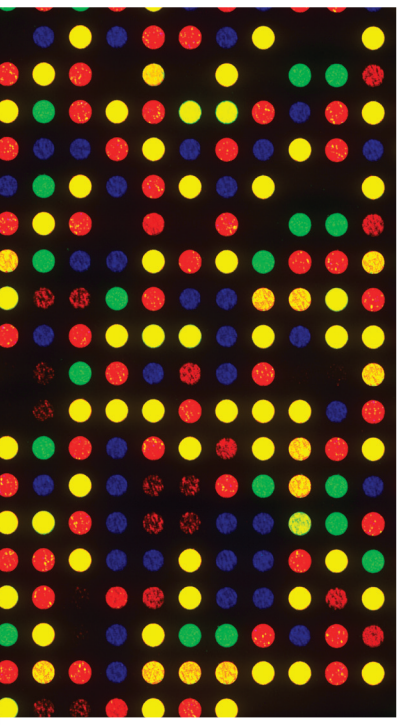
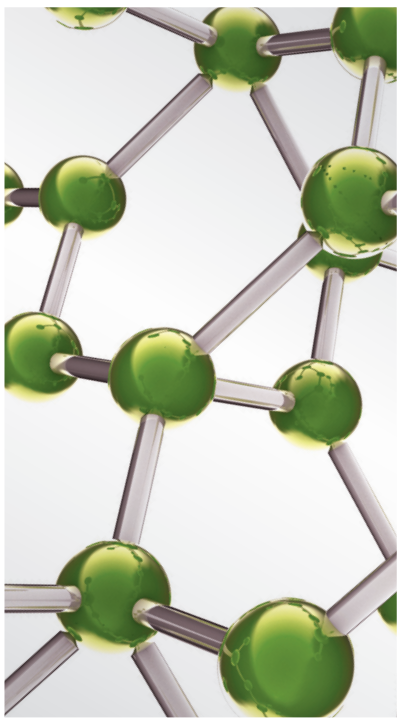
eCAM Evidence-Based Complementary and Alternative Medicine

Complementary and Alternative Medicine and Cancer Survivorship

Guest Editors: Alyson Huntley, Beverley de Valois, Tieraona Low Dog, and Francesca Borrelli



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Editorial Board

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Editorial

Complementary and Alternative Medicine and Cancer Survivorship

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In the UK, the Cancer Reform Strategy 2007 outlined the need for a National Cancer Survivorship Initiative to improve the care and support provided for those living with and beyond cancer. This is reflected across the world with health care research investigating new models of cancer care which include helping people to live healthily after cancer, helping them to prevent recurrence of cancer, to return to as normal a life as possible after treatment, and to support people living with active or advanced cancer.

The US National Cancer Institute defines an individual as a cancer survivor from the time of cancer diagnosis, through the balance of his or her life. Evidence from qualitative studies informs us that supportive care is wanted by cancer patients but it is felt there is a lack of appropriate support services. Complementary and alternative medicine (CAM) can play an important role in this approach.

This is why we felt it was important to propose a special issue on CAM and cancer survivorship. We also felt it was important to take a broad view not only across a wide range of therapies and interventions, some of which are unproven, but equally across a range of methodologies from in vitro studies to qualitative reports. We are pleased to say we achieved that with this special issue.

Four of the included papers discuss in vitro studies investigating the mechanisms of Traditional Chinese Medicine (TCM) and Ayurvedic medicine on cancer cell biology. Two reviews discuss the role of inflammation and its treatment in cancer. M. Sun and colleagues discuss Kushen, which has a long history of use in TCM to treat inflammatory diseases and cancer. This review consolidates the evidence base for Kushen in modulating molecular pathways in tumours. The review by V. N. Sumantran contains a discussion on the shared pathology of inflammation of cancer and metabolic syndrome in the context of the Ayurvedic concept of "Ama." A further review by Z. Wang and colleagues discusses the current understanding of the potential mechanisms of TCM in cancer therapy, and specifically the cancer glycolytic pathway. We have also included a study led by S. Sheikh which provides evidence for an Ayurvedic herbomineral preparation and its effects on the human cancer cell lines, and apparent lack of toxicity both in animals and human subjects.

Nutritional and herbal therapies are also covered in four clinical papers. H. Othman writes on a novel approach to the role of honey in health care in developing countries. Whilst the author discusses honey as a natural immune booster, anti-inflammatory and antimicrobial agent, cancer "vaccine," and a promoter for healing chronic ulcers and wounds, he also takes the argument further by suggesting that bee farming could provide both income and health benefits in developing countries.

M. C. S. Araujo controlled trial of *Uncaria tomentosa* shows that it may be effective in aiding recovery from chemotherapy-induced neutropenia for women with breast cancer. In a review of 1,217 case reports sourced from four Chinese databases (from 1958 to 2011), G. Yang et al. report that chemo-/radiotherapy-induced leukopenia was the most common type of condition treated by TCM. The paper by J. N. Lai and colleagues describes prescription patterns of TCM for breast cancer in Taiwan and shows that 81.5% of women

with breast cancer use TCM and 18% of them seek TCM for treating their breast cancer. Commonly used herbals were Jia-wei-xiao-yao-san, dang qui, and ren shen, and the authors conclude that the effects of these herbs should be taken into account by healthcare providers.

Two papers focus on the development of tools for CAM research. Patient reported outcomes (PROs) used in yoga intervention studies for cancer survivors from 2004–2011 are explored by S. N. Culos-Reed. This research provides new directions for examining clinical significance using PROs such as quality of life and psychosocial or symptom measures. In addition, J. J. Mao et al. report on the development and validation of a measure of cancer survivors' attitudes and beliefs about CAM. This 15-item instrument is based on the theory of planned behaviour and has a 3-factor structure: expected benefits, perceived barriers, and subjective norms related to CAM use by cancer patients. This study provides preliminary evidence that the instrument produces reliable and valid scores to measure attitudes and beliefs related to CAM use among cancer patients.

This special issue covers several aspects of physical and mind body therapies in cancer care. J. L. Ryan and colleagues look at CAM interventions for cancer related stress including mindfulness, yoga, Tai Chi Chuan, acupuncture, energy-based techniques, and physical activity. Whilst the evidence base for these studies is often limited, the authors conclude that some these approaches could be integrated into standard cancer care.

A novel mixed method review of dragon boat racing for breast cancer survivors provides a fascinating insight into this supportive therapy. This narrative review summarizes findings from quantitative and qualitative research supporting the hypothesis that dragon boat paddling is safe for women recovering from breast cancer, and showing that it has been embraced as a complementary exercise therapy by cancer survivors.

We have two studies which examined the role of massage for cancer patients using both quantitative and qualitative methodologies. A pilot study by N. A. Hodgson et al. investigates the effects of reflexology and Swedish massage therapy on physiologic stress, pain, and mood in older cancer survivors residing in nursing homes. They showed a significant decline in salivary cortisol and pain, and improvements in mood. S. L. Ackerman and colleagues describe parent caregivers' experience of the effects of massage and acupressure for their children undergoing haematopoietic cell transplantation. Benefits for both children and parents are described.

This special issue demonstrates the breadth of CAM research for cancer survivorship, including many novel and innovative approaches. We hope you find it stimulating and useful.

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Review Article

Yoga & Cancer Interventions: A Review of the Clinical Significance of Patient Reported Outcomes for Cancer Survivors

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Limited research suggests yoga may be a viable gentle physical activity option with a variety of health-related quality of life, psychosocial and symptom management benefits. The purpose of this review was to determine the clinical significance of patient-reported outcomes from yoga interventions conducted with cancer survivors. A total of 25 published yoga intervention studies for cancer survivors from 2004–2011 had patient-reported outcomes, including quality of life, psychosocial or symptom measures. Thirteen of these studies met the necessary criteria to assess clinical significance. Clinical significance for each of the outcomes of interest was examined based on 1 standard error of the measurement, 0.5 standard deviation, and relative comparative effect sizes and their respective confidence intervals. This review describes in detail these patient-reported outcomes, how they were obtained, their relative clinical significance and implications for both clinical and research settings. Overall, clinically significant changes in patient-reported outcomes suggest that yoga interventions hold promise for improving cancer survivors' well-being. This research overview provides new directions for examining how clinical significance can provide a unique context for describing changes in patient-reported outcomes from yoga interventions. Researchers are encouraged to employ indices of clinical significance in the interpretation and discussion of results from yoga studies.

1. Introduction

Physical activity is widely accepted as beneficial for cancer survivors both on and off treatment [1]. It is recommended that adult survivors engage in the same amount of physical activity as healthy older adults, with adaptations made as necessary [2]. This recommendation is supported by a substantive amount of evidence documenting the beneficial effects of PA on quality of life, psychosocial, and physical/symptom outcomes [1]. Within this growing body of physical activity and cancer research, there have been calls to examine modes of physical activity from the area of complementary medicine as a means of improving participation rates and long-term adherence [3]. This approach is particularly important when considering potential additional barriers experienced during a cancer diagnosis, its subsequent treatments, and ongoing recovery [3, 4].

Yoga is quickly emerging as an important complementary medicine therapeutic approach for cancer survivors. Ross and Thomas' [5] review of exercise and yoga highlights

that yoga is as beneficial as more traditional types of physical activity at improving a variety of health-related outcome measures (with the exception of physical fitness outcomes) in both healthy individuals and those with various health conditions (e.g., cancer). It concludes that yoga is a potentially beneficial gentle form of physical activity for cancer survivors and continues to receive growing research attention in cancer populations [5].

Additionally, four recent reviews have summarized findings specifically on yoga for cancer [6–9]. Smith and Pukall [6] conducted the first systematic review of the yoga and cancer research to date. This review reported both the characteristics and effect sizes of ten studies, including six randomized controlled trials. The authors documented large variability across studies (i.e., yoga type, population, sample size, and intervention duration) as well as methodological limitations. Despite these issues, generally positive results, especially in terms of psychological outcomes, were noted based on a calculation of effect sizes and narrative summary of reported results. In addition, a recently published meta-analysis aimed to determine effects of yoga on quality of life, psychological, and physical health in cancer survivors [7]. Ten studies were examined, including both yoga and mindfulness-based stress reduction (MBSR) interventions, due to the inclusion of yoga in MBSR. Although the results are preliminary and should be interpreted cautiously, intervention groups showed significantly greater improvements in psychological health than waitlist or supportive therapy control groups [7]. Results were inconclusive for quality of life and physical health outcomes. Undoubtedly, research examining yoga for cancer survivors is in its infancy. However, as research in this area continues to rapidly grow and yoga is increasingly integrated into cancer care, it is imperative the clinical benefits of yoga for cancer survivors are better understood and emphasized within clinical and posttreatment survivorship care. Thus the focus of the current study is to better determine the implications of the existing research on yoga for cancer survivors by evaluating additional indicators of clinical significance.

Reviews of the research on yoga for cancer survivors to date have relied on the interpretation of effect sizes and subjective observation of trends. Subjective interpretation of trends is often heavily influenced by reporting of the *P*-value, which is commonly used as a statistical indicator of the benefits of an intervention. However, the *P*-value, often set at .05, indicates only whether or not observed changes are large enough to conclude that such differences were not caused by chance [24]. In addition, the *P*-value is largely contingent on sample size, with larger studies more likely to report statistical significance. Clinical significance, or minimal clinically important difference (MCID), may not involve statistical significance [25] and is considered a marker of the effectiveness of interventions that takes into account the practical importance of treatment effects [26]. Clinical significance also gives meaning to observed changes in terms of their implications for patient care [27, 28]. In the case of our current paper, clinical significance may also be used as a comparative metric of treatment effects between studies.

There are a number of widely accepted assessments of the clinical significance of change in an intervention, using both anchor-based (i.e., clinical) and distribution-based (i.e., statistical) assessments [26, 28]. Anchor-based approaches are methods that relate change to an external event, rating, or condition, while distribution-based methods link clinical significance to a statistical parameter of group or individual data [28]. Examination of the yoga and cancer intervention literature reveals minimal reporting of anchor-based metrics. Given this an anchor-based anchor-based approach for understanding clinical significance was not employed in the current overview of the literature.

Commonly reported distribution-based methods include one standard error of the measurement (1 SEM), 0.5 standard deviation (0.5 SD), and effect sizes. The SEM provides an index that incorporates both the variation and reliability of a sample on any measure expressed in the original metric of the measure it describes [29]. When examining the mean difference from pre- to postintervention, a value greater than 1 SEM is considered clinically significant. One SEM has been shown to consistently correlate with anchor-based measures of important difference and with an effect size of 0.5, if the reported reliability is ≥ 0.75 [29]. Caution must be used in interpreting the SEM, as this criterion is often predetermined from other studies and may not be derived directly from the study sample.

Second, the assessment of the clinical significance is often determined using 0.5 SD of the baseline measure as a "rule of thumb" or guideline [30, 31]. Specifically, pre-post mean differences larger than 0.5 SD on that scale are considered clinically significant. It has been suggested [26] the 0.5 SD is best used as an indicator of "meaningful difference" versus "minimal difference," suggesting a change that cannot be ignored. Third, effect size (ES) is a simple way of quantifying the differences between two groups, and by association, how large a clinical response is observed [32]. Helpful exploratory criteria are Cohen's convention of 0.20 for a small effect, 0.50 for a moderate effect, and 0.80 for a large effect [33]. Of note, 0.5 SD of the preintervention score (in the case of pre-post within subjects) or 0.5 of control baseline (in the case of between-groups) can equate with 0.50 ES (provided these measures are calculated using these same baseline measures as the denominator).

Finally confidence intervals (CI) provide a range of possible scores for a population parameter. Thus, in the case of the oft reported 95% CI, we can be 95% confident that our CI includes the population parameter [34]. The width of the CI reflects the precision of the data, with more narrow confidence intervals being more precise. CIs are not just a surrogate for *P* value reported statistical significance, as they also give us a window into both the size of the difference and precision in estimating the true difference [35].

In all cases, it is important not to use these indices (1 SEM, 0.5 SD, ES, CI) in the way *P* values often are: as arbitrary cut-off values of a study's given significance [36]. Rather, these values should be used concurrently to triangulate on and describe the range of one's findings, their relative magnitude of effect, and generalizability. Such a thorough examination of the clinical significance of published studies

on yoga for cancer survivors has not been completed to date. The purpose of this paper was to clarify how findings from yoga interventions for cancer survivors should be interpreted by implementing multiple methods for calculating clinical significance of patient-reported outcomes, including measures of general quality of life, psychosocial factors, and symptoms. Interpretation of the studies' findings consisted of examining both within group pre-post change in both control and pre-post design studies, as well as determining the magnitude of difference between treatment and control groups in control design studies. Factors that may influence clinical significance related to the study design, sample, specific intervention, and method of measurement were also documented.

2. Methods

2.1. Selection of Publications. This literature review of yoga interventions for cancer survivors, both on and off treatment, was completed in July 2011. To this end, a systematic search was conducted of the relevant databases, including PubMed, PsychInfo, Medline, Annotated Bibliography of Indian Medicine, Cochrane Library, Web of Science, and Google Scholar. Key search terms included *yoga, cancer, survivor, patient, intervention, quality of life, well-being, clinical significance, important change(s), important difference(s), and/or patient reported outcomes*. The following inclusion criteria were applied to the search: (1) must include a yoga intervention; (2) have a sample of exclusively adult cancer survivors (on or off treatment); (3) report at least pre- and post-intervention assessments; (4) include patient-reported outcomes related to quality of life, psychosocial, and/or symptom outcomes. Publications were excluded if they incorporated intervention components in addition to yoga (e.g., MBSR, comprehensive lifestyle change programs, physiotherapy), were published in a non-peer reviewed journal, or were not written in English.

2.2. Data Synthesis. The common indices of clinical significance used in the current overview were (1) 1 standard error of the measurement (1 SEM); (2) 0.5 standard deviation (0.5 SD); (3) both within and between-group difference effect sizes (ES: Hedge's g) and their respective confidence intervals (CI). In order to examine the clinical significance of findings for each yoga intervention study, both pre-post means and the SDs or SEs had to be available in order to calculate 1 SEM, 0.5 SD, ES, and CI. No follow-up time periods (if included) were analyzed, and only published data were accessed. From the initial 19 eligible publications, a further six were dropped because (a) SDs or SEs were not available; or (b) the same data were reported in duplicate publications. Data were extracted to examine changes pre-post intervention in both the yoga and control groups, as well as the relative difference between groups in the case of control design studies. Clinical significance was determined using the following criteria. First, the SEM was calculated as (pre-intervention SD $*$ $\sqrt{1}-$ Cronbach's alpha). If the Cronbach's alpha was not cited in the study it was derived from either a clinically relevant population, or from prior psychometric evaluations of the instrument. Second, 0.5 SD values were calculated from the baseline SD. Third, ES were calculated using Hedges g for both within-groups effects (post-pre/pooled SD) and between-groups effects (treatment mean difference-control mean difference/pooled change SD). These effects were interpreted following Cohen's convention of small (0.2), medium (0.5), and large (0.8) [33]. Fourth, CIs were calculated for both treatment and control within-subjects mean differences, between-groups mean differences, and their accompanying ES. ES and CIs were calculated using Comprehensive Meta-Analysis (Version 2) software [37]. Pre-post differences were evaluated based on their respective 1 SEM, 0.5 SD ES, and CI, while between-group differences were evaluated based on the control group 1 SEM, 0.5 SD, and the between-groups calculated ES and CI. Finally, given the aforementioned correlation between 1 SEM and an effect size of 0.5 if the reported reliability is ≥ 0.75 [29], the Pearson product-moment correlation coefficients were calculated to determine the strength of the linear dependence between the 1 SEM and 0.5 SD. As our primary purpose was to evaluate patient-reported outcomes in the yoga literature and given the comparatively small number of studies, no computation of study quality was completed in the current paper. In addition, given our focus on a number of different indices of clinical significance, the small number of studies and heterogeneity in terms of type of yoga, dose response, length of intervention, and outcome measures, average effect sizes across studies were not calculated nor meta-analyses performed. Although we intended that the literature search be inclusive of all existing studies, it did not follow other methods necessary to be considered a systematic review so as not to be redundant with other recent publications [6, 7].

3. Results

3.1. Description of Studies. The initial literature search resulted in a total of 25 publications. A review of abstracts reduced the final number to 19 publications based on the inclusion and exclusion criteria. Of the 19 publications reviewed, 14 contained enough data to be included in this paper and are summarized in Table 1. Note that Vadiraja et al. [16, 17] are from the same study sample and are therefore reported as one study. The resulting 13 studies included a variety of yoga interventions (with respect to type of yoga and duration), cancer types, and timing and content of assessments. Seven of the 13 studies employed a randomized controlled trial design, including a control group for comparison to the yoga intervention ($n = 6$ with a waitlist control group, $n = 1$ with an active control group). Six studies were single-group pre-post designs. Table 2 details all study results.

3.1.1. Study Designs. In the randomized controlled trial studies, mean age ranged from 46–60 years. Sample size in the treatment group at time 2 ranged from 13–45 participants. Cancer diagnoses were comprised primarily of breast cancer, with one study focused on lymphoma. Many participants

Table 1: (a) Studies Reviewed from the Yoga-Cancer Literature—Control Design. (b) Studies Reviewed from the Yoga-Cancer Literature—Single Group Design.

(a)

Author	Sample	Cancer Type and Treatment	Yoga Intervention	Control Group	Outcome Measures Reported in Current Review
Chandwani et al., 2010 [10]	Treatment: T1 = 30, T2 = 27 Control: T1 = 31, T2 = 31 Age range: 31–68 Mean age = 53	Breast (Stages 0–3) Chemotherapy ($n = 47$) Radiation therapy ($n = 61$)	60-minute classes twice weekly for 6 weeks Type: Vivekananda Yoga	Wait-list control	Quality of Life -SF-36 Psychosocial -CES-D, STAI Symptom -BFI, PSQI
Cohen et al., 2004 [11]	Treatment: T1 = 19, T2 = 16 Control: T1 = 19, T2 = 14 Age range: NR Mean age = 51	Lymphoma (Stages I–IV) Previous 12 months receiving chemotherapy	Weekly classes for 7 weeks (class length not reported) Type: Tibetan Yoga	Wait-list control	Psychosocial -CES-D, STAI Symptom -BFI, PSQI
Culos-Reed et al., 2006 [12]	Treatment: T1 = 20, T2 = 18 Control: T1 = 18, T2 = 18 Age range: NR Mean age = 51	Breast ($n = 32$), Other ($n = 6$) ≥3 months post-treatment	75 minute weekly classes for 7 weeks Type: Iyengar Yoga	Wait-list control	Quality of Life -EORTC QLQ-C30 Psychosocial -POMS
Danhauer et al., 2009 [13]	Treatment:T1 = 22, T2 = 13 Control: T1 = 22, T2 = 14 Age range: 38–79 Mean age = 55	Breast (Stages I–IV) Radiation therapy ($n = 9$) Chemotherapy ($n = 11$)	75-minute weekly classes for 10 weeks Type: Integral Yoga	Wait-list control	Quality of Life -FACT-B, SF-12 Psychosocial -CES-D, PANAS, FACIT-Sp Symptom -FACT-F, PSQI
Littman et al., 2011 [14]	Treatment: T1 = 32, T2 = 27 Control: T1 = 31, T2 = 27 Age range: 33–74 Mean age = 60	Breast (Stages 0–III) >3 months post-hemotherapy and/or post-radiation	75-minute classes five times per week for 26 weeks (combination in-facility and home-based practice) Type: Viniyoga	Wait-list control	Quality of Life -FACT-G Symptom -FACT-F

(a) Continued.

Author	Sample	Cancer Type and Treatment	Yoga Intervention	Control Group	Outcome Measures Reported in Current Review
Moadel et al., 2007 [15]	Treatment: T1 = 45, T2 = 45 Control: T1 = 26, T2 = 26 Age range: 28–75 Mean age = 54	Breast (Stages I–III) Surgery (n = 95) Radiation Therapy (n = 10)Chemotherapy (n = 27)Anti-estrogen Therapy (n = 30)	90 minute weekly classes for 12 weeks. Home practice encouraged Type: Hatha Yoga	Wait-list control	Quality of Life -FACT-G Psychosocial -FACIT-Sp Symptom -FACT-F
Vadiraja et al., 2009a and b [16, 17]	Treatment: T1 = 44, T2 = 42 Control: T1 = 44, T2 = 33 Age range: 30–70 Mean age = 46	Breast (Stages II-III) Radiation therapy (n = 88)	Minimum of 3 in-person 60-minute individual yoga sessions per week for 6 weeks. Home practice encouraged. Type: Integrated Yoga Program	3-4 sessions of brief supportive therapy w/education	Quality of Life -EORTC QoL C30 Psychosocial -PANAS, HADS

(b)

Author	Sample	Cancer Type and Treatment	Yoga Intervention	Outcome Measures Reported in Current Review
Bower et al., 2011 [18]	T1 = 12, T2 = 11 Age range: 46–65 Mean age = 54	Breast (Stages 0–2) All had completed radiation therapy or radiation therapy + chemotherapy	90-minute classes twice weekly for 12 weeks Type: Iyengar Yoga	Quality of Life -SF-36 Psychosocial -BDI-II Symptom -PSQI, FSI
Danhauer et al., 2008 [19]	T1 = 51, T2 = 43 Age range: 34–82 Mean age = 59	Ovarian (n = 37) Breast (n = 14) Radiation therapy (n = 5) Chemotherapy (n = 29)	75-minute weekly classes for 10 weeks Type: Integral Yoga	Quality of Life -FACT-G, SF-12 Psychosocial -CES-D, FACIT-Sp, PANAS, STAI Symptom -FACT-F
Duncan et al., 2008 [20]	T1 = 24, T2 = 22 Age range: NR Mean age = 49	Breast (42%) Gynecologic (16.6%) Lymphoma (12.5%) Currently on or <6 months post treatment	90 minute weekly classes for 10 weeks Type: Iyengar Yoga	Quality of Life -FACT-G Psychosocial -FACIT-Sp
Galantino et al., 2011 [21]	T1 = 10, T2 = 10 Age range: 50–71 Median age = 58	Breast (Stages I–III) >4 weeks post-chemotherapy and/or post-radiation, all women taking aromatase inhibitors	90-minute classes twice weekly for 8 weeks, home practice encouraged Type: Iyengar-inspired	Quality of Life -FACT-B

(b) Continued.

Author	Sample	Cancer Type and Treatment	Yoga Intervention	Outcome Measures Reported in Current Review
Speed-Andrews et al., 2010 [22]	T1 = 17, T2 = 17 Age range: not reported Mean age = 54	Breast (Stages I–III) Surgery ($n = 23$) Radiation therapy ($n = 19$) Chemotherapy ($n = 18$) Hormone therapy ($n = 10$)	Two different sessions; 90 minute classes twice weekly for 6 weeks and 90 minute classes 22 times over 12 weeks Type: Iyengar Yoga	Quality of Life -FACT-B, SF-36 Psychosocial -CES-D, STAI
Ülger and Yağlı, 2010 [23]	T1 = 20, T2 = 20 Age range: 30–50 Mean age = 41	Breast >6 months post-chemotherapy	60 minute weekly classes for 8 weeks Type: Not specified ("Classical Yoga")	Quality of Life -NHP Psychosocial -STAI

Abbreviations: T1: baseline; T2: follow-up; SF-36 and SF-12: Medical Outcomes Study Short-Form Health Survey; EORTC QLQ C30: European Organization for Research and Treatment of Cancer-Quality of Life C30; FACT-B: Functional Assessment of Cancer Therapy—Breast; FACT-G: Functional Assessment of Cancer Therapy—General; NHP: Nottingham Health Profile; BDI: Beck Depression Inventory; CES-D 20: Center for Epidemiologic Studies Depression Scale—20 Item; STAI: State/Trait Anxiety Inventory; POMS: Profile of Mood States; PANAS: Positive and Negative Affect Schedule; FACIT-Sp: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being; HADS: Hospital Anxiety and Depression Scale; BFI: Brief Fatigue Inventory; PSQI: Pittsburgh Sleep Quality Index; FSI: Fatigue Symptom Inventory; FACT-F: Functional Assessment of Cancer Therapy-Fatigue. NR: Not Reported.

Table 2: (a) HRQL Measures—Control DesignTable. (b) Psychosocial Measures—Control Design. (c) Symptom Measures—Control Design. (d) HRQL Measures—Single Group Design. (e) Psychosocial Measures—Single Group Design. (f) Symptom Measures—Single Group Design.

(a)

Study	Outcome measure	Internal consistency (Cronbach α)	SEM (Baseline SD $\times \sqrt{1 -$ Cronbach α)		Baseline 0.5 SD		Baseline Mean (SD)		Within-Groups Mean Difference (95% CI)		Within-Groups Effect Size—Hedges' g (95% CI)		Between Groups Mean Difference (95% CI)	Between Groups Effect size—Hedges' g (95% CI)
			Yoga	Control	Yoga	Control	Yoga	Control	Yoga	Control	Yoga	Control		
Chandwani et al., 2010 [10]	SF36 PCS (Physical)	.90	2.60	3.40	4.10	5.30	41.50 (8.20)	41.8 (10.6)	1.60 [−1.74, 4.94]	−2.80 [−6.35, 0.75]	0.18 [−0.19, 0.54]	−0.27 [−0.62, 0.08]	4.40 [−0.52, 9.32][c]	0.46 [−0.06, 0.97]
	SF36 MCS (Mental)	.90	3.80	3.50	6.00	5.60	47.80 (12.00)	48.0 (11.1)	1.90 [−2.16, 5.96]	1.90 [−1.76, 5.56]	0.17 [−0.19, 0.54]	0.18 [−0.17, 0.52]	0.00 [−5.45, 5.45]	0.00 [−0.51, 0.51]
Culos-Reed et al., 2006 [12]	EORTC-QoL (Overall)	.89	8.50	4.26	12.82	6.43	64.58 (25.63)	62.04 (12.85)	13.66 [2.85, 24.47][ab]	0.46 [−6.16, 7.08]	0.56 [0.08, 1.04]*	0.03 [−0.41, 0.47]	13.20 [0.52, 25.88][cd]	0.67 [0.01, 1.32]*
	EORTC-Emo (Emotional)	.80	9.01	6.64	10.07	7.43	79.58 (20.14)	75.00 (14.85)	4.22 [−4.05, 12.49]	−4.17 [−11.57, 3.23]	0.23 [−0.22, 0.67]	−0.25 [−0.70, 0.20]	8.39 [−2.71, 19.49][cd]	0.48 [−0.16, 1.13]
Danhauer et al., 2009 [13]	FACT-B (Overall)	.90	6.30	7.70	10.00	12.20	104.90 (19.90)	101.1 (24.4)	9.90 [−0.71, 20.51][a]	−2.70 [−17.80, 12.40]	0.48 [−0.06, 1.02]	−0.09 [−0.58, 0.41]	12.6 [−6.12, 31.32][cd]	0.49 [−0.25, 1.24]
	FACT-SWB (Social)	.69	2.60	3.00	2.60	2.70	23.30 (4.70)	21.4 (5.4)	−0.20 [−2.84, 2.44]	−1.00 [−4.26, 2.26]	−0.04 [−0.55, 0.47]	−0.15 [−0.65, 0.35]	0.80 [−3.43, 5.03]	0.14 [−0.60, 0.87]
	FACT-FWB (Functional)	.86	2.60	3.10	2.90	3.50	18.70 (5.70)	18.0 (6.9)	3.20 [0.33, 6.07][ab]	−0.60 [−4.38, 3.18]	0.57 [0.01, 1.12]*	−0.08 [−0.57, 0.42]	3.80 [−1.00, 8.60][cd]	0.58 [−0.17, 1.34]
	FACT-EWB (Emotional)	.69	2.00	2.70	2.00	2.60	18.10 (3.90)	18.5 (5.2)	2.70 [0.74, 4.66][ab]	−0.30 [−3.29, 2.69]	0.70 [0.13, 1.28]*	−0.05 [−0.54, 0.44]	3.00 [−0.63, 6.63][cd]	0.61 [−0.15, 1.35]
	FACT-PWB (Physical)	.81	3.00	2.20	3.50	2.60	19.70 (7.00)	20.7 (5.1)	2.80 [−1.18, 6.78]	0.40 [−2.44, 3.24]	0.36 [−0.17, 0.89]	0.07 [−0.42, 0.56]	2.40 [−2.44, 7.24][c]	0.36 [−0.38, 1.10]
	SF-12 PCS (Physical)	.86	4.50	3.80	6.1 0	5.10	42.70 (12.10)	40.6 (10.1)	2.10 [−4.56, 8.76]	2.10 [−3.68, 7.88]	0.16 [−0.35, 0.67]	0.18 [−0.32, 0.68]	0.00 [−8.79, 8.79]	0.00 [−0.73.0.73]
	SF-12 MCS (Mental)	.81	4.40	4.50	5.10	5.10	43.40 (10.10)	49.9 (10.2)	8.80 [3.97, 13.63][ab]	−2.40 [−8.90, 4.10]	0.93 [0.30, 1.55]**	−0.18 [−0.68, 0.31]	11.20 [3.01, 19.39][cd]	1.00 [0.22, 1.78]**
Littman et al., 2011 [14]	FACT-B (Overall)	.90	2.97	4.49	4.70	7.10	89.00 (9.40)	87.8 (14.2)	1.30 [−2.58, 5.18]	−0.10 [−5.61, 5.41]	0.12 [−0.24, 0.49]	−0.01 [−0.37, 0.36]	1.40 [−5.34, 8.14]	0.11 [−0.42, 0.64]
	FACT-SWB (Social)	.69	2.84	3.01	2.60	2.70	21.70 (5.10)	21.7 (5.4)	0.40 [−1.51, 2.31]	−0.80 [−2.96, 1.40]	0.08 [−0.29, 0.44]	−0.14 [−0.50, 0.23]	1.20 [−1.68, 4.08]	0.22 [−0.31, 0.75]
	FACT-FWB (Functional)	.86	1.23	1.46	1.70	2.60	22.70 (3.30)	21.6 (5.1)	−0.10 [−1.47, 1.27]	0.10 [−1.75, 1.95]	−0.03 [−0.39, 0.34]	0.02 [−0.35, 0.39]	0.20 [−2.11, 2.51]	0.05 [−0.50, 0.57]
	FACT-EWB (Emotional)	.69	1.56	1.45	1.40	1.30	19.80 (2.80)	20.3 (2.6)	0.50 [−0.84, 1.84]	0.50 [−0.59, 1.59]	0.14 [−0.23, 0.51]	0.17 [−0.20, 0.54]	0.00 [−1.73, 1.73]	0.00 [−0.53, −0.53]
	FACT-PWB (Physical)	.81	1.00	1.7 0	1.20	2.00	24.70 (2.30)	24.2 (3.9)	0.70 [−0.08, 1.48]	0.10 [−1.47, 1.67]	0.33 [−0.05, 0.71]	0.02 [−0.34, 0.39]	0.60 [−1.16, 2.36]	0.18 [−0.35, 0.71]
Moadel et al., 2007 [15]	FACT-G (Overall)	.89	5.96	8.11	8.99	12.23	76.53 (17.98)	77.54 (24.45)	1.54 [−3.60, 6.68]	−7.16 [−16.25, 1.93]	0.09 [−0.20, 0.37]	−0.30 [−0.68, 0.09]	8.70 [−0.96, 18.36][c]	0.43 [−0.05, 0.91]
	FACT-SWB (Social)	.69	3.47	3.46	3.12	3.11	20.98 (6.23)	22.12 (6.22)	−0.30 [−1.99, 1.39]	−3.95 [−6.41, −1.49][ab]	−0.05 [−0.34, 0.24]	−0.60 [−1.00, −0.19]**	3.65 [0.75, 6.56][cd]	0.60 [0.11, 1.09]*
	FACT-FWB (Functional)	.80	2.85	3.45	3.19	3.86	18.33 (6.38)	18.19 (7.72)	−0.16 [−2.08, 1.76]	−1.98 [−4.88, 0.92]	−0.02 [−0.31, 0.26]	−0.26 [−0.63, 0.12]	1.82 [−1.53, 5.17]	0.26 [−0.22, 0.74]
	FACT-EWB (Emotional)	.74	2.43	3.03	2.39	2.97	16.36 (4.77)	16.50 (5.94)	1.83 [0.51, 3.14]**	−0.41 [−2.65, 1.83]	0.40 [0.10, 0.70]**	−0.07 [0.44, 0.31]	2.24 [−0.19, 4.67]	0.44 [−0.05, 0.92]
	FACT-PWB (Physical)	.82	2.24	2.98	2.64	3.52	20.87 (5.28)	20.73 (7.03)	0.16 [−1.51, 1.83]	−0.82 [−3.39, 1.75]	0.03 [−0.26, 0.32]	−0.12 [−0.49, 0.26]	0.98 [−1.96, 3.91]	0.16 [−0.32, 0.64]

(a) Continued.

Study	Outcome measure	Internal consistency (Cronbach α)	SEM (Baseline SD $\times \sqrt{1 -$ Cronbach α)		Baseline 0.5 SD		Baseline Mean (SD)		Within-Groups Mean Difference (95% CI)		Within-Groups Effect Size—Hedges' g (95% CI)		Between Groups Mean Difference (95% CI)	Between Groups Effect size—Hedges' g (95% CI)
			Yoga	Control	Yoga	Control	Yoga	Control	Yoga	Control	Yoga	Control		
Vadiraja et al., 2009 [16]	EORTC-Phys (Physical)	.71	12.49	16.68	11.60	15.49	73.20 (23.20)	62.72 (30.98)	0.06 [−7.30, 7.42]	6.24 [−4.19, 16.66]	0.00 [−0.29, 0.30]	0.20 [−0.14, 0.54]	6.18 [−6.24, 18.60]	0.23 [−0.23, 0.68]
	EORTC-Role (Role)	.52	24.15	25.22	17.43	18.20	72.72 (34.86)	71.59 (36.40)	7.16 [−3.32, 17.64]	1.26 [−11.81, 14.33]	0.20 [−0.10, 0.50]	0.03 [−0.30, 0.37]	5.90 [−10.64, 22.44]	0.16 [−0.29, 0.61]
	EORTC-Emo (Emotional)	.80	8.84	7.80	9.89	8.72	56.45 (19.77)	51.58 (17.44)	18.67 [12.47, 24.87][ab]	7.65 [0.48, 14.82]	0.89 [0.54, 1.25]***	0.36 [−0.01, 0.70]*	11.02 [1.57, 20.47][cd]	0.53 [0.07, 0.99]*
	EORTC-Cog (Cognitive)	.73	9.35	10.97	9.00	10.56	85.29 (18.00)	82.67 (21.12)	5.28 [0.13, 10.43]	−1.90 [−9.66, 5.86]	0.30 [0.00, 0.61]*	−0.08 [−0.42, 0.25]	7.18 [−1.83, 16.19]	0.36 [−0.10, 0.82]
	EORTC-Soc (Social)	.77	12.73	11.72	13.28	12.22	52.82 (26.55)	52.41 (24.43)	2.14 [−5.53, 9.81]	−2.48 [−10.78, 5.82]	0.08 [−0.22, 0.38]	−0.10 [−0.43, 0.23]	4.62 [−6.74, 15.98]	0.18 [−0.27, 0.64]

(b)

Study	Outcome measure	Internal consistency (Cronbach α)	SEM (Baseline SD $\times \sqrt{1 -$ Cronbach α)		Baseline 0.5 SD		Baseline Mean (SD)		Within-Groups Mean Difference (95% CI)		Within-Groups Effect Size—Hedges' g (95% CI)		Between Groups Mean Difference (95% CI)	Between Groups Effect size—Hedges' g (95% CI)
			Yoga	Control	Yoga	Control	Yoga	Control	Yoga	Control	Yoga	Control		
Chandwani et al., 2010 [10]	CES-D 20 (Depression)	.87	3.35	2.42	4.65	3.35	11.60 (9.30)	10.50 (6.70)	−5.00 [−8.85, −1.15][ab]	−3.50 [−7.23, 0.24][a]	−0.48 [−0.86, −0.09]*	−0.32 [−0.67, 0.03]	−1.50 [−6.87, 3.87]	−0.14 [−0.65, 0.37]
	STAI-State (Anxiety)	.94	3.36	2.45	6.85	5.00	36.30 (13.70)	32.70 (10.00)	−8.30 [−13.09, −3.51][ab]	−2.50 [−6.75, 1.75][a]	−0.63 [−1.04, −0.23]**	−0.20 [−0.55, 0.15]	−5.80 [−12.18, 0.58][cd]	−0.46 [−0.98, 0.05]
Cohen et al., 2004 [11]	CES-D 20 (Depression)	.93	2.91	2.27	5.50	4.29	10.20 (11.00)	9.60 (8.57)	−1.20 [−5.91, 3.51]	.10 [−3.79, 4.00]	−0.12 [−0.58, 0.35]	0.01 [−0.48, 0.51]	−1.30 [−7.52, 4.92]	−0.15 [−0.85, 0.55]
	STAI-State (Anxiety)	.95	2.75	3.26	6.15	7.30	34.30 (12.30)	37.80 (14.60)	−0.20 [−5.54, 5.14]	−4.00 [−10.65, 2.65][a]	−0.02 [−0.48, 0.45]	−0.30 [−0.80, 0.21]	−3.80 [−12.24, 4.64][c]	−0.31 [−1.02, 0.39]
Culos-Reed et al., 2006 [12]	POMS-D (Depression)	.95	1.76	1.14	3.93	2.55	4.70 (7.86)	5.44 (5.10)	−2.48 [−5.68, 0.72][a]	0.06 [−2.54, 2.66]	−0.34 [−0.80, 0.11]	0.01 [−0.43, 0.45]	−2.54 [−6.66, 1.58][c]	−0.39 [−1.04, 0.25]
Danhauer et al., 2009 [13]	CES-D 20 (Depression)	.93	2.57	3.89	4.85	7.35	16.30 (9.70)	16.60 (14.70)	−8.20 [−13.27, −3.17][ab]	1.20 [−7.14, 9.54]	−0.82 [−1.42, −0.22]**	0.07 [−0.42, 0.57]	−9.40 [−19.34, 0.54][cd]	−0.69 [−1.45, 0.06]
	PANAS-P (Positive Affect)	.87	3.17	3.53	4.40	4.90	32.70 (8.80)	30.60 (9.80)	5.50 [1.16, 9.84][ab]	1.20 [−4.21, 6.61]	0.64 [0.08, 1.21]*	0.11 [−0.39, 0.60]	4.30 [−2.71, 11.31][c]	0.45 [−0.29, 1.19]
	PANAS-N (Negative Affect)	.87	2.99	3.39	4.15	4.70	19.00 (8.30)	18.50 (9.40)	−5.00 [−8.91, −1.09][ab]	1.40 [−3.63, 6.43]	−0.65 [−1.22, 0.08]*	0.14 [−0.36, 0.63]	−6.40 [−12.84, 0.04][cd]	−0.73 [−1.49, 0.03]
	FACIT-Sp (Spiritual Well-Being)	.87	2.38	2.60	3.30	3.60	23.30 (6.60)	23.20 (7.20)	2.70 [−0.92, 6.31][a]	−1.70 [−6.16, 2.76]	0.38 [−0.15, 0.91]	−0.19 [−0.69, 0.31]	4.40 [−1.40, 10.20][cd]	0.56 [−0.19, 1.30]
Moadel et al., 2007 [15]	FACIT-Sp (Spiritual Well-Being)	.87	3.33	3.99	4.62	5.53	37.87 (9.24)	34.58 (11.06)	−1.02 [−3.59, 1.55]	−1.83 [−6.49, 2.83]	−0.11 [−0.40, 0.17]	−0.15 [−0.52, 0.23]	0.81 [−4.08, 5.70]	0.08 [−0.40, 0.56]
Vadiraja et al., 2009 [16]	PANAS-P (Positive Affect)	.87	2.62	2.66	3.64	3.69	24.05 (7.28)	21.81 (7.37)	3.80 [1.62, 5.98][ab]	1.52 [−1.17, 4.21]	0.52 [0.20, 0.84]***	0.19 [−0.15, 0.53]	2.28 [−1.14, 5.70]	0.30 [−0.15, 0.76]
	PANAS-N (Negative Affect)	.87	3.82	3.18	5.30	4.41	22.15 (10.60)	25.22 (8.82)	−9.24 [−12.41, −6.074][ab]	−3.37 [−6.78, 0.04][a]	−0.86 [−1.21, −0.51]***	−0.33 [−0.67, 0.01]	−5.87 [−10.56, −1.18][cd]	−0.57 [−1.03, −0.11]*

(b) Continued.

Study	Outcome measure	Internal consistency (Cronbach α)	SEM (Baseline SD $\times \sqrt{1}$ − Cronbach α)		Baseline 0.5 SD		Baseline Mean (SD)		Within-Groups Mean Difference (95% CI)		Within-Groups Effect Size—Hedges' g (95% CI)		Between Groups Mean Difference (95% CI)	Between Groups Effect size—Hedges' g (95% CI)
			Yoga	Control	Yoga	Control	Yoga	Control	Yoga	Control	Yoga	Control		
Vadiraja et al., 2009b [17]	HADS-A (Anxiety)	.79	1.77	1.82	1.94	1.99	8.05 (3.87)	9.35 (3.98)	−3.17 [−4.27, −2.07][ab]	−1.23 [−2.56, 0.10]	−0.86 [−1.21, −0.51]***	−0.31 [−0.65, 0.03]	−1.94 [−3.65, −0.23][c]	−0.51 [−0.97, −0.05]*
	HADS-D (Depression)	.87	1.45	1.25	2.01	1.74	7.57 (4.02)	8.00 (3.47)	−3.43 [−4.57, −2.29][ab]	−1.47 [−2.71, −0.23][a]	−0.89 [−1.25, −0.54]***	−0.40 [−0.74, −0.05]*	−1.96 [−3.65.−0.27][cd]	−0.52 [−0.98, −0.06]*

(c)

Study	Outcome measure	Internal consistency (Cronbach α)	SEM (Baseline SD $\times\sqrt{1}$ − Cronbach's α)		Baseline SD 0.5		Baseline Mean (SD)		Within-Groups Mean Difference (95% CI)		Within-Groups Effect size—Hedges' g (95% CI)		Between Groups Mean Difference (95% CI)	Between Groups Effect size—Hedges' g (95% CI)
			Yoga	Control	Yoga	Control	Yoga	Control	Yoga	Control	Yoga	Control		
Chandwani et al., 2010 [10]	BFI (Fatigue)	.94	0.39	0.54	0.80	1.10	2.30 (1.60)	2.30 (2.20)	−0.40 [−1.58, 0.78][a]	0.20 [−1.17, 1.57]	−0.12 [−0.49, 0.24]	0.05 [−0.29, 0.39]	−0.60 [−2.44, 1.24][c]	−0.17 [−0.68, 0.34]
	PSQI (Sleep)	.84	1.52	1.56	1.90	1.95	7.30 (3.80)	7.10 (3.90)	−0.70 [−2.46, 1.06]	−0.40 [−2.15, 1.35]	−0.15 [−0.51, 0.22]	−0.08 [−0.42, 0.27]	−0.30 [−2.79, 2.19]	−0.06 [−0.57, 0.45]
Cohen et al., 2004 [11]	BFI (Fatigue)	.96	0.48	0.44	1.20	1.10	3.10 (2.40)	2.80 (2.20)	0.00 [−1.03, 1.03]	0.30 [−0.72, 1.32]	0.00 [−0.47, 0.47]	0.15 [−0.35, 0.64]	−0.30 [−1.76, 1.16]	−0.14 [−0.84, 0.56]
	PSQI (Sleep)	.84	2.00	1.88	2.50	2.35	6.50 (5.00)	7.20 (4.70)	−0.70 [−2.82, 1.42]	0.90 [−1.23, 3.03]	−0.16 [−0.62, 0.32]	0.21 [−0.29, 0.71]	−1.60 [−4.62, 1.42]	−0.37 [−1.07, 0.34]
Danhauer et al., 2009 [13]	FACT- F (Fatigue)	.95	3.00	2.64	6.70	5.90	30.10 (13.40)	32.70 (11.80)	9.70 [2.87, 16.53][ab]	−0.10 [−7.45, 7.25]	0.72 [0.14, 1.30]*	−0.01 [−0.50, 0.49]	9.80 [−0.27, 19.87][cd]	0.71 [−0.04, 1.47]
	PSQI (Sleep)	.84	1.88	2.12	2.35	2.65	8.30 (4.70)	8.60 (5.30)	−2.20 [−4.65, 0.25][a]	−1.60 [−4.14, 0.94]	−0.46 [−1.00, 0.08]	−0.31 [−0.81, 0.20]	−0.60 [−4.14, 2.94]	−0.12 [−0.86, 0.61]
Littman et al., 2011 [14]	FACT-F (Fatigue)	.95	1.30	1.90	2.90	4.25	43.10 (5.8)	43.20 (8.50)	1.9 [−0.20, 4.00][a]	−0.10 [−3.69, 3.49]	0.33 [−0.05, 0.71]	−0.01 [−0.38, 0.36]	2.00 [−2.16, 6.16][c]	0.25 [−0.27, 0.78]
Moadel et al., 2007 [15]	FACT-F (Fatigue)	.95	2.75	3.22	6.16	7.21	34.27 (12.31)	35.88 (14.42)	2.29 [−1.11, 5.69]	−1.11 [−6.50, 4.30]	0.19 [−0.10, 0.48]	−0.08 [−0.45, 0.30]	3.40 [−2.66, 9.46][c]	0.27 [−0.21, 0.75]

(d)

Study	Outcome measure	Internal consistency (Cronbach α)	SEM (Baseline SD $\times\sqrt{1}$ − Cronbach's α)	Baseline 0.5 SD	Baseline mean (SD)	Within-Groups mean difference (95% CI)	Within-Groups Effect Size—Hedges' g (95% CI)
Bower et al., 2011 [18]	SF36 Gen Health (Overall)	.81	9.63	11.05	50.50 (22.10)	14.50 [1.44, 27.56][ab]	0.61 [0.00, 1.21]*
Danhauer et al., 2008 [19]	FACT-G (Overall)	.89	3.55	5.35	75.90 (10.70)	3.50 [0.33, 6.67]	0.32 [0.02, 0.63]*
	FACT-SWB (Social)	.69	2.39	2.15	24.00 (4.30)	0.80 [−0.53, 2.13]	0.18 [−0.12, 0.47]
	FACT-FWB (Functional)	.80	1.92	2.15	18.00 (4.30)	0.80 [−0.44, 2.04]	0.19 [−0.11, 0.49]
	FACT-EWB (Emotional)	.74	1.07	1.05	14.00 (2.10)	−0.20 [−0.81, 0.41]	−0.10 [−0.39, 0.20]
	FACT-PWB (Physical)	.82	2.42	2.85	20.00 (5.70)	2.10 [0.47, 3.73]	0.38 [0.07, 0.68]*

(d) Continued.

Study	Outcome measure	Internal consistency (Cronbach α)	SEM (Baseline SD $\times\sqrt{1}$ − Cronbach's α)	Baseline 0.5 SD	Baseline mean (SD)	Within-Groups mean difference (95% CI)	Within-Groups Effect Size—Hedges' g (95% CI)
	SF12 PCS (Physical)	.86	4.27	5.70	41.20 (11.40)	2.30 [−0.98, 5.58]	0.21 [−0.09, 0.50]
	SF12 MCS (Mental)	.81	3.75	4.30	48.40 (8.60)	3.60 [1.04, 6.16]	0.41 [0.11, 0.72]**
Duncan et al., 2008 [20]	FACT-G (Overall)	.89	4.70	7.30	64.6 (14.16)	10.63 [4.44, 16.82][ab]	0.69 [0.24, 1.14]**
Galantino et al., 2011 [21]	FACT-B (Overall)	.90	6.38	10.09	89.33 (20.18)	16.72 [−5.07, 28.37][ab]	0.81 [0.14, 1.48]*
Speed-Andrews et al., 2010 [22]	FACT-B (Overall)	.90	6.67	10.55	108.20 (21.10)	8.90 [−1.51, 19.31][a]	0.39 [−0.08, 0.86]
	FACT-SWB (Social)	.69	2.95	2.65	20.70 (5.30)	0.70 [−1.84, 3.24]	0.13 [−0.33, 0.58]
	FACT-FWB (Functional)	.86	1.83	2.45	19.90 (4.90)	1.80 [−0.29, 3.89]	0.39 [−0.08, 0.86]
	FACT-EWB (Emotional)	.69	2.67	2.40	15.80 (4.80)	2.10 [−0.37, 4.57]	0.39 [−0.09, 0.86]
	FACT-PWB (Physical)	.81	2.31	2.65	20.90 (5.30)	2.00 [−0.37, 4.37]	0.38 [−0.09, 0.85]
	SF-36 PCS (Physical)	.90	3.38	5.35	45.50 (10.70)	3.70 [−1.41, 8.81][a]	0.32 [−0.14, 0.79]
	SF-36 MCS (Mental)	.90	2.85	4.50	44.40 (9.00)	4.20 [−0.01, 8.41][a]	0.45 [−0.03, 0.93]
Ülger and Yağlı, 2010 [23]	NHP-Total (Overall)	.70	12.64	11.54	103.23 (23.08)	−17.32 [−26.70, −7.94][ab]	−0.77 [−1.26, −0.29]**
	NHP-Social (Social)	.56	20.01	15.08	43.01 (30.16)	−20.56 [−32.24, −8.88][ab]	−0.74 [−1.22, −0.26]**
	NHP-Emotion (Emotional)	.83	9.68	11.74	61.37 (23.47)	−26.61 [−36.35, −16.87][ab]	−1.15 [−1.70, −0.60]***
	NHP-Physical (Physical)	.72	11.86	11.21	44.51 (22.41)	−20.41 [−29.77, −11.05][ab]	−0.92 [−1.43, −0.41]***

(e)

Study	Outcome measure	Internal consistency (Cronbach α)	SEM (T1 SD $\times$ $\sqrt{1}$ − Cronbach's α)	Baseline 0.5 SD	Baseline mean (SD)	Within-Groups mean Difference (95% CI)	Within-Groups Effect Size—Hedges' g (95% CI)
Bower et al., 2011 [18]	BDI (Depression)	.81	3.49	4.00	15.40 (8.00)	−7.90 [−12.20, −3.60][ab]	−1.00 [−1.69, −0.32]**

(e) Continued.

Study	Outcome measure	Internal consistency (Cronbach α)	SEM (T1 SD $\times$ $\sqrt{1}$ − Cronbach's α)	Baseline 0.5 SD	Baseline mean (SD)	Within-Groups mean Difference (95% CI)	Within-Groups Effect Size—Hedges' g (95% CI)
Danhauer et al., 2008 [19]	CES-D 20 (Depression)	.93	2.27	4.30	12.30 (8.60)	−3.10 [−5.66, −0.54][a]	−0.36 [−0.66, −0.05]*
	STAI-State (Anxiety)	.95	2.39	5.35	34.20 (10.70)	−2.40 [−5.57, 0.77][a]	−0.22 [−0.52, 0.08]
	PANAS-P (Positive Affect)	.87	3.10	4.30	34.70 (8.60)	1.50 [−1.06, 4.06]	0.17 [−0.12, 0.47]
	PANAS-N (Negative Affect)	.87	1.80	2.50	15.80 (5.00)	−1.70 [−3.14, −0.26]	−0.35 [−0.65, −0.04]*
	FACIT-Sp (Spiritual Well-Being)	.87	2.56	3.55	38.70 (7.10)	1.40 [−0.74, 3.54]	0.19 [−0.10, 0.49]
Duncan et al., 2008 [20]	FACIT-Sp (Spiritual Well-Being)	.87	3.65	5.07	30.83 (10.13)	5.88 [1.93, 9.83][ab]	0.60 [0.16, 1.04]**
Speed-Andrews et al., 2010 [22]	CES-D 10 (Depression)	.85	0.23	0.30	31.00 (0.60)	−0.20 [−0.47, 0.07]	−0.34 [−0.81, 0.13]
	STAI-State (Anxiety)	.85	2.59	3.35	45.20 (6.70)	1.80 [−1.48, 5.08]	0.25 [−0.21, 0.71]
Ülger and Yağlı, 2010 [23]	STAI-State (Anxiety)	.95	1.75	3.92	55.05 (7.83)	−11.70 [−14.96, −8.44][ab]	−1.51 [−2.14, −0.88]***

(f)

Study	Outcome measure	Internal consistency (Cronbach α)	SEM (Baseline SD $\times$ $\sqrt{1}$ − Cronbach's α)	Baseline 0.5 SD	Baseline mean (SD)	Within-Groups mean difference (95% CI)	Within-Groups Effect Size—Hedges' g (95% CI)
Bower et al., 2011 [18]	FSI Average (Fatigue)	.97	0.19	0.55	6.3 (1.1)	−3.6 [−4.44, −2.76][ab]	−2.34 [−3.47, −1.22]***
	PSQI (Sleep)	.84	1.64	2.05	7.1 (4.1)	−0.7 [−2.99, 1.59]	−0.17 [−0.72, 0.38]
Danhauer et al., 2008 [19]	FACT-F (Fatigue)	.95	2.71	6.05	34.6 (12.1)	2.7 [−0.83, 6.27][a]	0.22 [−0.08, 0.52]
Ülger and Yağlı, 2010 [23]	NHP-S (Sleep)	.72	15.64	14.78	43.50 (29.55)	−23.47 [−34.69, −12.25][ab]	−0.88 [−1.38, −0.38]***

* $P < .05$, ** $P < .01$, *** $P < .001$ (Reported between group P values).

[a]Within-Group mean difference exceeds 1 SEM.

[b]Within-Group mean difference exceeds Baseline 0.5 SD.

[c]Between-Group mean exceeds control group 1 SEM.

[d]Between-Group mean exceeds control group Baseline 0.5 SD.

Abbreviations—α: alpha; SD: standard deviation; CI: confidence interval; SF-36 and SF-12: Medical Outcomes Study Short-Form Health Survey; EORTC QLQ C30: European Organization for Research and Treatment of Cancer-Quality of Life C30; FACT-B: Functional Assessment of Cancer Therapy-Breast; FACT-G: Functional Assessment of Cancer Therapy-General; NHP: Nottingham Health Profile; BDI: Beck Depression Inventory; CES-D 20: Center for Epidemiologic Studies Depression Scale-20 Item; STAI: State/Trait Anxiety Inventory; POMS: Profile of Mood States; PANAS: Positive and Negative Affect Schedule; FACIT-Sp: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being; HADS: Hospital Anxiety and Depression Scale; BFI: Brief Fatigue Inventory; FSI: Fatigue Symptom Inventory; PSQI: Pittsburgh Sleep Quality Index; FACT-F: Functional Assessment of Cancer Therapy-Fatigue.

were on active treatment or, in some cases, 3 months or more posttreatment. In the case of Moadel et al. [15] we reported on their secondary analysis that focused on women with breast cancer who were not receiving chemotherapy. Yoga classes were 60–90 minutes in length, and programs lasted 6 to 26 weeks. Yoga styles included Hatha, Integral, Iyengar, Tibetan, Viniyoga, and Vivekananda. The majority of control designs employed a waitlist control group except the Vadiraja study [16, 17], which utilized an active supportive therapy with education control group.

In the single group design studies, mean age ranged from 41–59 years. Sample size at time 2 ranged from 10 to 43 participants. Cancer diagnoses were comprised primarily of breast cancer, with one study focused on ovarian cancer. Many participants were on active treatment or, in some cases, six months or more posttreatment. Yoga classes were 60–90 minutes in length and programs lasted 6 to 10 weeks. Yoga styles included Integral, Iyengar, and "classical" yoga.

3.1.2. Instruments Reviewed. A total of 18 different instruments, assessing patient-reported outcomes in health-related quality of life (HRQL; six instruments), psychosocial (eight instruments), and symptom domains (four instruments) were reviewed. We acknowledge that there is some overlap in HRQL and psychosocial constructs. For the sake of simplicity and parsimony, we left HRQL subscales in the HRQL category even if they capture psychosocial constructs such as social or emotional well-being. Further, in order to minimize the number of categories of patient-reported outcomes, we included spiritual well-being in the psychosocial category. Table 2 presents a summary of the clinical significance for the patient-reported outcomes in the 13 reviewed studies and is divided into control design and pre-post single group design studies. Each table further distinguishes between patient, reported outcome categories: HRQL, Psychosocial, and Symptom variables.

3.2. Quality of Life Outcomes

3.2.1. Overall HRQL. Two control design studies, Danhauer et al. [13] and Culos-Reed et al. [12], met the 1 SEM and 0.5 SD criteria both pre-post and between yoga intervention and waitlist control. Medium between-group ES, ranged from 0.49 (95% CI −0.25, 1.24; P = NS) [13] to 0.67 (95% CI 0.01, 1.32; $P < .05$) [12]. Moadel et al. [15], while showing no evidence of clinically significant change pre-post, met the 1 SEM criteria with an overall small ES of 0.43 (95% CI −0.05, 0.91; P = NS), reflecting improvement in overall HRQL in the yoga group versus a worsening in the control group. Littman et al. [14] showed no significant differences either pre-post or between-groups. In single group design studies [18–23] clinically significant outcomes ranged from a small ES of 0.39 (95% CI −0.08, 0.86; P = NS) meeting the 1 SEM criteria [22], to a large ES of 0.81 (95% CI 0.14, 1.48; $P < .05$) [21], that met both 1 SEM and 0.5 SD criteria. Interestingly, overall HRQL in Danhauer et al. [19], while statistically significant ($P < .05$) with a small ES of 0.32 (95% CI 0.02, 0.63), met neither the 1 SEM nor 0.5 SD criteria.

3.2.2. Physical HRQL. Only two control design studies, Chandwani et al. and Danhauer et al. [10, 13], showed evidence of clinically significant differences. While both studies did not exhibit clinically significant pre-post changes, both studies showed clinically significant effects between groups that met the 1 SEM criteria, with small ES, ranging from 0.36 ES (95% CI −0.38, 1.10; P = NS) [13] to 0.46 ES (95% CI −0.06, 0.97; P = NS))[10]. Interestingly, although there was clinically significant change on the FACT physical wellbeing subscale in Danhauer et al. [13], there was no significant change on the SF-12 physical wellbeing subscale. Several other control design studies [14–16] exhibited no clinically significant differences in physical HRQL, either pre-post or between groups. Within the single-group design studies, only the Ülger and Yağlı study [23] showed a large ES of −0.92 (95% CI −1.43, −0.41; $P < .001$) and met both the 1 SEM and 0.5 SD criteria, indicating significant improvements in physical HRQL pre-post yoga intervention. Speed-Andrews et al. [22] met the 1 SEM criteria with a small ES of 0.32 (95% CI −0.14, 0.79; P = NS). Interestingly, Danhauer et al. [19] met neither 1 SEM nor 0.5 SD but was statistically significant ($P < .05$) with an effect size of 0.38 (95% CI 0.07, 0.68) on the FACT physical wellbeing subscale. There was no significant change on the SF-12 physical wellbeing subscale.

3.2.3. Mental HRQL. Large effects were seen in control group designs for Danhauer et al. [13] with pre-post and between-group mean differences meeting both 1 SEM and 0.5 SD criteria, with a between group ES of 1.00 (95% CI 0.22, 1.78; $P < .01$). Vadiraja et al. [16] did not meet the 1 SEM or 0.5 SD criteria but reported a statistically significant ($P < .05$) ES of 0.30 (95% CI 0.00, 0.61) pre-post yoga intervention. There were no clinically significant differences between groups. There were also no significant differences either pre-post or between groups in Chandwani et al. [10]. In single group designs, Danhauer et al. [19] pre-post differences did not meet the 1 SEM or 0.5 SD criteria but reported a statistically significant ($P < .01$) ES of 0.41 (95% CI 0.11, 0.72). Speed Andrews et al. [22] demonstrated a small clinically significant difference meeting the 1 SEM criteria with an effect size of 0.45 (95% CI −0.03, 0.93; P = NS).

3.2.4. Emotional HRQL. Values ranged from meeting both the 1 SEM and 0.5 SD criteria pre-post and between groups, with ES from 0.53 (95% CI 0.07, 0.99; $P < .05$) [16], to 0.61(95% CI −0.15, 1.35; P = NS) [13], between groups. There were no clinically significant differences pre-post for either Moadel et al. [15] or Culos-Reed et al. [12], however both exhibited between-group differences. Culos-Reed et al.[12]exhibited a small ES of 0.48 (95% CI −0.16, 1.13; P = NS) between groups that met both the 1 SEM and 0.5 SD criteria. Moadel et al. [15] met neither 1 SEM nor 0.5 SD criteria but demonstrated a small statistically significant ($P < .01$) pre-post ES of 0.40 (95% CI 0.10, 0.70). There were no differences between groups. Littman et al. [14] demonstrated no clinically significant differences either pre-post or between groups. Within single subject designs,

Ülger and Yağlı [23] reported large pre-post differences that met both 1 SEM and 0.5 SD with an effect size of −1.15 (95% CI −1.70, −0.60; $P < .001$). There was no clinically significant differences pre-post yoga intervention for either Danhauer et al. [19] or Speed-Andrews et al. [22].

3.2.5. Social HRQL. The majority of control design studies [13, 14, 16] report no clinically significant differences either pre-post or between yoga and waitlist control groups. Interestingly, Moadel et al. [15] demonstrated a moderate, clinically significant decline in the waitlist control group, with an ES of −0.60 (95% CI −1.00, −0.19; $P < .01$). This led to a moderate between group difference of 0.60 ES (95% CI 0.11, 1.09; $P < .05$), which met both the 1 SEM and 0.5 SD criteria, indicating a relative improvement in social HRQL for the yoga group versus a worsening of the waitlist control group. Within the single group designs, Ülger and Yağlı [23] demonstrated a moderate clinically significant difference of −0.74 ES (95% CI −1.22, −0.26; $P < .01$), meeting both the 1 SEM and 0.5 SD criteria, while Danhauer et al. [19] and Speed-Andrews et al. [22] demonstrated no clinically significant differences in social HRQL pre-post yoga intervention.

3.2.6. Functional HRQL. Only Danhauer et al. [13] reported pre-post improvement in Functional HRQL, with a moderate between-group ES of 0.58 (95% CI −0.17, 1.34; P = NS) that met both 1 SEM and 0.5 SD criteria. Littman, Moadel, and Vadiraja [14–16], indicated no clinically significant differences either pre-post or between yoga and waitlist control groups. Similarly no clinically significant differences are reported pre-post within single group designs [19, 22].

3.3. Psychosocial Outcomes

3.3.1. Depression. Clinically significant differences ranged from small, with a between-groups ES of −0.39 (95% CI −1.04, 0.25; P = NS), that met the 1 SEM criteria [12] to medium, with a between groups ES of −0.69 (95% CI −1.45, 0.06; P = NS), meeting both 1 SEM and 0.5 SD criteria [13]. Interestingly in the case of Vadiraja et al. [17] large clinically significant differences within the yoga group, −0.89 ES (95% CI −1.25, −0.54; $P < .001$), and small clinically significant differences within the supportive therapy control group, −0.40 ES (95% CI −0.74, −0.05; $P < .05$), indicated significant depression reduction in both groups. This led to a medium overall ES, −0.52 ES (95% CI −0.98, −0.06; $P < .05$) that met both the 1 SEM and 0.5 SD criteria, favoring overall depression reduction in the yoga group relative to the supportive therapy control. Within the Chandwani et al. study [10], small clinically significant differences in the yoga group, −0.48 ES (95% CI −0.86, −0.09; $P < .05$), and small clinically significant differences in the waitlist control group, −0.32 ES (95% CI −0.67, 0.03; P = NS), also indicated significant depression reduction in both groups. However, there were no overall clinically significant differences in depression reduction between yoga and waitlist control groups. Within the Cohen et al. [11] study there were no clinically significant differences in depression reduction pre-post or between groups. Within single group designs, ES ranged from small, −0.36 ES (95% CI −0.66, −0.05; $P < .05$) meeting the 1 SEM criteria [19], to large, −1.00 ES (95% CI −1.69, −0.32; $P < .01$) meeting both the 1 SEM and 0.5 SD[18]. In the case of Speed-Andrews et al. [22] no clinically significant differences in depression were indicated pre-post yoga intervention.

3.3.2. Anxiety. Within the control designs, Vadiraja et al. [17] indicated moderate clinically significant differences, with an overall between-groups ES of −0.51 (95% CI −0.97, −0.05; $P < .05$) that met the 1 SEM criteria. Chandwani et al.[10] indicated moderate clinically significant differences within the yoga group, −0.63 ES (95% CI −1.04, −0.23; $P < .01$) and small clinically significant differences in the waitlist control group, ES −0.20 (95% CI −0.55, 0.15; P = NS), indicating anxiety reduction in both groups. Overall, small clinically significant differences between yoga and waitlist control, with an ES of −0.46 (95% CI −0.98, 0.05; P = NS) that met both the 1 SEM and 0.5 SD criteria, suggest relative overall anxiety reduction in the yoga group relative to the waitlist control. Interestingly, within the Cohen et al. study [11], small clinically significant differences, with an ES of −0.30 (95% CI −0.80, 0.21; P = NS) that met the 1 SEM criteria, indicate significant overall anxiety reduction in the waitlist control versus the yoga group. Within single group designs Ülger and Yağlı [23] demonstrated large clinically significant reductions in anxiety, −1.51 ES (95% CI −2.14, −0.88; $P < .001$) that met both the 1 SEM and 0.5 SD criteria. Danhauer et al. [19] indicated small clinically significant reductions in anxiety, with an ES of −0.22 (95% CI −0.52, 0.08; P = NS) that met the 1 SEM criteria. No clinically significant differences were reported in Speed-Andrews et al. [22].

3.3.3. Positive Affect. Danhauer et al. [13]demonstrated a small clinically significant effect of 0.45 ES (95% CI −0.29, 1.19; P = NS) that met the 1 SEM criteria between yoga and waitlist control groups. Vadiraja et al. [16] reported a moderate clinically significant effect pre-post yoga intervention of 0.52 ES (95% CI 0.20, 0.84). However, although statistically significant ($P < .001$), the between-group difference met neither the 1 SEM nor 0.5 SD criteria. Within the single group designs, there were no significant differences in positive affect pre-post yoga intervention.

3.3.4. Negative Affect. Within the Danhauer et al. study [13], moderate clinically significant differences between groups, −0.73 ES (95% CI −1.49, 0.03; P = NS) meeting both the 1 SEM and 0.5 SD criteria, indicated significant overall reduction in negative affect in the yoga group. Within the Vadiraja et al. study [16], large clinically significant differences within the yoga group, −0.86, ES (95% CI −1.21, −0.51; $P < .001$) and small differences within the supportive therapy group, −0.33 ES (95% CI −0.67, 0.01; P = NS) suggested there was a clinically significant reduction of negative affect in both groups. However, moderate clinically significant differences

between groups, −0.57 ES (95% CI −1.03, −0.11; $P < .05$), that met both the 1 SEM and 0.5 SD criteria, suggest a significant overall reduction of negative effect in the yoga group relative to the supportive therapy control group. In the single group study designs, Danhauer et al. [19] met neither the 1 SEM nor 0.5 SD criteria but did exhibit a statistically significant ($P < .05$) ES of −0.35 (95% CI −0.65, −0.04).

3.3.5. Spiritual Well-Being. In Danhauer et al. [13] moderate clinically significant differences, 0.56 ES (95% CI −0.19, 1.30; P = NS) meeting both the 1 SEM and 0.5 SD criteria, indicated an increase in spiritual well-being in the yoga versus waitlist control group. Within the Moadel et al. study [15] there were no clinically significant differences in spiritual well-being pre-post or between groups. Within the single group designs moderate clinically significant differences, 0.60 ES (95% CI 0.16, 1.04; $P < .01$) were reported pre-post yoga intervention [20]. There were no clinically significant differences in spiritual well-being pre-post yoga intervention in Danhauer et al. [19].

3.4. Symptom Outcomes

3.4.1. Fatigue. Within the control group designs [10, 11, 13–15] clinically significant differences between the yoga intervention and control groups ranged from small ES, −0.17 ES (95% CI −0.68, 0.34; P = NS), meeting the 1 SEM criteria [10] to medium ES, 0.71 ES (95% CI −0.04, 1.47; P = NS), meeting both the 1 SEM and 0.5 SD criteria [13]. In the case of Cohen et al. [11] there were no clinically significant differences in fatigue pre-post or between yoga and control groups. Within the single group designs, effect sizes ranged from small, 0.22 ES (95% CI −0.08, 0.52; P = NS) meeting the 1 SEM criteria [19], to very large, −2.34 ES (95% CI −3.47 to −1.22; $P < .001$) meeting both the 1 SEM and 0.5 criteria [18].

3.4.2. Sleep. In the case of Danhauer et al. [13] despite small clinically significant differences pre-post, ES −0.46 ES (95% CI −1.00, 0.08; P = NS) there were no overall clinically significant differences in sleep between the yoga and waitlist control groups. There were no clinically significant differences in sleep pre-post or between groups in the Chandwani or Cohen studies [10, 11]. In the single group designs, there was a large effect, −0.88 ES (95% CI −1.38, −0.38; $P < .001$) meeting both 1 SEM and 0.5 SD requirements, for sleep pre-post yoga intervention [23]. In the case of Bower et al.[18] there were no clinically significant differences in sleep pre-post yoga intervention.

3.5. Clinical Significance Criteria

3.5.1. Consistency between SEM and SD. Within the control group designs, the correlation between the 1 SEM and 0.5 SD criteria for HRQL indices was $r = .92$, $P < .01$ for the treatment group and $r = .93$, $P < .01$ for the control group. For the single group designs the correlation between 1 SEM and 0.5 SD was $r = .92$, $P < .01$, indicating these criteria are highly correlated. For psychosocial indices within the control group designs, the overall correlation between the 1 SEM and 0.5 SD criteria was $r = .74$, $P < .01$ for the treatment group and $r = .83$, $P < .01$ for the control group. For the single group designs the correlation between 1 SEM and 0.5 SD was $r = .80$, $P < .01$, indicating these criteria are also highly correlated. Similarly, for the symptom indices, within the control group designs, the overall correlation between the 1 SEM and 0.5 SD criteria was $r = .91$, $P < .01$ for the treatment group and $r = .91$, $P < .01$ for the control group. Finally, for the single group designs the correlation between 1 SEM and 0.5 SD was $r = .97$, $P < .05$, indicating these criteria are highly correlated.

4. Discussion

The yoga and cancer literature is rapidly growing. This literature is characterized by studies published with small sample sizes and variability in the type and length of interventions, populations studied (e.g., cancer type, time during the treatment continuum), and measures used to assess the patient-reported outcomes of interest. Thus, to accurately characterize the results of the current literature in this area, reporting multiple indicators of clinical significance is of great value [38]. Studies evaluated for clinical significance show some consistency across this research, demonstrating the positive impact of yoga on quality of life, psychosocial, and, to a lesser degree, physical symptom indices.

Since this area of research is in its infancy, it is useful to utilize multiple criteria of clinical significance to explore the clinical efficacy of results from each study. We recommend the use of not only ES and CIs, but also validated metrics such as the 1 SEM and 0.5 SD criteria. A cursory look at our summary tables would indicate that to examine any of these studies by one criterion alone, particularly in the case of P-values, much information and insight into the results would be lost. Based on our current paper, we see emerging beneficial findings from yoga interventions in the areas of HRQL, including overall HRQL and its mental and emotional domains, and in psychosocial measures in the areas of anxiety, depression, negative affect, and spiritual well-being. There may also be some preliminary evidence for yoga's role in fatigue. Findings for the role of yoga in physical, functional, and social domains of HRQL remain far more inconclusive, as is the role of yoga in positive affect and sleep indices for cancer survivors. Thus, considering clinical significance indicates stronger support than previous reviews of the literature for the preliminary efficacy of yoga for improving overall HRQOL and its mental and emotional domains, in addition to psychosocial outcomes [6, 7].

The present paper highlights that yoga for cancer survivors results in a number of clinically significant improvements in select patient-reported outcomes. Specifically, multiple criteria, including a mean difference from pre- to postintervention greater than or equal to 1 SEM and/or 0.5 SD, and the respective ES and CI, were met for quality of life and psychosocial outcomes (e.g., anxiety, depression, positive and negative effect, and spiritual well-being), and

for some limited symptom outcomes (e.g., fatigue, sleep). These results suggest that indices vary in their sensitivity/conservatism for reporting clinical significance. For example, in cases where research participants patient-reported outcome pre-scores are subclinical or it has been established that smaller changes in patient-reported outcomes would be beneficial (e.g., palliation), using the mean difference criterion of greater than 1 SEM may be a more pragmatic index of clinically significant change. In addition, researchers may want to employ the respective smaller ES with the SEM when smaller changes would be considered meaningful.

4.1. Baseline Cut-offs Reported in Literature. One consideration for the discrepancies between clinical significance and statistical significance found for HRQOL and psychosocial patient-reported outcomes may be participant baseline characteristics. Baseline health status, as reflected in patient-reported outcome scores, has been shown to affect the overall responsiveness of an instrument [39]. For example, if participants are several months posttreatment, they may report preintervention scores that are relatively high (positive). Thus, there is less "room" for improvement and a ceiling effect is encountered on a given outcome. The patient cannot score any higher and so a given level of change necessary for clinical significance is not obtained [28]. Therefore, improvements in patient-reported outcomes must be contextualized within participant baselines scores.

While beyond the scope of this manuscript, the baseline values of all HRQL, psychosocial, and symptom measures varied for each study in comparison to established clinical cutoffs, where available. Clinical cut-off values are established to distinguish between people who have a clinically important level of the construct and to enable comparison between studies. Thus studies that had more room for improvement at baseline, which can be judged in comparison to clinical cut-off values, may have resulted in higher levels of clinical significance.

4.2. MIDs Reported in Literature. In addition to the 1 SEM, 0.5 SD, and ES measures reported in our results, for some instruments, MIDs currently exist in the literature. Thus it may also be of value to compare current results to literature-reported MIDs. Utilizing a combination of distribution-based methods and MIDs reported in the literature, as they are available, allows for unique insights into both the interventions and study members. While literature-based MIDs may allow for additional ease in comparing changes across studies, they are developed based on a large cross-section of studies and may not always be appropriate given any one study [38].

4.3. Limitations and Future Research. The current paper has some limitations. First, it is important to note calculations of clinical significance do not account for elements that can be controlled by the original study design. Differences between the studies—type of yoga, duration, assessment periods, number of assessments, type of control group (waitlist versus active comparison control), sample size, and cancer type—are all issues that should be considered in the interpretation of the results. For example, some studies may show clinically significant changes as a function of a longer duration (i.e., a time effect improvement in patient-reported outcomes) rather than a direct benefit of yoga. In addition, small sample sizes may also miss important clinical differences and mask significant improvement following an intervention. In contrast, studies with large sample sizes may produce significant findings that are clinically meaningless [40]. Future studies will be strengthened by the recruitment of larger, more homogenous samples to minimize this variability and lead to more consistent results. In addition, the research clearly has relied primarily on participation from breast cancer survivors, and minimal published work on yoga in other groups of cancer survivors exists to date.

The relative dearth of symptom-focused patient-reported outcomes illustrates a gap in the evaluation of the potential physical effects of yoga for cancer survivors. Whereas it is certainly important that yoga consistently demonstrates a positive influence on quality of life and psychosocial outcomes, research evaluation may be missing an important component of the potential benefits that may be gained in symptom alleviation, be it fatigue, sleep disturbance, or pain. Future research that focuses more in-depth on assessment of symptom patient-reported outcomes, in addition to fatigue and sleep, is warranted.

Comparing yoga to other types of interventions, either physical activity or psychosocial, may elucidate comparable effects or unique outcomes of yoga on patient-reported outcomes in cancer survivors. Notably, yoga was not originally intended to target specific outcomes. Thus, choosing which of the many yoga practices to implement (e.g., movement, breath, and meditation) and, based in part on these decisions, which psychophysiological outcomes to assess will be an ongoing challenge in the attempt to explore this holistic ancient practice with contemporary methods of scientific exploration [5].

Within this paper a total of 18 different instruments were used to assess patient-reported outcomes, including six instruments for HRQL alone. Recent research has advocated for a more coordinated use of measures to increase validity of constructs measured as well as to ensure the reliability of comparisons [41]. In this capacity, recent work by the Patient Reported Outcomes Measurement Information System (PROMIS) cooperative group provides new direction in collectively and parsimoniously measuring these phenomena [42]. Independent of the PROMIS initiative, the literature on yoga for cancer survivors is beginning to use some of the same measures within multiple interventions. This practice of consistent use of measures is valuable for furthering the evidence on yoga for cancer survivors. For example, recent studies have found clinically significant changes using the FACT-G and subscales, FACT-F, and FACIT-Sp [13, 20, 22]. Thus, we now have the benefit of inferring that it was not likely the measure alone, but perhaps other intervention-dependent factors, that influenced the results. In this capacity, we also strongly recommend the use of

disease-specific instruments in future research.

Identifying mechanisms that explain how yoga leads to clinically significant outcomes is another next step in understanding the ability of yoga to target specific desired outcomes. Little research attention has been paid to the psychophysiological mechanisms by which benefits are accrued via yoga practice. In this capacity, there have been recommendations to integrate patient-reported outcomes with biomedical endpoints as a means of better describing the complexity of these measures [43]. Before yoga can be broadly applied within oncology, both a strong theoretical understanding of how yoga practice causes change and carefully designed and executed research that convincingly evaluates not only the efficacy of yoga in clinical settings but also posits potential mechanisms of action underlying these interventions are required [44].

Finally, since the timing of the assessment of a patient-reported outcome may influence clinical significance, it is important for future studies of yoga to include measures that look at change before and after a single yoga practice session. Assessing these more acute effects of yoga would allow for documentation of the potential immediate impact of yoga on outcomes of interest [45].

5. Conclusion

There is a need across the research literature to assess a variety of indices that speak to a given study's clinical significance, a metric relevant to researchers, clinicians, and patients alike. The current analysis supports preliminary evidence of the clinical significance of yoga for improving quality of life, psychosocial, and limited symptom outcomes in cancer survivors. It behooves researchers to take these preliminary findings as a starting point to begin to explore, report and revise these purported indices of clinical significance further [30]. Identifying the clinical significance in studies of yoga for cancer survivors adds further description to the existing literature and highlights the promising benefits of a yoga intervention. While this study focused specifically on one type of intervention in a defined group (i.e., cancer survivors), there is the broader issue of the need to examine and present clinical significance data for other types of intervention studies in order to ensure that "significant" findings are truly meaningful to people, impacting various health outcomes and behaviors that are important to them.

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Research Article

Toxicity of a Novel Herbomineral Preparation Las01 on Human Cancer Cell Lines and Its Safety Profile in Humans and Animals

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Polyhedral formulations based on Rasayana therapy described in Charaka Samhita showed remarkable improvement in quality of life of various cancer patients who have been found to be refractory or poor responders to modern chemotherapy and radiation treatment. One of the most recent novel herbomineral preparation, Las01 prepared absolutely as per the instruction given in the ancient Ayurvedic literature has been found to be effective as a potent anticancer drug in the human cell lines, the MCF-7 and Hela cancer cell lines. This novel preparation of Las01 is also found to be devoid of toxicity both in animals as well as in human subjects, which is the main drawback of chemotherapeutic agents used in modern system of medicine. Our results warrant multicentric clinical trials on a large scale which seems to be a future promising drug to cure incurables cancer patients.

1. Introduction

Cancer has become one of the biggest challenges to the scientific community over the world, and despite development of drugs and other modalities for treatment of Cancer, however there are complexities at every level of treatment. Cancer chemotherapy is associated with many unwanted side effects such as nausea, loss of taste, lethargy, loss of hair, loss of libido, immunosuppression and myelosuppression, and tumorogenesis [1]. Thus there is need to find out relatively safe, effective, and economical solution for cancer. The scientific community is looking at traditional holistic system of the medicines for treatment of cancer. Herbomineral therapeutics is one of the most promising areas of treating diseases like cancer. The branch of Ayurveda deals with medicinal properties of herbometallic and herbomineral preparations known as Rasa shastra and the drugs which are used are known as Rasa Aushadhi. They were more popular during the period of Lord Buddha due to its faster relief, lesser and convenient doses, and mysterious efficacy as compared to only herbal drugs. Various constituents of Herbomineral compounds such as gold, silver, lead, iron, and arsenic are never used in the raw form as their raw form causes poisonous and toxic effects [2].

Modern science has now revealed that this process of anaerobic cooking used in preparing Herbomineral drugs converts the toxic mega particles of metal into safe and efficacious nanoparticles and even smaller picoparticles which explains the usefulness of Herbomineral drugs as effective medicines for cancer as prophylactic, palliative, curative, and supportive medicaments. Therefore, Rasayana therapy and its role in cancer management are being screened in almost all leading Ayurveda research institutes in this country. Polyhedral formulations based on Rasayana therapy described in Charaka Samhita showed remarkable improvement in quality of life of various cancer patients who were treated earlier with chemotherapy and radiotherapy. It was also effective in overcoming the side effects of chemotherapy and radiation such as hair loss, weight loss, stomatitis, and xerostomia [3, 4]. In the present study the safety and toxicity of Las01 were checked in animals as well as human beings and the therapeutic efficacy of its anticancer activity has been checked on breast cancer cell line MCF-7 and HeLa cervical cancer cell line job1041.

2. Material and Methods

2.1. Las01 Herbomineral Anticancer. The drug used in the present study was Las01 a Herbomineral preparation prepared by Lavanya Ayurvedic Hospital and Cancer Research Centre by its own manufacturing unit exactly as per the instructions laid down in our ancient Ayurvedic literature [5]. Accordingly Las01 preparation contains a number of herbs and different types of inorganic minerals such as mercury which has been extensively purified through 75 steps as per Kupipakva Rasayana technique yielding an anticancer drug in the form of bhasma. This Herbomineral drug was standardized by the use of physiochemical properties and transmission electron microscopy.

2.2. Animals, Feed, Dose, and Experiment. Charles-Foster strains of albino rats of either sex with an average body wt 150–200 gm were used in the experiment. 16 animals were taken in each group for acute toxicity study. Rats were randomly divided into four groups and one group served as control (2 animals/group of either sex) for 14 days in order to study the acute toxicity. For chronic toxicity study 36 rats were randomly divided into four groups and group one served as control and was kept normal (3 animals/group of either sex) for 90 days in order to study the chronic toxicity. The Sagar Institute of Technology and Management Lucknow animal house facility was used; all animal experiments were conducted after getting approval from institutional animal ethics committee of the institute. The standard animal conditions of room temperature 21 ± 20°C, relative humidity 60 ± 10%, and 12 h light/dark cycle were maintained. The commercial pellet diet and reverse osmosis water for rats were available *ad libitum*. The dose for experimental study of the test drug Las01 was calculated by extrapolating the human dose (1000 mg/day) to animal dose (88.02 mg/kg normal dose = 1x; 880.2 mg/Kg body wt. = Las01 10x; 3520.80 mg/Kg body wt. =Las01 40x) based on the body surface area ratio and the drug was administered orally to the animals [6].

The study was divided into two phases, acute and subchronic. In acute toxicity the animals were sacrificed on the 14th day while in subchronic studies they were sacrificed on the 90th day. During autopsy the shape, size, and colours of internal organ were visually observed for any signs of lesions. The blood was collected by cardiac puncture method and collected into EDTA-K3 and clot activator non-VAC. tubes of LabTech Company for haematological and biochemical analysis, respectively. Haematological parameters were checked by automated cell counter and haemoglobin by cyanmethemoglobin method [7] by blood. Serum was separated through centrifugation of blood at 3000 rmp for 10 minutes for biochemical analysis and was performed using prepared kits from Roche Diagnostic reagents. Serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), and alkaline phosphatase (ALP) were estimated by (International Federation of Clinical Chemistry) IFCC Method [8], bilirubin total and direct by Jen Drasik and Grof method, creatinine by Jaffe and Kinetic method, blood urea nitrogen by Glyceraldehyde dehydrogenase method [9], total protein by Biuret method, and albumin and globulin by Bromocresol Green method. Serum sodium and potassium were estimated by Biolyte 2000 ion elective electrolyte analyzer [10]. Histopathological analysis of the liver (Figure 1), kidney (Figure 3), heart (Figure 2), and lung was performed by cutting 2 mm section of the tissue fixed in 10% formaldehyde by a microtome and further staining with haematoxylin and eosin and was examined by a pathologist.

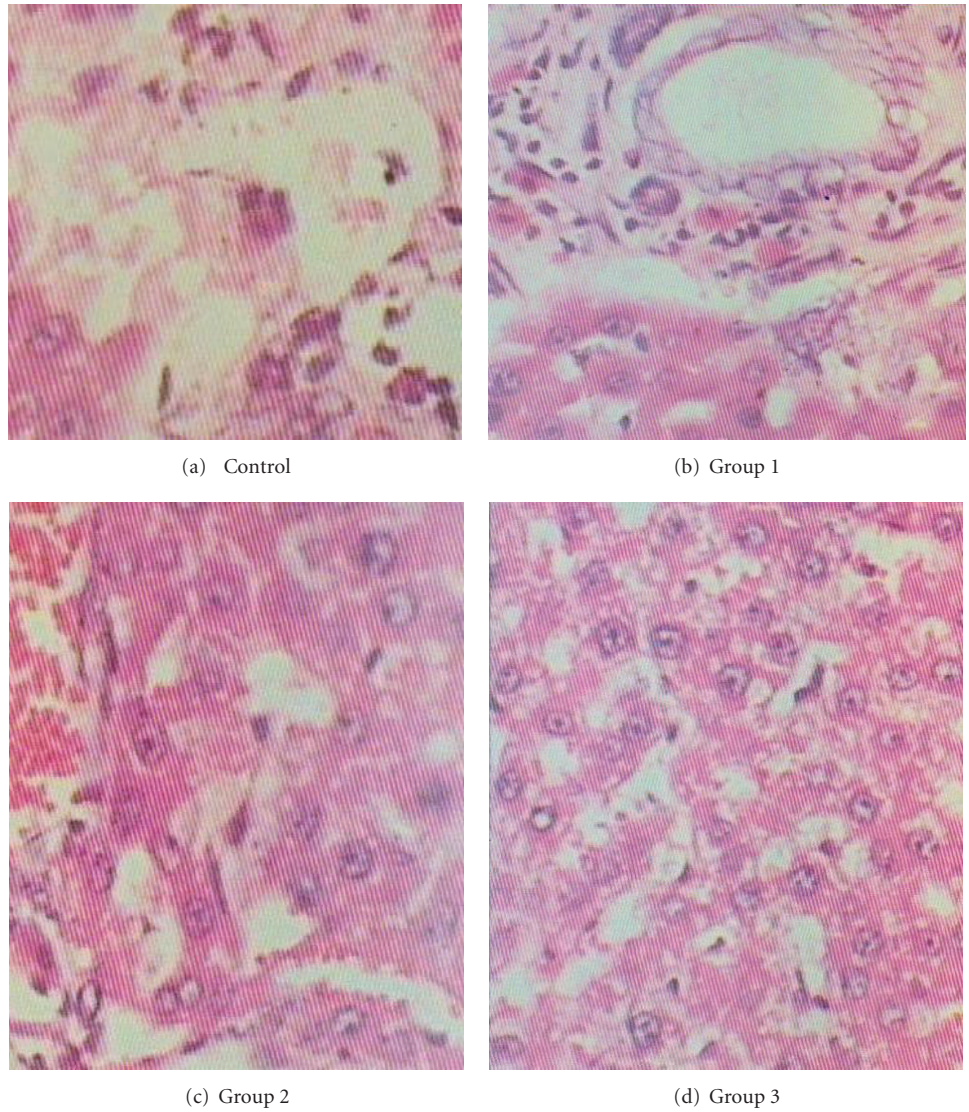
2.3. Safety Profile of Las01 in 25 Patients of Different Cancers. Lavanya Ayurvedic Hospital has been treating cancer patients with Las01 Herbomineral for the last several years. In the present study blood from 25 patients was taken for hematological and biochemical (hepatic and renal) toxicity of Las01 preparation. After obtaining written informed consent forms from patients and clearance from IEC, blood was analyzed before and after 1-year treatment of cancer patient by Las01 Herbomineral preparation.

2.4. In Vitro Anticancerous Activity

2.4.1. Cancer Cell Lines and Culture Conditions. Human HeLa cervical cancer cell lines and MCF-7 breast cancer cell lines (adenocarcinoma) were obtained from National Centre for Cell Sciences (NCCS) Pune, India. Both cell lines were cultured as monolayer cultures in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum and antibiotics (100 units/mL penicillin and 100 mg L^{-1} streptomycin) in a humidified atmosphere of 5% CO_2 at 37°C in T-75 flasks and were subcultured twice a week.

2.4.2. Cytotoxicity Assay. The cytotoxic effect of Las01 was assessed in human cervical cancer HeLa and MCF-7 breast cancer cell lines (adenocarcinoma) cells by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay [11]. Briefly, cells were seeded at a number of 2×10^4 cells per well on 96-well plates (200 μL/well) in triplicates and exposed to ethanol dissolved in Las01 different concentrations for 48 h (25 mg/L–500 mg/L). At the end of the treatment, the medium was removed and cells were incubated with 20 μL of MTT (5 mg/mL in PBS) in fresh medium for 4 h at 37°C. After four hours, formazan crystals, formed by mitochondrial reduction of MTT, were solubilized in DMSO (150 μL/well) and the absorbance was read at 570 nm after 10 min incubation on the iMark Microplate Reader (Bio-Rad, USA). Percent of inhibition of cytotoxicity was calculated as a fraction of control (without Las01) and the cytotoxicity of Las01 was expressed as % inhibition.

2.4.3. LDH Assay. Cytotoxic property of Las01 was also assessed by lactate dehydrogenase (LDH) leakage into the culture medium. Following exposure to the Las01, the culture medium was aspirated and centrifuged at 3000 rpm for 5 min in order to obtain a cell-free supernatant. The activity of LDH in the medium supernatant was determined using a commercially available *CytoScan* by using *LDH* Cytotoxicity Assay Kit. Percent of inhibition of cytotoxicity



(a) Control (b) Group 1

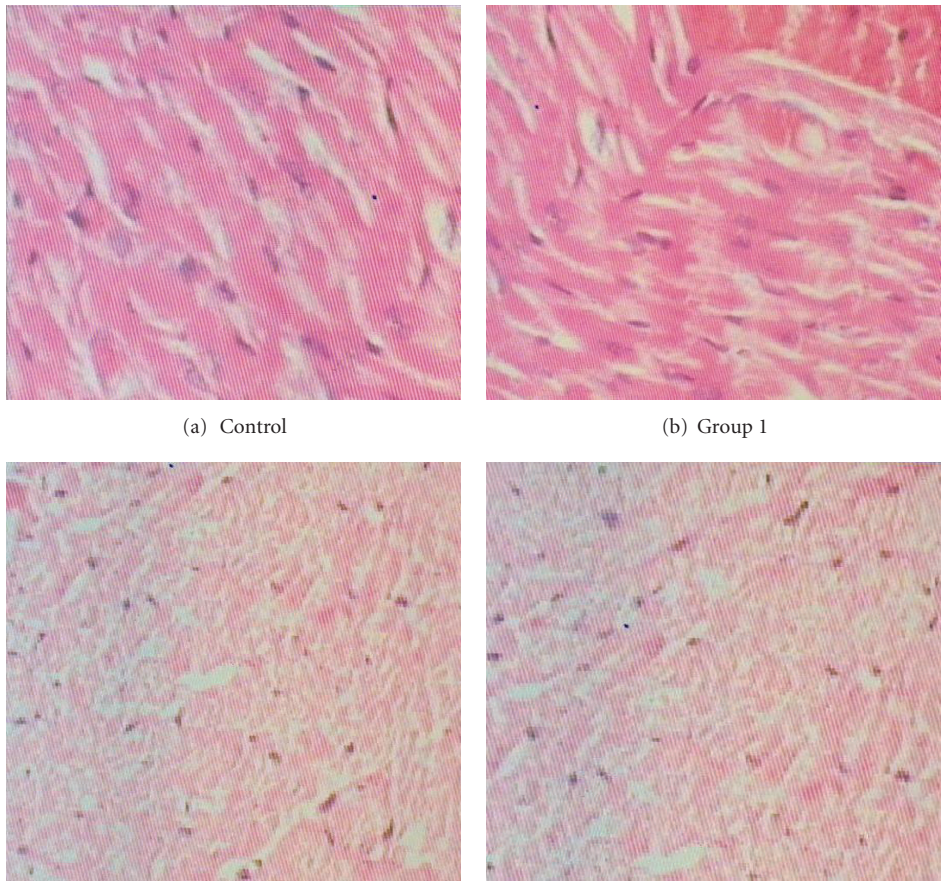
(c) Group 2 (d) Group 3

Figure 1: Histopathological pictures of liver after 90-day exposure of Las01. Magnification (40x). (a) Control normal Liver. (b) Group 1 treated liver (88.02 mg/Kg body wt. = Las01 1x). (c) Group 2 treated liver (880.2 mg/Kg body wt. = Las01 10x). (d) Group 3 treated liver (3520.80 mg/Kg body wt. =Las01 40x).

was calculated as a fraction of control (without Las01) and the cytotoxicity of Las01 was expressed as IC50.

2.4.4. Viability Staining by Trypan Blue Dye Exclusion Method. Cytotoxic activities of Las01 were analyzed by trypan blue dye exclusion method adopted by Ian Freshney, 1994. Cell lines in exponential growth phases were washed with PBS solution and trypsinized and resuspended in complete culture media. Cells were plated at 5000 cells/well in 6-well plates and incubated for 24 hrs during which partial monolayer was formed. After incubation the cells were exposed to various concentrations of the drug. The control well received only maintained media. The plates were incubated at 37°C in 5% CO_2 incubator for a period of 24 hrs. Morphological changes were examined using inverted microscope and compared with the cells serving as control. At the end of 24 hrs incubation cell viability was determined.

2.4.5. Determination of Apoptosis and Necrosis. Apoptotic and necrotic cells were analyzed with double staining to quantify the number of apoptotic cells in culture on the basis of scoring of apoptotic cell nuclei. HeLa cells (5000 cells per well) were placed in DMEM by using 6-well plates and treated with different concentrations of functional oligomers (about 0 to 200 $\mu g \cdot mL^{-1}$ in phenol red free medium) for 24 h period. Both attached and detached cells were collected, then stained with Hoechst dye 33342 (2 $\mu g \cdot mL^{-1}$), propodium iodide (PI) (1 $\mu g \cdot mL^{-1}$), and DNAse free-RNAse (100 $\mu g \cdot mL^{-1}$) for 15 min at room temperature [11]. Necrotic cells were stained red by PI. Necrotic cells lacking plasma membrane integrity and PI dye cross cell membrane,



(a) Control (b) Group 1

(c) Group 2 (d) Group 3

Figure 2: Histopathological pictures of heart after-90 day exposure of Las01. Magnification (40x). (a) Control normal Heart. (b) Group 1 treated heart (88.02 mg/Kg body wt. = Las01 1x). (c) Group 2 treated heart (880.2 mg/Kg body wt. = Las01 10x). (d) Group 3 treated heart (3520.80 mg/Kg body wt. =Las01 40x).

but PI dye does not cross nonnecrotic cell membrane. The number of apoptotic and necrotic cells was determined with DAPI and FITC filters of Fluorescence Inverted Microscope (Leica, Germany).

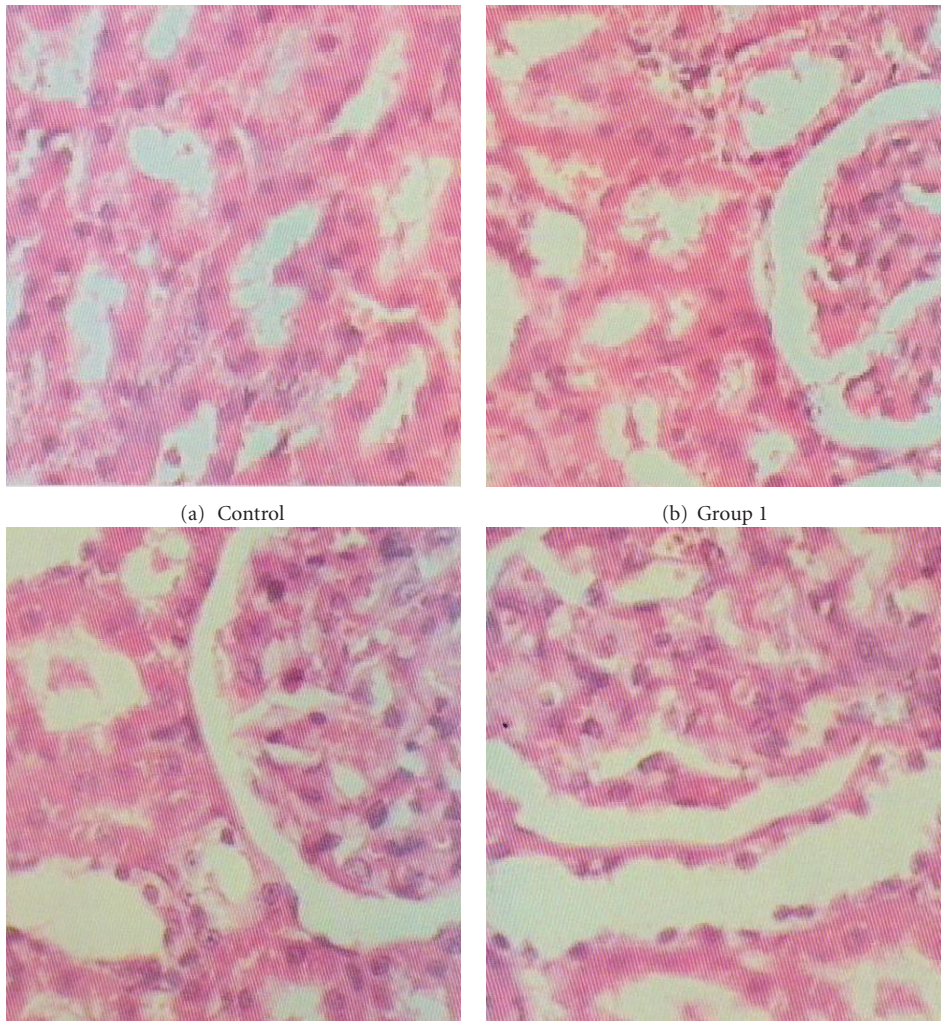
3. Results

3.1. Acute Toxicity

3.1.1. Effect of Las01 on Haematological and Biochemical Parameter. There was no significant change in total WBC count, haemoglobin content, and biochemical parameters in animals treated with Las01 upto 40-fold doses for a period of 14 days (Table 1). All the parameters are within the normal limits and animals did not show any sign of hyperactivity. ALD was not found up to 5 mg of Las01.

3.2. Chronic Toxicity. There was no significant change of WBC count, haemoglobin content, and differential counts. There was no significant alteration in hepatic and renal function parameters. Subchronic administration of these drugs did not produce any alteration in sodium, potassium, chloride, and bicarbonate levels (Table 2). No remarkable histopathological changes were noted in the internal organs of rats receiving these drugs in higher doses.

3.3. In Vitro Activity. Data on the cytotoxic effects of Las01 using MCF-7 and HeLa cell lines *in vitro* are shown in Table 3. Cytotoxic effects of Las01 on MCF-7 and HeLa cell lines *in vitro* by MTT and LDH methods, respectively, inhibited proliferation of both MCF-7 and HeLa cervical cancer cells in a dose-dependent manner. The cytotoxic effect of Las01 was determined using concentrations ranging from 10 mg L^{-1} to 500 mg L^{-1} for 48 h. After 48 h exposure, Las01 induced concentration-dependent cytotoxic effect about 78% at 500 mg/L in cervical cell lines and 77% at 500 mg/L in MCF-7 breast cancer cell line. Trypan blue was used to stain cells for observing the ratio of viable and dead cells. It was observed that increasing the concentration (10 to 500 mg/L) of Las01 decreases viability of cancer cells. Low concentrations of the Las01 produced low toxic effect on cells whereas at higher concentrations (500 mg/L) there was higher effect in toxicity so that in only 20% and 18% in MCF-7 and HeLa, respectively, viability was observed (see Table 4). The



(a) Control (b) Group 1

(c) Group 2 (d) Group 3

Figure 3: Histopathological pictures of kidney after 90-day exposure of Las01. Magnification (40x). (a) Control normal Kidney. (b) Group 1 treated kidney (88.02 mg/Kg body wt. = Las01 1x). (c) Group 2 treated kidney (880.2 mg/Kg body wt. = Las01 10x). (d) Group 3 treated kidney (3520·80 mg/Kg body wt. =Las01 40x).

Table 1: Effect of acute administration of Las01 in rats.

Parameters	Control	Las01		
		Group 1	Group 2	Group 3
Total WBCcount $\times 10^3$ mm^3	6293 ± 488	6342 ± 422	6321 ± 230	6234 ± 230
Haemoglobin (gm%)	11.91 ± 1.85	11.82 ± 1.33	11.75 ± 1.0	11.82 ± 1.0
Bilirubin total (mg/dL)	0.31 ± 0.13	0.30 ± 0.12	0.31 ± 0.15	0.32 ± 0.15
Bilirubin direct (mg/dL)	0.24 ± 0.32	0.29 ± 0.27	0.25 ± 0.25	0.27 ± 0.15
SGPT (U/L)	44.8 ± 11.5	45.7 ± 11.1	44.53 ± 12.38	46.11 ± 12.38
SGOT (U/L)	135.4 ± 19.6	139.3 ± 15.26	136.2 ± 17.25	133.4 ± 17.25
ALP (U/L)	161.8 ± 92.1	168.6 ± 93.2	170.7 ± 94.5	163.6 ± 91.5
Albumin (mg/dL)	3.53 ± 0.41	3.35 ± 0.46	3.71 ± 0.32	3.47 ± 0.32
Globulin (mg/dL)	4.03 ± 0.19	4.03 ± 0.36	4.00 ± 0.39	4.12 ± 0.39
Total protein (gm%)	7.56 ± 0.28	7.38 ± 0.22	7.71 ± 0.42	7.59 ± 0.42
BUN (mg/dL)	66.58 ± 7.45	63.13 ± 6.6	66.26 ± 7.48	65.32 ± 7.48
Creatinine (mg/dL)	0.45 ± 0.05	0.46 ± 0.04	0.44 ± 0.04	0.44 ± 0.04
Sodium (mEq/L)	146 ± 4.41	147.5 ± 2.82	144.3 ± 5.6	148.3 ± 5.6
Potassium (mEq/L)	4.15 ± 0.18	4.12 ± 0.39	4.14 ± 0. 23	4.16 ± 0. 23
Chloride (mEq/L)	104 ± 1.18	103 ± 1.68	101.8 ± 3.70	102.9 ± 3.70

Table 2: Effect of chronic administration of Las01 in rats.

Parameters	Control	Las01		
		Group 1	Group 2	Group 3
Total WBCcount $\times 10^3$ mm^3	7634 ± 520	7293 ± 488	7335 ± 230	7653 ± 422
Haemoglobin (gm%)	13.13 ± 1.0	12.10 ± 2.85	12.65 ± 1.0	13.16 ± 1.23
Bilirubin total (mg/dL)	0.29 ± 0.12	0.28 ± 0.14	0.30 ± 0.02	0.31 ± 0.12
Bilirubin direct (mg/dL)	0.25 ± 0.15	0.21 ± 0.12	0.28 ± 0.15	0.33 ± 0.14
SGPT (U/L)	45.11 ± 11.12	46.8 ± 10.5	45.66 ± 11.35	44.6 ± 12.1
SGOT (U/L)	74.2 ± 12.25	73.1 ± 12.6	74.2 ± 19.33	75.4 ± 14.16
ALP (U/L)	210.2 ± 22.5	218.3 ± 44.1	219.8 ± 42.5	228.2 ± 39.5
Albumin (mg/dL)	3.27 ± 0.32	3.31 ± 0.41	3.26 ± 0.12	3.25 ± 0.41
Globulin (mg/dL)	4.15 ± 0.19	4.11 ± 0.10	4.10 ± 0.28	4.64 ± 0.11
Total protein (gm%)	7.32 ± 0.42	7.42 ± 0.28	7.36 ± 0.42	7.89 ± 0.22
BUN (mg/dL)	65.12 ± 6.29	67.22 ± 6.87	64.26 ± 7.09	65.15 ± 5.8
Creatinine (mg/dL)	0.41 ± 0.02	0.42 ± 0.03	0.46 ± 0.01	0.41 ± 0.06
Sodium (mEq/L)	145.1 ± 2.1	144.4 ± 2.39	143.6 ± 3.5	145.8 ± 2.45
Potassium (mEq/L)	4.8 ± 0. 33	4.9 ± 0.34	4.2 ± 0. 76	4.9 ± 0.01
Chloride (mEq/L)	104.1 ± 1.10	108 ± 1.08	103.5 ± 4.20	104.6 ± 1.34

Table 3: Determination of cytotoxicity by MTT assay.

	MCF-7			HeLa		
Laso1 conc. mg/L	Absorbance	% inhibition	% viability	Absorbance	% Inhibition	% viability
10	2.009	4%	95%	2.008	5%	92%
25	2.001	10%	90%	2.002	12%	89%
50	1.991	15%	84%	1.990	16%	80%
100	1.850	35%	64%	1.850	38%	65%
150	1.720	41%	59%	1.719	45%	55%
200	1.562	46%	45%	1.561	47%	42%
250	1.320	51%	48%	1.321	57%	38%
300	1.250	66%	39%	1.252	68%	32%
350	1.110	70%	32%	1.109	70%	29%
400	1.001	72%	30%	1.002	74%	25%
450	1.000	75%	24%	1.001	76%	20%
500	.950	77%.	20%	.951	78%	18%

results obtained with double staining of control and treated cells are presented in Figure 4. The control cells fluoresced uniformly green and had normal features. Most of the cells treated with Las01 fluoresced red and indicated apoptotic features such as cell shrinkage, chromatin condensation, nuclear fragmentation, and apoptotic body formation. A few cells indicated necrotic features such as cell swelling and lysis in higher concentration of Las01 1000 mg/L.

The results obtained with double staining of control and treated cells are presented in Figure 4. The control cells fluoresced uniformly green and had normal features. Most of the cells treated with Las01 fluoresced green and indicated apoptotic features such as cell shrinkage, chromatin condensation, nuclear fragmentation, and apoptotic body formation comparatively less in 250 mg/l than in 500 mg/L.

4. Discussion

Ayurveda is a traditional medical system used by the majority of India's 1.1 billion populations. The word Ayurveda literally means science of life. It is time tested and trusted through thousands of years of usage. Ayurveda, from the days of Charaka and Sushruta, was primarily used as medicinal plants for the preparation of therapeutic agents. It is only in the 8th century AD that Indian alchemist Nagrjuna prescribed the use of metals (e.g., mercury, lead, cadmium, iron, and zinc) and minerals (e.g., mica) as medicinal agents. Since these were very effective, quick in action, even in smaller dosage, palatable, and having longer shelf life, the use of minerals and metals became the backbone of Ayurvedic therapeutics [12].

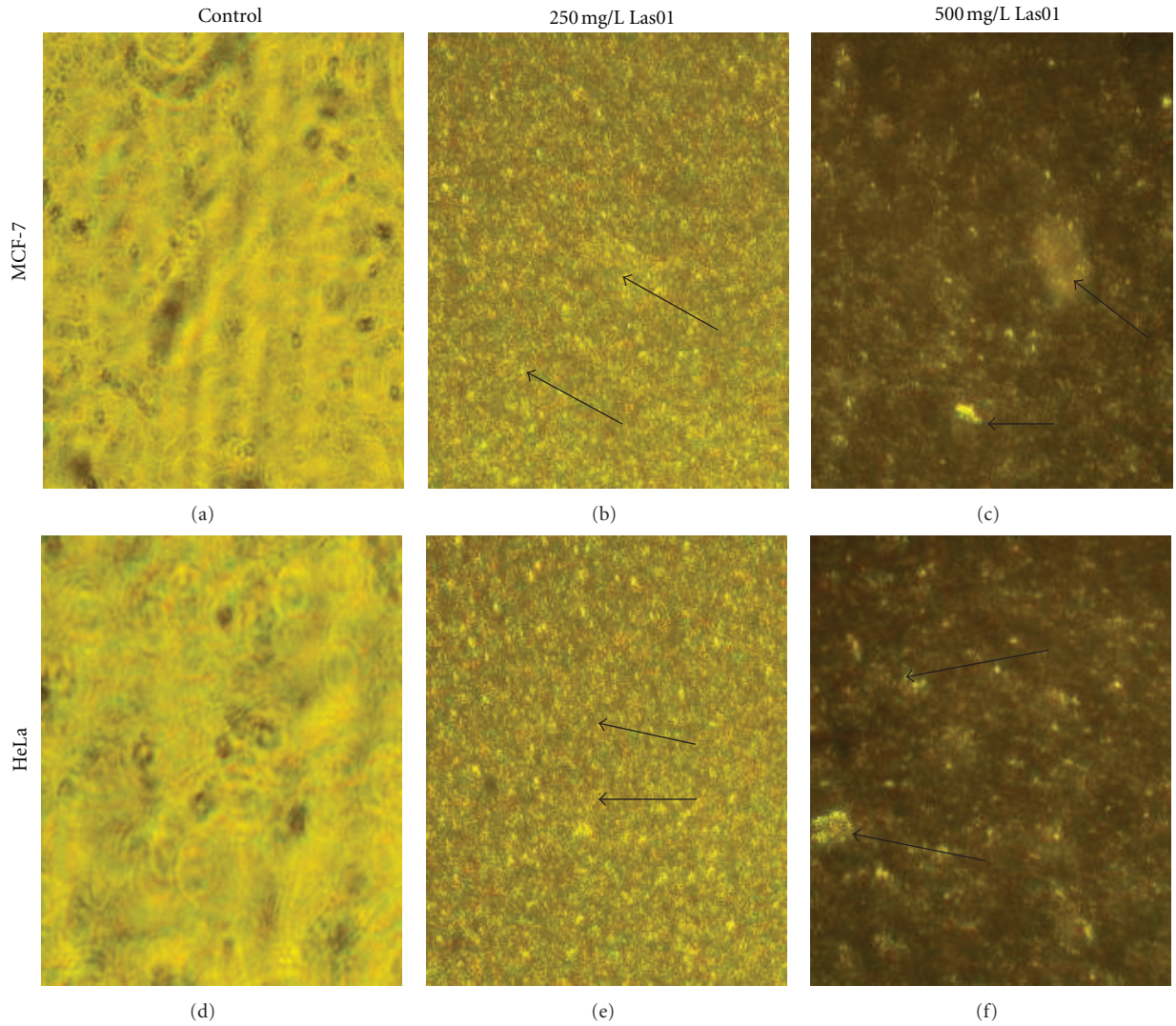


Figure 4

Cancer is a major cause of death or morbidity in human populations [13]. The human body is made up of different cells. Cells divide and multiply as per the need of body system. However, when balance between protooncogenes and tumor suppressor gene is disturbed due to several factors these cells continue to divide needlessly resulting in tumor formation [14]. There is evidence that potentially toxic macro- or microparticles of heavy metals could be nontoxic if these particles are converted into nanoparticles [15]. The search for novel antitumor compounds in phytotherapy is a promising strategy for the prevention of cancers [16]. Cellular proliferation depends on the rates of cell division and death and, thus, many anticancer drugs have been used to prevent cancer cell division in order to inhibit cancer cell proliferation. *In vitro* cytotoxicity assays can be used to predict human toxicity and for the general screening of chemicals [17, 18]. It has been previously reported that different cytotoxicity assays can give different results depending on the test agent used and the cytotoxicity assay employed [19]. Our present study demonstrates not only the efficacy of Las01 in *in vitro* tests on human cervical cancer cell line (HeLa) and breast cancer cell line (adenocarcinoma MCF-7) but also the safety of Las01 on variety of haematological and biochemical parameters both in animal experiments as well as in human beings. Las01 dosage formulation prepared by Lavanya Ayurvedic Hospital and Cancer Research Centre as per the instructions described in our ancient Ayurvedic literature is also supported by the observations of Dasgupta and Cuenca [14, 15]. Our *in vitro* experiments on apoptosis also demonstrate that the characteristic immortal cancer cells are converted into mortal cells indicating carcinostatic as well as carcinocid activity of Las01. In view of the efficacy and safety of Las01, a Herbomineral standardized preparation, its extensive clinical trial is warranted in a variety of carcinomatous conditions.

5. Conclusion

One of the most recent novel Herbomineral preparations, Las01, prepared absolutely as per the instruction given in

Table 4: Effect of administration of Las01 on biochemical parameters of cancer patients.

	Normal range	Pretreatment	1 year after treatment
LFT			
Serum bilirubin (T)	0.2–1.0 mg/dL	0.75	0.78
Serum bilirubin (D)	0.0–0.3 mg/dL	0.32	0.34
Bilirubin (ID)	0.1–1.0mg/dL	0.43	0.44
SGOT	0–37 (M) 0–31 (F) lu/L	31	28
SGPT	0–37 (M) 0–31 (F) lu/L	29	30
S-Alkaline phosphatase	100–275 lu/L	192	185
KFT			
Blood urea	15–50 mg%	22.6	22.7
S. uric acid	2.0–6.0 mg%	3.9	3.82
Creatinine	0.0–2.0 mg%	0.6	0.7
RBS	70–150 mg%	75	80
Total protein	6.0–9.0 mg%	7.2	7.1
Albumin	3.0–6.0 gm%	3.2	3.0
Globulin	2.0–5.0 gm%	4.0	4.1
Electrolyte			
Serum sodium	135–145 meq/L	140.2	141.1
Serum potassium	3.0–6.0 meq/L	4.21	5.0

the ancient Ayurvedic literature has been found to be an effective drug on the human cell lines MCF-7 and HeLa cancer cell line. This novel preparation of Las01 is also found to be devoid of toxicity both in animals as well as in human subjects, which is the main drawback of chemotherapeutic agents used in modern medicine. In view of our encouraging results, multicentric clinical trials are warranted on a large scale which seems to be a novel and future promising drug to cure incurable cancer patients.

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Review Article

Antitumor Activities of Kushen: Literature Review

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To discover and develop novel natural compounds with therapeutic selectivity or that can preferentially kill cancer cells without significant toxicity to normal cells is an important area in cancer chemotherapy. Kushen, the dried roots of *Sophora flavescens* Aiton, has a long history of use in traditional Chinese medicine to treat inflammatory diseases and cancer. Kushen alkaloids (KS-As) and kushen flavonoids (KS-Fs) are well-characterized components in kushen. KS-As containing oxymatrine, matrine, and total alkaloids have been developed in China as anticancer drugs. More potent antitumor activities were identified in KS-Fs than in KS-As *in vitro* and *in vivo*. KS-Fs may be developed as novel antitumor agents.

1. Introduction

To discover and develop novel natural compounds with therapeutic selectivity or that can preferentially kill cancer cells without significant toxicity to normal cells is an important area in cancer chemotherapy. Because of their wide range of biological activities and low toxicity in animal models, some natural products have been used as alternative treatments for cancers. Many anticancer drugs are derived from naturally occurring compounds. Vinca alkaloids (e.g., vinblastine, vincristine) and taxol are examples of such compounds.

The traditional Chinese medicine kushen is the dried roots of *Sophora flavescens* Aiton (Leguminosae). It was first described in the Chinese book *Shen Nong Ben Cao Jing* in 200 A.D. as a treatment for solid tumors, inflammation, and other diseases [1]. The traditional use of kushen includes the decoction or powder of dried plant roots. It is commonly used for the treatment of viral hepatitis, cancer, enteritis, viral myocarditis, arrhythmia, and skin diseases (e.g., colpitis, psoriasis, eczema) [2].

The known chemical components of kushen include alkaloids (3.3%), flavonoids (1.5%), alkylxanthones, quinones, triterpene glycosides, fatty acids, and essential oils [2, 3]. Kushen alkaloids (KS-As) and kushen flavonoids (KS-Fs) are well-characterized components in kushen. KS-As have been developed as anticancer drugs in China. More potent antitumor activities have been identified in KS-Fs than in KS-As [4].

2. KS-As

KS-As have been well studied and are considered to be the major active components of kushen as demonstrated in experimental animal models [5–8] and clinical studies [9–14]. The bioactivities of kushen (including antitumor, antiviral and anti-inflammatory activities) have been shown in the KS-As fraction [6].

KS-As containing oxymatrine, matrine (Figure 1), and total alkaloids were approved for the treatment of cancer patients by the Chinese State Food and Drug Administration (SFDA) in 1992. Multiple KS-As products have been used

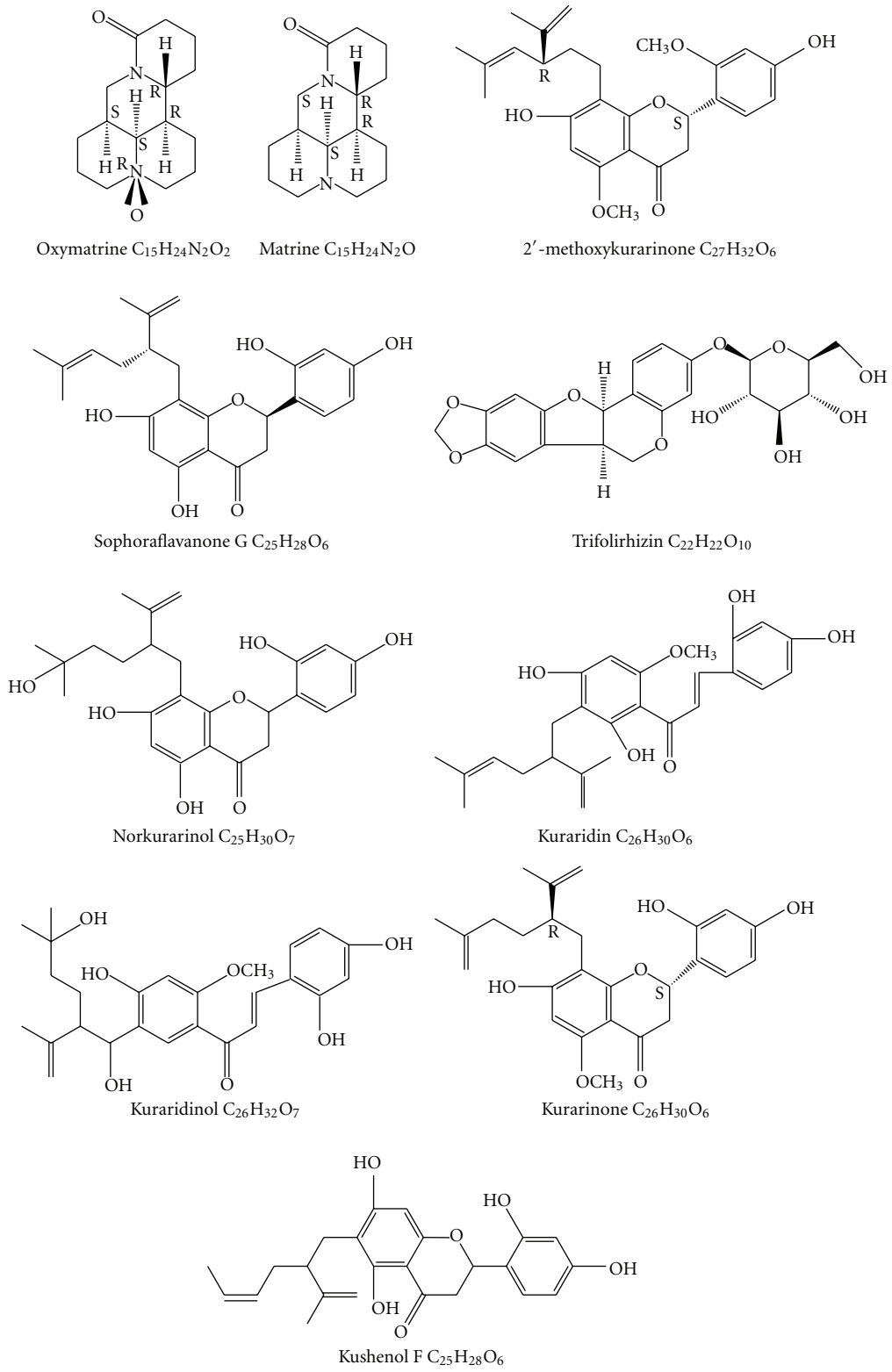

Figure 1: The molecular structure of antitumer compounds derived from *Sophora flavescens*.

widely in China for the treatment of cancers and hepatitis. The SFDA-approved KS drugs for oncology are all KS-As used as single agents or in combination with chemotherapy or radiotherapy. Few studies focused on the efficacy of KS-As in animal models and clinical trials before 1992, when KS-As was first approved.

Several clinical studies reported that KS-As were efficacious in the treatment of various types of solid tumors (including lung, liver, and gastrointestinal tract). The treatment responses were comparable to, or better than, that of chemotherapy drug-treated patients (Table 1) [11, 14–32]. KS-As demonstrates a good safety profile in cancer patients, such as reduced toxicity in the bone marrow when used in combination with chemotherapy agents [33]. Long-term survival data for KS-As-treated cancer patients remains to be demonstrated with well-controlled clinical studies and large patient cohorts.

3. Matrine and Oxymatrine

Matrine and oxymatrine (Figure 1) are the two major alkaloid components found in the roots of Sophora species. They are obtained primarily from *Sophora japonica* (kushen), *Sophora subprostrata* (shandougen), and from the overground portion of *Sophora alopecuroides*. The matrines were first isolated and identified in 1958; they are unique tetracyclo-quinolizidine alkaloids found only in *Sophora* species thus far [52–56].

In vitro studies have demonstrated that matrine and oxymatrine weakly inhibit the growth of various human tumor cell lines with a half-maximal inhibitory concentration (IC_{50}) of 1.0–4.0 mg/mL [57–61].

In vivo studies have shown that KS-As, oxymatrine, and matrine inhibit the growth of murine tumors, including H22, hepatoma, S180, sarcoma, and MA737 breast cancer cells [58, 60, 62, 63]. In a human xenograft tumor model using the SGC-7901 cell line, matrine enhanced the inhibition of 5-fluorouracil in the tumor [33].

Matrine can also inhibit the invasiveness and metastasis of the human malignant melanoma cell line A375 and cervical cancer HeLa cells, as well as induce differentiation of leukemia K-562 cells [64–66]. In addition, matrine-induced autophagy in rat C6 glioma cells has been observed by electron microscopy [67].

The antitumor response of KS-As was further demonstrated in several clinical studies in various types of cancers, including stomach, esophagus, liver, colon, lung, cervix, ovary, and breast cancers, as a single agent [9–14] or in combination with chemotherapy [15–18] or radiotherapy [68]. It has been reported that matrine exerts its antitumor effects by inhibiting the proliferation and inducing the apoptosis of gastric and cervical cancer cells as well as leukemic and glioma cells [34, 67–70].

Several *in vitro* and *in vivo* studies have tried to elucidate the mechanism of action of matrine. Matrine promotes apoptosis in leukemic [35], breast cancer [36], nonsmall-cell lung cancer [37], hepatocarcinoma, and gastric cancer cells [38] by a mitochondrial-mediated pathway [39]. Beclin 1 is involved in matrine-induced autophagy, and the proapoptotic mechanism of matrine may be related to its upregulation of Bax expression [39]. Recent evidence indicates that matrine also has appreciable effects in modulating the immune response by reducing the invasion and metastasis of HCC cells [40, 41, 71].

Tissue homeostasis requires a balance between the division, differentiation and death of cells. A tumor is a type of "cell cycle disorder" that has the abnormal interface of division, differentiation and death [42]. As a "biological modifier" of cells, matrine can reverse the abnormal biologic behavior of tumor cells and recover the balance between the division, differentiation, and death of cells.

Matrine can also inhibit the invasiveness and metastasis of the human malignant melanoma cell line A375 [43]. Some studies reported that matrine reduced the adhesion and migration of HeLa cells [72]. The mechanisms of action of matrine against cancer cell proliferation and invasion are associated with epidermal growth factorvascular endothelial growth factor vascular endothelial growth factor receptor 1 Akt–nuclear factor-kappa B (EGF/VEGF—VEGFR1—Akt—NF-κB) signaling [36] (Table 2).

Matrine displays synergistic effects with the anticancer agents celecoxib (cyclooxygenase-2 inhibitor), trichostatin A (histone deacetylase inhibitor) and rosiglitazone against the tumor proliferation and VEGF secretion. Matrine may have broad therapeutic and/or adjuvant therapeutic applications in the treatment of human nonsmall-cell lung cancer, breast cancer, and hepatoma [36, 37] (Table 2).

Some studies have also reported upon the anticancer activity of oxymatrine in human gastric cancer cells, pancreatic cancer, and human breast cancer cells [73–75]. Oxymatrine can induce the apoptosis death of human pancreatic cancer cells, which might be attributed to the regulation of Bcl-2 and IAP families, release of mitochondrial cytochrome C, and activation of caspase-3 [74] (Table 2).

Compound kushen injection (CKI), commonly known as Yanshu injection, is extracted from two herbs, kushen (Radix Sophorae Flavescentis) and Baituling (Rhizoma Smilacis Glabrae), with the primary components being oxymatrine and matrine [75]. CKI has been used extensively alone or in combination with chemotherapy or radiotherapy for many years in China. Clinical studies have shown that CKI attenuates the side effects of chemotherapy and radiotherapy by improving the quality of life and regulating the immune function of cancer patients, as well as synergizing the therapeutic effects of chemotherapy and radiotherapy (Table 1) [15–32, 76]. It has been demonstrated that CKI suppresses the growth of tumor cells by inducing apoptosis and inhibiting the migration, invasion, and adhesion, of such cells [77].

Cancer stem cells (CSCs) play an important part in the initiation, relapse and metastasis of cancer. A specific agent has not been found to target CSCs because they are resistant to most conventional therapies and proliferate indefinitely. In one study, CKI suppressed the size of the side population (SP; ~90%) and downregulated the main genes of the Wnt signaling pathway in MCF-7 SP cells. CKI suppressed tumor growth by downregulating the Wnt/b-catenin pathway,

Table 1: Clinical trials using compound kushen injection.

	Dose and course of treatment	Combined medication	Case/control	Cancer type	Indications and symptoms	Efficacy	Positive control	Side effect	Reference
1	1,000–1,500 mg + GS 500 mL, i.v., q.d., 30–45 days	No	68/37	Gastric cancer	Fever, pain, GI reactions, ascites	Relief	MMC + UFT	Abdominal distention, constipation	[11]
2	1,000–1,500 mg + GS 500 mL, i.v., q.d., 30 days, total dose of 30–45 g	No	44	Hepatocarcinoma	Evaluation of curative effect, immune effect, toxic effect	Effective treatment, reduction in tumor size, improvement in symptoms and signs, improvement in immune function	No	Nausea	[14]
3	30 mL + GS 250 mL, i.v., q.d., 10 days	Hydroxycamptothecin	20/20	Hepatocellular carcinoma	Recurrence rate	HCPT and CKI postoperative arterial infusion may be helpful for reducing intrahepatic recurrence after curative resection for HCC	PDD and 5-FU	No	[15]
4	1,000 mg + GS 500 mL, i.v., q.d., 30 days	Carboplatin or 5-FU	21	Malignant ascites	Evaluation of curative effect (ascites)	Lessening of ascites	Carboplatin or 5-FU	Abdominal distention	[16]
5	50 mL intrapleural injection or 100 mL peritoneal injection, b.i.w., 3 weeks	Dexamethasone	24	Virulent succus inside the thorax and belly: lung cancer, breast cancer, ovarian cancer	Ascites	Lessening of ascites, effective rate (CR and PR) 68.8%	No	Mild abdominal pain	[17]
6	1,000 mg + GS 500 mL, i.v., q.d., 30 days, 2–4 cycles	MVP/FAM/CAF/FP	65/61	Malignant tumor: lung, esophageal, liver, gastric, breast, colon, nasopharyngeal	Toxic effect, QoL	Improvement in QoL, reduce the toxic effects (leukopenia, GI reactions) of chemotherapy	MVP/FAM/CAF/FP	No	[18]
7	12–15 mL + NS 250 mL, i.v., q.d., 10 days	No	52/52	Malignant tumor: lung, breast, gastric, esophageal, colorectal, pancreatic	Pain	Pain relief	Sustained-release indomethacin or tramadol hydrochloride	No	[19]
8	15 mL + NaCl 250 mL, i.v., q.d., for 12 days	Fentanyl	31/31	Advanced cancer: gastric, esophageal, breast	Pain	Pain relief and KPS better than fentanyl, $P < 0.05$	Fentanyl alone	No	[20]
9	20 mL + NaCl 250 mL, i.v., q.d., for 14 days, 3 cycles	Oxaliplatin and capecitabine	36/30	Advanced gastric cancer in senile subjects	KPS; toxic effect	KPS better than oxaliplatin and capecitabine, $P < 0.05$; CKI has a low incidence rate for leukopenia, pain and hepatotoxicity, $P < 0.05$	Oxaliplatin and capecitabine	No	[21]
10	20 mL, i.v., q.d., 10–14 days	Chemotherapy: CAVP or CAP	61/60	Lung cancer	Immune	Improvement in immune function	Chemotherapy: CAVP or CAP	No	[22]

Table 1: Continued.

	Dose and course of treatment	Combined medication	Case/control	Cancer type	Indications and symptoms	Efficacy	Positive control	Side effect	Reference
11	30 mL + NaCl 250 mL, i.v., q.d., 7 days	Taxol and epirubicin	34/34	Breast cancer	Immune	Improvement in immune function	Taxol and epirubicin	No	[23]
12	20 mL + GS/NaCl 250 mL, i.v., q.d., 14 days, 2 cycles	TACE (5-FU 1,000–2,000 mg, MMC 10–20 mg, EP I60–100 mg)	27/23	Liver cancer	KPS; toxic effect	KPS better than TACE, $P < 0.05$; The incidence rate of nausea and vomiting hepatotoxicity were significantly lower than for TACE chemotherapy, $P < 0.05$	TACE	No	[24]
13	30 mL + GS/NaCl 250 mL, i.v., q.d., 10 days, 4 cycles	FOLRIRI chemotherapy	50/50	Advanced colorectal cancer	Pain, toxic effect, KPS	Pain relief, reduced toxic effect (leukopenia, GI reactions, hepatotoxicity and renal toxicity) of FOLFIRI chemotherapy; improved QoL	FOLRIRI chemotherapy	No	[25]
14	20 mL, i.v., q.d., 14 days, 3 cycles	Radiotherapy	33/33	Cervical cancer	Evaluation of curative effect, KPS, immune toxic effect	Improve therapeutic effects, QoL, immune function; attenuate myelosuppression	Radiotherapy alone	No	[26]
15	10 mL + NaCl 250 mL i.v. q.d. 10 days	DA/TA/MA chemotherapy	35/35	AML	KPS, hematotoxicity	Improve QoL; attenuate hematotoxicity (leukopenia) of chemotherapy	DA/TA/MA chemotherapy	No	[27]
16	20 mL intrapleural injection; keep 48 h q2W and 20 mL + 100 mL NaCl, i.v., q.d., 4 weeks	No	32/32	Malignant pleural effusion	KPS, evaluation of curative effect, toxic effect	Improve QoL and therapeutic effects; reduce toxic effects	Cisplatin	No	[28]
17	100 mL, i.v. b.i.d., 10 days	Gastric cancer: TPF chemotherapy; colorectal cancer: FOLFOX or FOLFRI chemotherapy; breast cancer: TA or CAF chemotherapy; lung cancer: GP/TP/NP chemotherapy	83/83	Malignant tumors: gastric, lung, colorectal, breast	Hepatotoxicity	CKI can effectively prevent hepatic injury caused by chemotherapy (incidence and degree of hepatic injuries)	Chemotherapy: gastric cancer: TPF; colorectal cancer FOLFOX or FOLFRI; breast cancer: TA or CAF; lung cancer GP/TP/NP	No	[29]

Table 1: Continued.

	Dose and course of treatment	Combined medication	Case/control	Cancer type	Indications and symptoms	Efficacy	Positive control	Side effect	Reference
18	20 mL + NaCl 250 mL, i.v., q.d., 21 days, 2 cycles	FOLFOX4 chemotherapy	27/21	Gastric cancer	Toxic effect	Incidence rate of alopecia lower than for FOLFOX4 chemotherapy, $P < 0.05$.	FOLFOX4 chemotherapy	No	[30]
19	20 mL + NaCl 200 mL, i.v., q.d., 14 days, 2 cycles	FOLFX chemotherapy	30/30	Gastric cancer	Toxic effect, QoL, symptoms	Promote reduction of symptoms, reduce chemotherapy side effects (alopecia, leukopenia, thrombocytopenia, GI reactions), improve QoL and prolong median survival time	FOLFX chemotherapy	No	[31]
20	20 mL in NaCl 250 mL, i.v., q.d., for 3-4 weeks, 2-3 cycles	Chemotherapy and radiotherapy	75/75	Mid-late-stage cancer: lung, breast, esophageal, nasopharyngeal, colorectal, pancreatic, ovarian	Immune, CBR, KPS, toxic effect	Improvement in immune function, increase the CBR and QoL and reduce adverse reactions of chemotherapy in patients with midlate-stage cancer.	Chemotherapy and radiotherapy (lung cancer: NP/GP/TP + radiotherapy; breast cancer: CAF/TA + radiotherapy: esophageal cancer: PF + radiotherapy; nasopharyngeal carcinoma: DDP + radiotherapy; colorectal cancer: oxaliplatin + 5FU + CF/oxaliplatin + xeloda; pancreatic cancer: GP; ovarian cancer: CAP/TP)	No	[32]

AML: acute myeloid leukemia; CAF: cyclophosphamide, adriamycin, and fluorouracil; CAP: cyclophosphamide, doxorubicin, and cisplatin; CAVP: cyclophosphamide, doxorubicin, and etoposide; CBR: clinical benefit rate; CF: calcium 5-formyletrahydrofolate; CR: complete remission; DA: daunorubicin and cytarabine; DDP: cisplatin; FAM: fluorouracil, adriamycin, and mitomycin; FOLFOX: oxaliplatin, calcium folinate, and fluorouracil; FOLFOX4: oxaliplatin, calcium folinate and fluorouracil; fOLFRI: irinotecan, calcium folinate and fluorouracil; FOLFX: oxaliplatin, calcium folinate and fluorouracil; FOLRIRI: leucovorin, fluorouracil, and irinotecan; FP: fluorouracil and cisplatin; 5-FU: fluorouracil; GI: gastrointestinal; GP: gemcitabine and cisplatin; HCC: hepatocellular carcinoma; HCPT: hydroxycamptothecin; KPS: karnofsky performance scale; MA: mitoxantrone and cytarabine; MMC: mitomycin; MVP: mitomycin, vinblastine, and cisplatin; NP: vinorelbine and cisplatin; PDD: cisplatin; PR: partial remission; QoL: quality-of-life; TA: paclitaxel and epirubicin; TA(9): pirarubicin and cytarabine; TACE: fluorouracil, mitomycin, and epirubicin; TP: paclitaxel and cisplatin; TPF: paclitaxel, fluorouracil, and cisplatin; UFT: Tegafur-Uracil.

Table 2: Mechanism of action of the chemotherapy of kushen compounds.

Compound	Mechanisms of action	Reference
Matrine	Promotes apoptosis via mitochondria	[34–38]
	Modulates the immune response	[39–41]
	Inhibits EGF/VEGF—VEGFR1—Akt—NF-κB signaling	[35, 42, 43]
Compound kushen injection	Inhibits cancer stem cells	[44]
Kuraridin, sophoraflavanone G, kurarinone, kushenol F, and norkurarinol	Strong tyrosine kinase inhibitory activity	[45–49]
Kurarinone	Inhibits TNFαl-induced NF-κB activation and enhances apoptosis	[45, 50, 51]
Kurarinone and kuraridin	Attenuate NF-κB activation by inhibition of IκBα proteolysis and p65 nuclear translocation as well as phosphorylation of ERK1/2, JNK, and p38 MAP kinases	[45, 51]

whereas cisplatin activated the Wnt/b-catenin pathway and could spare SP cells. These data suggested that CKI may serve as a novel drug targeting CSCs, but further studies are recommended [44].

4. KS-Fs

The antitumor effects of some flavonoid compounds (Figure 1) have been demonstrated *in vitro* and *in vivo* [78–82]. Surprisingly, the antitumor activities of KS-Fs were more potent than those of KS-As, which have been considered to be the major active components in the plant [83]. KS-Fs such as kurarinone, 2′-methoxykurarinone, and sophoraflavanone G (lavandulyl flavanones isolated from *S. flavescens*) (Figure 1) can inhibit cell proliferation in A549, NCI-H460 (nonsmall-cell lung), SK-OV-3 (ovary), SK-MEL-2 (skin), XF498 (central nerve system), HCT-15 (colon) HL-60 (myeloid leukemia) and SPC-A-1 (lung) cells with IC_{50} values between 2 μg/mL and 36 μg/mL [80, 82, 83].

Antitumor efficacies were confirmed in mice models of H22, S180 and Lewis lung tumors as well as nude mice models of human H460 and Eca-109 xenografted tumors [45, 83]. Moreover, KS-Fs and kurarinone enhanced the antitumor activities of Taxol *in vitro* and *in vivo* [83, 84]. The oral or intravenous maximum tolerated dose of KS-Fs was >2.8 g/kg or 750 mg/kg, respectively, appreciably more than the oral median lethal dose of KS-As ($\leq$1.18 g/kg). Adverse reactions were not observed. In addition, peripheral blood cell counts were not significantly affected in normal mice treated with KS-Fs at 200 mg/kg/day for 2 weeks [45, 83].

Kuraridin, sophora flavanone G, kurarinone, kushenol F, and norkurarinol have extremely strong tyrosinase inhibitory activity [45–49]. Kurarinol, kuraridinol, and trifolirhizin markedly inhibited (>50%) melanin synthesis [48, 49].

The mechanism of action of KS-Fs and kurarinone involves inhibition of tumor necrosis alpha one (TNFαl)-induced NF-κB activation and enhance apoptosis [45, 50, 51]. The apoptosis-inducing effect was enhanced in the presence of taxol. In H460 xenograft mice treated with kurarinone, downregulation of Bcl-2 and upregulation of caspase 8 and caspase 3 in tumors were observed [45]. KS-Fs and kurarinone induce apoptosis in tumors by acting on multiple cellular targets, including inhibition of NF-κB activation and multiple receptor tyrosine kinase activities [45]. Kurarinone and kuraridin attenuate NF-κB activation by inhibition of IκBα proteolysis and p65 nuclear translocation, as well as phosphorylation of extracellular signal-regulated kinase (ERK)1/2, c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinases [45, 51]. Constitutive NF-κB and RSK2 activities are important hallmarks of human cancers (including hematopoietic malignancies and solid tumors), so prenylated flavanones represent an attractive class of natural inhibitors of the ERK/RSK2 signaling pathway for cancer therapy [85] (Table 2).

Fifty-six flavonoids have been identified from KS-Fs. Twenty-one of the KS-Fs have been found to have antitumor activities. Studies have demonstrated that more potent antitumor activities are observed in KS-Fs instead of KS-As fractions. KS-Fs were more than 10-fold more potent than KS-As in the cell proliferation assay. Further evaluation of the safety and efficacy of KS-Fs in clinical oncology settings is warranted. KS-Fs could be developed as botanical drugs for solid tumors, and kurarinone could be used as a marker compound. Additional structural modifications of KS-Fs compounds could also generate more potent drug candidates.

5. Conclusions and Future Perspectives

This paper summarized the antitumor efficacy and mechanism of action of kushen and its constituents *in vitro* and *in vivo*. Many Patents of kushen extracts have been applied in USA, China and other countries (Table 3). These results strengthen the hypothesis that kushen (or its components) alone or combination with chemotherapy agents could modulate various molecular pathways in tumors or be used to treat cancer. Studies described here and elsewhere highlight the use of flavonoids of kushen as novel chemoprevention agents for cancer intervention. It is expected that future studies with kushen will help to define various molecular mechanisms and targets for the inhibition and apoptosis of tumor cells. The number of multicenter, large sample,

Table 3: Patents of kushen extracts.

Patent	Patent number
Extract of *Sophora flavescens* flavonoids and uses thereof	US20050226943
Prenylated flavonoid derivatives having anti-inflammatory properties and *Sophora flavescens* extracts	Korea1020000077932
Extract of *Sophora flavescens* flavonoids and uses thereof	US20050226943
Compositions comprising matrine and dictamnine for treating or preventing cancer and other diseases	US2004192579A1
Medicine preparation containing matrine or epimatrine and its application in analgesic medicines	CN1347694A
Use of oxidized matrine in preparation of chemicals for treating venereal diseases	CN1530108A
A process for the manufacture of a herbal composition comprising a matrine	WO02067955A3
Use of oxidized matrine in preparation of chemicals for treating viral myocarditis	CN1530109A
Double salt formed by inosine and matrine or oxymatrine and application thereof in field of medications	CN101724002A
Pharmaceutical purpose of compound comprising ferulic acid and matrine alkaloid in prevention and treatment of osteoarthropathy	CN101669946A
Application of oxidized matrine in preparing medicine for treatment of hepatitis B	CN1157717A
Joint synergy of ferulic acid and matrine alkaloid and medical application thereof	CN101669945A
Medicinal use of matrine alkaloid for promoting digestive tract power	CN1850075A
Medicine composition containing silymarin and kurarinone or matrine and use thereof	CN101357129A
Pharmaceutical composition comprising kurarinone, magnolia vine fruit, and ginseng for treating hepatitis	CN1970001A
Use of kurarinone in preparation of medicine for postoperative intestine functional restoration	CN1923198A
Combination of medication of containing kurarinone and glycyrrhetic acid, and application	CN1695624A
Oxymatrine compositions and related methods for treating and preventing chronic infectious diseases	US2010022575A1
Pharmaceutical composition comprising oxymatrine and baicalin	CN1919205A
Medicinal composition of oxymatrine and polysaccharide	CN101081240A
Complex salt of silybin and oxymatrine or matrine and uses thereof	CN101157689A
Double salt formed by inosine and matrine or oxymatrine and application thereof in field of medications	CN101724002A
Method for separating matrine and oxymatrine from total matrines	CN101585837A
Application of oxymatrine in preparing medicine for treating acute chronic cardiac insufficiency disease	CN101185647A
Application of oxymatrine in preparing medicine to treat viral hepatitis C	CN1350848A
Application of oxymatrine in preparing medicine to treat liver fibrosis	CN1350849A
Use of alkaloids extracted from *Sophora flavescens* in preparing medicine for treating diseases reduced by mycoplasma, chlamydia and fungus	CN101336958A
Compositions for improving skin conditions comprising matrine or its oxidized derivatives	US2010099698A1
Oxymatrine compositions and use thereof for treating and preventing chronic infectious diseases	WO2010011975A1
Preparation and use of silybin bis bias succinate oxymatrine double salt and matrine double salt	CN101297802A
Medication with spermicidal effect *in vitro* and bacteriostatic action and preparation method and application thereof	CN101757140A
Chinese medicine for hepatitis B and its preparation	CN1244409A
Medicinal composition for preventing tumors	CN101073611A
Application of kushen (*Sophora flavescens*) flavone in preparing antihypoglycemic agents	CN1348762A

randomized, double-blind, controlled chemoprevention clinical trials with kushen are very limited. Extensive clinical research is warranted to evaluate further the safety and chemoprevention efficacy of kushen alone or in combination with chemotherapy agents.

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Research Article

Reflexology versus Swedish Massage to Reduce Physiologic Stress and Pain and Improve Mood in Nursing Home Residents with Cancer: A Pilot Trial

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Objective. The purpose of this pilot study was to investigate and compare the effects of reflexology and Swedish massage therapy on physiologic stress, pain, and mood in older cancer survivors residing in nursing homes. *Methods*. An experimental, repeated-measures, crossover design study of 18 nursing home residents aged 75 or over and diagnosed with solid tumor in the past 5 years and following completion of cancer treatments. The intervention tested was 20 minutes of Swedish Massage Therapy to the lower extremities, versus 20 minute Reflexology, using highly specified protocols. Pre- and post-intervention levels of salivary cortisol, observed affect, and pain were compared in the Swedish Massage Therapy and Reflexology conditions. *Results*. Both Reflexology and Swedish Massage resulted in significant declines in salivary cortisol and pain and improvements in mood. *Conclusions*. Preliminary data suggest that studies of Swedish Massage Therapy and Reflexology are feasible in this population of cancer survivors typically excluded from trials. Both interventions were well tolerated and produced measurable improvements in outcomes. Further research is needed to explore the mechanisms underlying the potential benefits of these CAM modalities in this patient population.

1. Introduction

Cancer is a leading cause of morbidity and mortality in the older population. Demographic trends in the aging of the population, coupled with trends in cancer diagnoses and treatment, will shift much of the care of older cancer survivors to the nursing homes setting. Older cancer survivors suffer many long-term side effects of cancer and its treatment that threatens their quality of life [1]. Pain and distressing symptoms are common and often difficult to treat pharmacologically. Thus, investigations into the care of nursing home cancer survivors are particularly relevant.

Complementary therapy interventions have shown great promise in reducing distress and promoting comfort in cancer survivors [2, 3]. Two of the most widely accepted manual CAM therapies are reflexology and massage therapy. Recent reviews suggest that these modalities may have beneficial effects such as decreasing pain and increasing qualify of life in patients who have cancer [4, 5]. However, study limitations (small sample size, lack of adequate control groups) and conflicting results made firm conclusions impossible [6, 7]. Moreover, while results of earlier studies are encouraging, these studies have not compared the physiologic responses to these treatments and have typically excluded older cancer survivors. Thus, in order to advance this area of research, the next step is to test the feasibility and compare the efficacy of these interventions using physiological and behavioral measures of distress. This pilot study served as a first step to evaluating the use of a Swedish Massage and a Reflexology

protocol for relief of distress in nursing home cancer survivors.

2. Materials and Methods

An experimental, repeated-measures, crossover design study of 18 older cancer survivors residing in nursing homes was conducted from 2009–2011. This design was selected because it offered advantages over parallel group trials including: (a) that each subject acted has his or her own control, eliminating among-subject variation; (b) that fewer subjects were required to obtain the same power; (c) that every subject received both conditions [8].

Directors of nursing at 3 large nursing home facilities in Pennsylvania approached residents for permission to be contacted for the study. The medical director at each facility gave final approval to contact the residents, and their responsible party for consent. Subjects were included if they were (a) residents of the nursing home for at least 6 months, (b) aged 75 or over, (c) diagnosed with a solid tumor (lung, prostate, colorectal, breast) in the last 5 years (d) completed cancer treatments, and (d) capable of giving informed consent, or had an acceptable surrogate capable of giving consent on the subjects behalf. Exclusion criteria were based on the relevant literature that outlines suitability for elders receiving massage-based treatments and included [9, 10] (a) evidence of rapid terminal decline, recent traumatic injury, or hospitalization within the 2 weeks, (b) skin diseases: acute psoriasis, eczema, severe bruises, skin infection or ulceration, open wound, recent burn or fracture, (c) inflammatory conditions: acute rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Reiter's syndrome, (d) cardiovascular conditions: history of deep vein thrombosis, phlebitis, angina, a pacemaker, (e) recent discontinuation (less than 2 weeks) of physiotherapy that included massage therapy, (f) fever (recent temperature >102° within past 24 hours), or (g) currently prescribed anticoagulant medication (e.g., Coumadin, Heparin, or derivative substances).

Consenting subjects were randomized into two conditions. Those assigned to the first group received one week of friendly visits (for baseline assessment) followed by four weekly sessions of Swedish Massage, a one-week washout period, then 4 weekly sessions of Reflexology. Those assigned to the second group received one week of friendly visits followed by four weekly sessions of Reflexology, a one-week washout, then 4 weekly sessions of Swedish Massage. The protocols were developed based on Standards of practice and expert guidelines of the American Massage Therapy Association (AMTA) and National Certification Board for Therapeutic Massage and Bodywork standards of practice [11]. To reduce the extraneous effects of multiple interventionists, the friendly visits, massage, and reflexology were provided by a single, certified, reflexology/massage therapy provider. The protocols were offered at the same time (between 2 and 4 pm) on the same day each week. All subjects received an equal number and duration of sessions in the privacy of their room in the nursing home. There was no script for any of the sessions. It was normal for the practitioner to converse with the subject and give a brief overview of the session. The subject would normally "lead" the conversation.

2.1. Intervention Protocols. The Swedish Massage protocol was prespecified and involved a combination of 10 minutes of light stroking and light pressure using the whole hand to plantar and dorsal surfaces and all tissue from the toes to the knee of each leg (20 minutes total). The Reflexology Intervention was based on the original Ingram method and used a combination of finger pivot and thumb walking techniques to the base of the foot and the toes that correspond with reflex points. The sole, instep, and lateral aspects of the foot were stimulated 5 times, each foot for a total of 10 minutes per foot (20 minutes total). The interventionist was licensed and certified in both modalities and underwent additional training in the detailed protocols and was assessed for fidelity as random intervals [12].

2.2. Study Outcomes. Baseline data collection began in September 2009 and included an intake assessment of demographic and medical information. Data collectors blind to group condition performed follow-up data collection. Each data collection encounter was designed to take less than 15 minutes and was completed at four intervals across the day: (1) early morning: 7–7:30 am, (2) mid morning: 11–11:30 am, (3) early afternoon 1–1:30 pm, (4) late afternoon: 4–4:30 pm. These times were selected to maximize the opportunities to observe the subjects mood and to capture the diurnal variation in salivary cortisol, while avoiding interruption of the interventionists' presence.

Over the course of the intervention day, 3 distinct types of data were collected: (1) saliva samples from which salivary cortisol was measured; (2) 5-minute observation of affect (e.g., positive and negative mood) using the Apparent Affect Rating Scale (AARS) [13, 14]; (3) pain using the checklist of nonverbal pain indicators (CNPI) [15, 16]. Measures were then averaged to provide daily mean values for each outcome of interest.

2.2.1. Salivary Cortisol. The primary outcome of interest was physiologic distress as measured daily average salivary cortisol [17]. Since cortisol possesses diurnal qualities, samples (of .5–1 mL volume each) were collected across the day to capture the circadian patterns. Assays were collected using oral swabs made of a nontoxic, inert polymer shaped into a 30 × 10 mm cylinder designed to help filter mucus and other matter from the sample. The swabs were held under the tongue for one minute starting on awakening (7–7:30 am) and at 3 additional intervals (midmorning, early afternoon, late afternoon). Care was taken when collecting saliva to avoid collection after mouth cleaning, meals, snacks, or medications. Saliva samples were transferred to 2 mL cryovials and stored frozen (at least −20°C) until assayed. All samples were assayed for cortisol using a highly sensitive enzyme immunoassay 510 K cleared for use as an in vitro diagnostic measures of adrenal function (Salimetrics, PA). The test had lower limit of sensitivity of .007 ug/dL, range of sensitivity from .007–3.0 ug/dL, and an average intra- and

Table 1: Group means and SDS for outcomes, difference scores (change in treatment values), and effect size estimates.

Outcome of interest	Arm	Means ± SD			ES	P°
		Baseline	Post-treatment	Change from baseline		
Salivary cortisol (ug/dL)[1]		.257 ± 1.1				
	R		.157 ± .09	−0.10*	−.13	
	M		.209 ± .08	−0.05*	−.10	0.23
Positive affect[2]		1.58 ± 0.93				
	R		2.25 ± 0.9	+0.67*	+.73	
	M		1.94 ± 1.0	+0.36*	+.30	0.16
Negative affect[3]		1.17 ± .95				
	R		.823 ± .72	−0.35*	−.42	
	M		.941 ± .82	−0.23*	−.30	0.16
Pain[4]		2.29 ± 1.2				
	R		2.00 ± .79	−0.29*	−.35	
	M		1.58 ± 1.2	−0.71*	−.77	0.22

[1] Higher score: higher physiologic stress.
[2] Higher score: higher positive affect.
[3] Higher score: worse negative affect.
[4] Higher score: higher observed pain
R: Reflexology, M: Swedish Massage; SD: standard deviation; ES: standardized effect sizes.
$^{\circ}$ t-test comparing Reflexology and Swedish Massage Conditions.
* Indicates paired t-test results demonstrating significant change from baseline ($P < .05$).

interassay coefficients of variation of less than 5.0% and 10.0%.

Observation of Affect. Positive and negative mood was measured by the AARS scale which consists of five items (positive mood: alertness, pleasure; negative mood: sadness, anxiety, anger), requires 5 minutes of observation, and provides reliable and valid readings of positive and negative affect and levels of alertness for both cognitively intact and impaired nursing home residents [13, 14]. Psychometric properties have been well demonstrated in the sample population and documented in earlier studies, including interobserver reliability (ICC = 0.91 for the current study), convergent and discriminant validity, and support for its two-factor (positive mood, negative mood) structure [14].

Pain. The CNPI, a behavioral observation scale for nonverbal older adults with cognitive impairment, is one of the more rigorously tested pain assessment instruments [15, 16]. The CNPI is composed of six items (nonverbal vocal complaints, facial grimacing/wincing, bracing, restlessness, rubbing, and verbal vocal complaints), that are rated as presence or absence of pain and has good face validity with verbal, horizontal visual, vertical visual, and faces pain scales, and established interrater reliability for periods of rest and movement [15, 16].

2.2.2. Statistical Analysis. The feasibility of the study was assessed by examining the rates of recruitment, retention and suitability of the outcome measures. The efficacy of Swedish Massage Therapy versus Reflexology were compared to baseline values for each outcome variable based on subjects who had available data for both pre- and post-treatment time points. The treatment effect size was computed on all change scores with a Cohen's d [18],based on difference between the averages of the post-treatment values minus the average of the baseline values for each condition. Paired t-tests were used to compare Swedish Massage Therapy versus Reflexology with respect to their mean change baseline to post-treatment values as described above (Table 1). Since cortisol is not normally distributed, all analyses used the log-transformed hormone values; however, nontransformed data are reported in the tables and text to facilitate interpretation.

3. Results and Conclusion

Of the 45 residents approached for consent, 20 consented, 12 declined, 11 did not return consents, 1 resident died, and 1 resident was hospitalized while invitations to participate were in the mail. Of the 20 that consented, 2 were hospitalized prior to baseline data collection and were unable to participate, thus we randomly assigned 18 individuals to the 2 groups. The ages of participants averaged 90 years and ranged from 85 years to 98 years. Approximately 66% (N = 12) were female and 33% (N = 6) were male. Mental status as measured by the Mini-Mental State score ranged from 0 to 18 with an average score of 10.17, indicating significant cognitive impairment. The types of cancer represented in the sample were: breast cancer (n = 7,39%), prostate cancer (n = 5,28%), colorectal cancer (n = 5,28%), and lung cancer (n = 1,5%). All study procedures were well tolerated by the study participants. No drop outs occurred during the study period and no adverse events or outcomes were observed.

Table 1 shows the group means and difference scores associated with the outcomes of interest for the Reflexology and Swedish Massage conditions, along with Cohen's d effect size estimates. Within group, comparison of the treatment results revealed that both conditions were associated with a statistically significant changes in salivary cortisol, negative affect, positive affect, and pain ($P < .05$), when post-treatment values were compared to the baseline values, with a slight advantage indicated for Reflexology. Cohen's d effect size estimates ranged from $d = .1$ to $d = .77$, and on average were in the medium range of effect [18]. According to between-group t-tests, no significantly greater improvement in outcomes resulted when the two treatment conditions were compared.

4. Discussion

The results demonstrated the feasibility of providing and studying manual CAM modalities in nursing home residents with cancer and indicate the need for larger trials. Although our sample size was small, the data suggested some efficacy of the Massage and Reflexology intervention, particularly related to a reduction in observed pain, observed affect, and measures of stress. Although most of the effectsizes noted were in the medium range, a larger study would be needed to determine whether the effect sizes suggested in this pilot study can be confirmed with statistically significant results. Reflexology appeared to offer a slight benefit on outcomes when compared to Swedish Massage, although this benefit was not significant. The mechanism underlying this potential benefit may be attributed to the stimulation of the acupressure points during Reflexology treatments. This hypothetical mechanism may deserve further investigation in a larger trial.

The study has several important limitations. Participants may not be representative of nursing home residents with cancer. The three recruitment sites served a relatively homogenous population of Caucasian older adults. Also, by design the study included only English-speaking residents who were medically stable and not actively undergoing cancer treatments. Thus the subjects may systematically differ from residents with cancer who did not meet eligibility criteria. Moreover, because the sample was not randomly selected from the nursing home population, it is unclear whether the responses we observed are generalizable to other groups of older cancer survivors. In addition, we were unable to assess clinically significant improvements in cortisol, pain, or mood since clinically significant change of the measures used in this study has not been determined. Moreover, the lack of normative data on measures of salivary cortisol in this population limited our ability to test for clinical meaningful changes in this biomeasure. The sample size did not permit us to explore the interaction of covariates in this sample. We were unable to include a usual care control group due to sample size and budget restrictions. Another limitation of this study is the concern that small samples may not be truly representative of the range of subject heterogeneity that can be observed in a larger sample; thus, the effect-size estimates may be larger than would be observed in a larger replication study [19].

These limitations notwithstanding, this pilot study had a number of strengths, which included a randomized design, stringent manualized conditions, and evaluations that were blind to treatment assignment. The results suggest that both Swedish Massage and Reflexology were well tolerated and potentially beneficial in reducing distress and pain and improving mood in older cancer survivors residing in nursing homes. Previous research has supported the value of CAM modalities such as massage and reflexology for relieving distress in older adult patients with cancer and offer guidelines for therapists [20, 21]. For example, the REST study demonstrated significant benefits of massage on pain and mood in adults with advanced cancer [22]. However, given that few clinical trials of massage or reflexology in a frail, institutionalized, older patient population have been published, few direct comparisons are available. Nonetheless, our results confirm earlier studies on CAM modalities in cancer survivors and extend the findings to a sample of participants typically excluded from earlier trials.

These preliminary findings support further study of manual CAM modalities as part of a palliative approach to institutionalized cancer survivors. Developing additional insights into physiological effects and mechanisms of manual CAM interventions is a crucial component of the scientific evidence base needed to guide future clinical practice for older cancer survivors.

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Review Article

Cancer-Related Stress and Complementary and Alternative Medicine: A Review

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A cancer diagnosis elicits strong psychophysiological reactions that characterize stress. Stress is experienced by all patients but is usually not discussed during patient-healthcare professional interaction; thus underdiagnosed, very few are referred to support services. The prevalence of CAM use in patients with history of cancer is growing. The purpose of the paper is to review the aspects of cancer-related stress and interventions of commonly used complementary and alternative techniques/products for amelioration of cancer-related stress. Feasibility of intervention of several CAM techniques and products commonly used by cancer patients and survivors has been established in some cancer populations. Efficacy of some CAM techniques and products in reducing stress has been documented as well as stress-related symptoms in patients with cancer such as mindfulness-based stress reduction, yoga, Tai Chi Chuan, acupuncture, energy-based techniques, and physical activity. Much of the research limitations include small study samples and variety of intervention length and content. Efficacy and safety of many CAM techniques and some herbs and vitamin B and D supplements need to be confirmed in further studies using scientific methodology. Several complementary and alternative medicine therapies could be integrated into standard cancer care to ameliorate cancer-related stress.

1. Introduction

Cancer-related distress is defined as an "unpleasant emotional experience of a psychological, social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment" [1]. Several factors can cause stress during the cancer experience; a cancer diagnosis itself is a strong stressor associated with "disbelief, anxiety, depression," and disturbances of sleep, appetite, and routine daily activities [2]. In addition to uncertainty about the disease and its treatment, there is also fear of death, disease progression, reduction in quality of life (QOL) and relationships, a loss of sense of control [3–10], and impacts on decision-making ability and treatment compliance [1]. Cancer patients experience a broad spectrum of individual and cooccurring symptoms such as pain, anxiety, depression, fatigue, nausea, diarrhea, wasting, and cognitive impairments, which both promote and indicate distress [11]. Regardless of treatment regimen, distressing symptoms such as fatigue, insomnia, pain, depression, hot flashes, sexual dysfunction, and cognitive deficits frequently occur and often persist following treatment [12, 13]. Overall, a cancer diagnosis creates a vicious and compounding cycle of stress.

Although all patients with a history of cancer experience variable level of stress across the continuum of disease [1], often information sharing on this topic does not happen during interaction of patients with their healthcare professionals [1]. The reported prevalence of cancer-related distress is 24–59% depending on the type of cancer [10], stage of disease, patient population studied, and study setting [14, 15]. A recent study of newly diagnosed cases reported distress in about 67% of lung cancer patients and 50% of breast cancer patients [16]. Another study found self-reported distress in 25% of cancer outpatients, 59% of patients with advanced

cancer undergoing palliative care, and 16% of cancer patients in the general community [14]. Psychosocial interventions including experiential-existential group psychotherapy and cognitive-behavioral stress management [17–22] have shown positive results in coping with daily stressors. Additionally, pharmacologic treatments for some of the cancer-related psychiatric symptoms are available. Some resources are available in the form of information on its identification and possible counseling services recommended by various national societies and institutions [1]. However, only a small percentage of patients with distress are detected and referred for treatment [1]. The use of complementary and alternative medicine (CAM) has increased among cancer patients at the time of diagnosis, during treatment, and even after treatment is complete [23]. The primary reasons for CAM use by cancer patients are pain relief, immune-system boost, symptom management [24], and better quality of life [25]. However, there are concerns about the use of CAM techniques related to cancer experience since the efficacy of several of these techniques/products has not been documented or due to possibility of interaction with treatment. This paper reviews aspects of cancer-related stress and CAM interventions for the amelioration of stress during and after the cancer experience. Researchers over time have used the words "stress" and "distress" interchangeably, and in this paper, the term "stress" will be used unless the referenced study used the word "distress".

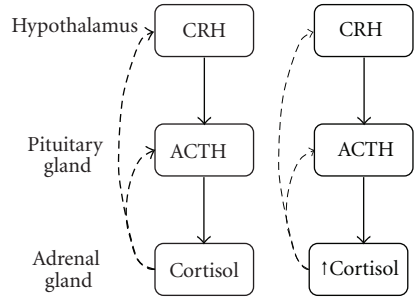
2. Neuroendocrine and Immunological Aspects of Stress and Cancer

Stress is characterized by psychophysiological processes in response to an event or circumstance that is perceived as threatening, harmful, or challenging [26]. The hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) are involved in the physical stress response. The HPA axis functions through a negative feedback system: increased cortisol and other glucocorticoid (GC) levels inhibit release of corticotrophin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) from the neurons of the hypothalamus and pituitary gland, respectively, leading to a reduction in GC levels (Figure 1(a)). A chronic or repeated exposure to a stressor decreases CRH, ACTH, and GC levels [27, 28] indicating a reduction in negative feedback in the HPA axis. In cancer patients, such dysregulation of the HPA axis and the SNS may be related to the development, maintenance, and recurrence of cancer. For instance, norepinephrine has been linked to the etiology of cancer [29], and epinephrine has been shown to protect against cellular apoptosis in cancer cells [30]. In women with metastatic breast cancer, HPA axis dysregulation was characterized by increased resting cortisol levels (Figure 1(b)) and decreased inhibition of the pituitary gland and the hypothalamus [31]. Although a linear relationship between resting cortisol levels and stage of cancer was observed, ACTH levels were normal in both early and late stages [31]. Other studies have shown that some cancer patients have a flattened diurnal cortisol rhythm compared to healthy controls [32, 33], which is associated with shorter survival times [33].

Stressful events like cancer have been shown to lead to increased risk of disease progression and decreased survival [34–37], and they can contribute to dysregulation of the immune system, chronic inflammation, and numerous adverse effects [38]. Psychological stress and altered HPA axis function can influence the activity of a variety of immune cells, including natural killer (NK) cells, T cells, and macrophages [39]. Disrupting the balance of immune cells leads to a chronic proinflammatory cytokine-mediated cascade of events resulting in enhanced psychological stress, depression, anxiety, fatigue, sleep disturbance, cognitive impairments, and ultimately reduced quality of life [40–44]. Stress hormones can impair the immune response and may affect tumor progression and cancer prognosis. Chronically elevated stress hormones shift the balance between the Th1 (cellular) and Th2 (humoral) immune responses toward the Th2 response. Expression of Th1 cytokines IFN-γ and IL-12 decreases during stress, while Th2 cytokines IL-4, IL-5, IL-6, IL-10, and IL-13 increase (reviewed in [45, 46]). These changes are associated with decreased cytotoxic T-lymphocyte and natural killer (NK) cell activity [47, 48]. Evidence from animal models suggests that these types of immune deficiencies can lead to tumor progression. For example, mice subjected to social isolation stress had decreased splenic NK cell activity [49]. In the same mice, metastasis required less time after tumor cell injection in stressed animals than in controls. Stressed animals also did not respond as well to chemotherapy [50].

Stress hormones can also alter cell-signaling pathways, which have been implicated in cancer progression. Many studies suggest that stress hormones can decrease apoptosis in certain cancer cells through decreased activity of pro-apoptotic caspases-3, 8, and 9 [51] and protein BAD [52]. Increases in vascular endothelial growth factor (VEGF), which is important for tumor vascularization and survival [53], have been shown in cancer cell culture models as a result of norepinephrine-dependent β-adrenoreceptor activation of the cAMP/PKA signaling pathway [54–56], and this could be critical in tumor progression. In an animal model of ovarian cancer, psychological stress simultaneously increased VEGF expression and tumor burden [57].

Metastasis relies on tumor cell invasion, which requires proteins that can break down the extracellular matrices of the invaded tissues; preliminary evidence of the same is provided by norepinephrine-stimulated ovarian cell invasion and increased matrix-metalloproteinase- (MMP-)2 and 9 expression through activation of the β-adrenergic receptor [58] and an increase in MMP-2 and 9 associated with psychological stress in the ovarian cancer mouse model [57]. Thus, it is conceivable that stress management might reduce disease progression and improve quality of life in patients with cancer. We note that while this is a plausible hypothesis, the evidence supporting it in cancer patients is lacking. Several modalities for stress reduction have shown promise; use of other options can be considered based on evidence provided by recent research on complementary and alternative medicine (CAM) techniques/products.



(a) Normal HPA-axis regulation

(b) Proposed HPA-axis dysregulation for high cortisol levels

Figure 1: Overview of the hypothalamus-pituitary-adrenal axis in relation to the stress response in healthy individuals (a) and those with cancer (b). CRH: corticotrophin-releasing hormone; ACTH: adrenocorticotropic hormone. Thin dashed lines represent reduced feedback inhibition.

3. Complementary and Alternative Medicine Utilization in Cancer

CAM has been defined by the National Center for Complementary and Alternative Medicine (NCCAM) as "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine" [59]. Such techniques include mind-body medicine, natural products, nutritional supplementation, manipulative body-based practices, energy-based techniques, and traditional medical systems (e.g. Chinese, Ayurved, and American-Indian). These modalities have recently been classified as integrative medicine as they are not an alternative to conventional medicine use; however, for the purpose of this paper the term CAM will be employed. CAM use has been increasing among cancer patients [23] and currently ranges from 22% to 73% [60]. Based on 2002 National Health Interview data, 26% of female survivors and 13.7% of male cancer survivors reported using CAM [61]. A more recent study revealed that 62% of female breast cancer survivors used CAM [62]. CAM use in cancer patients is associated with high levels of distress and failure of conventional medicine to meet psychosocial needs [63]. Although emotional distress along with other psychological indices significantly predicted CAM use in male and female survivors of colon cancer [64], a study of predictors of CAM use in early-stage breast cancer within a year of diagnosis suggested that such use may be motivated by the expected benefits and may not necessarily indicate distress or dissatisfaction [65].

4. Mind-Body Medicine

Mind-body medicine (MBM) includes a variety of practices that enable the mind to influence body functions. Some of the early works in the area of MBM include research on transcendental meditation (TM) [66–69] and application of meditation techniques for stress reduction by Kabat-Zinn [70]; the latter was called mindfulness-based stress reduction (MBSR). MBM is increasingly used by breast cancer patients [71]. A recent study reported that 64.2% of breast cancer patients practiced mind-body techniques following their diagnosis, and this usage was associated with Hispanic race, higher education, low income, and other CAM use [72]. Research on MBM in cancer has grown in the past decade, although the majority of studies have been conducted in the breast cancer population. Moreover, studies have used a variety of designs, intervention programs, and measures to evaluate effects, and most of the research has involved small sample sizes. Larger studies are needed to confirm the effects of many mind-body techniques on common symptoms of cancer and its treatment.

Several studies in cancer patients have examined the effect of meditation and yoga on quality of life, fatigue, and sleep [73–80]. Mindfulness-based stress reduction (MBSR), a program that includes meditation, yoga postures, and relaxation [81], helps patients understand their personal responses to stress and teaches them how to modify their responses. A program of MBSR reported lower levels of total mood disturbance and distress [82] as well as significant improvements in mood, sleep quality, and fatigue in a mixed cancer population [83]. Other studies using MBSR interventions in cancer patients have shown decreases in stress symptoms and cortisol levels and improvements in patient-reported quality of life [74]. A recent randomized controlled trial of a 6-week MBSR program for breast cancer survivors reported reduced anxiety, depression, and fear of recurrence and better perception of physical functioning in the intervention group [78].

Sixteen studies have shown that participation in programs consisting of traditional holistic yoga results in statistically significant improvements in stress, anxiety, irritability, emotional well-being, sadness, energy, invigoration, cognitive function, relaxation, pain, sleep, mood, depression, fatigue, symptom severity, hot flashes, appetite, bowel function, nausea, vomiting, QOL, and tolerance of cancer treatment [73, 75, 76, 84–96]. The yoga interventions typically lasted from 6 to 24 weeks and most often involved

weekly sessions of 75–120 minutes. The types of yoga used in the interventions also varied; the majority of the interventions used systems of yoga that involved meditation, breathing, gentle yoga, and restorative yoga. These studies indicate that clinicians and patients are very receptive to stress reduction programs, including yoga, as a treatment modality in traditional cancer centers and that it is feasible to recruit patients and conduct these types of interventions in a wide variety of communities. A large community-based trial of a yoga program in cancer survivors was found to improve their sleep, fatigue, quality of life [97], circadian rhythm, anxiety, and mood [98]. Some studies of yoga have examined its effects on measures of stress and its physiologic parameters. Yogic relaxation training has been found to reduce perceived stress after surgery in breast cancer [99]; another study of yoga during radiation treatment in breast cancer patients observed a 27% reduction in perceived stress score [84]. A recent study of Iyengar yoga in breast cancer survivors observed reduced morning and evening cortisol levels along with improved fatigue, emotional well-being [73], and vitality and reduced pain [96] following eight- and twelve-week interventions.

Tai Chi Chuan (TCC) is a form of martial arts used for centuries in China as a health exercise involving a series of individual movements continuously linked together and performed in conjunction with deep breathing and mental concentration. At least 20 prospective, randomized, controlled clinical trials in a number of populations including the elderly, cardiovascular patients, and patients with chronic diseases have been conducted using TCC [100]. TCC as an intervention may provide benefits to cancer survivors related to physical deconditioning, cardiovascular disease risk, and psychological stress. In a randomized, controlled clinical trial conducted by Mustian et al., women who completed treatment for breast cancer and received TCC demonstrated significant improvements in functional capacity, aerobic capacity, muscular strength and flexibility, self-esteem, bone health, immune function, and QOL [101–106]. Thus, physical activity seems to be an intervention capable of reducing anxiety and distress associated with the cancer experience. Conversely, higher levels of anxiety may reduce the likelihood of participation in physical activity following cancer treatment.

Acupuncture, a mind-body technique that is also classified as manipulative body-based technique and energy-based technique, has been shown to ameliorate distress in healthy adults [107]. It has also been found to reduce fatigue and distress in patients with advanced breast and ovarian cancer [108]. A recent systematic review of 15 studies of CAM interventions (acupuncture, massage, yoga and relaxation, hypnosis, vitamins, and medical qigong) in cancer-related fatigue reported most benefits from acupuncture [109]. Acupuncture has also been found beneficial in cancer-related vasomotor symptoms [110] and anxiety associated with hot flashes [111] and other symptoms associated with cancer such as pain, nausea and vomiting, fatigue that could be related to stress [112]. Another MBM technique, hypnosis, combined with cognitive behavioral therapy prevented the increase of fatigue in breast cancer patients compared to standard medical care during radiation therapy [113] and reduced fatigue in women who underwent lumpectomy for breast cancer [114].

5. Herbal and Natural Products

The use of herbal and natural supplements has dramatically increased over the last ten years. Herbal (or natural) supplements are commonly used to combat stress-related symptoms such as anxiety, depression, insomnia, and fatigue [115–117]. Herbal supplements are one of the three most common forms of CAM used by cancer patients [116–119]. In a recent study conducted by MD Anderson Cancer Center, 52% of 309 cancer patients reported using one or more forms of CAM modalities, and 26% reported herbal supplement usage [118]. Unfortunately, little evidence supports the effectiveness of herbal interventions for long-term reduction in stress [115, 116].

Sedative herbal and natural supplements have been used since the middle ages to reduce stress and improve quality of life. Herbal supplements are usually ingested as extracts (i.e., tea) or capsules or inhaled as essential oils (i.e., aromatherapy). Commonly used herbal supplements for stress include lemon balm, kava, valerian root, lavender, St. John's wort, and passionflower [115–117]. Lemon balm has proven effective and safe for relieving stress with long-term use [116, 120–123]. Substantial evidence indicates that kava reduces anxiety and stress; however, it has been implicated in liver failure and is therefore not clinically recommended but may be safe for short-term use in patients with mild to moderate anxiety [115, 116, 119, 122, 124, 125]. Although valerian is considered safe at low doses for less than one month, no clinical evidence supports its use for anxiety or distress [116, 121–123, 125]; however, combined with lemon balm and kava it has been associated with reduction in stress-related insomnia [120, 121, 125]. Lavender aromatherapy is recommended to relieve anxiety and depression and promote calmness and positivity, but definitive evidence for efficacy is lacking [117, 123, 124]. A randomized controlled trial which combined lavender essential oils with massage in patients with cancer reported reductions in distress, but the study was not able to conclude whether lavender aromatherapy supplemented the effects of massage [124]. Likewise, passionflower demonstrated a reduction in anxiety compared to oxazepam [116, 126]. St. John's wort is used mostly for depression and is less popular for treating anxiety and distress [116]. Some evidence suggests that Siberian ginseng and European mistletoe may reduce side effects of cancer treatment and improve quality of life [127–129]. Possible mechanisms of some herbals in stress are depicted in Figure 2. Thus patients with high levels of stress could benefit from herbal supplements [116–118, 124] but patients should discuss any proposed supplement use with their physician to ensure safety.

Researchers have studied the effects of numerous vitamins, minerals, and dietary supplements on psychological stress. The most promising include the B vitamins (folic acid, B6 and B12) and vitamin D. However, there is a

dearth of investigation of the effects of these compounds on psychological distress in cancer patients, perhaps due to the reluctance of oncologists to prescribe vitamin and mineral supplementation during treatment, believing that the antioxidant effects of these supplements might decrease treatment efficacy. Nevertheless, the few studies available show that vitamin and mineral supplementation administered during treatment do not reduce treatment efficacy [130, 131]. Following the completion of treatment, cancer survivors use vitamin and mineral supplementation at a higher rate than the general population, with 64–81% of cancer survivors using supplements compared to approximately 50% of the general population [132].

A large amount of the literature reports the effects of B vitamins (folic acid (B9), pyridoxine (B6), and cobalamins (B12)) on psychological stress, particularly depression. There is a biological rationale for the association of B vitamins with psychological stress. B vitamin deficiency can lead to an increase in homocysteine levels [133], which is associated with increased depression rates [134]. Cross-sectional studies commonly find that patients with psychological stress disorders have deficient folic acid levels [135–137]. Similar findings were reported for vitamin B12, with low levels seen in patients with psychological distress [138–140]. Evidence from cross-sectional studies also indicates that psychologically stressed patients have low levels of vitamin B6 [141, 142], but the evidence is not as strong as for folic acid or vitamin B12. Other studies show that individuals deficient in B vitamins have a poorer response to antidepression therapy and higher rates of relapse of depression. Randomized trials have shown that adding folic acid and vitamin B12 supplementation to existing treatments increases the efficacy of antidepressant treatment [143–145].

Recent research has shown that vitamin D may be involved in psychological well-being. Vitamin D plays a crucial role in brain development and function [146, 147]. A recent study in fibromyalgia patients found a significantly higher rate of vitamin D deficiency in patients with anxiety [148]. Other studies have associated vitamin D deficiency with cognitive impairment [149, 150], mood disorders [150], and depression [148, 151]. Vitamin D deficiency has also been associated with seasonal affective disorder (SAD), a condition with depression-like symptoms that occur in winter, when vitamin D levels are typically at their lowest [152]. Randomized trials also show that vitamin D supplementation may ameliorate symptoms of depression [151] and SAD [153, 154]. Thus, research indicates that individuals with low levels of folic acid, vitamin B12, and vitamin D have higher rates of psychological stress, and limited evidence from randomized trials show that supplementation with these vitamins may improve anxiety, mood disorders, and depression.

6. Manipulative and Other CAM Therapies

Research on massage therapy, a manipulative body-based technique, for stress reduction in cancer populations has not provided consistent results [164–167]. Polarity Therapy, Reiki, therapeutic touch, healing touch, and Qigong involve manipulation of the body energy fields. Polarity therapy (PT) has been shown to reduce cancer-related fatigue during radiation treatment [168] when compared with modified massage therapy and standard care [169]; the potential for its use in management of cancer-related stress can be explored since PT has been shown to decrease stress in caregivers of dementia patients [170]. The fact that Reiki ameliorates pain in advanced cancer patients [171] and reduces cancer-related fatigue [172] may indicate that it can also lower cancer-related stress, although there is no supporting evidence. The trials of music in reducing stress in cancer have not yielded consistent results; one study in women with metastatic breast cancer showed no significant differences in the music therapy led by a therapist and the usual care groups [173]. However, one study of music imagery intervention has suggested reduction of anxiety in adults undergoing chemotherapy, particularly those with lower initial stress levels [174].

7. Exercise

Exercise training improves resilience to stress [175, 176]. A 6-week exercise intervention in patients receiving chemotherapy was found to have beneficial effects on psychological distress [177]. Similarly, in postoperative breast cancer patients receiving chemotherapy, a 12-week home-based exercise intervention was found to improve mood disturbance compared to a nonexercise control group [178]. Researchers have found that cancer patients who exercised before undergoing treatment for cancer experienced lower levels of anxiety and depression [179]. Early-stage breast cancer patients undergoing a 6-week walking exercise intervention during radiation treatment also noted improvements in anxiety [180]. In colorectal cancer survivors, a relationship was established between psychological distress, anxiety, and participation in physical activity. Cancer survivors with higher levels of anxiety are less likely to participate in physical activity [181].

8. CAM in Children, Adolescents, and the Elderly with Cancer

A recent systematic review estimated that the prevalence of CAM use by children with cancer ranges from 6% to 91%, with significant variation between studies [182]. Children's and adolescents' use of CAM has been linked to parents' use of CAM [183, 184]. Parents with higher educational backgrounds are more likely to consider [185] and to use [182] CAM approaches for their children, although no consistent correlations between CAM use and parental income, child age, or ethnicity have been reported [182]. CAM use and consideration were shown to be positively related to a lower survival perspective [186] and fewer days since relapse [185], respectively, suggesting that CAM therapies may be a coping strategy for families in an attempt to try every possible approach for curing or alleviating pain and distress in their children. A review by Sencer and Kelly [187] suggests that families' use of CAM may increase their

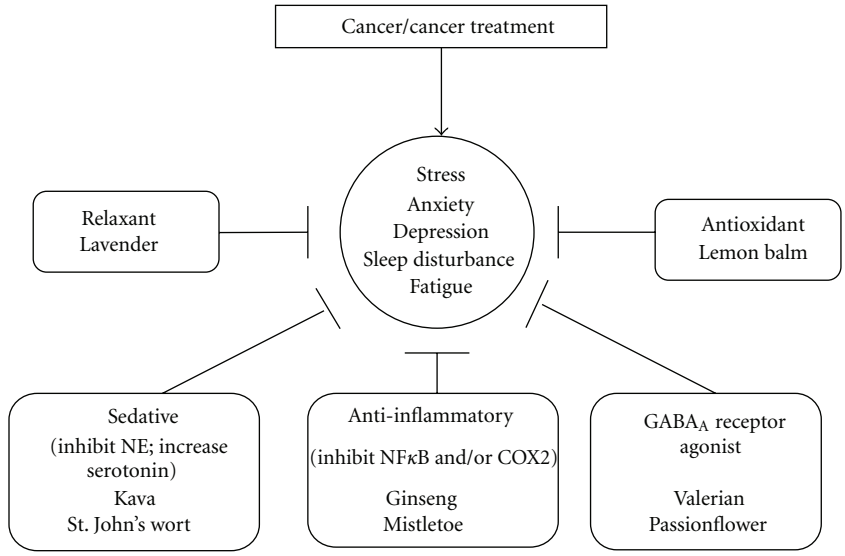


Figure 2: Mechanisms of herbal supplements for stress. Cancer and cancer treatment affect a patient's quality of life resulting in various symptoms of stress, such as anxiety, depression, sleep disturbance, and fatigue [155]. The human body's response to such stressors involves many different mechanistic pathways. This diagram outlines the mechanisms by which herbal supplements reduce stress-related symptoms in cancer patients. The majority of herbal supplements have anti-inflammatory properties, but their primary target of action is different. Lavender acts as vascular smooth muscle relaxant through nitric oxide/cGMP phosphorylation and myosin light chain dephosphorylation [156]. Lemon balm is an immune stimulating agent with potent free radical scavenging properties [157–159]. Kava and St. Johns's wort function reduce norepinephrine (NE) and increase serotonin levels, similar to antianxiety drugs such as benzodiazepines [116, 122, 160]. Valerian and passionflower are $GABA_A$ receptor agonists that produce a sedative effect [161, 162]. Ginseng and mistletoe are potent anti-inflammatory agents that inhibit NFkB and/or COX2 [127, 163].

sense of control and active participation in treatment, and therefore open discussion of CAM should be useful for physicians in building relationships with families and in understanding all potential influences on the child's care.

The quality of research related to CAM use in pediatric oncology has varied greatly from study to study. Within the past 10 years, there has been considerable movement towards more rigorous research testing, including randomized clinical trials conducted through the Children's Oncology Group or other multisite studies [188–191]. There is a great need for rigorous safety and efficacy trials, particularly for biologically based therapies [188, 192]. Research has reported physical and psychological benefits from a massage intervention for children with various cancers and blood disorders [193]; however, another randomized trial of a combined massage and humor intervention found no significant differences across groups in children undergoing stem cell transplants [190]. A trial of music video compared to audiotape and usual care in adolescents and young adults undergoing stem-cell transplantation suggested less distress in music group at 100-day follow-up [194]. Thus, several promising CAM therapies are available to help children with cancer to manage emotional and physical distress related to cancer and its treatment; however, much work is needed to document their efficacy and safety.

Aging alone is associated with declines in physical function, including reduction in functional capacity [195, 196], reduced muscular strength [197], arthralgia [198], and reductions in bone mineral density [199]. Depression [200], anxiety [201], and cognitive difficulties [202] also affect older adults. Cancer treatments can further exacerbate these age-related declines and stressors. Cancer survivors aged 65 and older report more limitations in activities of daily living [203], a lower quality of life [204], lower self-rated health [204], a greater incidence of frailty [203], and higher rates of dementia, depression, falls, incontinence, and osteoporosis [203]. Other stressors in this population include relocation, financial changes with retirement, caring for grandchildren and/or a spouse, the death of friends and family members, chronic illnesses, and the fear of losing independence [205–208]. Stress is associated with depression in the elderly [209]. Emotional stress is also a potential trigger impairing the mechanisms responsible for balance, increasing the risk of falls that can lead to hip and femur fractures [210]. These additional declines in physiological and psychological function likely exacerbate the stress experienced by older cancer survivors.

Physical activity and social interactions reduce functional decline in the elderly [211]. Physical activity is also associated with a reduction in stress and anxiety. The American College of Sports Medicine (ACSM) recommends that older adults, even those with chronic medical conditions, participate in regular aerobic exercise training (150–300 minutes per week) and resistance exercise training (at least 2 days a week) [212]. The exercise prescription for those older adults who are functionally limited should be tailored and progressed gradually [213]. The literature supports the use of physical activity in cancer survivors younger than 65, but little has

been done to determine the benefits of physical activity or other forms of complementary and alternative medicine for cancer survivors who are 65 years of age and older. Researchers have investigated the benefits of Tai Chi Chuan in older adults without a history of cancer, finding that Tai Chi can reduce depression [214], improve self-efficacy [215], improve muscular strength and endurance [216], and improve balance and reduce falls [217]. Yoga can improve gait [218], quality of life [219], and depression [220] in the elderly. Research is limited concerning the implementation of CAM in older cancer survivors in particular, despite its promising impact on physiological and psychological function. Stress in particular has received very little research focus in older cancer survivors, but because the benefits of physical activity are so profound in older adults, it is an important and promising area of research.

9. Conclusions and Future Directions

Cancer-related stress affects all patients with cancer and negatively impacts cancer outcomes in terms of response to treatment, quality of life, disease progression, and survival in different phases of their experience. Feasibility of intervention with several CAM techniques and products commonly used by cancer patients and survivors has been established in some cancer populations: for example, mind-body techniques of meditation, yoga, Tai Chi Chuan, acupuncture, manipulative techniques massage, energy-based polarity therapy and Reiki, and some natural products. Efficacy of some CAM techniques and products in reducing stress and/or stress-related symptoms in patients with cancer has been documented

(1) Mindfulness-based stress reduction program with components similar to yoga showed reduction of stress levels in population of breast cancer and prostate cancer patients and improvements in endocrine indices of stress were also reported. Some studies of yoga intervention have shown significant stress reduction while some have shown beneficial effects on symptoms associated with stress for example, fatigue, sleep disturbances, hot flashes, and quality of life. However, the majority of studies of yoga were conducted in small samples of patients and there was a wide range of the length of intervention. This area of mind-body intervention seems to be promising in cancer; however, lack of uniformity of the intervention program in terms of its length and content makes it difficult to compare study results. Larger study samples with the use of comparable intervention programs may be more conclusive.

(2) Acupuncture can relieve anxiety, fatigue, and distress associated with advanced cancer.

(3) Practice of Tai Chi Chuan may be helpful in improving quality of life.

(4) Some herbs like lemon balm may be used, long in the term for relieving stress. Most current research suggests that patients with high levels of stress benefit the most from herbal supplements; therefore, studies are needed to examine their efficacy as well as safety.

(5) Most research on vitamins and supplements conducted in noncancer patients show promise in relieving stress; further trials in cancer patients are needed to demonstrate the safety of vitamin B and D supplementation in cancer patients receiving treatment before testing their efficacy on psychological stress.

(6) Physical activity may be helpful in reducing anxiety and distress in cancer survivors; however, the role of anxiety in affecting physical activity should be given consideration while designing intervention studies in cancer population.

(7) Research on CAM therapies for stress in childhood cancers is insufficient. Several promising CAM therapies may help children with cancer manage emotional and physical distress related to cancer and its treatment after the safety and utility of such therapies has been established.

(8) Stress in older cancer survivors is an important and promising area that is desperately needed to be examined as older adults are at much greater risk of developing cancer than young adults. It is especially important since by the year 2030, 70% of cancer patients will be elderly.

Although some CAM techniques/products could be integrated into cancer care, much more research is needed to confirm their efficacy. Moreover, the wide variety of study designs and types of interventions are an obstacle to reach effective conclusions. Additionally, there is a need to study mechanisms of action of various techniques and products using innovative designs such as research on the effects of CAM on apoptotic and angiogenesis pathways; this may be helpful in understanding tumor development and its progression and applying CAM as a part of personalized medicine to ensure cancer-free and better quality of life.

CAM is primarily used by cancer patients to relieve disease- and treatment-related side effects. Although many of the symptoms usually subside after treatment, CAM utilization could help maintain a symptom-free and good quality of life during cancer treatment. The word "stress" cannot be over emphasized when associated with cancer experience. Stress reported by cancer patients could potentially alert healthcare providers about the impending negative outcomes of cancer treatments. Most CAM techniques are relatively inexpensive, simple to administer or practice, and encompass the holistic nature of healing. CAM for stress management could restore a patient's sense of control, maintain quality of life, reduce risk of cancer recurrence, and minimize physician visits. The first prescription following a cancer-related visit with a healthcare provider may be for stress management technique/product. Further research on CAM and stress can help healthcare professionals as well as patients with their understanding of the significance of safe use of integrative modes of treatment, better compliance with conventional treatment, improve treatment outcomes and survival, and possibly reduce the risk of recurrence of cancer. Thus, CAM

for stress management could be a critical component of cancer care.

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Review Article

Emerging Glycolysis Targeting and Drug Discovery from Chinese Medicine in Cancer Therapy

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Molecular-targeted therapy has been developed for cancer chemoprevention and treatment. Cancer cells have different metabolic properties from normal cells. Normal cells mostly rely upon the process of mitochondrial oxidative phosphorylation to produce energy whereas cancer cells have developed an altered metabolism that allows them to sustain higher proliferation rates. Cancer cells could predominantly produce energy by glycolysis even in the presence of oxygen. This alternative metabolic characteristic is known as the "Warburg Effect." Although the exact mechanisms underlying the Warburg effect are unclear, recent progress indicates that glycolytic pathway of cancer cells could be a critical target for drug discovery. With a long history in cancer treatment, traditional Chinese medicine (TCM) is recognized as a valuable source for seeking bioactive anticancer compounds. A great progress has been made to identify active compounds from herbal medicine targeting on glycolysis for cancer treatment. Herein, we provide an overall picture of the current understanding of the molecular targets in the cancer glycolytic pathway and reviewed active compounds from Chinese herbal medicine with the potentials to inhibit the metabolic targets for cancer treatment. Combination of TCM with conventional therapies will provide an attractive strategy for improving clinical outcome in cancer treatment.

1. Introduction

Cancer is the second leading cause of mortality in human diseases worldwide. According to a national statistic report on the incidence and mortality in the USA, there were a total of 1,529,560 new cancer cases and 569,490 deaths from cancer occurring in 2010 [1]. Surgery, chemotherapy, and radiotherapy, either alone or in combination, have been considered as conventional strategies for cancer treatment in the last century. With the rapid development of molecular medicine, novel therapeutic approaches, such as immunotherapy, molecular targeted therapy, and hormonal therapy, have been proposed to improve clinical outcomes for cancer patients [2–4]. However, those therapeutic approaches are not always effective and clinical outcome in survival rates is still poor. One of the major problems is that cancer cells gradually develop resistances to those therapies. Seeking for new therapeutic approaches to improve outcome of cancer treatment is timely important.

Complementary and alternative medicine (CAM) attracts much attention for drug discovery in current cancer research [5, 6]. Among CAM modalities, TCM is particularly appreciated in both rural and well-developed urban areas of China based on its 5000-year-old history and a well-established theoretical approach [7, 8]. In China, Chinese herbal medicine is widely used as an adjunct therapy to reduce the resistances and side effects of cancer cells to chemotherapy and radiotherapy. Chinese herbal medicine in combination with chemotherapy and radiotherapy potentially improves clinical outcome in cancer treatment [9]. However, the relatively poor designs in many clinical reports, such as lack of quality standardization of herbal products, shortage of well-designed randomized controlled trials (RCT), and the limited sample size, bring difficulty to evaluate the benefits or disadvantages of herbal medicine for cancer treatment [10, 11]. TCM approaches have always been met with much skepticism and pessimism by the West. In fact, medicinal herbs are very important

resources for drug discovery in cancer treatment. The direct experience from TCM on human subjects and its long history provide important cues for drug development. Of the 121 prescription drugs in use today for cancer treatment, 90 are originally derived from medicinal plants. Almost 74% of those drugs were discovered from folk medicine [12, 13]. In a previous review article, 48 out of 65 new drugs approved for cancer treatment during 1981–2002 were natural products, leading from natural products, or mimicked natural products in one form or another [14]. Among the drugs, the most well-known examples include *Vinca* alkaloids (vincristine, vinblastine, vindesine, vinorelbine), taxanes (paclitaxel, docetaxel), podophyllotoxin and its derivative (etoposide, teniposide), camptothecin and its derivatives (topothecan, irinothecan), anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin), and others [15]. There is an impressive revival of seeking natural lead compounds for the generation of semisynthetic derivatives. Current progress in this aspect not only provide a chemical bank from natural sources for drug discovery but also bring better understanding for the chemical basis of Chinese herbal medicine for cancer treatment.

With its multiple components, TCM formulas and therapies are generally considered to regulate multiple cellular signal pathways [16]. Herbal medicine and their active components are promising sources for the designs of more effective and less toxic agents in cancer chemoprevention and treatment [17]. Many TCM products or single active components have been reported to inhibit a variety of processes in cancer cell growth, invasion, and metastasis by modulating a wide range of molecular targets, including cyclooxygenase-2 (COX-2), nuclear factor kappa B (NF-κB), and nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant signaling pathways. A previous review article summarized the therapeutic targets of traditional Ayurvedic medicine for inflammation and cancer. The targets include growth factor signaling (e.g., epidermal growth factor); prostaglandin (e.g., COX-2); inflammation factors (e.g., inflammatory cytokines: TNF, IL-1, IL-6, chemokines); drug resistance genes (e.g., multidrug resistance); cell cycle proteins (e.g., cyclin D1 and cyclin E); angiogenesis factors (e.g., vascular endothelial growth factor); invasion mediators (e.g., matrix metalloproteinases); apoptosis related genes (e.g., bcl-2, bcl-X(L), XIAP, survivin, FLIP); proliferation factors (e.g., c-myc, AP-1, growth factors), [18]. With the development of systematic biology and bioinformatics, more attention has been paid to the synergistic effects of herbal medicine on "common" signal pathways involved in the proliferation, invasion, metastasis, and apoptosis of cancer cells. It is interesting to ask the question whether herbal medicine and it's derivatives can specially target on tumor biomarkers and affect survival of cancer cells.

Molecular targeted therapy has been attracted much attention in cancer treatment [19]. Ideally, the identified targets should be preferentially expressed or activated in cancer cells but not in normal cells. Combining molecular and genetic technologies, a number of small molecular inhibitors and antibodies targeting on kinases or oncogenes has been designed and synthesized [20, 21]. The most well-known examples include the small molecule Gleevec (targeting on BCR-ABL translocation associated with chronic myelogenous leukemia), and antibody-based molecule Herceptin (c-erbB-2 overexpression related to breast cancer), [22, 23]. However, primary and secondary resistances to these targeted molecules severely reduce their therapeutic efficacy [24, 25]. Therefore, seeking more distinctive molecular targets and their corresponding drug candidates become important tasks for oncologists.

Cancer cells can be distinguished from normal cells in several hallmarks. One of hall marks is that cancer cells have a fundamentally different bioenergetic metabolism from that of nonneoplastic cells. In normal cells, energetic metabolism mostly relies upon the process of mitochondrial oxidative phosphorylation which consumes glucose and oxygen to produce energy. In contrast, cancer cells have developed an altered metabolism that allows them to sustain higher proliferation rates [26]. Cancer cells could predominantly produce energy by glycolysis followed by lactic acid fermentation, even in the presence of oxygen—this is known as the "Warburg Effect" [27, 28]. Cancer glycolysis is a critical step in carcinogenesis and oncogenic activation [29, 30]. Targeting on glycolysis becomes an attractive strategy in cancer diagnosis and treatment clinically [31]. The inhibitors targeting some key enzymes showed promising anticancer effects and have been approved for clinical trials [32]. Chinese herbal medicine could specifically target on the molecules in the metabolic pathways of cancer. Recent progress leads to the discoveries of many active compounds derived from Chinese herbs with the properties of inhibiting cancer cell glycolysis activity. Therefore, in the present paper, we intend to review current progress about TCM-derived phytochemicals which specifically target the key enzymes and proteins involved in cancer glycolysis.

2. Glycolytic Pathway as a Target for Cancer Therapy

Otto Heinrich Warburg, a pioneer in the study of respiration, made a striking discovery in the 1920s from extensive observation on the metabolic behavior of cancer cells. Even in the presence of oxygen, cancer cells prefer to metabolize glucose by glycolysis, a less efficient pathway for producing ATP [33]. The respiratory behavior was subsequently demonstrated in a various kinds of cancer cells and was called aerobic glycolysis [34–36]. The exact reasons why tumor cells exhibit elevated glycolysis and use this primitive and less energy-efficient pathway to generate ATP is still unclear. Accumulating evidences have suggested multiple mechanisms contributing to the unique phenomenon: (1) mitochondrial DNA mutations; (2) nuclear DNA mutations; (3) oncogenic transformation; (4) influences of the tumor microenvironment [37–39]. All these factors result in mitochondrial dysfunction and make cancer cells generate ATP much more dependently on the glycolytic pathway. Given the mitochondrial respiratory abnormality, cancer cells have to uptake much more glucose to produce enough

ATP supporting rapid proliferation needs. At present, the phenomenon has been exploited clinically for the detection of tumors by fluorodeoxyglucose positron emission tomography (FDG-PET) [40]. Inhibition of aerobic glycolysis becomes an important strategy to preferentially kill cancer cells and to find anticancer agents based on Warburg hypothesis [41, 42]. As illustrated in Figure 1, cancer cells in the tumor mass could be divided into oxygenated and hypoxic cells. Hypoxic cancer cells predominately depend on glycolysis to produce energy. The glycolytic pathway is a series of metabolic reactions catalyzed by multiple enzymes or enzyme complexes. From the original glucose uptake to the final lactate production, the key steps include: (1) the increasing uptake of glucose by elevated expression of glucose transporter-1 (GLUT1) and sodium glucose cotransporter-1 (SGLT1); (2) active ATP generation reaction by upregulation of phosphoglycerate kinase (PGK) and pyruvate kinase (PK); (3) regeneration of NAD^+ by lactate dehydrogenase (LDH); (4) out-transport and reuptake of lactate by monocarboxylate transporter (MCT), mainly MCT1 and MCT4 [43, 44]. In oxygenated cancer cells, the reuptaken lactate could be metabolized to pyruvate and reentered the mitochondrial tricarboxylic acid cycle to produce ATP. Each reaction in the glycolytic pathway is activated by a specific enzyme or enzyme complex. Interrupting any of the above proteins could lead to metabolism blockade followed by cell death. The activities of many enzymes in the pathway are controlled by two factors including c-myc and hypoxia inducible factor-1α (HIF-1α) [45, 46]. Many studies have demonstrated an increase in the activities of the glycolytic enzymes such as hexokinase, lactate dehydrogenase A (LDH-A), and glyceraldehydes-3-phosphate dehydrogenase (GAPDH) in various types of tumors and cancer cell lines [47–49]. In addition, silencing of these overexpressed enzymes, such as LDH-A or pyruvate kinase (PKM2), has been documented efficiency for inhibiting cancer cell proliferation, inducing apoptosis and reversing multidrug resistance [50–52]. Furthermore, some glycolytic enzymes are multifunctional proteins. For example, hexokinase and enolase play critical roles in transcription regulation [53, 54], while glucose-6-phosphate isomerase may affect cell motility [55]. Therefore, developing novel glycolytic inhibitors is an important direction in current cancer research. As TCM has held an important position in primary health care in China and been recently recognized by the West as a fertile source for revealing novel lead molecules for modern drug discovery, more and more herb-derived bioactive compounds have been identified for cancer therapy. Among them, several have been proved to be effective in suppressing cancer glycolytic activity by targeting on particular enzymes. Herein, we review current evidence on the studies of herbal medicine related to regulate several key enzymes in the glycolytic pathway including HIF-1α, hexokinase, and LDH-A.

3. Glycolytic Molecular Targets and Herb-derived Inhibitors

3.1. HIF-1α. HIF-1 is a basic helix-loop-helix heterodimeric transcriptional factor composed of α and β subunits [56]. HIF-1 is overexpressed in various types of cancer, and the levels of its activity have already been demonstrated closely to tumorigenicity, angiogenesis and also glycolytic activity [57, 58]. HIF-1α levels are primarily induced by hypoxia, growth factors, and oncogenes. As shown in Figure 2, under normoxia, HIF-1α is rapidly and continuously degraded by the ubiquitin-proteasome pathway. The prolyl hydroxylation of oxygen-dependent degradation domain (ODD) and binding with Von Hippel-Lindau (VHL) play a critical role in regulation of HIF-1α degradation. However, under hypoxic condition, the absence of oxygen prevents the prolyl hydroxylase process, allowing HIF-1α to accumulate and translocate to the nucleus, where it forms an active complex with HIF-1β and activates a series of downstream gene transcription [59, 60]. Besides hypoxia, the expression of HIF-1 was also regulated by other factors including oncogenes (p53, VHL, etc.), cytokines (EGF, TGF-α, IGF-1, and -2, etc.) and some posttranslational modifications including hydroxylation, ubiquitination, acetylation, and phosphorylation, [61, 62]. A number of glycolytic related genes are regulated by HIF-1α, such as GLUT-1, hexokinase, LDH-A, and PDK1. Interruption of HIF-1α signaling revealed to inhibit cancer growth in both *in vitro* and *in vivo* experimental models [63].

Recently, a remarkable progress has been made to seek selective HIF-1α inhibitors for cancer treatment from herbal medicine. Apigenin, a plant flavonoid compound, is considered as a typical HIF-1α inhibitor [64–72]. Apigenin is isolated from a traditional Chinese herb *Apium graveolens var.dulce*. Apigenin has been shown to inhibit proliferation and induce apoptosis in a wide range of malignant cells including breast, ovarian, prostate, and lung cancer, [65–68]. Apigenin suppressed tumor angiogenesis by downregulating VEGF, a proangiogenic protein regulated by HIF-1α [69, 70]. Apigenin inactivated the PI3K/Akt pathway in prostate cancer cells [71, 72]. Apigenin reduced HIF-1α stability and HIF-1α mRNA expression in human prostate cancer PC3-M cells *via* PI3K/Akt/GSK-3β pathway [73]. Apigenin promoted HIF-1α degradation *via* disrupting HIF-1α-Hsp90 interaction under hypoxia [74]. Oral administration of apigenin resulted in tumor growth abrogation in prostate cancer xenografts, accompanied by inactivation of Akt, and induction of apoptosis [72]. Another study also revealed that apigenin *in vivo* administration significantly limited tumor growth and angiogenesis in both prostate and ovarian cancer models. Meanwhile, the expression of HIF-1α and VEGF were also down-regulated in apigenin-treated tumor samples [69]. Chrysin, isolated from *Oroxylum indicum (L.)Vent*, mediated apoptosis in various types of cancer including prostate, thyroid, and leukemia malignancies [75–77]. Chrysin significantly inhibited prostate cancer growth and angiogenesis with a decreased HIF-1α expression [78]. The suppression of HIF-1α expression could be related to different mechanisms including stimulation of PHD activity, disruption of HIF-1α-HSP90 interaction and direct inhibition of HIF-1α protein synthesis [78]. Epigallocatechin gallate (EGCG) is a widely spread flavonoid in Chinese herbs. The anticancer effects of EGCG were well documented [79, 80]. Many of its intracellular molecular targets, such

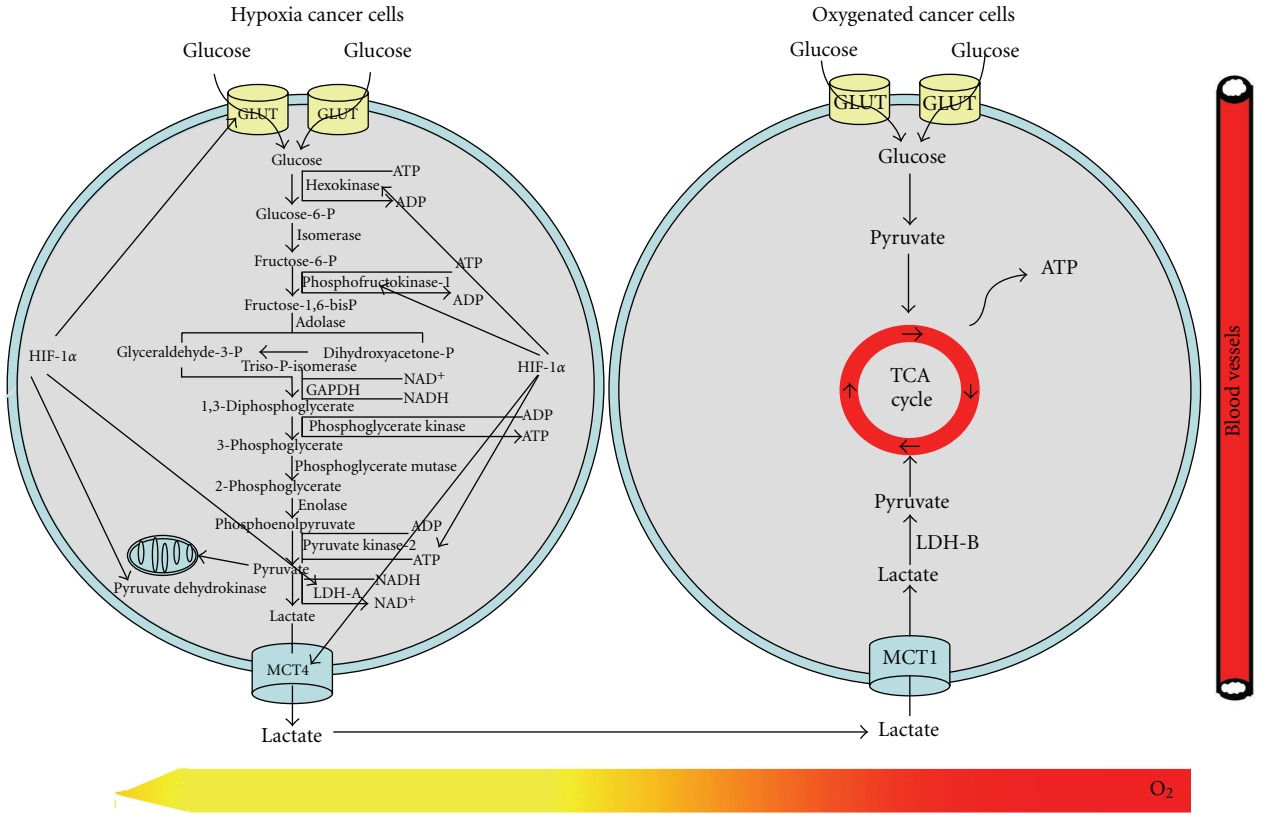

Figure 1: Glycolytic pathway and the role of HIF-1α in regulating glycolysis. Glucose was uptaken by increased expression of GLUT in hypoxia cancer cells. Through a series of enzyme reaction, glucose was finally metabolized into lactate and ATP, NAD^+ was also regenerated by LDH-A for maintaining continuous glycolysis. Lactate was exhausted out of cancer cells by MCT4 and then uptaken by oxygenated cancer cells through MCT1. In the presence of oxygen, lactate is oxidized into pyruvate by LDH-B and pyruvate enters the tricarboxylic acid (TCA) cycle to produce ATP. HIF-1α was the main regulator of some enzymes expression in the glycolytic pathway, including GLUT-1, hexokinase, phosphofructokinase, pyruvate kinase, pyruvate dehydrogenase, LDH-A, and MCT.

as proteasomes, MAP kinases, VEGF, erythropoietin, and glucose transporters, are directly or indirectly regulated by HIF-1α [81, 82]. Several studies indicate that EGCG could inhibit HIF-1α expression by both blocking PI3K/Akt signaling pathway and reducing interaction between Hsp90 and HIF-1α [83]. Besides, curcumin, a well-validated anticancer compound extracted from *Curcuma longa*, has been found to interact directly with more than 30 different proteins including transcriptional factors (NF-κB, AP-1, STAT, and β-catenin, etc.), growth factors and protein kinases (EGFR, ErbB-2, VEGF, EGF, MAPKs, and CXCR-4, etc.), inflammatory factors (TNF-α, IL-1β, IFN-γ, and COX-2, etc.), adhesion molecules (integrins, fibronectin, vitronectin, and collagen IV, etc.) and apoptosis-related proteins (death receptors, Bax, Bcl-2, and survivin, etc.) [84, 85]. Several studies also demonstrated that curcumin dose-dependently inhibited HIF-1α and HIF-1β gene at transcription level [86, 87]. Using luciferase reporter gene assay, an Indian herb *Ophiorrhiza trichocarpon* was identified to have the strongest HIF-1α inhibitive effects among more than 6,000 crude natural products. The extracts of *Ophiorrhiza trichocarpon* were shown to reduce hypoxia-induced HIF-1α accumulation to 22% relative to the normal control. Following bioactivity-guided fractionation assay validated camptothecin to be the best HIF-1α inhibitor among 84 fractions isolated from the medicinal plant [88]. Since the primary molecular target of camptothecin is established as human DNA topoisomerase I, its anticancer effects need to be further verified in animal experiments. Detail mechanisms in regulation of HIF-1α transcription activity remain to be further investigated. Terpenoids were also reported to inhibit HIF-1α activity. Nguyen et al. carried out screening assay for HIF-1α inhibitors from *Salvia miltiorrhiza* extracts by using luciferase gene reporting system. Diterpenes including sibiriquinone A, sibiriquinone B, cryptotanshinone, and dihydrotanshinone were finally identified to be strong HIF-1α inhibitors [89]. Although many herb-derived compounds are effective in suppressing HIF-1α activity, little compound is identified to specifically bind to HIF-1α. The structure-activity relationship and chemical optimization study are important topics for further studies on this direction. In addition, as many studies were conducted with cell systems, *in vivo* animal experiments are essentials to verify the bioactivities of targeting on HIF-1α activity contributing to their anticancer effects for drug development.

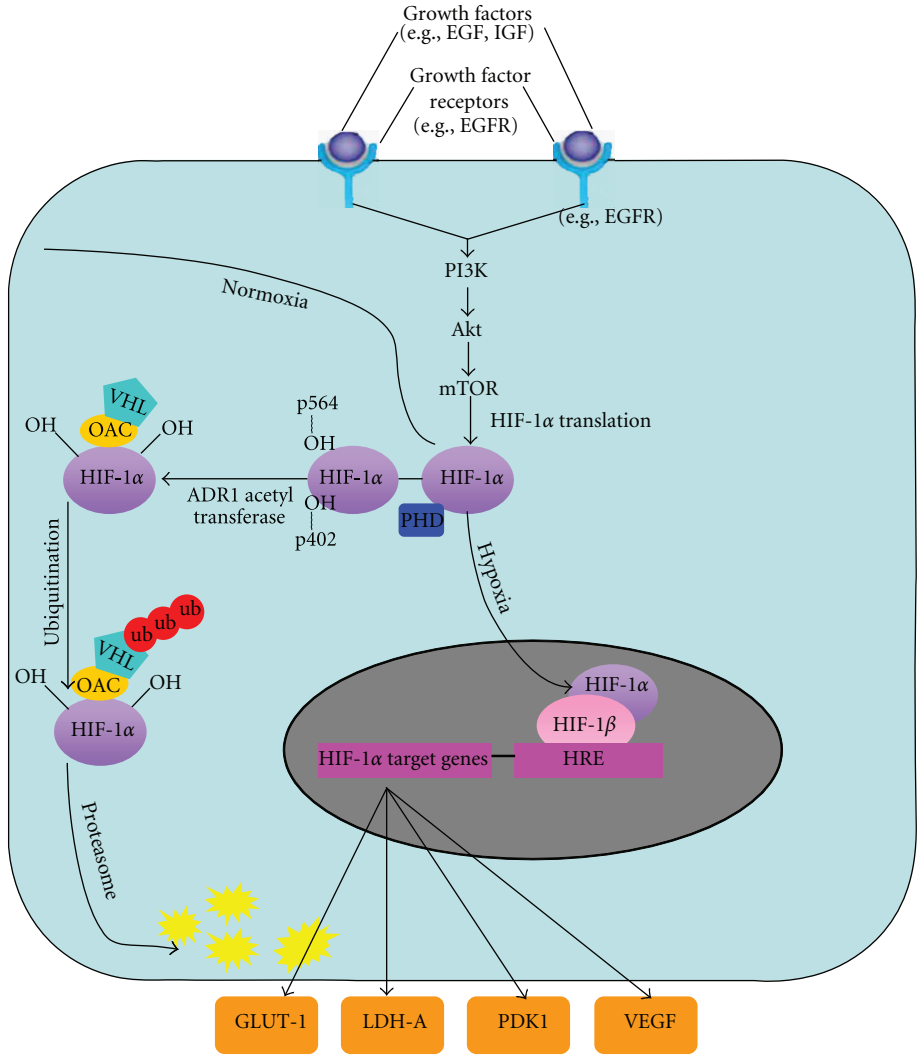

Figure 2: The intracellular HIF-1α regulation pathway in normoxia and hypoxia. Under normoxia, HIF-1α will be constituently ubiquitinated and subsequently degraded via proteasomal pathway after recruitment of von Hippel-Lindau protein (pVHL), which depends on the hydroxylation of proline residues on 564 and 402. However, under hypoxia, the praline hydroxylation of HIF-1α will be inhibited, HIF-1α will be translocated into the nucleus and combine with HIF-1β, then activate the transcription of a series of downstream genes including LDH-A, PDK1, GLUT-1, and VEGF. The levels of HIF-1α were also influenced by the PI3K/AKT pathway after stimulation of growth factors such as EGF and IGF.

3.2. Hexokinase. Hexokinase (HK) controls the conversion of glucose to glucose-6-phosphate (G6P), which serves as the starting point for sugar to enter the glycolytic pathway or for glycogen synthesis [90]. Four isoforms of hexokinase have been identified in mammals, among which hexokinase II (HKII) is a major form responsible for maintaining the high glucose catabolic rates of malignant cells [91]. HKII overexpression was found in various types of cancers such as liver, breast, and lung cancers [92]. In addition to its glucose phosphorylation activity, HKII is capable of binding to the voltage-dependent anion channel (VDAC) on the mitochondrial outer membrane [93]. The specific binding not only allows efficient use of mitochondrial-generated ATP served as glycolytic fuel, but also stabilizes the mitochondrial membrane and prevents the release of pro-apoptotic factors, such as cytochrome C [94]. Disrupting the interaction between HKII and VDAC could inhibit cell proliferation and induce apoptosis through decreasing ATP supply and destabilization of mitochondrial membranes (Figure 3). Therefore, developing inhibitors targeting HKII is an interesting topic in anticancer drug development. 2-deoxyglucose (2-DG) and 3-bromopyruvate (3-BrpA) are well known HKII inhibitors [95, 96]. These pharmacological inhibitors have been proved to be effective in disrupting the binding of HKII to the mitochondrion, depleting ATP, inhibiting cell cycle progression, and inducing cell death. A TCM formula Ben Cao Xiao Ke Dan was revealed a strong inhibitory effect on HKII activity. However, exact

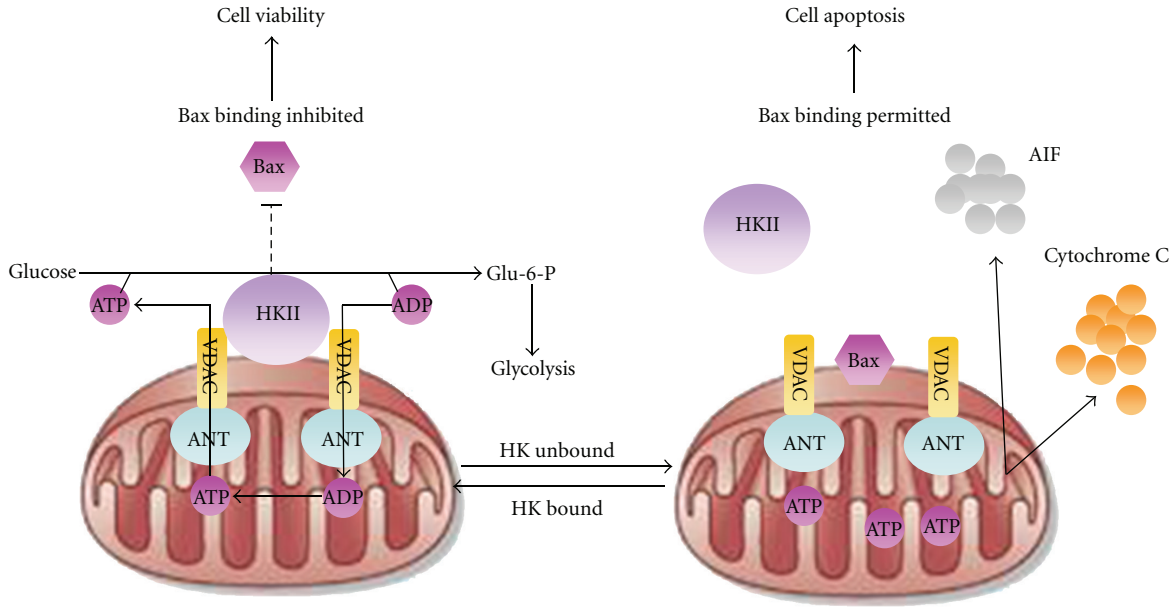

Figure 3: Antiapoptotic and metabolic roles for mitochondrial hexokinase II (HKII). (Left panel) Specific binding of HKII to the outer mitochondrial membrane (OMM) promotes ATP exchanges through complexes consisting of voltage-dependent anion channel (VDAC) and adenine nucleotide (ANT). The effluxed ATP could directly participate the transition from glucose to glucose-6-phosphate, which accelerates the glycolytic activity. Meanwhile, HKII binding to OMM also antagonizes Bax interaction with mitochondrial contact site, which prevents apoptosis occurrence; (Right panel) HKII unbound resulted in the "close" of VDAC-ANT channel, which induces Bax integration and potential changes between outer and inner mitochondrial membrane, and finally leading to release of cytochrome C and apoptosis-inducing factors (AIF) from mitochondrion.

phytochemicals in the formula accounting for this inhibitory effect remains unclear [97]. Methyl jasmonate, a plant lipid derivative, exists in many herbs and functions as a signaling molecule in the stress response. Methyl jasmonate was shown to induce apoptosis in various malignancies including prostate, cervical, and bladder cancers [98–100]. Recent studies found that its apoptosis-induction effects are closely correlated to the disruption of the interactions between HKII and VDAC [101]. Although some HKII inhibitors, such as 2-DG and 3-BrpA, were approved for clinical trials, the nonspecific inhibitions on all isoforms of HKs and normal cells might result in toxic effects when they are applied in patients. Therefore, to develop agents specifically targeting on HKII of cancer cells is a direction for further studies.

3.3. LDH-A. LDH-A is emerging as a novel therapeutic target in the glycolytic pathway. LDH has two subtypes: LDH-A, also called the skeletal muscle type or LDH-M, and LDH-B, also known as the heart type or LDH-H. LDH-A exhibits kinetic features suitable for conversion of pyruvate into lactate, whereas LDH-B has kinetic features suitable for conversion of lactate into pyruvate. LDH-A is an attractive target for cancer therapy because its expression is largely confined to skeletal muscle [102]. Moreover, human subjects with LDH-A deficiency show myoglobinuria under intense anaerobic exercise, and individuals with complete lack of LDH-A subunit have been documented with no apparent increase in hemolysis [103]. Numerous studies also demonstrated the overexpression of LDH-A in various types of cancer [104]. Considering the role of LDH-A in maintaining cancer cell energy metabolism, once its activity is inhibited, the energy-producing burden will be transferred to mitochondria, which may result in elevated oxidative stress and induce mitochondrial pathway apoptosis. Several studies have already found that the inhibition of LDH-A in cancer cells could stimulate mitochondrial respiration, decrease mitochondrial membrane potentials and finally lead to cancer cell death [105, 106]. Given LDH-A inhibition has no significant toxic effect on normal tissue, it is promising to develop novel LDH-A inhibitors. Gossypol is a polyphenolic compound isolated from cotton seeds, which are traditionally used in TCM for improving immunity. Gossypol is initially applied as a male antifertility agent. Following studies suggest its anticancer, antioxidant, antiviral and antiparasitic activities [107–109]. Gossypol preferentially acts on redox reactions catalyzed by NAD^+/NADH-based enzymes such as LDH-A. Gossypol is a nonselective competitive LDH-A inhibitor and its anticancer activity appears to be associated with LDH-A inhibition [110, 111]. However, gossypol revealed significant toxicities including cardiac arrhythmias, renal failure, muscle weakness, and even paralysis, resulting in the stop of further development [112]. Galloflavin, a gallic acid derivative, was recently found to directly bind with LDH-A and LDH-B. Biological studies found that galloflavin could block aerobic glycolysis and trigger apoptosis in cancer cells without interfering cellular respiration. [113]. An antimalaria drug FX-11 was also reported to inhibit LDH-A activity and induce cancer growth arrest in both *in vitro* and

in vivo experiments[114]. To explore active compounds from herbal medicine as LDH-A inhibitors, we investigated the effects of *Spatholobus suberectus,* a natural Chinese herb, on LDH-A activities in breast cancer cells. Our results showed that *Spatholobus suberectus* extractions significantly inhibited LDH-A activity in the breast cancer cells (unpublished data). Furthermore, we have conducted bioactivity-guided screening and epigallocatechin was identified as the main compound accounting for the herb anti-LDH-A function, the mechanism of which is correlated to accelerated HIF-1α proteasome degradation (unpublished data).

3.4. Others. Glucose transporters (GLUTs) are important channels expressed on cell membrane for mediating glucose and other substrates entering into cells as nutrients. A total of six GLUT isoforms have been identified. Among them, GLUT-1 is closely related to cancer stages and chemo- or radiotherapy responses [115]. GLUT-1 silencing reduced cancer cell proliferation and mediated apoptosis [116]. For herb-derived inhibitors, apigenin, and genistein were proved to inhibit GLUT-1 [117, 118]. GAPDH is a classical glycolytic enzyme encoded by a "housekeeping gene" which is constitutively expressed in most cells. GAPDH is responsible for transforming glyceraldehydes-3-phosphate to 1,3-bisphosphoglycerate coupled with the reduction of NAD^+ to NADH. Beside glycolytic function, GAPDH also participated in endocytosis, membrane fusion, vesicular secretory, nuclear tRNA transport, and DNA replication or repair. GAPDH inhibition resulted in induction of apoptosis [119]. Arsenic was demonstrated to abolish ATP generation in GAPDH-catalysing reaction process, although it is not in a direct binding mode [120]. AMP-activated protein kinase (AMPK) serves as a critical sensor in monitoring intracellular energy supply [121]. AMPK contributes to the increase of glycolytic activity in cancer cells. Thus, AMPK becomes a novel therapeutic target for cancer treatment. Herb-derived compounds curcumin and quercetin were demonstrated to induce apoptosis *via* AMPK pathway in cancer cells [122, 123]. In addition, other glycolytic enzymes including pyruvate kinase M2, glucose-6-phosphate isomerase, and transketolase-like enzyme 1, also participate in maintaining vitality of cancer cells. Development of small molecular inhibitors derived from herbs or natural plants targeting on these enzymes will be a new direction for anticancer research. The potential glycolysis inhibitors discussed above are summarized in the Figure 4.

In summary, recent research progress indicate that many active compounds derived from herbal medicine have the potentials to regulate key metabolic enzymes, such as HIF-1α, GLUT-1, hexokinase, LDH-A, and PDK1. Those enzymes and proteins are important signaling molecules in the glycolytic pathways of cancer cells. The unique glycolytic pathways could provide cancer cells sufficient energy and ATP for their rapid proliferation and growth. In the meantime, the unique metabolic characteristics of cancer cells raise great opportunities for the development of anticancer agents targeting on aerobic glycolysis. With this strategy, the compounds derived from herbal medicine or synthesized novel chemicals would preferentially kill cancer cells instead of normal cells by blocking aerobic glycolysis, greatly facilitating the drug discovery for molecular target therapy.

4. Perspectives

The elucidation of specific molecular signaling involved in cancer initiation, development, and metastasis have provided the grounds for molecular targeting based therapeutic strategy. Glycolysis is an important hallmark of cancer cells differentiated from normal cells. The metabolic alternations and adaptations of cancer cells have been extensively studied in last decades. Tumor cells exhibit altered metabolic behavior due to tumor cell intrinsic properties and tumor microenvironment. With Warburg effect, tumor cells have increased glucose uptake and preferentially metabolize glucose through glycolysis even in the presence of oxygen, allowing them to sustain higher proliferation rates and fast growth. Therefore, targeting on glycolysis can be an important strategy in cancer prevention and treatment. For example, cancer cells acquire and develop resistance in many patients when receiving chemotherapy or radiotherapy. A recent study investigated the antitumor effects of trastuzumab (a monoclonal antibody against EGFR-2) in combination with glycolysis inhibitor 2-DG in ErbB2-positive breast cancer. Trastuzumab inhibited glycolysis *via* downregulation of heat shock factor 1 (HSF1) and LDH-A in ErbB2-positive cancer cells, resulting in tumor growth inhibition. Moreover, increased glycolysis *via* HSF1 and LDH-A contributed to trastuzumab resistance. Combining trastuzumab with glycolysis inhibition synergistically inhibited trastuzumab-sensitive and -resistant breast cancers *in vitro* and *in vivo*, due to more efficient inhibition of glycolysis [124]. Thus, inhibition of glycolysis may offer a promising strategy to overcome the resistances of cancer cells toward chemotherapy [125, 126]. Similarly, glycolysis based on Warburg effect also links to radioresistance [127]. Given many herb-derived phytochemicals exhibit properties of antiglycolysis and reversal of drug-resistance, Chinese herbal medicine targeting cancer glycolysis can be developed as an adjunct treatment for cancer patients by combining chemotherapy and radiotherapy. It will provide an opportunity to increase clinical outcome in cancer treatment.

There are 250,000 to 300,000 plant species in the world. Although large efforts are made, only 5,000 plant species have been studied for their possible medical applications. With the long history of application in human subjects, Chinese herbal medicine enjoys a unique position for molecular targeting-based therapeutic strategy. Based on histological documents and case reports in cancer treatment, Chinese herbal medicine provides a fast track and important source in drug discovery for molecular targeting based therapeutic strategy. It is anticipated that in the years to come, more and more medicinal herbs will be screened targeting on glycolytic-related molecular targets or other therapeutic targets. Establishing well validated high throughput screening platform is necessary and essential for the purpose, greatly accelerating the process of drug development. In conclusion, molecular-targeted screening strategy is critical and efficient

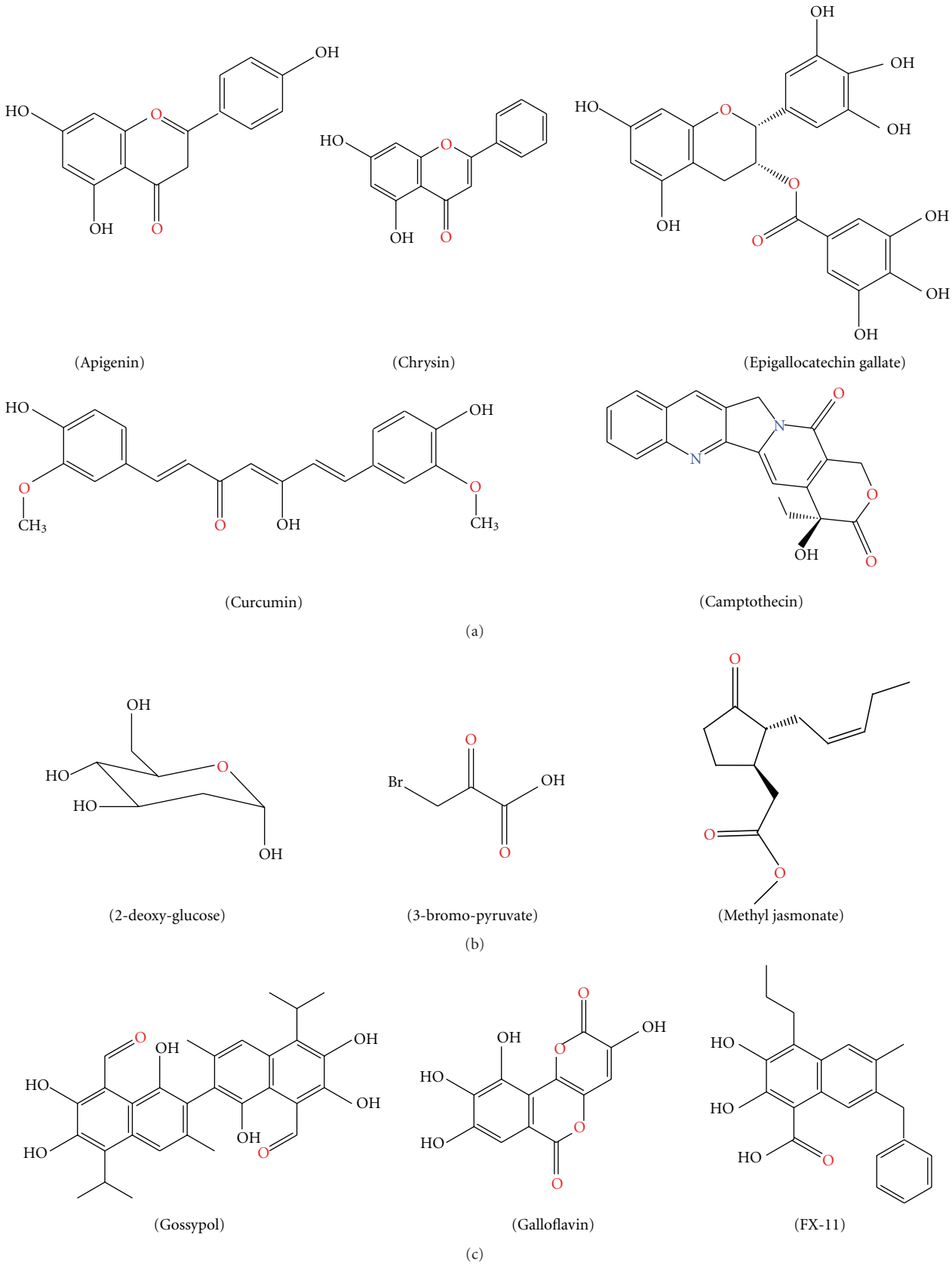

Figure 4: Chemical structures of glycolytic inhibitors derived from Chinese herbs. (a) Chemicals targeting on HIF-1α; (b) HKII inhibitors; (c) Chemicals targeting on LDH-A.

strategy for exploring the active compounds from Chinese herbal medicine for anticancer drug discovery. It will not only bring the discoveries of new anticancer drugs with more target specific and low toxic, but also make contributions to the globalization and modernization of traditional Chinese medicine.

Abbreviations

TCM: Traditional Chinese medicine
CAM: Complementary and alternative medicine
RCT: Randomized controlled trials
GLUT-1: Glucose transporter-1
SGLT-1: Sodium glucose cotransporter-1
PGK: Phosphoglycerate kinase
PK: Pyruvate kinase
LDH: Lactate dehydrogenase
MCT: Monocarboxylate transporter
GAPDH: Glyceraldehydes-3-phosphate dehydrogenase
PKM2: Pyruvate kinase, muscle
HIF-1: Hypoxia inducible factor-1
ODD: Oxygen-dependent degradation domain
VHL: von Hippel-Lindau
EGCG: Epigallacatechin gallate
HK: Hexokinase
VDAC: Voltage-dependent anion channel
2-DG: 2-Deoxy-glucose
3-BrpA: 3-Bromo-pyruvate
AMPK: AMP-activated protein kinase
HSF1: Heat shock factor 1.

Conflict of Interests

The authors declare that there are no conflict of interests.

Acknowledgments

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Review Article

Cancer, Inflammation, and Insights from Ayurveda

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A recent, exciting discovery relates to the concept of "shared pathology" between cancer and metabolic syndrome. One major pathway common to cancer and metabolic syndrome is chronic inflammation, which is a major driving force in carcinogenesis. Indeed, chronic inflammation precedes most cancers and is considered a "hallmark" of the neoplastic process. We discuss molecular and biochemical evidence which links diet, obesity, abnormal lipid metabolism, and type 2 diabetes mellitus with chronic inflammation. We also explain how each of these factors is linked with biochemical aberrations of carcinogenesis and the prevalence and risk of cancer. While there are reliable biomarkers for chronic inflammation, there are few markers for a mechanistic link between early inflammation and digestive disorders. Discovery of such a marker could lead to identification of a new subtype of patients with digestive disorders that predispose them to cancer and/or metabolic syndrome. In this context, we discuss the ayurvedic concept of "*Ama*" which is thought to be a toxic, proinflammatory waste-product of improper digestion. We then develop hypotheses and outline preclinical and clinical experiments designed to prove whether "*Ama*" can serve as a novel and reliable biomarker that links abnormal digestive status, with the onset of chronic inflammation.

1. Introduction

The vast amounts of data from the omics revolution has led to the concept of translational medicine, wherein well-documented biological discoveries are used to produce new drugs and medical devices. Another outcome of the omics revolution is "personalized medicine" for individual patients or subtypes of patients. Indeed, both translational and personalized medicine are "hot fields" for today's pharmaceutical industries, and the race to find "personalized drugs" for cancer patients is well underway. Notably, the identification of certain sub-types of breast cancer has already resulted in some degree of personalized treatment for these patients. However, there is a gap between the quantity of genomic information and our ability to interpret it. One critical review states that "without a truly robust mechanism for selecting personalized medicine-we will continue to see only incremental improvements. Therefore, it is now imperative that future clinical trials be designed with a plan to incorporate biomarker development" [1]. Thus, the experts acknowledge limitations in the fields of translational and personalized medicine. These limitations have significant impact on cancer treatment, since cancer is a complex, multifactorial, and heterogenous disease which requires innovative approaches in translational and personalized medicine.

1.1. Personalized Medicine and Ayurveda. Although personalized medicine is new to modern medicine, it is well established in *Ayurveda*, the traditional system of Indian medicine which is still being practiced. Ayurvedic physicians perform careful analysis of host-drug interactions in order to prescribe personalized drugs for each patient. We have discussed the sophisticated nature of Ayurvedic personalized medicine with two examples [2]. First, we explained how individuals with different sub-types of osteoarthritis can be treated with different drugs. Next, we illustrated the dynamic nature of Ayurvedic medicine by explaining how a sequence of personalized drugs can be used to treat different stages of asthma in a single patient [2]. Since there are limitations in the current research on personalized medicine, it is important to carefully evaluate Ayurvedic concepts and develop hypotheses

which may lead to novel methods of cancer diagnoses and biomarker development.

1.2. "Shared Pathology" between Cancer and Metabolic Syndrome. A recent, exciting discovery is the concept of "shared pathology" between cancer and metabolic syndrome. Thus, Hirsch et al. found several similarities between gene signatures for cancer and gene expression signatures from inflammatory, cardiovascular, and gastrointestinal diseases. Many of the genes common to these diseases regulate lipid metabolism and cholesterol biosynthesis [3, 4]. One major pathway common to both these diseases is chronic inflammation [5]. In fact, chronic inflammation is now considered a critical "hallmark" of carcinogenesis [6], and the molecular and biochemical mechanisms linking inflammation, lipid metabolism, and cancer are the subject of intense research. Therefore, this article reviews evidence for the newly discovered links between inflammation, lipid metabolism, and cancer. We also discuss relevant Ayurvedic concepts and outline experimental approaches that can contribute towards the development of new biomarkers for chronic inflammation. Before we describe the "shared pathology" between cancer and metabolic syndrome, we explain how chronic inflammation develops and contributes to tumorigenesis. Indeed, chronic inflammation precedes most cancers and is associated with at least 20% of all cancers [5, 6].

2. Chronic Inflammation in Cancer

2.1. Generation and Maintenance of Chronic Inflammation in Tumors. Short-term inflammation has anti-infective and anticancer effects, whereas prolonged or chronic inflammation can promote disease. Preclinical and clinical research, over the past decade, strongly suggests that chronic inflammation is associated with serious lifestyle and age-related diseases such as cancer and metabolic syndrome. Indeed, evidence also suggests that inflammatory microenvironment in and around tumors is an essential part of tumorigenesis. The molecular nature of the causal relationship between inflammation and cancer is only now being understood. Thus, there are two main ways in which the tumor microenvironment undergoes chronic inflammation. First, an intrinsic pathway of inflammation is driven by cells transformed by various genetic events (oncogenes, gene amplification, or inactivation of tumor-suppressor genes). In the second pathway, external inflammatory or infectious conditions increase the risk of developing cancer at certain sites (e.g., the colon, prostate, and pancreas) [5, 6]. These two pathways activate transcription factors such as nuclear factor-kappaB (NF-κB), signal transducer and activator of transcription 3 (STAT-3), and hypoxia-inducible factor 1alpha (HIF-1 alpha), in tumor cells [6, 7]. Next, these transcription factors coordinate the overexpression, elevated secretion, or abnormal activation of proinflammatory mediators such as cytokines, chemokines, cyclooxygenase-2 (COX-2), prostaglandins, inducible nitric oxide synthase (iNOS), and nitric oxide. Inflammatory cells, such as tumor-infiltrating leukocytes and tumor associated macrophages (TAMs), are now recruited into the tumor stroma. TAMs in particular are considered prime regulators of cancer inflammation [5, 6]. The resulting inflammatory microenvironment directly promotes tumor progression by increasing tumor growth and survival, increasing evasion of apoptosis, and accelerating the processes of angiogenesis, invasion, and metastasis [5, 6]. Figure 1 summarizes the major tumor promoting effects of NF-κB, STAT-3, and HIF-1 alpha.

2.2. Maintenance of Chronic Inflammation in Tumors. Once the inflammatory microenvironment has been created in tumors, there are mechanisms which sustain it. First, the cytokines which activated the transcription factors NF-κB and STAT-3 in tumor cells also activate these same transcription factors in inflammatory cells and tumor-stromal cells, which in turn results in more inflammatory mediators being produced. Thus, the cancer-related inflammatory microenvironment is enhanced by activation of inflammation in cells surrounding the tumor. This sustained "smouldering" cancer-related inflammation has many tumor-promoting effects [5–7]. Another mechanism for maintaining the cancer-related inflammation involves inflammation induced by reactive oxygen and nitrogen species. These free radicals damage DNA, proteins, and lipids and result in gene mutation and accumulation of advanced glycation end products (AGE). Interaction of AGE with its receptor (RAGE) triggers chronic inflammation by activation of NF-κB, at sites of tissue damage. The activated NF-κB, overrides endogenous anti-inflammatory mechanisms and leads to sustained inflammation [7–9]. Indeed, the importance of the RAGE-AGE interaction was proved by showing that transgenic mice lacking RAGE protein, developed small skin tumors with low levels of pro-inflammatory mediators and reduced numbers of infiltrating immune cells, when compared with wild type mice. These data strongly suggest that the AGE-RAGE interaction is essential for maintaining the inflammatory microenvironment in tumors [8].

In addition to its direct tumor promoting effects, chronic inflammation can indirectly enhance tumor formation. For example, immunosuppression, which is a serious risk factor for initiation and promotion of tumors, results from chronic inflammation [5, 6]. Although the mechanisms are unknown, there is now good evidence that a chronic systemic inflammatory response results in progressive loss of weight in cancer patients, which is known as cachexia [10]. Thus, immunosuppression and cachexia are two important indirect effects of chronic inflammation on cancer.

2.3. Anti-Inflammatory Drugs for Cancer. Although our understanding of signaling pathways and transcription factors in chronic inflammation primarily comes from preclinical studies, these data have clinical relevance since certain anti-inflammatory drugs (such as nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 specific inhibitors) have proven anticancer effects in pre-clinical tumor models and clinical trials. These anti-inflammatory drugs interfere with eicosanoid signaling and metabolism, suppress the neoplastic process, and can decrease oxidative stress and

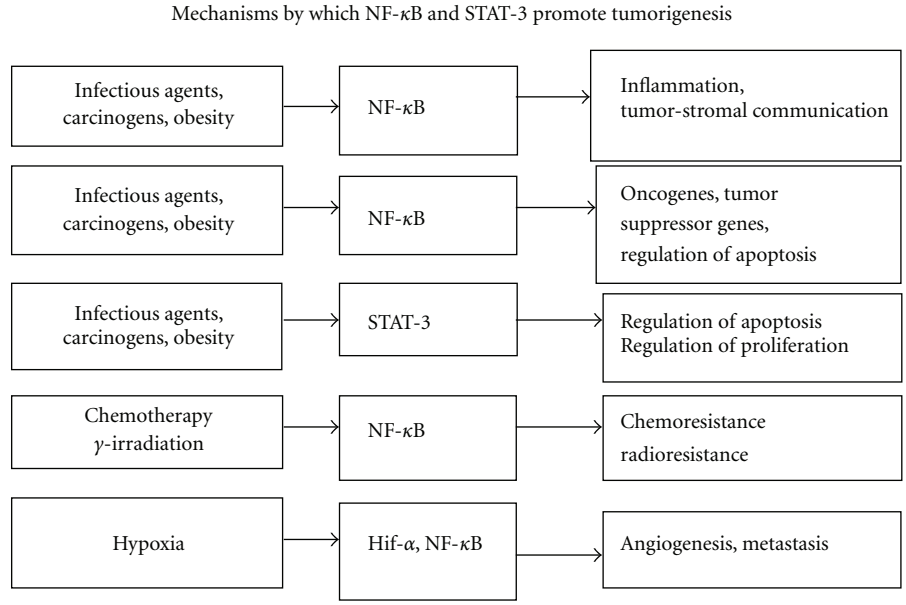

Figure 1: NF-κB and STAT3 control inflammation and cancer. Nuclear factor-κB (NF-κB) and signal transducers and activators of transcription 3 (STAT3), are transcription factors which activate pathways causing inflammation, transformation, angiogenesis, and metastasis. NF-κB and STAT3 are constitutively active in most cancers, and their suppression results in inhibition of tumor proliferation and invasion. Most chemopreventive agents act by inhibition of NF-κB and STAT3 pathways.

angiogenesis [11]. Interestingly, the potent antitumor effects of phytochemicals, such as curcumin, from turmeric, the green tea polyphenol epigallocatechin gallate (EGCG), and resveratrol from grapes, are in large part attributed to their anti-inflammatory activities [12]. Guggulsterone, the major active component of the gum resin from *Commiphora wightii* (or *Commiphora mukul*), is used to treat internal tumors, obesity, liver disorders, and malignant sores and ulcers in *Ayurveda*. Notably, guggulsterone was shown to induce apoptotic cell death and suppress proliferation, invasion, angiogenesis and metastasis of tumor cells [12]. Interestingly, all four phytochemicals (curcumin, EGCG, resveratrol, and guggulsterone) inhibit inflammation by suppressing the transcriptional activity of NF-κB [12, 13]. In addition, guggulsterone may also inhibit the transcriptional activity of STAT-3 [13].

3. Cancer and Metabolic Syndrome

3.1. Abnormal Lipid Metabolism and Cancer. Having explained the importance of chronic inflammation in tumor formation and progression, we review the evidence on the concept of "shared pathology" between cancer and metabolic syndrome [3, 4]. Metabolic syndrome refers to a cluster of related diseases (type 2 diabetes mellitus, cardiovascular disease, and obesity) which share abnormalities such as chronic inflammation and dyslipidemia. Therefore, in the next two sections, we discuss abnormalities of lipid metabolism in tumors, obesity, and how these processes lead to chronic inflammation.

Tumor cells metabolize large amounts of lipids, and lipid biosynthesis and desaturation of lipids are required for tumor cell survival. Indeed, enzymes, such as fatty acid synthase [14] and stearoyl-CoA desaturase [15], are often overexpressed in tumor cells and are potential targets for anticancer drugs. Cholesterol which serves as a precursor for the synthesis of many sex hormones has been linked to increased risk of prostate cancer [16]. However, the mechanisms which link cancer and cholesterol remains controversial, because antineoplastic therapies influence one's lipid profile, and anti-hyper lipidemic drugs, in turn, may influence the processes of malignancy [17]. However, recent data point to a direct link between Oxidized LDL receptor 1 (OLR-1) and cancer. Thus, OLR-1 may act as an oncogene, by activating the NF-κB, which, in turn, induces expression of its target genes responsible for lipogenesis, cell proliferation, cell migration, inflammation, and inhibition of apoptosis [3, 18]. In addition, oxidized LDL itself can directly promote tumors by enhancing the generation of reactive oxygen species which damage and mutate DNA [19]. Oxidized LDL also indirectly promotes tumors by inducing proinflammatory changes in macrophages and reducing their phagocytic capacity towards dying tumor cells. In this context, it is important to note that oxidized LDL is generated in the body by several pathways [18, 19].

3.2. Obesity, Cancer, and Inflammation. Epidemiological data have linked a high body mass index (BMI) and obesity in both genders to an enhanced risk of colorectal, esophageal, kidney cancer, non-Hodgkin's lymphoma, and multiple myeloma. Multiple myeloma and large B-cell lymphoma were especially linked to obesity in males, whereas cancer of the breast and cervix have been linked to obesity in females. Indeed, approximately 30–50% of deaths caused by breast

cancer are due to obesity. There is also an association between obesity and cancers of the digestive tract [20], because obesity-associated hormones and growth factors contribute to the pro-inflammatory environment created by crosstalk between epithelial tumor cells, adipocytes, and inflammatory cells [21]. Specifically, dysregulation of cytokines such as TNF-α and interleukin-6 (IL-6) and adipokines such as lectin and adiponectin contribute to the low-grade inflammation that is a hallmark of obesity [22]. Leptin is mainly regulated by insulin-induced changes of adipocyte metabolism and helps to prevent weight gain, whereas adiponectin can increase insulin sensitivity and reduce adipogenic inflammation [23]. Thus, adiponectin can oppose the actions of pro-inflammatory cytokines such as TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1) [24].

3.2.1. Clinical Studies on Obesity and Inflammation. Studies on obese patients show varying results due to differences in study design and the population being analyzed. However, a majority of studies confirm that cytokines and adipokines can regulate obesity-associated inflammation [21–25]. One study found that obese patients have increased concentrations of the C-reactive protein (CRP), the pro-inflammatory cytokine TNF-α, and decreased concentrations of adiponectin. However, levels of adiponectin did increase during weight loss, suggesting that weight loss maybe able to restore an anti-inflammatory condition [25]. Strong clinical evidence linking obesity, adipokines, and carcinogenesis comes from a report which found that very obese patients suffering from cancer and/or cardiovascular events had a 30% reduction in mortality following surgery for weight loss [24].

These data on chronic inflammation and abnormal lipid metabolism have important clinical implications because patients are usually diagnosed and stratified on the basis of markers for three separate diseases (type 2 diabetes mellitus, cancer, or metabolic syndrome). In contrast, markers for chronic inflammation and abnormal lipid metabolism are "shared abnormalities" which precede these diseases and therefore allow for earlier diagnoses of these related diseases.

3.3. Nuclear Receptors, Lipid Metabolism, Inflammation, and Cancer. While lipids such as cholesterol and oxidized LDL can play a significant role in tumorigenesis, nuclear receptors are equally important. Nuclear receptors are a unique family of transcription factors which bind DNA and also bind a lipid ligand. Thus, nuclear receptors sense specific lipids and accordingly regulate the expression of specific target genes within adipose tissue. The nuclear receptors regulating lipid metabolism and chronic inflammation are discussed below [26].

3.3.1. Liver X Receptors (LXRs). LXRs are cholesterol-sensing nuclear receptors that regulate lipid metabolism and transport and also suppress inflammatory signaling in macrophages by modulating activity of NF-κB [27]. Recent reports suggest that agonistic ligands of LXR suppress proliferation of multiple human cancer cell lines *in vitro* and inhibit the growth and progression of prostate tumor xenografts in nude mice. Notably, phytosterols are agonists for LXRs and are associated with a reduced incidence of colon cancer [28].

3.3.2. Peroxisome Proliferator-Activated Receptors (PPARs). PPARγ is a transcription factor which regulates insulin sensitivity, adipocyte differentiation, and lipid utilization in adipocytes. In addition to regulating gene transcription, PPARγ binds various lipids (fatty acids, bile acids, and/or sterols) and functions as a major sensor of lipid metabolism. Interestingly, several pre-clinical studies demonstrate that ligands which activate PPARγ receptors (particularly thiazolidinedione derivatives) exert a broad spectrum of anti-tumoral, anti-inflammatory, antiangiogenic, and immunomodulating activities [29]. The anti-inflammatory effects of PPARγ ligands include stimulation of adiponectin production, which in turn opposes the action of pro-inflammatory cytokines [30]. Indeed, PPARγ nuclear receptors are considered an important component of the molecular pathways interconnecting cancer development with metabolic syndrome [31].

3.3.3. Farnesoid X Receptor (FXR). Activation of another nuclear receptor, FXR, can also have anti-tumor effects. Thus, FXR deficient mice show increased susceptibility to intestinal tumorigenesis [32] and are more susceptible to inflammation induced by the endotoxin, lipopolysaccharide (LPS) [33]. FXR is a specific bile acid receptor and serves as an important drug target for prevention of colorectal can-cer [34], because elevated excretion of secondary bile acids is a strong risk factor for colorectal cancer. Interestingly, guggulsterone's efficacy against hyperlipidemia and its ability to bind FXR also make it a potentially useful drug for colon cancer [13]. Together, these data suggest that normal levels of FXR expression and activity have important anti-inflammatory and anti-tumor effects.

In summary, all three types of nuclear receptors (LXR, PPARs, and FXR) detect signals derived from dietary lipids, pathogenic lipoproteins, or essential fatty acid metabolites and respond by regulating lipid metabolism and suppressing inflammation [26–34]. Since lipid metabolism and inflammation have a major impact on tumor development and progression, drugs which modulate the activities of these nuclear receptors are important anticancer drugs. Having discussed the role of lipid metabolism and inflammation in cancer, we now explain how obesity and diabetes are linked to cancer.

3.4. Obesity, Diabetes, and Cancer. Epidemiological data point to a link between type 2 diabetes mellitus (T2DM) and cancer, which can be independent of obesity. Thus, a large prospective study in the USA conducted a 16-year followup study on a cohort of almost 1million men and women who had no reported history of cancer. The results showed that independent of obesity, T2DM was a strong predictor of mortality from cancer of the colon, pancreas, female breast, male liver, and bladder. In the case of pancreatic cancer, it

was unclear whether diabetes was the cause or outcome of pancreatic cancer [20].

The physiological link between obesity, T2DM, and cancer arises, because the adipose tissue in obese individuals produces high levels of free fatty acids, triglycerides, leptin, and pro-inflammatory cytokines. These metabolic changes increase insulin secretion and can lead to insulin resistance which is common in diabetes. Obesity and elevated insulin levels also induce more secretion of insulin like growth factor 1 (IGF-1), which stimulates cell growth and proliferation [20]. A biochemical link between cancer and T2DM exists, because signaling through insulin receptor and insulin like growth factor 1 receptor (IGF-1R) is increased in the hyperinsulinemic condition of diabetics [20]. The hyperactive IGF-1/IGF-IR axis in diabetic individuals can drive proliferation, survival, and growth of tumor cells. Indeed, overexpression of IGF-1R is common in several cancers, and preclinical studies show that downregulation of IGF-IR signals can reverse the neoplastic phenotype and sensitize cells to anticancer treatments. Accordingly, several IGF-IR inhibitors have entered clinical trials [35].

Another biochemical link between cancer and T2DM arises because hyperglycemia generates oxidative stress, which in turn leads to accumulation of modified forms of DNA, protein, and lipids. These modified macromolecules can function abnormally and initiate carcinogenesis. Certain products of oxidative stress, such as advanced glycation end products (AGE), have pro-inflammatory effects. AGE, which consists of glycated, carbonylated, and nitrosylated proteins, accumulates due to aging and diabetes. AGE interacts with its receptor (RAGE) and further enhances oxidative stress and induces inflammation, thus significantly increasing the risk for cancers in diabetic patients [9, 36].

4. Diet, Inflammation, and Cancer

4.1. Diet, Digestion, and Inflammation. Thus far, we have explained how the "shared pathology" across obesity, metabolic syndrome, and cancers involves biochemical aberrations in signaling pathways which regulate lipid metabolism and chronic inflammation. However, diet can also contribute to the pathophysiology of metabolic syndrome and cancer. Therefore, this section reviews the evidence linking cancer with diet and inflammation. Many human studies have found high levels of systemic markers of inflammation (high-sensitivity C-reactive protein (Hs-CRP), interleukin-6 (IL-6), and TNF-α) in individuals with low-fiber, high-fat diets [37]. A recent study of healthy men and women found that the ratio of omega-6/omega-3 fatty acids showed the strongest positive correlations with increased levels of most inflammation markers, suggesting that this ratio may constitute a predictor of low-grade, chronic inflammation [38].

Although there are several studies on the effects of diet on inflammation markers and the risk of cancer, the influence of digestion on the risk of contracting cancer remains unclear. Studies suggest that the gut microflora (which is influenced by diet and digestion) can influence the pathways linking diet and low-grade inflammation. Thus, fat depots from mice with colitis showed increased expression of inflammatory cytokines and the nuclear receptors PPARγ and FXR [30–33]. Administration of probiotics reversed these pro-inflammatory effects and normalized the gut microflora [39]. Therefore, normal gut microflora potentially have important anti-inflammatory effects. Another interesting study showed that PPARγ, LXR, and FXR are important components of a molecular defense mechanism to protect against accumulation of toxic endogenous lipids and bile acids which accumulate in diet induced hyperlipidemia [40]. As mentioned earlier, drugs modulating FXR activity [32, 33] and guggulsterone [13] have a potential role in treatment of colon cancer, which is associated with fatty diets and elevated secretion of bile.

5. Basic Principles of Ayurveda

5.1. Doshas, Prakriti, and Disease. Thus far, we reviewed evidence linking inflammation, lipid metabolism, diabetes, and cancer. Before we discuss how ayurveda may provide new biomarkers of chronic inflammation, we explain the basic concepts of ayurvedic physiology.

Ayurveda defines three dynamic pathophysiological entities (Doshas), as the basis for all body function. The three Doshas are termed as Vata, Pitta, and Kapha, respectively. *Kapha Dosha* governs the nervous and musculo-skeletal systems [41–43]. At the cellular level, Vata Dosha can be associated with signaling pathways regulating cell growth, differentiation, and cell death. Vata Dosha also governs movements of cells, molecules, nutrients, and wastes [44, 45]. The Pitta Dosha is responsible for transformative processes such as digestion, metabolism, energy production, and maintenance of immunity [41–43]. At the cellular level, *Pitta Dosha* can be associated with actions of enzymes, growth factors, hormones, and the reactions required for energy homeostasis and maintenance of basal metabolism [44, 45]. *Kapha Dosha* acts to form and maintain body mass, shape, and flexibility [41–43]. At the cellular level, anabolic processes (such as biosynthesis of macromolecules) and coordination of gene and protein function maybe associated with *Kapha Dosha* [44–46].

In ayurveda, one's basic "body constitution" is termed as "*Prakriti*." *Prakriti* arises due to a unique combination of fixed amounts of the three *Doshas* at the time of conception. Thus, *Prakriti* determines individuality and is akin to one's genotype. *Ayurveda* recognizes seven main types of *Prakritis*, based on the different combinations of the three *Doshas* at conception. Experimental analysis of the *Prakriti* concept revealed statistically significant correlations between an individual's *Prakriti* and the expression of specific genes and biochemical parameters [44]. Another study found correlations between *Prakriti* and HLA gene polymorphisms [47]. Although one's *Prakriti* (genotype) is fixed, one's *Doshas* are in dynamic equilibrium, and optimal function of each *Dosha* and normal interactions between *Doshas* are essential for good health. Accordingly, individuals with "balanced" *Doshas* (*Sama Prakriti*) are less susceptible to disease than individuals with abnormal *Doshas*. In fact, imbalances or

disturbed interactions between *Doshas* are considered a major cause of disease. An abnormal *Dosha* can be inhibited, excessive, or vitiated (disturbed) [48]. Indeed, the type and nature of disease, are primarily determined by the *Dosha* which is affected. For example, inflammatory diseases are associated with vitiation of *Pitta Dosha* [48], whereas obesity and metabolic syndrome are associated with vitiation of *Kapha Dosha* [45, 46]. A specific illness manifests when the vitiated *Dosha(s)* interact with weaknesses in specific organs (*Dhatus*). Conversely, pathogenic factors can also trigger abnormality of the *Doshas* and weaken the *Dhatus* [48]. Severe diseases, such as cancer, affect the entire body and usually involve vitiation of all three *Doshas* [48, 49].

5.2. Doshas, Agni, and Immunity. In addition to the concepts of *Doshas* and *Prakriti*, the Ayurvedic concept of *Agni* is important. *Agni* is the primary entity responsible for metabolic and transformative processes at the physiological and cellular levels. There are thirteen types of *Agni* which control all metabolic functions. When *Agni* is strong, digestion of food is normal, and even vitiated *Doshas* can be converted into nontoxic components [50]. "Incompatible foods" (*Viruddha Ahara*) can disturb *Agni* and lead to vitiation *of Doshas*. Indeed, certain useful foods can be pathogenic if ingested in certain combinations or in specific situations. For example, fruits and milk are each useful, but their combination is difficult to digest and can vitiate *Kapha Dosha* and lead to *Agnimandya* (weak *Agni*) [51]. A complex interplay between diet and host factors regulates *Agni* and is in turn influenced by *Agni*. Thus, the nature and composition of diet, quantity of food, timing of food intake, and the intrinsic properties of food are important. In addition, an individual's ability to digest and process food depends on host factors such as *Prakriti*, status of *Doshas*, *Agni*, tolerance, and digestive factors [48, 50, 51]. Thus, a feedback loop mechanism links diet and host factors with the strength and activity of *Agni*. Long-term consumption of incompatible foods can impair this feedback mechanism and increase susceptibility for various metabolic diseases and acute or fatal conditions [48, 50–52]. A weakened *Agni* can also result in decreased immune surveillance, which is a major risk factor for diseases such as cancer. Therefore, maintenance of *Agni* at optimum levels is important for avoiding pathogenesis [50, 51].

5.3. Ayurveda and Cancer. Ayurveda does not consider cancer as a distinct disease or set of diseases. Rather, ayurveda states that all diseases result from gross, systemic imbalances and malfunctions of the three *Doshas*. As mentioned above, specific diseases (including cancer) originate from interactions between abnormal *Doshas* and weakened *Dhatus* [48, 49]. For example, vitiation of *Kapha Dosha* is a common link between cancer and diabetes; however, the organs (*Dhatus*) which are affected differ [53, 54]. Thus, weak *Shukra Dhatu* (tissue regeneration and cell division) interacting with vitiated *Vata Dosha* and *Kapha Dosha* could lead to cancer, whereas excess and improperly formed *Meda* (adipose tissue) interacting with vitiated *Kapha Dosha*, can cause diabetes [54]. The magnitude of illness and clinical presentation of cancer are thought to vary, because each person has different patterns of exposure to pathogens and has dynamic changes in the functioning of *Dhatus* [53].

Instead of using targeted therapies for destruction of the tumors, ayurvedic drugs/modes of treatment attempt to correct metabolic defects and restore normal tissue functions ("*Sama Dhatu Parampara*"). Like most forms of traditional medicine, ayurvedic medicine is holistic, since immunotherapy (*Rasayanaprayoga*) for rejuvenating the body's support systems, forms a significant component of cancer therapy [41, 43, 48, 49]. A review of Ayurvedic concepts of cancer and herbal anti-cancer drugs is available in the literature [49].

Table 1 compares the modern and ayurvedic concepts of cancer. It highlights new molecular evidence which validates certain ayurvedic concepts of cancer. Earlier, cancer was thought to result from sequential genetic events regulating cell growth and death. It is now clear that abnormalities involving epigenetic regulation, diet, environmental factors, and immune function significantly affect the phenotype of a cancer patient (Table 1). Ayurveda also considers diet and environmental factors as important regulators of *Agni* and immunity, which in turn can increase risk for cancer. The concept of "shared pathology" between cancer and metabolic syndrome [3, 5, 6] has some similarities to the Ayurvedic view that interactions between vitiated Doshas and weak tissues (*Dhatus*) lead to systemic malfunctions which can manifest as cancers of specific organs (Table 1). As discussed in Sections 2.3 and 3.3, certain anti-inflammatory drugs [11–13] and antidiabetic drugs [29–31] are effective against cancers because of the "indirect" involvement of inflammation and dyslipidemia in carcinogenesis. Ayurveda also uses "indirect" approaches to treat cancers because therapies aim to eliminate vitiated Doshas, rejuvenate body functions, and restore immunity (*Rasayanaprayoga*) (Table 1). Modern, cutting edge, anti-cancer therapy also uses immunotherapy and cancer vaccines.

6. The Ayurvedic Concept of "*Ama*" and Intestinal Autointoxication

As mentioned above, abnormal *Doshas*, weakened *Dhatus*, and weakened *Agni* are major risk factors which weaken immune status and predispose an individual to serious diseases such as cancer. We also explained how chronic inflammation, a hallmark of carcinogenesis [5–7], is associated with poor diets [37–39], abnormal lipid metabolism [9, 18–33], *Kapha Dosha* [45, 46], and metabolic syndrome [20–24]. We now discuss the Ayurvedic concept of "*Ama*" since it pertains to the origin of chronic inflammation.

"*Ama*" is a toxic, heavy, unctuous, and sticky juice which originates as a waste-product of digestion and metabolism. Indeed, the word "*Ama*" can be translated to mean "immature" or "incompletely digested." "*Ama*" builds up in individuals whose digestion is either weak or overloaded with the wrong foods [55]. Since one's digestive powers (*Agni*) are in part determined by one's *Prakriti* (genotype), individuals with strong digestive powers (a characteristic associated with *Pitta Prakriti*) can eat larger quantities and richer foods

Table 1

Medicines' earlier concepts of cancer	Ayurvedic concepts of cancer	Evidence supporting ayurvedic concepts of cancer
Cancer results from sequential genetic events which lead to uncontrolled cell growth and resistance to cell death.	Cancer results when abnormal interactions between *Prakriti* (genotype) and environmental factors vitiate the *Doshas* and impair immunity.	Abnormalities besides aberrant cell growth and cell death cause cancer. Epigenetic regulation, diet, environmental factors, and immunity affect phenotypes.
Most cancers arise due to sporadic mutations in specific tissues, and spread to other organs.	Interaction between vitiated *Doshas* and weak tissues (*Dhatus*) manifests as cancers of specific organs.	Shared molecular pathology between cancer and metabolic syndrome.
High-fiber diets associated with lower risk of heart disease and cancer. Inflammation process was not linked to cancer.	Links between improper diet, digestion, metabolism, inflammation, and disease. "*Ama*" maybe a novel biomarker for early inflammation.	Chronic inflammation actively promotes all stages of carcinogenesis.
Chemotherapy or radiotherapy are not selective for cancer tissue. These therapies also destroy normal tissue and have severe side effects.	Therapies indirectly target cancer tissue by eliminating vitiated *Doshas*, rejuvenating *Dhatus*, and restoring immunity.	Anti-inflammatory and antidiabetic drugs indirectly destroy cancer tissue. Immunotherapy. Cancer vaccines.

without forming "*Ama*." In contrast, individuals with weak *Agni* have weak digestive powers (a characteristic associated with *Kapha Prakriti*) and produce "*Ama*" more easily. Ayurveda states that simple foods minimize formation of "*Ama*," whereas foods with high protein or fat content result in increased production of "*Ama*" because such foods are intrinsically difficult to digest and are therefore more likely to be partially digested [55]. Food or water consumption before complete digestion of previously consumed food also causes "*Ama*" and leads to vitiation of all three *Doshas*. Overall, a weakened *Agni* is the root cause of "*Ama*," which is a major risk factor for disease [56].

The Ayurvedic concept of "*Ama*" is similar to the Egyptian concept of "*Ukedu*," and the old theory of intestinal auto-intoxication propounded by *Metchnikoff* [48]. Thus, *Metchnikoff* believed that proteolytic gut bacteria can produce toxic byproducts (phenols, indoles, and ammonia), from digestion of dietary proteins. These toxic byproducts of digestion accumulated with age and caused disease [57]. Interestingly, modern evidence supports *Metchnikoff*, since bacterial species which metabolize dietary carcinogens (heterocyclic amines) from cooked meat and fish are associated with increased risk of tumors [58]. The link between intestinal auto-intoxication and disease is concordant with Ayurvedic concepts on "*Ama*" and its pathogenic potential (please see the next two sections).

6.1. Diagnoses and Treatment of "Ama". An ayurvedic practitioner diagnoses "signs and symptoms" of "*Ama*." Typically, "*Ama*" manifests as a sticky, white coating on the tongue, which obstructs various internal microchannels and is associated with characteristic symptoms such as inability to taste food, local or general inflammation, sudden fatigue, heaviness, pain, abdominal discomfort, lethargy, indigestion, and constipation [48, 59]. Since "*Ama*" is considered the root cause of disease, it must be fully digested before one can rectify vitiated *Dosha(s)* [59]. Accordingly, strengthening of *Agni* and complete digestion of "*Ama*" are major goals of ayurvedic treatment. Thus, therapies such as purgation, enema, or therapeutic emesis lead to complete digestion of "*Ama*" and separation of the vitiated *Dosha* from various channels [55]. Improved *Agni* results in complete digestion of "*Ama*," and causes the condition known as "*Nirama*" (free from "*Ama*"). The "*Nirama*" stage is favorable for additional treatments aimed at resolving vitiated or depleted *Dosha* and *Dhatus* and reversing the disease pathology[55]. Notably, the popular *Panchakarma* procedures for eliminating vitiated *Doshas* are only effective if preexisting "*Ama*" has been completely digested [55].

6.2. "Ama" and Pathogenesis. The obstruction of microchannels by "*Ama*" is responsible for loss of homeostasis, inflammation, and tissue damage [60]. Accordingly, ayurveda believes that "*Ama*" is the root cause of several diseases since it blocks important micro-channels (*Srotas*) which nourish tissues (*Dhatus*) [61]. Being a sticky substance, "*Ama*" is usually conjugated with *Doshas* or *Dhatus*. For example, *Pitta Dosha* in conjunction with "*Ama*" is termed as "*Sama Pitta*," which can trigger pathogenesis and hamper physiological functions [50]. Excessive "*Ama*" can circulate and interact with excretory products to produce a reactive and toxic form with antigenic and pro-inflammatory properties. This form of "*Ama*"can potentially disrupt the immune system and increase severity of the initial disease [48]. In this context, it is intriguing to note that modern science also finds that chronic inflammation may be caused by nondigestible particles [11].

6.3. Experimental Approaches for Investigating "Ama". In the context of cancer and inflammation, it is important to study "*Ama*" because it is believed to have antigenic and pro-inflammatory properties [48]. Pre-clinical experiments can

be done to determine if "*Ama*" can serve as a reliable, early biomarker of chronic inflammation. Isolation of pure "Ama" maybe problematic because it is primarily localized in microchannels of the body. According to Ayurveda, excess "*Ama*" can be found on the tongue and in urine. Therefore, it is important to properly identify and collect samples of tongue secretions and urine after "clinical" characterization and confirmation of "*Ama*" stages of disease as described in Ayurveda [48]. If available, one should use samples from the same individual prior to disease ("*Nirama*" stage), as controls. These paired samples can then be tested for potential toxicity, immunogenicity, and pro-inflammatory activity, *in vitro*, and in appropriate animal models. This can be done by adding different concentrations of "*Ama*" containing samples versus "*Nirama*" controls, to cell lines derived from various tissue types. One can then determine if "*Ama*" is cytotoxic by doing MTT and/other assays for cell viability and cell death (apoptosis and necrosis assays) [62]. Since most cell lines are immortalized or transformed, it is also important to assess the potential toxicity of "*Ama*" on primary cultures derived from normal tissues. If "*Ama*" is cytotoxic *in vitro*, these toxicity experiments should also be replicated in animal models.

In order to determine if "*Ama*" can induce inflammation, one can add different concentrations of "*Ama*" containing samples versus "*Nirama*" controls, to different cell types and measure various pro-inflammatory molecules (cytokines, adipokines, eicosanoids, NF-κB, and STAT-3) [5–7, 21–25]. If these results suggest that "*Ama*" has pro-inflammatory properties, one can inject different concentrations of "*Ama*" containing samples versus "*Nirama*" controls, into separate groups of mice, and measure these various pro-inflammatory molecules [5–7, 21–25] and inflammation markers (CRP and ratio of omega-6/omega-3 fatty acids) [22, 24, 37, 38]; in experimental animals versus controls. If these results also show that "*Ama*" containing samples induce inflammation when compared with "*Nirama*" controls, then the concept of "*Ama*" as a pro-inflammatory molecule would be proved.

6.4. Candidate Molecules for "Ama". If the above experiments show that "*Ama*" containing samples can trigger chronic inflammation, one can comparatively analyze the biochemical composition of "*Ama*" versus "*Nirama*" samples. One should be also able to compare the biochemical composition of "*Ama*" with various endogenous, pro-inflammatory molecules produced during digestion, metabolism, and energy production. There are at least five types of endogenous pro-inflammatory molecules which may represent "*Ama*". First, improperly digested foods in obese individuals are excellent candidate molecules for "*Ama*", because they are associated with altered composition of gut microflora [37, 39, 57, 58], which in turn can induce chronic inflammation through activation of the lipopolysaccharide toll-like receptor-4 axis [11, 63]. The link between high fat diets, increased secretion of bile acids (such as deoxycholic acid), and increased risk for colon cancer is known [28, 34]. However, a direct link between bile reflux, inflammation, and cancer comes from a study showing that unconjugated bile acids potently stimulate expression of cyclooxygenase-2 (COX-2), a major pro-inflammatory enzyme in oesophageal adenocarcinoma-derived cells [64]. Thus, specific bile acids can have a pro-inflammatory nature and therefore represent a second molecular candidate for "*Ama*" [34, 64]. The pro-inflammatory nature of abnormal bile acids is also suggested by the fact that modulation of bile acid receptor (FXR) has anti-inflammatory effects (Section 3.3). The third molecular candidate for "*Ama*" represents advanced glycation end-products (AGE) which accumulate in diabetes, ageing, and cancer. AGE may represent "*Ama*," because interaction of AGE with its receptor (RAGE) triggers chronic inflammation [8, 9, 36]. The fourth molecular candidate for "*Ama*" consists of protein-lipid peroxide (P-LPO) adducts, since LPO (which accumulate during oxidative stress) can form adducts with lysine residues of certain proteins and induce the expression of the pro-inflammatory cytokine, TNF-α [65]. Lipid peroxides can also react with DNA to produce promutagenic adducts such as etheno-deoxyadenosine. Increased levels of such etheno-DNA adducts in human blood and urine, may serve as biomarkers of chronic inflammation in individuals who are prone to cancer due to prior exposure to carcinogens [66]. Hence, such etheno-DNA adducts could represent a fifth molecular candidate for "*Ama*."

The above experiments may reveal that "*Ama*" is enriched in one of these five candidate molecules. On the other hand, "*Ama*" may consist of a heterogenous mixture of these five candidate pro-inflammatory molecules (partially digested food particles, specific bile acids, AGE, peptide-peroxidized lipid adducts, and etheno-DNA adducts) derived from abnormal digestion and metabolism in organs and cells.

6.5. Potential Clinical Significance of Ama. According to ayurveda, excess "*Ama*" can be found on the tongue, and in urine [48]. Therefore, comparative and quantitative biochemical analysis of "*Ama*" from healthy individuals versus patients suffering from different cancers, metabolic syndrome, or both diseases can be done. In addition, one could measure the levels of pro-inflammatory markers and degree of immunosuppression in patients with different cancers and in patients with metabolic syndrome and a specific type of cancer. Such clinical studies may find statistically significant correlations between the biochemical composition and levels of "*Ama*," and the severity of metabolic syndrome and/or cancers. Since Ama' originates from improper digestion and metabolism in normal, non-obese, individuals [48, 55, 56] it should be detectable at early stages. Accordingly, increased levels of "*Ama*" may well precede the expression of the major pro-inflammatory molecules discussed above. If levels of "*Ama*" (as diagnosed by Ayurveda) significantly correlate with the levels of one or more of the five candidate molecules mentioned above, then "*Ama*" may prove to be a reliable biomarker of early inflammation in patients at risk for metabolic syndrome and/or cancers. If "*Ama*" can serve as a reliable biomarker of early inflammation, it may lead to identification of a new sub-type of patients with digestive disorders, inflammation, and high risk for cancer and metabolic syndrome. Such a discovery could have enormous clinical

significance, because it implies that "wellness therapies" (diet and life-style changes, detoxification therapies) may lead to reduced "*Ama*," and prevent onset of chronic inflammation and its associated diseases (cancer and metabolic syndrome).

In summary, the pre-clinical experiments and clinical experiments outlined above can determine if "*Ama*" is a reliable biomarker of early inflammation. Although C-reactive protein, TNF-α, and IL-6 are well-established inflammation markers associated with high fat diets, these markers reflect later stages when immune dysfunction has already occurred [22, 24, 37]. Similarly, the ratio of omega-6/omega-3 fatty acids [38] and AGE [8, 9, 36] are highly reliable inflammation markers for dietary status and levels of oxidative stress, respectively. It is estimated that 80% of cancer in USA have a nutrition/diet component suggesting a great impact of functional food and food components on incidence and treatment of cancer [67]. Currently, no single marker is available to predict the outcome of a dietary intervention on the resistance to infection or to other immune-system-related diseases [68]. If "*Ama*" proves to be a reliable biomarker of early inflammation, it could potentially link inflammation with improper diet and digestion. Thus far, altered gut microflora represent the only biomarker linking digestive status with inflammation [39, 57, 58]. There are no established biochemical markers linking weak/abnormal digestive and metabolic status with inflammation. "*Ama*" may well prove to be this missing "biochemical marker."

7. Conclusions

In the introduction we cited a review which warned that advances in personalized medicine may only occur with incremental improvements, due to lack of biomarkers for patient stratification. One way to avoid this scenario is to develop innovative concepts and approaches in the fields of translational and personalized medicine, by tapping into the wisdom of traditional systems of medicine. Thus far, research on ayurveda has focused on identifying and validating the bioactivities of phytochemicals isolated from various medicinal plants. However, ayurveda and other traditional systems of medicine are not merely sources of "raw materials" for potential drug candidates. Rather, the principles and practices of traditional systems of medicine could be developed into hypothesis which can be tested by modern scientific methods. This approach may provide evidence which validates some traditional concepts and may lead to the development of novel biomarkers for wellness and disease.

Evidence from the omics revolution and systems biology clearly point to a strong degree of connectivity between physiological and molecular pathways that were considered independent. For example, the newly discovered links between inflammation, lipid metabolism, and cancer were unexpected. Therefore, this paper explains and analyzes the links between two major diseases (cancer and metabolic syndrome). These new findings vindicate the holistic approach of ayurveda and other traditional systems of medicine, because it proves that a disease cannot be considered as a sequence of defective genetic and biochemical steps. Indeed, the links between inflammation, metabolic syndrome, and cancer suggest that even seemingly distinct diseases can arise from fundamental aberrations in metabolism, homeostasis, and immune function. Thus, the advances in omics analysis and systems biology are providing concrete evidence for some of the holistic concepts in traditional systems of medicine. If diseases are diagnosed and analyzed in a holistic manner, then treatment of disease is also holistic. Accordingly, ayurvedic drugs/treatment regimens are largely designed to restore the body's natural defense mechanisms and self-healing powers. These therapies are aimed at ensuring long-term recovery from disease by strengthening and rejuvenating major body systems. This holistic approach of ayurveda is also true of other traditional systems of medicine and is precisely what attracts people to alternative medicine. Indeed, we are in an exciting phase of modern medicine, wherein rigorous scientific evidence supports some aspects of holistic, traditional medical systems. Sustained and collaborative efforts between ayurvedic physicians, clinicians, and basic sciences researchers may lead to a deeper understanding and even convergence of certain modern and traditional principles underlying health and disease.

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Review Article

"We're All in the Same Boat": A Review of the Benefits of Dragon Boat Racing for Women Living with Breast Cancer

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This narrative review summarizes findings from quantitative and qualitative research literature that has been published over the past 15 years since an initial, community-based pilot study first challenged the long-held medical belief that vigorous, upper-body exercise would lead to lymphedema in women who were at risk due to treatments for breast cancer. Dragon boat racing originated in China more than 2000 years ago and has become a popular recreational and competitive support around the world. From the advent of the world's first breast cancer survivor dragon boat team, *Abreast in a Boat* launched in Vancouver, British Columbia, in 1996, there are now more than 140 breast cancer survivor dragon boat teams paddling and competing in 12 different countries. The wealth of quantitative and qualitative research that has ensued since that pilot study further supports the initial hypothesis that resistance exercise, for example, dragon boat paddling, is not only *safe* for women recovering from conventional breast cancer therapies but also shows that dragon boating has been embraced as a complementary exercise therapy by the cancer survivors participating in this magical sport.

"In any adventure, who people are can be determined not by what happens to them but by how they deal with it."
MacPhee, 1994

1. Introduction

Dragon boat racing originated in China more than 2000 years ago and is steeped in culture and powerful rituals. Traditionally, dragon boats raced from the north of China, the region of death, to the south—the realm of life [1]. Hong Kong hosted the first international dragon boat festival in 1976, and, 10 years later, the sport came to North America as part of Expo 86 in Vancouver, British Columbia. According to Barker: "Hosting dragon boat races is thought to bring health, happiness and prosperity, as well as offer protection for the unfriendly spirits of the sea" [1].

In 1996, Vancouver hosted the first international dragon boat festival held outside China. Among more than 130 teams entered from around the world was a novice team comprised entirely of women who had been treated for breast cancer, aptly named *Abreast in a Boat*—to signify not only the 24 paddlers' seated positions within the large, 700-kg boat but also the fact that many of them each had only "*a* breast." The brainchild of Dr. Donald McKenzie, a sports medicine physician and exercise physiologist at the University of British Columbia [2], the goal of *Abreast in a Boat* that first year was to determine whether women at risk for upper extremity lymphedema could progressively train for and partake in this repetitive, resistive sport without developing lymphedema—the chronic, irreversible swelling of the arm for which they were at greatly increased risk [3].

The purpose of this narrative review is to summarize the research, both quantitative and qualitative, that has ensued in the 16 years since *Abreast in a Boat* first took to the water in Vancouver. The quantitative research will trace the trajectory from the initial pilot study that examined whether or not this vigorous, repetitive upper-body sport was safe for women at risk for lymphedema through to recent, more

rigorous studies, for instance, randomized controlled trials and systematic reviews, which have continued to explore the safety and benefits of resistive exercise for breast cancer survivors. The qualitative research to be summarized explores the meanings of participating in this sport to some of the several thousand women around the world who are living with breast cancer and who have paddled and competed in dragon boat racing since those initial 24 pioneers first raised their paddles in Vancouver.

2. Potential Risks of Vigorous, Repetitive Upper-Body Exercise

For years prior to the launch of *Abreast in a Boat*, rehabilitation and oncology health professionals had warned women who had undergone axillary dissection for the staging of breast cancer to avoid strenuous, repetitive upper-body activity under the long-held presumption that such type of exercise would lead to development of lymphedema, a chronic and irreversible swelling of a limb [4–7]. This longstanding belief was based on the fact that exercise increases blood flow and would thereby increase lymph production, possibly leading to lymphedema [8]. Although removal of axillary lymph nodes and axillary radiation are known risks for developing lymphedema in the affected extremity, there was no evidence that exercise would actually induce lymphedema in those at risk or exacerbate preexisting lymphedema, and yet this myth has continued to prevail.

In a recent survey of 175 Australian women who had been treated for breast cancer, 70% reported that they intended to avoid strenuous activity with the involved upper extremity, due to "fear of lymphedema" [9].

The first study to challenge this longstanding belief was a case series involving upper-extremity measurements that was conducted on 20 of the 24 paddlers in *Abreast in a Boat* during their first paddling season in 1996. Results of that small pilot study have been supported by a number of subsequent studies involving larger samples and more rigorous research designs. These studies will be described and summarized in the following section.

3. Quantitative Research on Upper-Body Exercise for Women with Breast Cancer

3.1. The Pilot Dragon Boat Study. Although *Abreast in a Boat* began primarily as a community recreational activity to enable women living with breast cancer to reclaim their formerly healthy selves, two physical therapists—one a team member and the other a team coach—quantitatively studied the effects of resistance training and paddling on the risk of developing lymphedema by taking serial measurements of the paddlers' arm circumferences at four standardized anatomical locations at three time points: prior to paddling training, 2 months after commencement of training, and 7 months after the race season [10]. There were no clinically significant interlimb circumferential differences at the final time-point [10].

These results led the authors to conclude that women who had undergone axillary dissection and, in almost two-thirds of cases in the sample, radiation to the breast and/or axilla may be able to partake safely in strenuous upper body exercise. In a commentary accompanying the published article, a renowned surgical oncologist remarked that the study "should serve as the impetus for a more formalized randomized trial to confirm the authors' hypothesis, and again put a surgical myth to the test of a scientific study" [11]. Fortunately, that is exactly what happened in the decade following publication of this landmark initial study.

3.2. Other Quantitative Studies on Dragon Boat Racing. Whereas the initial pilot study [10] took place entirely within a community setting, the first sub-sequent dragon boat study was laboratory-based and more rigorously controlled, albeit also a case-series design [12]. Lane and colleagues examined the effects of a 20-week resistance and aerobic exercise program, supplemented at week 8 with addition of dragon boat training, for 16 breast cancer survivors [12]. Upper-extremity circumference and volume and upper-body strength were assessed at baseline, week 8 and week 20. In contrast to findings in the pilot study [10], all outcome measures increased significantly between times 1 and 3 for women in the combined exercise program [12]. However, as Lane et al. concluded, changes were consistent across both upper extremities and the increases in arm volume were likely due to the accompanying strength changes and not to lymphedema.

In 2009, McNeely et al. studied the effects of an acute bout of moderate-intensity exercise on upper-extremity volume in 23 breast cancer survivors regularly participating in dragon boat racing [13]. Each participant had undergone unilateral axillary lymph node dissection or sentinel lymph node biopsy, with 17 also having had radiation treatments. Five of the 23 participants had preexisting lymphedema. The independent variable was 20 minutes of continuous exercise on an arm ergometer. Although limb volume increased bilaterally immediately following the exercise bout, it reduced to levels slightly below baseline 60 minutes after exercise completion. The study authors concluded that moderate-intensity bouts of exercise are safe for breast cancer survivors with and without lymphedema but that their findings could be generalized only to women who had been participating already in vigorous upper-body exercise, that is, dragon boat racing.

Unfortunately, all of the research to date that has explicitly involved dragon boat racing as an intervention (or dragon boat paddlers as participants) has employed case-series designs with small samples [10, 12, 13]. However, this early line of inquiry that challenged the longstanding belief that vigorous, repetitive exercise was unsafe for women at risk for lymphedema [10] led to a number of larger and more rigorous studies examining the effects of other types of upper-body resistance training on lymphedema risk and other outcome variables.

3.3. Other Research on Upper-Body Resistance Training. Over the past 5 years, at least seven systematic reviews (SRs) have been published examining the effects of resistance training

and other forms of exercise on survivors of breast and other types of cancer [14–21]. The two most relevant to the focus of the current article are a 2008 SR by Cheema and colleagues, summarizing the effects of progressive resistance training on health-related benefits and potential adverse effects, for instance, lymphedema, in women with breast cancer [14], and a 2011 review by Kwan et al. examining the safety of resistance exercise for breast cancer patients with or at risk for lymphedema [15].

In their SR of 10 studies published between 1966 and 2007, Cheema et al. found no incidence or exacerbation of quantified or self-reported lymphedema as a result of resistance exercises or a combination of resistance and aerobic exercise [14]. In the more recent SR, Kwan and colleagues included 17 studies or SRs (2004–2010) of resistance and/or aerobic exercise training as well as other interventions, for instance, shoulder range of motion and manual lymph training; the authors of this SR concluded that slowly progressive resistance exercise is safe at any time following breast cancer surgery [15]. Both SRs reported improvements in muscle strength as a result of resistance training [14, 15].

Although the studies included in these two SRs [14, 15] were not limited to those involving resistance exercises used in dragon boat racing, their results support the findings from the original *Abreast in a Boat* case series [10], that is, that vigorous, repetitive upper body exercise does not initiate lymphedema or exacerbate preexisting lymphedema. Given that the studies reviewed included 11 randomized controlled trials (RCTs), many with samples much larger than that in the original pilot study, there is reasonable substantiation that resistance exercise or programs involving a combination of aerobic and resistance exercise are safe for women who have had axillary lymph nodes removed and, in many cases, radiation to the breast and/or axilla. The fact that three of the studies included in the most recent SR [15] were well-powered RCTs [22–24] provides further compelling evidence for the safety and efficacy of resistance exercises in women with pre-existing lymphedema [22] or those at risk for the disorder [23, 24].

3.4. Summary. Since the 2000 publication of the first small study to challenge the belief that vigorous upper-body exercise could lead to lymphedema, an impressive body of quantitative research on similar types of resistance exercise has continued to support the original hypothesis "that women who have undergone axillary dissection and, in many cases, radiation for the treatment of breast cancer *may* be able to safely engage in strenuous, repetitive upper body exercise" [10]. This subsequent line of research has shown also that resistance exercise, either alone or in combination with aerobic exercise, has positive benefits on muscle strength, body composition, self-esteem, and most importantly the participants' quality of life [14, 15, 21].

4. Qualitative Research on the Experience of Dragon Boat Racing

Since *Abreast in a Boat* first took to the water in 1996, dragon boat racing for women with breast cancer has become a worldwide phenomenon. According to the *Abreast in a Boat* website [25], there are now 143 breast cancer dragon boat teams in 12 different countries. With approximately 25 paddlers per team, these figures suggest that more than 3500 breast cancer survivors are enjoying the mysticism, camaraderie, and overall good fun that this magical sport engenders.

Because there is much more to dragon boat racing than getting fit and challenging long-held myths about the dangers of vigorous sport, a number of qualitative researchers have chosen to study this powerful phenomenon by exploring what the sport means to the paddlers themselves [26–31]. Published between 2002 and 2011, these six studies involving 67 women resulted in a number of themes, several of which were remarkably similar: feelings of camaraderie, a sense of renewed fitness and health, opportunities to promote awareness of a full and enjoyable life after breast cancer, and enhanced self-confidence and control of one's life.

Feelings of *camaraderie* were echoed by a number of participants, as seen in the following quote:

> *"The feeling of racing, giving it your all using every ounce of muscle that you possibly have. That feeling of strength, the camaraderie. Getting us all together. You can do it if there's 22 people in the boat, you can go anywhere. It's everybody, all working paddling the same..." [26, page 53].*

Within the predominant theme of physical and emotional well-being, one woman described her *renewed feelings of self-confidence, fitness, and taking back control of her life* [27]:

> *...That's why I think dragon boating is so important to women because it starts to build their confidence back that they can do something, taking control of their lives and puts them in fantastic physical shape...through all of the accomplishments you have a feeling of control back and of confidence back. Then you start feeling great from a physical aspect...comes the confidence and from the confidence comes the control, it's all weaved together [27, page 143].*

In another study [30], a participant described how the experience of dragon boat racing gave her a sense of *renewed health*:

> *I found [dragon boat racing] actually improved my physical condition. I used to have very severe osteoporosis, and I had lower back pain, and when I started paddling, because you use your whole body and you use your lower back, I was worried that it would cause too much strain on my back and it would be difficult, but it had the opposite effect. After a while, my back pain actually went away, so it was really beneficial [30, page 229].*

Although dragon boat racing has not been included in lists of more standard complementary therapies for cancer, it clearly fits within definitions provided by leading experts

in that area in that it serves as an "adjunct to mainstream cancer care" [32, page 80] and is aimed at enhancing well-being (and controlling symptoms) of its participants [32]. As can be seen from both the quantitative and qualitative studies summarized in the foregoing two sections, involvement in this sport has enhanced the well-being of its participants and assisted in controlling their symptoms.

Not only has physical exercise been shown to contribute to increasing muscle strength and enhancing overall fitness and well-being, it has been shown also to improve overall quality of life and to prolong survival in women who have been diagnosed with breast cancer.

5. Benefits of Physical Activity on Quality of Life and Survival after Breast Cancer

Two recent meta-analyses have summarized the benefits of physical activity/exercise interventions on health-related quality of life (HRQoL) [33] and mortality after a breast cancer diagnosis [34]. Duijts and colleagues reported a summary effect size of 0.298 ($P < 0.001$) based on 13 studies examining the effect of physical exercise on HRQoL [33], thus providing quantitative support for some of the participants' quotes in the preceding section that summarized qualitative research findings for dragon boat racing. Other statistically significant effects of physical exercise interventions were reported in decreasing fatigue and depression and enhancing body image.

In their meta-analysis of six studies on physical activity and survival after breast cancer diagnosis, Ibrahim and Al-Homaidh found that postdiagnosis physical activity reduced breast cancer deaths by 34%, all cause mortality by 41%, and breast recurrence by 24%; however, when women with estrogen-receptor-negative breast cancer were analyzed separately, there were no significant effects for that sub-group which comprises about one-quarter of women with the disease [34]. The authors surmised that the greater benefits of physical activity for women with estrogen-receptor-positive disease were likely due to the effects on reducing estrogen levels.

6. Discussion

Although the quantitative and qualitative studies included in this paper had different aims, their combined findings support dragon boat racing as a beneficial complementary therapy for women who have experienced breast cancer, regardless of whether or not they have lymphedema. Results of the quantitative research, both on dragon boating specifically as an intervention [10, 12, 13] and on other types of resistance exercises [14–24], suggest that these recreational pursuits are safe for individuals who have undergone axillary surgery and/or radiation to the breast, chest wall, or axilla and do not lead to development of lymphedema or exacerbation of pre-existing lymphedema. In addition, resistance exercise positively influences muscle strength, body composition, self-esteem and quality of life. Improvement in self-esteem and quality of life certainly fits with the aim of complementary therapies for cancer, that is, to enhance participants' well-being [32]. In their 2009 systematic review on the effects of exercise on quality of life in women with breast cancer, Bicego and colleagues included nine RCTs of moderate to high methodological quality and concluded that there was "strong evidence that exercise positively influences QOL in women living with breast cancer" [21, page 45].

Although exercise had not previously been considered as a *typical* complementary therapy for cancer, the 2009 clinical practice guidelines developed by the Society for Integrative Oncology included among their 20 overall recommendations a specific recommendation on exercise and physical activity: "Regular physical activities can play many positive roles in cancer care. Patients should be referred to a qualified exercise specialist for guidelines on physical activity to promote basic health." [35, page 96]. The authors commented further that the strongest evidence for this recommendation was for breast cancer survivors and that resistance exercise is particularly beneficial during adjuvant cancer therapy [35].

Following completion of cancer treatments, the practice guideline authors recommend standard public health guidelines for cancer survivors [36], that is, to exercise at least 20–30 minutes at moderate-to-vigorous intensity on at least 3 to 5 days of every week. Because training regimens for dragon boat racing typically include both aerobic and resistive exercises, each of 20–30 minutes duration on 3 to 5 days of the week [10], this is an ideal recreational program for breast cancer survivors to maintain and/or regain post-treatment fitness. Furthermore, a recent systematic review has shown that exercise helps to mitigate the effects of cancer-related fatigue among breast cancer survivors [37], thus enhancing quality of life.

Whereas quantitative research showed that dragon boating is *safe* for women who have undergone treatments for breast cancer, and enhances a number of physical and psychosocial outcomes, findings from qualitative research describe the tremendous joy, support, and camaraderie that this sport engenders [26–31]. Although qualitative research does not aim at generalizability, per se, most of the studies took place in Canada and involved primarily Caucasian, well-educated women.

Despite this limitation, quantitative studies have shown that exercise and physical activity are complementary therapies commonly used by breast cancer survivors of different ethnic origins. Based on a questionnaire administered to over 5,000 Chinese women with breast cancer, Chen et al. reported that physical activity was the third most common complementary therapy used, with walking the most popular type of physical activity [38]. In a study of 125 Hispanic women living in the southwestern USA (with educational level averaging less than 10 years and income less that $20,000 per year), Owens and colleagues reported that 65% used exercise as a complementary therapy during breast cancer treatment [39]. Furthermore, in a South Korean survey of 425 breast cancer survivors, of the 57.4% that reported use of complementary/alternative medicine, exercise therapy was the most common type used by 43.2% [40]. Certainly the fact that there are breast cancer survivor dragon boat teams in Malaysia, Shanghai, and Singapore suggests that paddlers

are not all Caucasian [25], although this is the ethnic group most heavily represented in the qualitative studies conducted to date.

7. Conclusion

Beginning with the "fledgling research efforts of a group of Canadian investigators" [41, page 710], a longstanding medical myth that had threatened to negatively influence the quality of life in breast cancer survivors was first challenged in Vancouver in 1996. The published, community-based pilot study from that initial research [10] spawned a host of subsequent and far more rigorous quantitative studies, including RCTs and systematic reviews that went on to support the initial hypothesis that vigorous, repetitive upper-body exercise was safe for women who had been treated for breast cancer. In addition, that original case-series led to a half-dozen qualitative studies that further supported the effects of dragon boating in enhancing participants' quality of life.

Because exercise and physical activity have recently emerged as *mainstream* complementary therapies, the compelling line of research supporting the safety and positive effects of dragon boat racing and other forms of resistance exercise suggests that these are *evidence-based* complementary treatments. The universal joy of participating in dragon boating, as witnessed by participant quotes from the qualitative studies included in this paper, lends further support to the importance of making all women who have been treated for breast cancer aware of this wonderful recreational opportunity:

> *"When I am in a dragon boat, when I am dragon boating, I feel free, exhilarated, (pause) in control, powerful, all those good things." [28, page 133].*

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Research Article

Uncaria tomentosa—Adjuvant Treatment for Breast Cancer: Clinical Trial

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Breast cancer is the most frequent neoplasm affecting women worldwide. Some of the recommended treatments involve chemotherapy whose toxic effects include leukopenia and neutropenia. This study assessed the effectiveness of *Uncaria tomentosa* (Ut) in reducing the adverse effects of chemotherapy through a randomized clinical trial. Patients with Invasive Ductal Carcinoma—Stage II, who underwent a treatment regimen known as FAC (Fluorouracil, Doxorubicin, Cyclophosphamide), were divided into two groups: the UtCa received chemotherapy plus 300 mg dry Ut extract per day and the Ca group that only received chemotherapy and served as the control experiment. Blood samples were collected before each one of the six chemotherapy cycles and blood counts, immunological parameters, antioxidant enzymes, and oxidative stress were analyzed. *Uncaria tomentosa* reduced the neutropenia caused by chemotherapy and was also able to restore cellular DNA damage. We concluded that Ut is an effective adjuvant treatment for breast cancer.

1. Introduction

Breast cancer is the most frequent neoplasm affecting women worldwide, both in terms of incidence and mortality. The disease is more common in developed countries with its highest incidence being observed in the United Kingdom, Australia, USA, and Canada. From invasive tumors, ductal carcinoma and its variants represent 80% of cases [1] and the proportion of women with tumors in clinical stages I and II increased from 41 to 65% in the last decade [1, 2]. About 70% of breast cancers express Estrogen hormone receptors and/or Progesterone receptor [3]. These markers along with the HER-2 receptor (c-erbB2) provide information about the tumor and how it might respond to different treatments [4].

Chemotherapy is among the recommended treatments for breast cancer, which can be a single or combination therapy with multiple drugs. Chemotherapy drugs have very narrow therapeutic indexes in terms of nonselective toxic effects on normal tissues, with neutropenia being the most frequently observed adverse reaction, which increases the risk of infections [5].

Pharmacological interventions that reduce or prevent adverse effects may have a substantial impact on cancer treatment. According to World Health Organization (WHO), 80% of the population use medicinal plants as alternative or complementary procedures for the treatment of their diseases [6].

Studies have reported the use of herbal medicines in cancer patients to minimize the effects of chemotherapy. *Uncaria tomentosa* (Utor Cat's Claw) is a medicinal herb that has been used in the treatment of different diseases including cancer.

Patients who use Cat's Claw along with traditional cancer therapies, such as chemotherapy and radiation, reported fewer adverse effects to those therapies [7]. Uthelps in the restoration of cellular DNA, preventing mutations and cell damages caused by chemotherapy drugs [8]. It modulates the activity in the immune system, such as the proliferation of normal T and B lymphocytes [9], also modulating certain cytokines, including IL-1 and IL-6, TNF-α [10]. In addition, it has antioxidant properties [11]. Its direct myelostimulating effects, through myelopoiesis stimulation and Colony-Stimulating Factors (G-CSF) [8, 12], seem to be a beneficial option to minimize the risks associated with neutropenia.

Numerous reports present a theoretical understanding of Ut action mechanisms, but none of these studies consisted of clinical trials. Thus the objectives of this study are situated in this context, which consisted of a clinical trial using *Uncaria tomentosa* Herbarium tablets, as adjuvant treatment for breast cancer.

2. Methods

2.1. Design and Patients. A randomized interventional study was performed. It was carried out with 40 patients who had undergone complete breast cancer resection, which was histologically diagnosed as Invasive Ductal Carcinoma—Stage II [2], and who were going to begin adjuvant chemotherapy with Doxorubicin-based scheme for six cycles, at the Santa Maria University Hospital, Brazil.

Patients were randomly divided into two groups: the CaUt group, which was treated with six cycles chemotherapy + Ut and the cancer group (Ca), which only received six cycles of chemotherapy, according to the date treatment was started, as follows: the first patient who agreed to participate in the study was included into the CaUt group, the second, into the Ca group, and, thus, successively, until the end.

For the control group were invited to participate healthy women, classified by clinical trial, with similar age of the patients and that did not receive any medication in the last 30 days or have chronic disease.

Patients were part of the study during 6 chemotherapy cycles, of 21 days each. Medication dosage in the CaUt group was as follows: FAC (Fluorouracil, Doxorubicin, and Cyclophosphamide) and 3 tablets of Ut (Unha de Gato Herbarium), daily, from day 2 to day 21. The dose of Ut was similar to that used in previous studies, with 250–350 mg C-MED-100, in aqueous Ut extracts [13].

The calculation to estimate the sample size required for randomized clinical trial was performed according to Greenberg et al. [14], with constant significance level (α) of 5%, and statistical power of 90% (β 10%), using as reference the studies of Sheng et al. [15].

The Human Ethics Committee of the Santa Maria University Hospital, Brazil, approved the present study and informed consent was obtained from all participants (protocol number: 0169.0.0242.000-07.). All subjects were invited to participate and were informed in detail about the design of this study through a Statement of Consent signed by the researcher and participants. They were informed that they could be selected randomly for the Ca or UtCa group.

2.2. Materials. Each tablet of *Unha de Gato* Herbarium contained 100 mg of dry *Uncaria tomentosa* extract. Biological materials used in the tablets were derived from plants in their natural habitat. The *Uncaria tomentosa* extract was prepared by Ultra-turrax Extraction (Biotron, Kinematica AG) from ground bark (Centroflora) using 70% ethanol (Dipalcool). The HPLC analysis of the Ut dry extract presents 2.57% pentacyclic oxindole alkaloids (POAs) content, which was calculated with reference to external calibration curves of mitraphylline. The extract analysis showed absence of tetracyclic oxindole alkaloids in the sample, allowing its use for therapeutic and research purposes in accordance with the U.S. Pharmacopeia.

2.3. Sample Collection. Blood was collected into citrate, EDTA, heparin Vacutainer tubes, without any anticoagulants, before chemotherapy and after each of the 6 cycles.

2.4. Biochemical Parameters. A COBAS INTEGRA system was used for the quantitative determination of the blood chemical constituents, and data were acquired through a COBAS INTEGRA 400 Plus apparatus (USA).

2.5. Hemograms. Blood samples were analyzed using a Pentra apparatus (France). The lowest values were confirmed by observation of slides, using a May Grünwald-Giemsa Stain and optical microscopy.

2.6. CD3+, CD4+, and CD8+ Cells. Samples were collected in EDTA and analyses were performed using a three-color fluorescence-activated cell sorter (FACSCalibur, Becton Dickinson Biosciences, United States) and a Multiset software (Becton Dickinson). FITC-conjugated anti-CD4, PE-conjugated anti-CD8, and PerCP-conjugated anti-CD3 were used. Immune subpopulations were measured as a percentage of the total CD3+ cell number.

2.7. Interleukin 6 (IL-6). ELISA assays of IL-6 were carried out according to a previously published method [16], at room temperature in Microtiter 96-Well Plates (Nunc-Immuno Plate MaxiSorp) and optical densities (O.D.) at 490 nm, which were determined using a Microplate Reader (Thermo Scientific Multiskan FC, Vantaa, Finland).

2.8. Single Cell Gel Electrophoresis (Comet Assay). The alkaline comet assay was performed as described by Singh et al. [17] in accordance with the general guidelines for use of the comet assay [18, 19]. Lymphocytes were suspended in 0.7% low-melting-point agarose and phosphate-buffered saline (PBS) at 37°C and placed on microscopic slides with a layer of 1% agarose. The slides were immersed in lysis solution at 4°C for 1 h and followed by electrophoresis at 25 V, 300 mA, for 40 min at steady temperature. The slides were then silver-stained, as described by Nadin et al. [20]. All steps, from sample collection to electrophoresis, were conducted under yellow light to minimize the possibility of cellular DNA damage. One hundred cells (50 cells from each of the two replicate slides) were selected and analyzed. Cells were

Table 1: Clinical characteristic of patients. It represents age, body mass index (BMI), total cholesterol levels, estrogen receptor (ER), and progesterone receptors (PR), as well as the HER-2 status in different groups.

Clinical parameters	Control ($n = 20$)	Ca ($n = 20$)	UtCa ($n = 20$)
Age interval	32–79	32–71	40–75
Mean age	56.5 ± 11.6	55.0 ± 9.7	54.4 ± 11.0
BMI	25.0 ± 1.93	27.27 ± 1.49	26.82 ± 5.03
Cholesterol levels	202.5 ± 1.90	238.9 ± 57.9	244.2 ± 44.5
Estrogen receptor status (ER)			
Positive	—	+14	+17
Negative	—	−6	−3
Progesterone receptor status (PR)			
Positive	—	+10	+11
Negative	—	−10	−9
HER-2 receptor status (HER2)*			
Positive	—	+2	+6
Negative	—	−16	−12

The results for ER, HER2, and REP are represented as positive and negative numbers for the expression of receptors by number of women, while other parameters are expressed as mean ± standard deviation. UtCa group: patients treated with chemotherapy +300 mg *Uncaria tomentosa* daily ($n = 20$); Ca group: patients received chemotherapy ($n = 20$); control group ($n = 20$).
*To HER-2 receiver only data were obtained from 18 patients.

visually scored according to tail length and received scores from 0 (no migration) to 4 (maximal migration). Therefore, the damage index for cells ranged from 0 (all cells with no migration representing a damage index of 0%) to 400 (all cells with maximal migration, representing a damage index of 100%). The slides were analyzed under blind conditions by at least two different individuals [21].

2.9. Carbonylation of Serum Protein. The carbonylation of serum proteins was determined by a modified Levine's method [22]. The absorbance of the supernatant at 370 nm was measured using a spectrophotometer. Carbonyl content was calculated using $22 \times 10^3\,\mathrm{mM^{-1}\,cm^{-1}}$ as the molar extinction coefficient, and the results were expressed as nanomoles of carbonyl groups per milligram protein.

2.10. Determination of Lipid Peroxidation. Lipid peroxidation was estimated by measuring TBARS levels in plasma samples according to a modified method of Jentzsch et al. [23]. The concentration of malondialdehyde (MDA) was determined by measuring the absorbance at 532 nm using a spectrophotometer. The results were expressed as nanomoles of MDA per milliliter of plasma.

2.11. Catalase (CAT) and Superoxide Dismutase (SOD) Activities. CAT activity was determined in accordance with a modified method of Nelson and Kiesow [24]. The change in absorbance at 240 nm was measured for 2 min. CAT activity was calculated using the molar extinction coefficient ($0.046\,\mathrm{mM^{-1}\,cm^{-1}}$), and the results were expressed as picomoles of CAT per milligram of protein.

SOD activity was determined based on the inhibition of the radical superoxide reaction with adrenaline as described by McCord and Fridovich [25]. SOD activity is determined by measuring the rate of adrenochrome formation, observed at 480 nm, in a medium containing glycine-NaOH (50 mM, pH 10) and adrenaline (1 mM).

2.12. Statistics. Results are expressed as mean ± standard deviation. The statistical analysis was performed with GraphPad Prism 5.0 (GraphPad Prism 5.0 Software Inc., USA) using the Student's t-test. $P < 0.05$ was considered to represent a significant difference in all tests.

3. Results

All patients (40) included in the trial had Breast Cancer, Invasive Ductal Carcinoma—Stages II A or II B, according to the American Joint Committee on Cancer (AJCC) and the American Cancer Society (ACS) staging systems [2].

The general characteristics of patients and controls who participated in the study are described in Table 1.

To evaluate the effectiveness of Ut as adjuvant treatment for breast cancer, haematological parameters were used and analyzed (Table 2). At day zero, the results of the haematological parameters analyzed in the blood count did not significantly differ among the Control, the Ca, and the UtCa groups. A greater reduction in the white blood cell (WBCs) and the neutrophil counts were observed in the Ca group along the treatment, differently from the UtCa group, which remained closely the reference values, obtained in the control group (Figure 1). Considering the lymphocytes number, a significant difference between the control group and the groups of patients with breast cancer, either treated or not with Ut in the chemotherapy cycles, was observed. ($P < 0.05$). Monocytes number in patients with breast cancer (treated and not treated with Ut) at 5-6 chemotherapy cycles were higher than control group, but in the UtCa group, this increase was more strong (Table 2).

Table 2: Leukocytes, neutrophils, lymphocytes, and monocytes levels in breast cancer patients before treatment and after 6 cycles of chemotherapy without *Uncaria tomentosa* supply (Ca group) or receiving 300 mg/day of *Uncaria tomentosa* (UtCa group).

Parameters	Cycles			
(cells/mm^3)	0	1-2	3-4	5-6
Leukocytes				
Control	6800 ± 1458			
UtCa	6800 ± 1458	7890 ± 1615	6636 ± 2578	5469 ± 1626
Ca	6653 ± 1158	6617 ± 1504	4092 ± 1047*#	3247 ± 1117*#
Neutrophils				
Control	3510 ± 1077			
UtCa	3496 ± 1108	4335 ± 1626	3937 ± 1992	4016 ± 1545
Ca	3588 ± 1081	2663 ± 1351*	2028 ± 512*#	1083 ± 368*#
Lymphocytes				
Control	2264 ± 490,6			
UtCa	2276 ± 503,3	2376 ± 708,1	1627 ± 578,7*	1411 ± 596,6*
Ca	2177 ± 453,3	2284 ± 867,9	1460 ± 512,5*	1208 ± 395,1*
Monocytes				
Control	487,6 ± 128,9			
UtCa	515,3 ± 169	560 ± 322	814,9 ± 309#	817 ± 444,6
Ca	541,6 ± 161	526,6 ± 154	654,1 ± 310*#	500,9 ± 226*#

Data expressed asmean ± standard deviation.
*Represent difference significant between the Ca and UtCa groups, $P < 0.05$.
#Represent difference significant of the control group, $P < 0.05$ (Student's t-test).

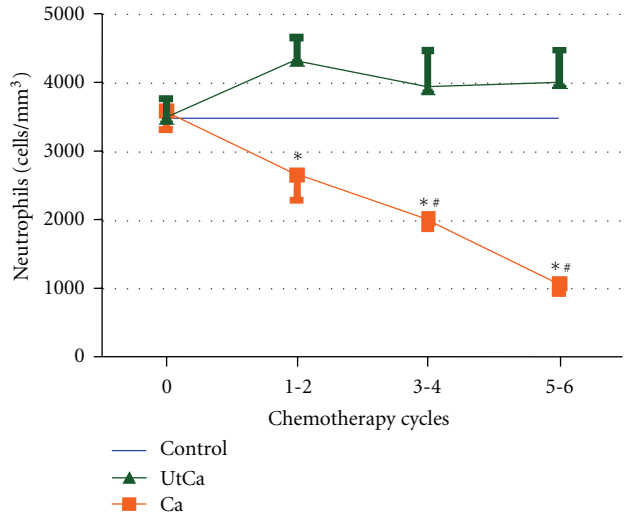

Figure 1: Values neutrophil granulocytes in patients with breast cancer undergoing chemotherapy with (UtCa) and without (Ca) supplementation with *Uncaria tomentosa* and reference values (control). Data are expressed as mean ± standard deviation.

To evaluate the immune response of patients with breast cancer, CD4$^+$ T cells, CD8$^+$ T cells (absolute count and ratio) and IL-6 levels were analyzed. During the chemotherapy treatment cycles, no significant difference was observed between groups. There was no difference between groups for any of the parameters analyzed (Table 3).

No correlation between the IL-6, CD4$^+$ T/CD8$^+$ T ratio and age, body mass index, and hormone receptor status was found (data not shown).

Antioxidant defenses were analyzed by the activity of Superoxide Dismutase (SOD) and Catalase (CAT) compared to treatment cycles zero and six, as well as between the UtCa and the Ca groups. There were no statistically significant differences among groups. An increase in SOD enzyme when compared to treatment cycles zero and six for the group supplemented with Ut was observed, but that difference was not observed between the groups (UtCa = 11.53 U/mg protein, Ca = 11.43 U/mg protein) or at the end of treatment (17.32 U/mg protein, 11.74 U/mg protein). Lipid Peroxidation was also estimated by the TBARS scale and the carbonylation of serum proteins, but there was no difference between groups (UtCa and Ca).

The protective effect of chemotherapy to extract Ut was evaluated by the Comet Assay. In the start of the treatment (zero cycle), the Ca group and UtCa group showed no significant difference in the Comet assay index. However, in the sixth cycle (end of the treatment), it was observed a significant decrease in the index test in the UtCa group, when compared to the Ca group ($P < 0.05$) Figure 2.

4. Discussion

Uncaria tomentosa enables the stimulation of the immune system, increasing resistance to diseases when the body is immunosuppressed due to stress, malnutrition, or due to the effect of some medication.

Table 3: Immune status of breast cancer patients before treatment and after 6 cycles of chemotherapy without *Uncaria tomentosa* supply (Ca group) or receiving 300 mg/day of *Uncaria tomentosa* (UtCa group).

Parameters	Group	Chemotherapy cycles	
		0	6
$CD4^+$ T cells	UtCa	1008.25 (379.21)	786.60 (310.49)
Cells/μL	Ca	1053.00 (620.81)	798.00 (366.14)
$CD8^+$ T cells	Ut Ca	568.81 (295.60)	459.87 (246.46)
Cells/μL	Ca	679.84 (273.22)	565.62 (231.05)
$CD4^+$ T/$CD8^+$ T ratio	UtCa	2.044 (0.62)	1.858 (0.89)
	Ca	1.630 (0.69)	1.652 (0.49)
IL6	UtCa	3.4 (4.50)	2.1 (6.6)
pg/mL	Ca	5.6 (5.53)	3.8 (7.312)

Data expressed as mean ± standard deviation; UtCa group: patients treated with chemotherapy +300 mg *Uncaria tomentosa* daily ($n = 20$); Ca group: patients received chemotherapy ($n = 20$).

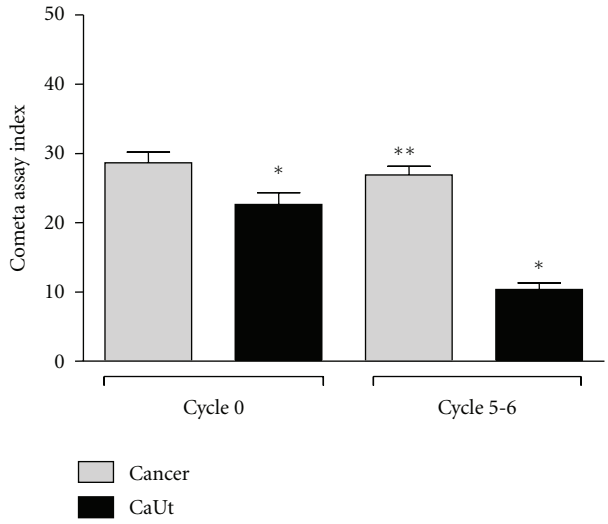

Figure 2: Index test of blood cells in patients with breast cancer treated and not treated with Ut. *Represents significant difference between all groups ($P < 0.05$). **Represents significant difference between the UtCa group (cycle 0) and the UtCa group (cycle 5-6) $P < 0.05$ (Student's t-test).

Many herbal medicines are used for various purposes, in various combinations (along with allopathic and homeopathic, medicines, etc.) based on historical or personal evidences generally not being associated with any adverse effects [26]. Therefore, this study, through a randomized clinical trial, evaluated the efficacy of Ut as a complementary therapy to chemotherapy.

The cytotoxic effect of chemotherapeutic agents is not selective for neoplastic cells, being also harmful to other body cells. Hematopoietic suppression is the major complication limiting dosage of such cytostatic agents; neutropenia and thrombocytopenia are the most frequent ones [1]. Treatment should be discontinued when neutrophil count is below 500 cells/mm^3 [27]. Thus, the success of the treatment process depends on the neutrophils content. Prevention of chemotherapy-induced neutropenia should be considered a clinical priority [28]. Once it is known that neutropenia predisposes to serious infections, often resulting in delays in treatment cycles and dose reductions.

Treatment using a daily dose of 300 mg dry Ut extract was effective in reducing the main chemotherapy effect, which is neutropenia. The effects of chemotherapy on blood cells tend to become more pronounced during treatment. However, our results show that in cycle six, which corresponds to the end of chemotherapy, the differences in the leukocytes and neutrophils counts were even more significant, as the group that was supplemented with Ut presented values twice as high of neutrophils when compared to the cancer group (without supplementation). In the group without supplementation, 67.89% of patients had neutropenia. Similarly, there was an increase in activated monocytes, as the activated precursors were common to both strains.

Our findings are corroborated by other studies that had already shown that the Ut extract has a stimulating effect on growth and differentiates the CFU-GM from mice bone marrow and spleen, using the model for listeriosis [29]. Increased leukocytes numbers were also detected using Ut aqueous extract for six consecutive weeks in volunteers [13]. The recovery of leukocytes was also observed in mice using a model for chemotherapy-induced leukopenia (Doxorubicin) using Granulocyte Colony-Stimulating Factor (Neupogen) as a positive control [15].

Our group confirmed these results using a model for ifosfamide-induced neutropenia in mice, which caused a severe neutropenia. Bioassays showed that treatment with Ut significantly increased neutrophils counts, and a power of 85.2% was calculated in relation to Filgrastim (rhG-CSF) at the corresponding doses tested (5 and 15 mg/day of Ut, and 3 and 9 mcg/day Filgrastim, resp.) [13]. Through *in vitro* assays in human hematopoietic stem precursor cells (hHSPCs) obtained from umbilical cord blood (UCB), we reach the conclusion that this effect happened due to proliferation of Forming Units-Granulocyte-Macrophage (CFU-GM) [13].

In this study, no differences were observed in lymphocyte counts between groups, either supplemented or not with Ut, over the chemotherapy cycles; however, its counts presented decrease due to chemotherapy when compared to the control

group. These differences were not observed in the CD4+ and CD8+ subpopulations.

This paper reports the effects of different *Uncaria tomentosa* extracts. The aqueous extract that has the highest concentration of quinic acid and low concentrations of oxindole alkaloids, being related to immunomodulatory properties is mediated by cytokines such as TNF-α [30]. Clinical studies using 20 mg/day of *Uncaria tomentosa* extract for 2 to 5 months in patients with HIV, receiving no other therapy, showed an increase in total peripheral lymphocytes without significant changes in the proportion of CD4+ and CD8+ [31]. Healthy volunteers receiving 350 mg of aqueous Ut extract for 8 weeks showed leukocytosis, with a tendency to higher proliferation of lymphocytes [15]. In an animal model, using aqueous extract, which has the highest concentration of quinic acid and low concentrations of oxindole alkaloids, an increase in lymphocytes was also observed [15, 32].

Furthermore, alcoholic extracts and/or pentacyclic oxindole alkaloids have higher myeloproliferative effects [33, 34]. Other studies have shown that the increase in the lymphocyte counts happens due to increased survival rates rather than proliferation [32].

Thus, changes observed in lymphocytes are associated with the chemically active components defined as quinic and bioactive acid esters *in vivo*, as quinic acid present in the aqueous extract used by authors. In our study, hydroalcoholic extract was used.

High levels of circulating IL-6 are associated with worse survival rates for patients with metastatic breast cancer, being correlated to the extent of the disease [30].

The patients who comprised our sample did not present a negative progression during the treatment cycles, that is, there was no occurrence of relapses or increased lesion extent, which could lead to an increase in IL-6.

Different *Uncaria tomentosa* extracts were tested *in vitro* in order to determine their antioxidant activity. Aqueous and alcoholic extracts prevent the production of reaction products with thiobarbituric acid (TBARS) and, therefore, damage the cytoplasmic membrane (lipids) and DNA by the nonformation of free radicals [35, 36] among the evaluated parameters of oxidative stress, such as SOD, CAT, TBARS, and carbonylated proteins.

Women with breast cancer present an increase in blood concentrations of oxidized substances, such as products derived from lipids peroxidation, proteins, and DNA [32, 33].

The only observed differences were in the SOD enzyme between groups, either with or without supplementation with Ut. These results were also found in an animal model, where an increase in the activity of this enzyme [10] was perceived. In a study on women with breast cancer, SOD activity showed a significant increase regardless of clinical stage and menopausal status [31]. There is evidence that the state of oxidative stress is higher than the greater degree of the disease stage is [37, 38].

Similar to results found in IL-6, the fact that all patients in the study had Stage II cancer may explain the results found.

The ability of doxorubicin to bind itself to the cell membrane lipid can affect a variety of cellular functions. The reaction of the doxorubicin enzymatic reduction by a variety of oxidase, reductase, and dehydrogenases genes generates ROS and, thus, may result in damage to DNA and proteins, triggering apoptosis [39, 40].

The performance of antioxidants *in vivo* depends on the types of free radicals formed, where and how these radicals are generated, and what are the doses for optimal protection. So it is entirely possible for an antioxidant to act as a protector in any given systems, but it is also possible for it to fail to protect, or even increase lesions induced in other systems or tissues. Thus, the use of antioxidants in cancer treatment is controversial.

Ambrosone and colleagues [41] observed that women having breast cancer with genotypes that result in higher levels of ROS had better survival rates than those with genotypes associated with lower generations of ROS. Such results indicate that an increased oxidative stress may increase the effects of chemotherapy and/or radiotherapy, resulting in improved treatment efficacy and, thus, better survival rates. The overexpression of SOD is associated with better survival rates for patients diagnosed with colorectal cancer [42].

Cleveland and Kastan suggest that a promising treatment for some types of cancer could happen by increasing ROS levels and inhibiting SOD levels [43, 44]. Other authors report that the overexpression of SOD has presented resistance to doxorubicin [43, 44], but not 5-fluorouracil in gastric cells [41]. Another study on breast cancer cells showed an increased resistance to Adriamycin with the intracellular level of glutathione (GSH) [45].

The protective effect of Ut on DNA was observed during the breast cancer cycles of treatment, by the Comet test analysis.

Doxorubicin has its own mechanism of action related to its binding to the DNA and the inhibition of nucleic acid synthesis. Studies have shown that aqueous Ut extracts present DNA repairing activities [15]. Mammone et al. (2006) showed the ability to modulate *Uncaria tomentosa* and repair of DNA in human skin and organ cultures [46].

In the present study, the results of comet test suggest that Ut had a protective effect of the DNA during the treatment cycles. However, it is necessary for other studies to confirm these effects.

5. Conclusions

Uncaria tomentosa, used at dose of 300 mg dry extract per day, is effective in the recovery from neutropenia induced by chemotherapy in women diagnosed with Invasive Ductal Carcinoma—Stage II. It is also able to restore cellular DNA. Thus, it is a safe and effective adjuvant treatment in reducing adverse chemotherapy effects.

Conflict of Interests

All authors deny any conflict of interests.

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Review Article

Honey and Cancer: Sustainable Inverse Relationship Particularly for Developing Nations—A Review

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Honey and cancer has a sustainable inverse relationship. Carcinogenesis is a multistep process and has multifactorial causes. Among these are low immune status, chronic infection, chronic inflammation, chronic non healing ulcers, obesity, and so forth. There is now a sizeable evidence that honey is a natural immune booster, natural anti-inflammatory agent, natural antimicrobial agent, natural cancer "vaccine," and natural promoter for healing chronic ulcers and wounds. Though honey has substances of which the most predominant is a mixture of sugars, which itself is thought to be carcinogenic, it is understandable that its beneficial effect as anticancer agent raises skeptics. The positive scientific evidence for anticancer properties of honey is growing. The mechanism on how honey has anticancer effect is an area of great interest. Among the mechanisms suggested are inhibition of cell proliferation, induction of apoptosis, and cell-cycle arrest. Honey and cancer has sustainable inverse relationship in the setting of developing nations where resources for cancer prevention and treatment are limited.

1. Cancer: The Global Epidemic

Cancer is a global epidemic. In 2008, it was estimated there were 12,332,300 cancer cases of which 5.4 million were in developed countries and 6.7 million were in developing countries [1] (Figure 1). Over half of the incident cases occurred in residents of four WHO regions. The world population increased from 6.1 billion in 2000 to 6.7 billion in 2008 [2]. The increase in populations was much more in developing countries than in developed countries. Even if the age-specific rates of cancer remain constant, developing countries would have a higher cancer burden than developed countries.

Cancer trends are showing upward trends in many developing countries [3–5] and a mixed pattern in developed countries [6–8]. By 2050, the cancer burden could reach 24 million cases per year worldwide, with 17 million cases occurring in developing countries [9]. Cancers which are associated with diet and life style are seen more in developed countries while cancers which are due to infections are more in developing countries. According to the World Health Organization (WHO), death from cancer is expected to increase to 104% worldwide by 2020.

While the number of total cancer is increasing, the trend of certain cancers is changing in developed and developing countries. In developed countries, the trend is declining [10] since infections by microorganisms are declining and screening facilities are available. In Singapore, there was an average annual increase of 3.6% for breast cancers in women in the 1988–1992 period [11]. In Qatar, there was a 57.1% rise of cancers 1991–2006 [12], and in Netherlands, there was an increase between 1.9% (females) and 3.4% (males) per year for oesophageal cancer 1989–2003 [13].

In order to understand the usefulness of honey in cancer, we need to understand the various factors which could cause cancer. Carcinogenesis is a multi-step process and has multi-factorial causes. Development of cancers takes place long after initiation, promotion, and progression steps (Figure 2) have taken place. The cellular damage could be by one factor or multiplicity of these factors. The latter is more frequent. Cancer development could occur 10–15 years after exposure to the risk factors.

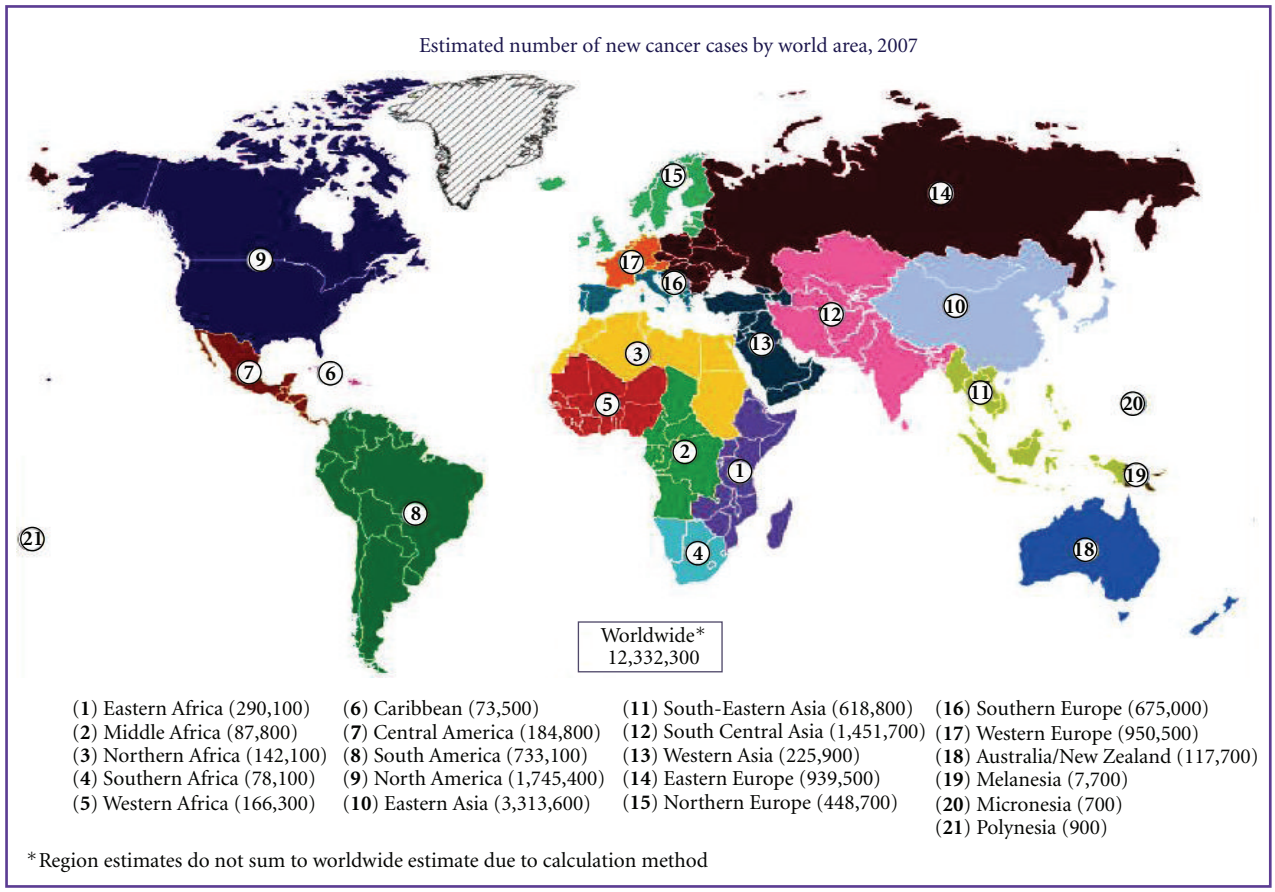

Figure 1: Estimated new cancer cases by world areas (source: Global Cancer Facts and Figures 2007).

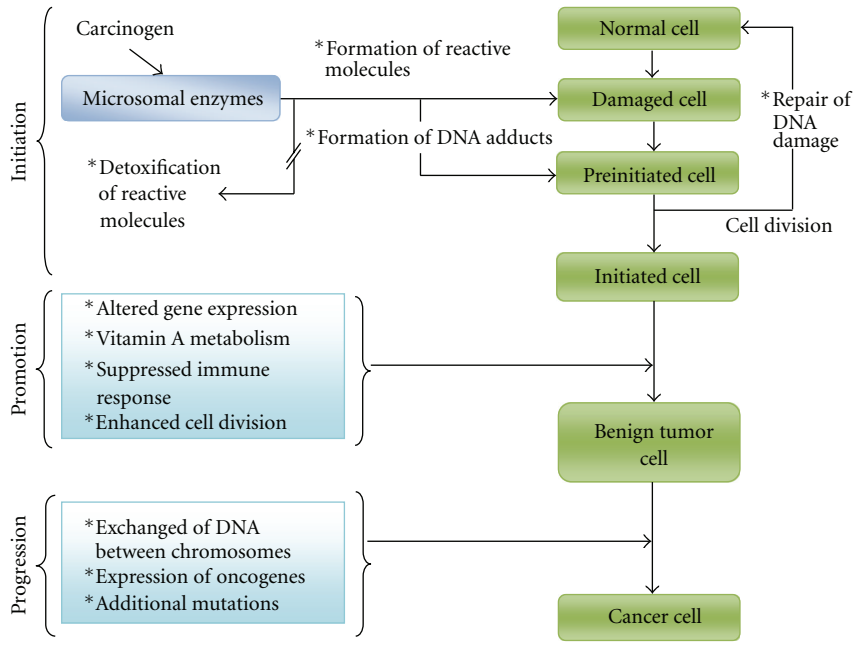

Figure 2: Steps in carcinogenesis. *Steps altered by alcohol consumption (Source: Garro et al. Alcohol Health & Research World 16(1):81–86, 1992).

1.1. Life-Style Habits/Diseases as Risks to Cancer Development. Cancer is caused by genetic damage in the genome of cells. This damage is either inherited or acquired throughout life. The acquired genetic damage is often "self-inflicted" through unhealthy lifestyles. Essentially one-third of cancer is due to tobacco use, one-third due to dietary and lifestyle factors, and one-fifth due to infections. Other factors include chemical carcinogens, environmental pollutants, and alcohol (Figure 3). In the developing countries, cancers caused by infections by microorganisms such as cervical (by human papilloma virus) [14], liver (by hepatitis viruses) [15], nasopharynx (by Epstein-Barr virus) [16], and stomach (by *Helicobacter pylori*) [17] are more common than those in developed countries [18]. While cancers of the prostate, breasts, and colorectal are clearly more prevalent in developed than developing countries, the distinction is not very apparent as that for cancer of the lung which is as prevalent as that in more or less developed nations. Except for breast cancers, the top 5 cancers in males and females of developing nations are due to life-styles or infections [18].

1.1.1. Smoking and Tobacco Use. Association of cancer to cigarette smoking is beyond doubt. The prevalence of smoking is higher in developing than that in developed countries [19]. Smoking is associated with a number of cancers such as larynx, bladder, breasts, oesophagus, and cervix. While in developed countries the prevalence of smoking is decreasing [20], the scenario is the reverse in developing countries. The initiation and the influence to start smoking are similar to those in developed countries [21]. Smoking increases the risk of colorectal carcinomas by 43% [22]. Ever-smokers were associated with an 8.8-fold increased risk of colorectal cancers (95% confidence interval, 1.7–44.9) when fed on well-done red meat diet if they have NAT2 and CYP1A2 rapid phenotypes [23]. No similar association was found in never-smokers [23].

1.1.2. Obesity and Physical Inactivity. Obese subjects have an approximately 1.5–3.5-fold increased risk of developing cancers compared with normal-weight subjects [24]. Obesity is associated in a number of cancers [25, 26] particularly endometrium [27, 28], breasts [29, 30], and colorectal cancers [31]. Adipocytes have the ability to enhance the proliferation of colon cancer cells in vitro [32]. The trend of prevalence of overweight/obesity is rising in many developed and developing countries [33]. In a study conducted in 2005 [34] in the Kota Bharu district in the state of Kelantan Malaysia, the overall prevalence of overweight/obesity was 49.1% [34], much higher than the figure reported earlier in 1996 [35]. In this community, the rise of cancer is exponential in the period from year 2002 to 2007 (143.6% increment) compared to the previous 5-year period of 1996–2001 [36].

Obesity is not a social problem but a disease. The greatest risk is for obese persons who are also diabetic, particular those whose body mass index is above 35 kg/m^2. The increase in risk is by 93-fold in women and by 42-fold in men [37].

1.1.3. Diabetes Particularly Type 2 as Risk for Cancer Development. Obesity is closely related with diabetes [38]. A community that has high prevalence of obesity also has high prevalence of diabetes [36]. In Kelantan, Malaysia, the prevalence of diabetes in 1999 was 10.5%, and impaired glucose tolerance was 16.5% [39]. Kelantan is ranked highest in prevalence of diabetes in Malaysia in which the overall national prevalence is 8.3% [40], thus it was not a surprise to see a rapid rise of cancer prevalence in the state [36]. According to a review on diabetes, the WHO has estimated that, by 2030, there would be 2.48 million diabetics in Malaysia, a jump of 164% from 0.94 million in 2002 [41]. One of the most common cancers noted in community that has high diabetics and obesity is colorectal cancer [42–45].

In a study of 138 colorectal cancers (CRC) seen in Hospital Universiti Sains Malaysia, 47.8% had metabolic diseases, of which 13.8% were diabetes type 2 [42]. Those diabetics with CRC often have distal cancers [42].

1.2. Chronic Infections as Risk for Cancer Development. There are a number of microorganisms which could cause cancer. Common viruses causing cancers [46] are Epstein-Barr virus (EBV) [47] (nasopharyngeal carcinomas), human papilloma virus (cervical cancers and other squamous cancers) and Hepatitis B viruses (liver cancers). Viruses are oncogenic after long period of latency [48].

Bacteria which has been studied to have associations with cancer are *Helicobacter pylori* infections (stomach cancer) [17], *Ureaplasma urealyticum* (prostate cancer) [49], and chronic typhoid carrier (gall bladder cancer) [50]. Chronic fungi infections have also been studied to be associated with cancer [51]. Parasites such as *Schistosoma haematobium* are associated with carcinoma of the urinary bladder; liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis* associated with cholangiocarcinoma and hepatocellular carcinoma. There are three main mechanisms by which infections can cause cancer. They appear to involve initiation as well as promotion of carcinogenesis [52]. Persistent infection within host induces chronic inflammation accompanied by formation of reactive oxygen and nitrogen species (ROS and RNOS) [52]. ROS and RNOS have the potential to damage DNA, proteins, and cell membranes. Chronic inflammation often results in repeated cycles of cell damage leading to abnormal cell proliferation [53]. DNA damage promotes the growth of malignant cells. Secondly, infectious agents may directly transform cells, by inserting active oncogenes into the host genome, inhibiting tumour suppressors or stimulating mitosis [52]. Thirdly, infectious agents, such as human immunodeficiency virus (HIV), may induce immunosuppression [52].

2. Low Immune Status as Risk of Cancer Development

2.1. Cancer and Aging. The most important change that would occur in the world population in the next 50 years is the change in the proportion of elderly people (more than 65 years): 7% in 2000 to 16% in 2050 [54]. Many cancers

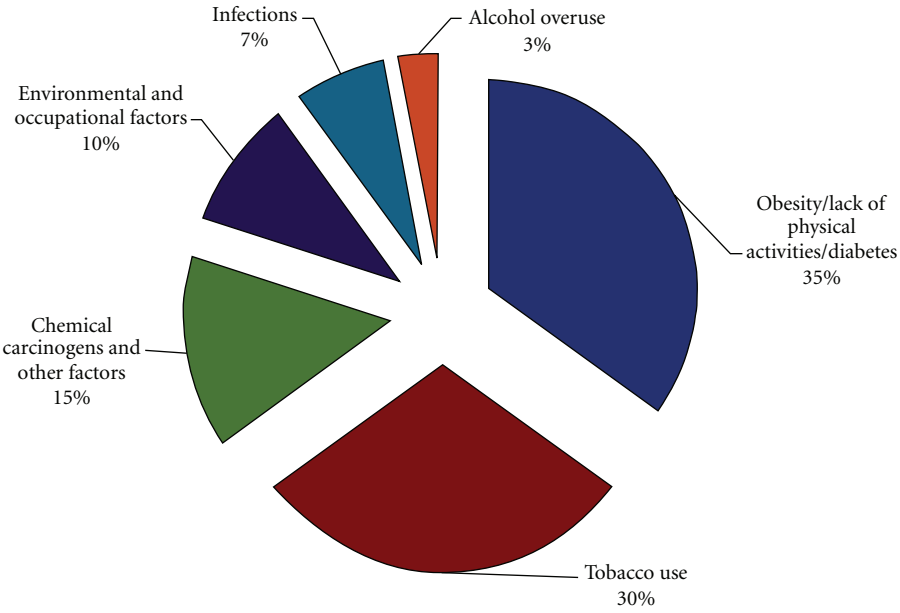

Figure 3: The acquired risk factors of cancer development.

are associated with aging. Although age per se is not an important determinant of cancer risk, it implies prolonged exposure to carcinogen [55]. By the year 2050, 27 million people are projected to have cancer. More than half of the estimated number will be residents of developing countries [54]. Aging is also associated with reduced immune system.

2.2. Low Immune Status due to Chronic Diseases. Patients who have low immune system are at risk for cancer development. This explains why diabetics are more at risk than non-diabetics to get epithelial cancers. HIV patients are at risk to develop epithelial and nonepithelial cancers. These persons are also at risk to develop multiple chronic infections implying the multiplicity in cancer genesis. Patients with autoimmune diseases are also at risk to develop cancers such as colorectal carcinomas in ulcerative colitis and Crohn's disease and thyroid cancer in autoimmune thyroiditis.

2.3. Chronic Ulcers and Wounds. Chronic ulcers have risk to develop cancer. The most common is Marjolin's ulcer [56], and they are common in developing nations especially in rural areas with poor living conditions [57]. This risk factor is related to chronic infections as most if not all chronic ulcers are not healing because of persistent infections.

3. What Is Honey and Why Is It Useful against Cancer? (See Figure 4)

Honey is known for centuries for its medicinal and health-promoting properties. It contains various kinds of phytochemicals with high phenolic and flavonoid content which contribute to its high antioxidant activity [58–60]. Agent that has strong antioxidant property may have the potential to prevent the development of cancer as free radicals and oxidative stress play a significant role in inducing the formation of cancers [61]. Phytochemicals available in honey could be narrowed down into phenolic acids and polyphenols. Variants of polyphenols in honey were reported to have antiproliferative property against several types of cancer [62].

4. Honey As a Natural Immune Booster

Honey stimulates inflammatory cytokine production from monocytes [63]. Manuka, pasture, and jelly bush honey were found to significantly increase TNF-α, IL-1β, and IL-6 release from MM6 cells (and human monocytes) when compared with untreated and artificial honey-treated cells ($P < 0.001$) [63]. A 5.8 kDa component of manuka honey was found to stimulate cytokine production from immune cells via TLR4 [64]. Honey stimulates antibody production during primary and secondary immune responses against thymus-dependent and thymus-independent antigens in mice injected with sheep red blood cells and *E. coli* antigen [65]. Consumption of 80 g daily of natural honey for 21 days showed that prostaglandin levels compared with normal subjects were elevated in patient with AIDS [66]. Natural honey has been shown to decrease prostaglandin level, elevated NO production in patients with a long history of AIDS [66]. It was reported that oral intake of honey augments antibody productions in primary and secondary immune responses against thymus-dependent and thymus-independent antigens [67].

These studies suggest that daily consumption of honey improves one's immune system.

5. Honey As Natural Anti-Inflammatory Agent

In routine everyday life, our cells may be injured by irritants from outside or within our bodies (by microbes or nonmicrobes). Cellular/molecular injuries result in inflammatory

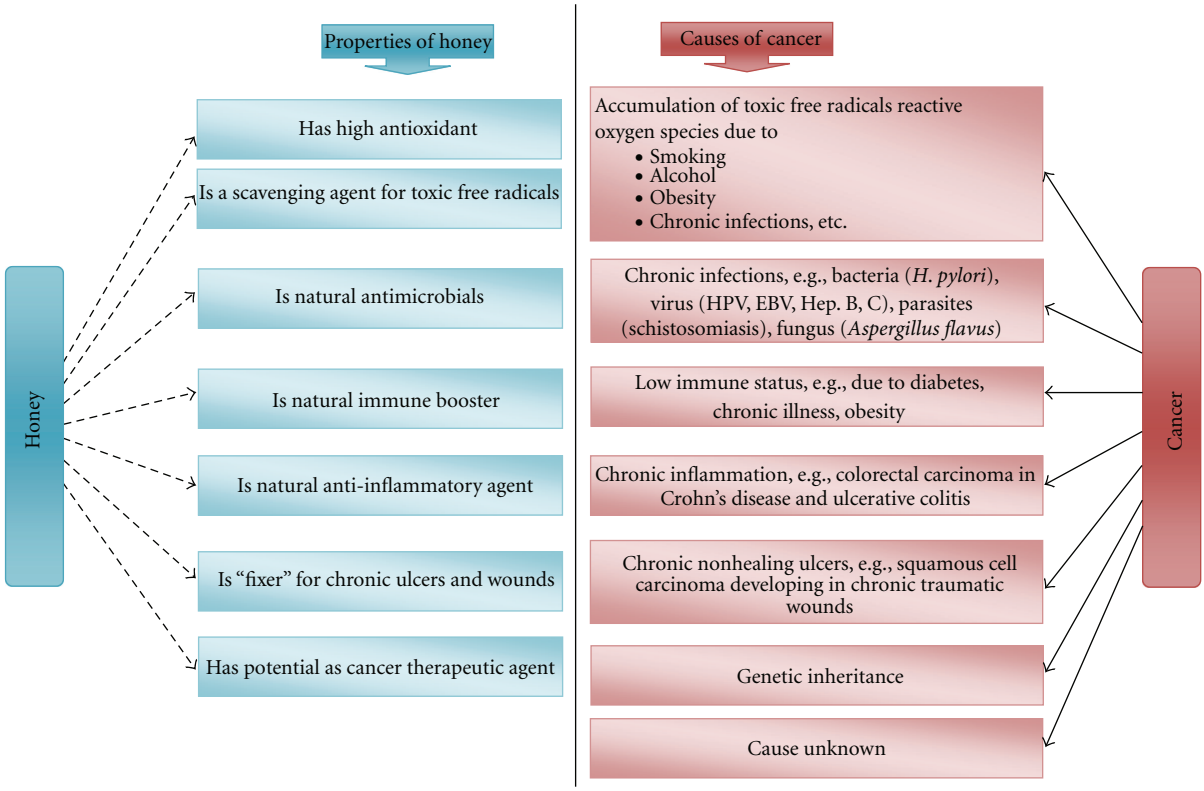

Figure 4: The inverse relationship of honey and cancer.

response, the body defense mechanisms in trying to rid of the irritants. In general inflammatory responses are beneficial and protective to us, but at times, inflammatory responses are detrimental to health. Honey is a potent anti-inflammatory agent. Infants suffering from diaper dermatitis improved significantly after topical application of a mixture containing honey, olive oil, and beeswax after 7 days [68]. Honey provides significant symptom relief of cough in children with an upper respiratory tract infection (URTI) [69]. It has been shown to be effective in management of dermatitis and *Psoriasis vulgaris* [70]. Eight out of 10 patients with dermatitis and five of eight patients with psoriasis showed significant improvement after 2 weeks on honey-based ointment [70]. Honey at dilutions of up to 1 : 8 reduced bacterial adherence from 25.6 ± 6.5 (control) to 6.7 ± 3.3 bacteria per epithelial cell ($P < 0.001$) in vitro [71]. Volunteers who chewed "honey leather" showed that there were statistically highly significant reductions in mean plaque scores (0.99 reduced to 0.65; $P = 0.001$) in the manuka honey group compared to the control group suggesting a potential therapeutic role for honey for gingivitis, periodontal disease [72], mouth ulcers, and other problems of oral health [73].

A case report of a patient who had chronic dystrophic epidermolysis bullosa (EB) for 20 years healed with honey impregnated dressing in 15 weeks [74] after conventional dressings and creams failed. This illustrates the usefulness of honey as an anti-inflammatory agent. Chronic inflammatory process has risk of cancer development.

6. Honey As Natural Antimicrobials

Everyday we are exposed to all kinds of microbial insults from bacteria, viruses, parasites, and fungi. Honey is a potent natural antimicrobial. The most common infections humans get are from staphylococcal infection. Antibacterial effect of honey is extensively studied. The bactericidal mechanism is through disturbance in cell division machinery [75]. The minimum inhibitory concentration (MIC) for *Staphylococcus aureus* by *A. mellifera* honey ranged from 126.23 to 185.70 mgml^{-1} [76]. Honey is also effective against coagulase-negative staphylococci [77]. Local application of raw honey on infected wounds reduced signs of acute inflammation [78], thus alleviating symptoms. Antimicrobial activity of honey is stronger in acidic media than in neutral or alkaline media [78]. The potency of honey is comparable to some local antibiotics. Honey application into infective conjunctivitis reduced redness, swelling, pus discharge, and time for eradication of bacterial infections [78]. When honey is used together with antibiotics, gentamycin, it enhances anti-*Staphylococcus aureus* activity, by 22% [79]. When honey is added to bacterial culture medium, the appearance of microbial growth on the culture plates is delayed [80]. Mycobacteria did not grow in culture media containing 10% and 20% honey while it grew in culture media containing 5%, 2.5%, and 1% honey, suggesting that honey could be an ideal antimycobacterial agent [81] at certain concentrations.

Honey is also effective in killing hardy bacteria such as *Pseudomonas aeruginosa* (PA) and could lead to a new approach in treating refractory chronic rhinosinusitis [82]. Daily consumption of honey reduces risk of chronic infections by microorganisms. Chronic infections have risk for cancer development.

There are three main mechanisms by which infections can cause cancer. They appear to involve initiation as well as promotion of carcinogenesis [52]. Persistent infection within host induces chronic inflammation accompanied by formation of reactive oxygen and nitrogen species (ROS and RNOS) [52]. ROS and RNOS have the potential to damage DNA, proteins, and cell membranes. Chronic inflammation often results in repeated cycles of cell damage leading to abnormal cell proliferation [53]. DNA damage promotes the growth of malignant cells. Secondly, infectious agents may directly transform cells, by inserting active oncogenes into the host genome, inhibiting tumour suppressors [52]. Thirdly, infectious agents, such as human immunodeficiency virus (HIV), may induce immunosuppression [52].

The effectiveness of honey is best when used at room temperature. Heating honey to 80 degrees for 1 hour decreased antimicrobial activity of both new and stored honey. Storage of honey for 5 years decreased its antimicrobial activity, while ultraviolet light exposure increased its activity against some of microorganisms [78].

Honey also has been shown to have antiviral properties. In a comparative study topical application of honey was found to be better than acyclovir treatment on patients with recurrent herpetic lesions [83]. Two cases of labial herpes and one case of genital herpes remitted completely with the use of honey while none with acyclovir treatment [83].

7. Honey As Possible Agent for Controlling Obesity

Obese individuals are at risk to develop cancer. There is a close link among obesity, a state of chronic low-level inflammation, and oxidative stress [84]. Obese subjects have an approximately 1.5–3.5-fold increased risk of developing cancers compared with normal-weight subjects [24–26] particularly endometrium [27, 28], breasts [29, 30], and colorectal cancers [31]. Adipocytes have the ability to enhance the proliferation of colon cancer cells in vitro [32]. The greatest risk is for obese persons who are also diabetic, particularly those whose body mass index is above 35 kg/m^2. The increase in risk is by 93-fold in women and by 42-fold in men [37]. One of the most common cancers noted in community that has high diabetics and obesity is colorectal cancer [42–45].

In a clinical study on 55 overweight or obese patients, the control group (17 subjects) received 70 g of sucrose daily for a maximum of 30 days and patients in the experimental group (38 subjects) received 70 g of natural honey for the same period. Results showed that honey caused a mild reduction in body weight (1.3%) and body fat (1.1%) [85]. Beneficial effect of honey on obesity is not well established thus far.

8. Honey as "Fixer" for Chronic Ulcers and Wounds

Increasing numbers of antibiotic-resistant bacteria has made simple wounds become chronic and non-healing and as such honey provides alternative treatment options [86]. Honey absorbs exudates released in wounds and devitalized tissue [87]. Honey is effective in recalcitrant surgical wounds [88]. It increases the rate of healing by stimulation of angiogenesis, granulation, and epithelialization, making skin grafting unnecessary and giving excellent cosmetic results [89]. In a randomized control trial, Manuka honey improved wound healing in patients with sloughy venous leg ulcers [90]. Honey was shown to eradicate MRSA (Methylene resistant *Staphylococcus aureus*) infection in 70% of chronic venous ulcers [91]. Honey is acidic and chronic non healing wounds have an elevated alkaline environment. Manuka honey dressings is associated with a statistically significant decrease in wound pH [92]. Available evidence in meta-analysis studies indicates markedly greater efficacy of honey compared with alternative dressings for superficial or partial thickness burns [93]. Honey is an inexpensive moist dressing with antibacterial and tissue-healing properties suitable for diabetic foot [94]. The average cost of treatment per patient using honey dressing is much cheaper with conventional dressing [95].

9. Honey As Natural Cancer "Vaccine"

Synthetic vaccines like BCG or polio vaccine work by preventing vaccinated subjects from contracting tuberculosis and poliomyelitis. Honey has the element of a "natural cancer vaccine" as it can reduce chronic inflammatory processes, improve immune status, reduce infections by hardy organisms and so forth. Some simple and polyphenols found in honey, namely, caffeic acid (CA), caffeic acid phenyl esters (CAPE), chrysin (CR), galangin (GA), quercetin (QU), kaempferol (KP), acacetin (AC), pinocembrin (PC), pinobanksin (PB), and apigenin (AP), have evolved as promising pharmacological agents in prevention and treatment of cancer [62]. The antioxidant activity of *Trigona carbonaria* honey from Australia is high at 233.96± 50.95 microM Trolox equivalents [96]. The antioxidant activity of four honey samples from different floral sources showed high antioxidant properties tested by different essay methods [97]. Dark honey had higher phenolic compounds and antioxidant activity than clear honey [98]. The amino acid composition of honey is an indicator of the toxic radical scavenging capacity [99].

10. Honey as Potential Use in "Cancer Therapy"

Honey may provide the basis for the development of novel therapeutics for patients with cancer and cancer-related tumors. Jungle honey fragments were shown to have chemotactic induction for neutrophils and reactive oxygen species (ROS), proving its antitumor activity [67]. Recent studies on human breast [100], cervical [100], oral [101], and

osteosarcoma [101] cancer cell lines using Malaysian jungle honey showed significant anticancer activity. Honey has been shown to have antineoplastic activity in an experimental bladder model in vivo and in vitro [102].

Honey is rich in flavonoids [62, 103]. Flavanoids have created a lot of interests among researchers because of its anticancer properties. The mechanisms suggested are rather diverse such as various signaling pathways [104], including stimulation of TNF-alpha (tumor necrosis factor-alpha) release [105], inhibition of cell proliferation, induction of apoptosis [106], and cell cycle arrest [107] as well as inhibition of lipoprotein oxidation [108]. Honey is thought to mediate these beneficial effects due to its major components such as chrysin [104] and other flavonoids [109]. These differences are explainable as honeys are of various floral sources, and each floral source may exhibit different active compounds. Though honey has other substances of which the most predominant are a mixture of sugars (fructose, glucose, maltose, and sucrose) [110] which itself is carcinogenic [111], it is understandable that its beneficial effect on cancer raises skeptics. The mechanism on how honey has anti-cancer effect is an area of great interest recently. The effects of honeys on hormone-dependent cancers such as breast, endometrial, and prostate cancer and tumors remain largely unknown. There is a lot we can learn from nature [112]. For example, phytochemicals, such as genistein, lycopene, curcumin, epigallocatechin-gallate, and resveratrol have been studied to be used for treatment of prostate cancer [113]. Phytoestrogens constitute a group of plant-derived isoflavones and flavonoids, and honey belongs to plant phytoestrogen [112, 114].

11. Conclusion

There is now a sizeable evidence that honey is a natural immune booster, natural anti-inflammatory agent, natural antimicrobial agent, natural cancer "vaccine," and natural promoter for healing chronic ulcers and wounds; some of the risk factors for cancer development. Bee farming is a lucrative business. Honey and cancer have sustainable inverse relationship in the setting of developing nations where resources for cancer prevention and treatment are limited.

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Review Article

Traditional Chinese Medicine in Cancer Care: A Review of Case Series Published in the Chinese Literature

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Traditional Chinese medicine (TCM) has been widely used in cancer in China. Case series report a series of cases exposed to a certain intervention. To understand the current situation of case series of TCM for cancer, we performed this review. We included case series of cancer patients treated with TCM therapy. Electronic searches were conducted in four main Chinese databases until February 2011. A total of 1,217 reports of case series (92,945 patients) were included. The top five types of cancer were lung cancer, liver cancer, stomach cancer, leukemia, and esophageal cancer. Leukopenia and hiccup treated by TCM were the most common adverse reactions after surgery or induced by chemo/radiotherapy. More than half of the patients were treated with TCM therapies alone. The application of herbal medicines especially formula based on syndrome differentiation was highly prevalent, and the typical administration route was oral usage. 1,182 reports were published in a structured format. The quantity of TCM case series for cancer treatment is substantial. Further studies should focus on the most common types of cancer and the most frequently applied TCM therapies. We presented a recommendation from the methodological point of view for the format of reporting.

1. Introduction

Cancer is a leading cause of death worldwide. According to the World Health Organization, it has accounted for 7.6 million deaths (around 13% of all deaths) in 2008, and deaths from cancer worldwide are projected to continue to rise to over 11 million in 2030 [1].

Conventional treatment for cancer, such as surgery and chemo/radio therapy, aims at curing the disease or prolonging life while improving the patient's quality of life (QOL) [1]. However, it is acknowledged that most cancer patients suffer from both the disease itself and symptoms induced by conventional treatment.

Traditional Chinese medicine (TCM) is a holistic system of medicine including herbal medicine, acupuncture and moxibustion, *tuina*, dietary therapy, and *qigong*. TCM has unique theories of the diagnosis and treatment, which is mostly the syndrome differentiation and prescription of herbal formula. A systematic review of case reports showed rich information of case reports about TCM therapies for cancer and suggested potential benefit [2].

Case series, a classical type of observational study, retrospective or prospective, report and examine the medical results of a series of cases exposed to a certain intervention (prevention or treatment) [3]. According to Oxford grading of evidence, case series are graded level 4, which is generally considered as low strength-level evidence [4]. However, all or none of the case series ("met when all patients died before the Rx (intervention) became available, but some now survive on it, or when some patients died before the Rx became available, but none now die on it") are graded up to 1c of all 5 levels [5].

There have been a considerable number of case series concerning TCM for cancer published in Chinese journals,

yet no systematic summary has been done. Without analyzing these publications, we will not detect any possible valuable information from the considerable amount of evidence. Therefore, this review aims to systematically identify, collect, and summarize case series on TCM in the treatment of cancer published in Chinese journals to provide an overview of current evidence of TCM for cancer treatment. Through this review, we hope to find potentials for further studies and to make recommendations for further TCM case series report from the methodology point of view.

2. Material and Methods

2.1. Source of Literature and Search Strategy. Two authors (G. Yang and X. Li) searched the major Chinese electronic databases, including China National Knowledge Infrastructure (CNKI) (1911–February 2011), Chinese Scientific Journal Database (VIP) (1989–February 2011), Chinese BioMedical Literature Database (CBM) (1978–February 2011), and Wanfang Database (Wanfang) (1994–February 2011).

The searching terms used included "*zhong_yi*" (Chinese medicine), "*zhong_yao*" (Chinese herbs), "*zhong_yi_yao*" (traditional Chinese medicine), "*zhong_cheng_yao*" (Chinese patent medicine), "*zhong_cao_yao*" (Chinese herbal medicine), "*zhen_ci*" (acupuncture), "*zhen_jiu*" (acupuncture and moxibustion), "*zhong_xi_yi_jie_he*" (integrated traditional Chinese and western medicine), "*an_mo*" (massage), "*tui_na*" (*Tuina*), "qi_gong" (*Qigong*), "*gua_sha*" (skin scraping therapy), "*ba_guan*" (cupping), "*xue_wei*" (acupuncture point), "*min_zu_yao*" (ethnomedicine), "*min_jian*" (folk), "*ai*" (cancer), "*liu*" (tumor), "*e_xing*" (malignant), "*e_xing_zhong_liu*" (malignant tumor), "*bai_xue_bing*" (leukemia), "*gu_sui*" (bone marrow) and "*lin_ba*" (lymph). No language restriction was applied.

2.2. Inclusion Criteria

(1) Types of study: case series published in Chinese journals.

(2) Types of participants: patients with cancer, including malignant tumor and malignant hematologic disease, or patients in precancerous condition.

(3) Types of interventions: Chinese medicine (herbal medicine, patent medicine, acupuncture, moxibustion, *tuina,* dietary therapy, *qigong* and other folk therapies used in China). Chinese medicine integrated with conventional medicine was also included if detailed data of TCM in cancer care were available.

(4) Types of outcome measures: survival, relapse or metastasis, complication, symptoms, quality of life, adverse reactions induced by surgery or chemo/radio therapy, or safety.

2.3. Literature Selection. Three authors (G. Yang, X. Li, and L. Wang) screened titles for the eligibility and relevance independently, and full-text versions of the relevant papers were retrieved and reviewed for selection of case series according to the inclusion and exclusion criteria. If there was any uncertainty during the study selection, a fourth author (J. Liu) was consulted.

2.4. Data Extraction and Analysis. A structured data extraction form was designed. It consisted of the following sections.

(1) Basic Bibliometric Information. It included full citation and year of publication.

(2) Type(s) of Cancer and Related Condition. In reports on cancer, cancer names were extracted and classified into ten categories: musculoskeletal (including bone marrow), dermatological, neurological, endocrine (including breast), hematologic and lymphatic, respiratory, digestive (including liver, gallbladder and pancreas), urinary and reproductive systems, head and neck cancer, and others. In reports on precancerous conditions, symptoms induced by conventional therapies, and other cancer-related conditions, the names were also extracted.

(3) Diagnostic Criteria. It was examined whether the three items reported: diagnostic criteria, gold diagnostic standard (pathological diagnosis), and syndrome differentiation (*bianzheng*) based on TCM theory.

(4) Type(s) of Intervention. TCM therapy was at first place classified into TCM alone and TCM therapy integrated with conventional therapy. Then, TCM therapy was further classified into herbal medicine, acupoint stimulation, dietary therapy, *tuina*, and *qigong*. Herbal medicine was further classified into formula based on syndrome differentiation (common types of formula in textbook [6]), self-prescribed formula (prescribed by practitioners), Chinese patent medicine, preparation used in specific hospital, injection extracted from herbs, and single-herb preparation. Acupoint stimulation was further classified into manual acupuncture, moxibustion, ear-acupuncture, cupping, electroacupuncture, and acupuncture point injection (injection with western medicine was defined as integrated therapy). We examined whether there was a detailed description of treatment regimens, administration, dosage, and course of the TCM therapy.

(5) Outcome Measures. Data of outcome were extracted including survival, relapse and/or metastasis, symptom (including cancer pain and tumor size), quality of life, adverse reaction after surgery or induced by chemo/radio therapy, and safety. For quality of life, we examined whether a standardized measurement was reported. We also examined whether the result was reported as composite outcome with defined grades, which combined more than one outcome criterion in each grade. We also examined whether the author(s) recommended for clinical application.

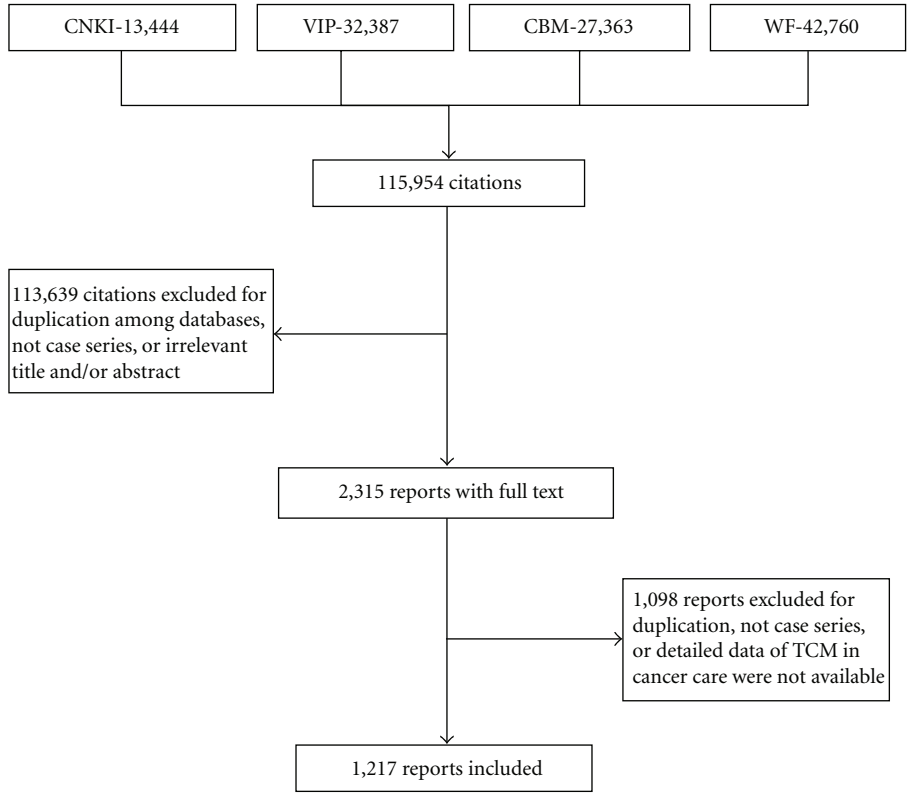

Figure 1: Flowchart of literature search and study selection.

(6) Structure of Reporting. We examined whether the study reported in a structured manner, concerning objective, material and methods (participants, treatment regimens, and outcome measures), results, discussion, and/or conclusion in different sections.

Data were extracted by ten authors and then verified by one author (G. Yang). Any discrepancies were discussed and consensus was reached with involvement of the other authors. Data were presented as counts, percentage, or frequency (calculated by number of publications and by patients respectively due to a wide range of patients number involved in case series).

3. Results

3.1. Bibliometric Information. A total of 115,954 citations were identified and screened by two authors (G. Yang and X. Li) based on the searching of the four electronic databases, and 113,639 citations were excluded due to duplication, irrelevant title, and/or abstract. Full texts of the remaining 2,315 citations were retrieved and evaluated according to the inclusion and exclusion criteria, and 1,098 citations were excluded. In total, 1,217 reports of case series involving 92,945 cancer patients were included in this review (Figure 1).

Among the retrieved reports from 1958 to 2011, only 2 [7, 8] were published before 1969. However, the number of publications concerning cancer patients per year appeared to increase from 1972 with the peak of 110 reports in 2008 (no publications were found in 1959 and in 1961–1971) (Figure 2). The number of patients involved in the 1,217 reports varied from 5 to 18,963 patients per study [9, 10]. 1086 (89.24%) reports involved less than 100 patients.

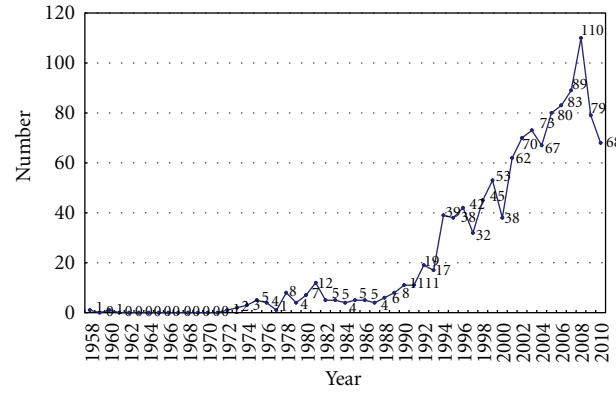

Figure 2: Publications number of case series on TCM for cancer in Chinese journals.

3.2. Types of Cancer and Cancer-Related Conditions. Out of the 1,217 reports of case series, 652 reported the treatment of cancer, 16 reported the treatment of precancerosis (8 for chronic atrophic gastritis and 6 for myelodysplastic syndrome, mainly for the prevention of stomach cancer and

Table 1: Cancer and cancer-related conditions in case series published in Chinese journals.

Name of condition	No. of publications (a)	Frequency (a/1,217)	No. of patients (b)	Frequency (b/92,945)
Cancer	652	53.57%	61,035	65.67%
Subtotal	652	53.57%	61,035	65.67%
Precancerosis	16	1.31%	848	0.91%
Subtotal	16	1.31%	848	0.91%
Pain	92	7.56%	7,275	7.83%
Leukopenia	35	2.88%	1,864	2.01%
Effusion in thoracic or abdominal cavity	38	3.12%	1,363	1.47%
Hiccup	36	2.96%	1,231	1.32%
Inflammation	21	1.73%	1,038	1.12%
Nausea and vomiting	13	1.07%	902	0.97%
Intestinal obstruction	10	0.82%	463	0.50%
Edema	11	0.90%	400	0.43%
Fever	9	0.74%	274	0.29%
Diarrhea	8	0.66%	212	0.23%
Depression	2	0.16%	100	0.11%
Subtotal	275	22.60%	15,122	16.27%
Other adverse reactions or complications	274	22.51%	15,940	17.15%
Subtotal	274	22.51%	15,940	17.15%
Total	1,217	100%	92,945	100%

leukemia), and 549 reported the treatment of adverse reactions after surgery or induced by chemo/radio therapy and complications, of which cancer pain, leucopenia, effusion in thoracic cavity or abdominal cavity, and hiccup were most frequently reported (Table 1).

Among all the 652 reports covering ten categories of cancer, a total of 27 different types of cancer were included. The top three categories were digestive cancer, respiratory cancer and hematologic/lymphatic cancer (Table 2).

Lung cancer, liver cancer, and stomach cancer were the top three cancer types according to frequency both calculated by number of publication, and patients. Leukemia was the 5th and 4th most frequent cancer calculated by number of publications and by patients, respectively (Figure 3).

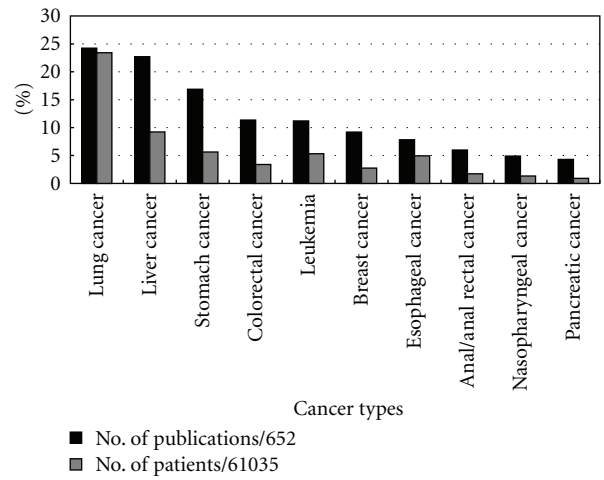

Figure 3: Top ten types of cancer treated by TCM in case series published in Chinese journals.

3.3. Diagnostic Criteria. In the 652 case series reports on cancer treated by TCM, 542 (83.13%) described the diagnostic criteria, 478 (73.31%) described the gold standard (pathological diagnosis), 407 (62.42%) described the cancer stage, and 364 (55.83%) described TCM syndrome differentiation.

In the remaining 565 reports on precancerous diseases, symptoms induced by chemo/radio therapies or other cancer-related conditions, 396 (70.09%) described the diagnostic criteria, 245 (43.36%) described the gold standard (pathological criteria), 135 (23.89%) described the cancer stages, and 247 (43.72%) described TCM syndrome differentiation.

3.4. Types of Intervention. Among the 1,217 reports, 678 (55.71%) with 61,529 (66.20%) cancer patients reported the application of TCM therapy alone and 539 (44.29%) with 31,690 (34.10%) cancer patients reported the integration of TCM and conventional medicine.

A total of 4912 (5.28%) patients have received more than one type of TCM therapy in 73 (6.00%) reports. Out of the 1,217 reports, herbal medicine and acupoint stimulation were most frequently applied. The top three applications of herbal medicine were formula based on syndrome differentiation, self-prescribed formula, and Chinese patent medicine. Types of acupoint stimulation mainly involved manual acupuncture, acupuncture point injection, and electroacupuncture (Table 3).

Table 2: Type of cancer treated by TCM in case series published in Chinese journals.

Type of cancer	No. of publications (a)	Frequency (a/652)	No. of patients (b)	Frequency (b/61,035)
Digestive system				
Liver	148	22.70%	5,627	9.21%
Stomach	110	16.87%	3,431	5.62%
Intestine	74	11.35%	2,076	3.40%
Anus/anal rectum	39	5.98%	1,059	1.73%
Esophagus	51	7.82%	3,019	4.94%
Pancreas	28	4.29%	550	0.90%
Gallbladder	4	0.61%	21	0.03%
Subtotal	454	69.62%	15,783	25.84%
Respiratory system				
Lung	158	24.23%	14,298	23.40%
Subtotal	158	24.23%	14,298	23.40%
Hematologic/lymphoid system				
Leukemia	73	11.20%	3,250	5.32%
Malignant lymphoma	16	2.45%	480	0.79%
Subtotal	89	13.65%	3,730	6.11%
Urinary and reproductive systems				
Cervix	24	3.68%	1,457	2.38%
Ovary	17	2.61%	295	0.48%
Bladder	9	1.38%	222	0.36%
Prostate	15	2.30%	217	0.36%
Kidney	5	0.77%	25	0.04%
Penis	1	0.15%	4	0.01%
Subtotal	71	10.89%	2,220	3.63%
Endocrine system				
Breast	60	9.20%	1,677	2.75%
Thyroid	12	1.84%	153	0.25%
Head and neck cancer				
Brain	10	1.53%	92	0.15%
Parotid gland	1	0.15%	2	0.00%
Oral cavity	11	1.69%	83	0.14%
Nasopharynx	32	4.91%	807	1.32%
Larynx	5	0.77%	17	0.03%
Subtotal	59	9.05%	1,001	1.64%
Skeletal and muscular systems	11	1.69%	178	0.29%
Skin cancer	11	1.69%	164	0.27%
Multiple myeloma	7	1.07%	137	0.22%
Malignant mole	4	0.61%	8	0.01%
Total*	652		61,035	

* Some reports involved more than one type of cancer.

Among the 652 reports for the treatment of cancer, herbal medicine was mostly reported in 640 (98.16%) reports involving 59,918 (98.17%) patients, while *tuina* was not used.

For the administration of herbal medicine in the 1,217 reports, oral medication applied in 912 (74.94%) reports with 77,080 (82.93%) patients, external application in 163 (13.39%) with 8,802 (9.47%), and injection in 158 (12.98%) with 7,559 (8.13%) were most frequently reported types. Oral medication was most frequently applied for formula based on syndrome differentiation. The administration of injection was applied for either injection extracted from herbs (including angelica injection, astragalus injection, and Shenmai injection) or injection of western medicine (including dexamethasone, lidocaine, vitamin B1, vitamin B6, vitamin B12, vitamin K1, vitamin K3, and anticholinergic agent).

Out of the 1,217 reports, 1,193 (98.03%) described the detailed TCM treatment regimens, 1,017 (83.57%) described dosage, and 784 (64.42%) described treatment course.

Table 3: TCM therapies for cancer in case series published in Chinese journals.

TCM therapy	No. of publications (a)	Frequency (a/1217*)	No. of patients (b)	Frequency (b/92945)
Herbal medicine	1102	90.55%	86,741	93.33%
Formula based on syndrome differentiation	703	57.76%	59,454	63.97%
Self-prescribed formula	127	10.44%	26,632	28.65%
Chinese patent medicine	140	11.50%	12,804	13.78%
Preparation used in specific hospital	107	8.79%	7,058	7.59%
Injection extracted from herbs	114	9.37%	5,753	6.19%
Single-herb preparation	30	2.47%	1,234	1.33%
Classical formula or concerted formula	22	1.81%	833	0.90%
Acupoint stimulation	160	13.15%	8,371	9.01%
Manual acupuncture	79	6.49%	3,801	4.09%
Acupuncture point injection	57	4.68%	2,900	3.12%
Electroacupuncture	11	0.90%	1,029	1.11%
Moxibustion	19	1.56%	799	0.86%
Ear acupuncture	12	0.99%	721	0.78%
Cupping	2	0.16%	92	0.10%
Dietary therapy	12	0.99%	667	0.72%
Qigong therapy	7	0.58%	2,117	2.28%
Massage (*Tuina*)	6	0.49%	214	0.23%

* Combination of TCM therapies was described in some reports.

Altogether there were 732 (60.15%) reports described that completed the description of the treatment.

The conventional therapies were mainly chemotherapy, surgery, and radiotherapy. Transcatheter arterial chemotherapy applied in 24 (4.45%) reports was to treat liver cancer and lung cancer mainly.

3.5. Outcome Measures Reported. Symptom relief was the most frequently reported outcome measure in 1,120, (92.03%) reports with 84,380 (90.78%) patients, followed by survival in 410 (33.69%) reports with 48,213 (51.87%) patients, quality of life in 228 (18.73%) reports with 13,143 (14.14%) patients, reducing adverse reactions induced by chemo/radiotherapy in 168 (13.80%) reports with 7,539 (8.11%) patients, relapse in 73 (6.00%) reports with 3,726 (4.01%) patients, metastasis in 53 (4.35%) reports with 2,478 (2.67%) patients, reducing adverse reactions after surgery in 17 (1.40%) reports with 1,079 (1.16%) patients, and safety in 169 (13.89%) reports with 27,230 (29.30%) patients.

Among the 652 reports for treatment of cancer, symptom relief was the most commonly reported outcome in 576 (88.34%) reports with 54,563 (89.40%) patients. Survival was reported in 360 (53.68%) reports with 44,772 (73.35%) patients, in the way of reporting the exact length of survival or rate of survival. In the rest, symptom relief was also the most commonly reported in 544 (96.28%) reports with 29,837 (92.70%) patients. Survival was reported in 51 (9.03%) reports with 3,481 (10.81%) patients.

Totally 228 (18.73%) reports reported quality of life, 153 (67.11%) mentioned the Karnofsky performance status scale, a standardized measurement for quality of life, and 6 (2.63%) mentioned other status scales (ECOG-WHO performance status EORTC QLQ-C30 and self-designed scales) [11]. The rest were considered as unclear reports with typical descriptions: "the patient is in high quality of life now" or "the patient is in a stable condition now" [12].

Out of the 1,217 reports, 414 (34.02%) reported composite outcomes, which described outcomes as predefined grades such as cured, improved, and ineffective, within each grade involved the evaluation of more than one original outcome [13]. All of the 1,217 reports were retrospective studies, in which data were collected basically from medical records and without clear description of follow-up.

3.6. Adequacy of Reporting. Out of the 1,217 reports, 1,182 (97.12%) reported structurally, but not in a structured manner including objective, methods and material (involving participants, treatment regimens, and outcome measures), results, discussion, and/or conclusion. Most of the reports lacked subheadings such as objectives, conclusion, and discussion. 12 (0.99%) reports lacked subheading of result, 95 (7.81%) reports lacked subheading of conclusion, and 37 (3.04%) lacked subheading of discussion.

There were 29 (2.38%) reports that lacked data of patients' baseline information concerning age, sex, and cancer or cancer-related conditions, 7 (0.58%) reports lacked data of treatment regimens concerning dosage, administration, and course. A total of 169 (13.89%) reports provided recommendation for clinical application in conclusion or discussion section, while the rest objectively reported the advantages and disadvantages or did not provide.

4. Discussion

4.1. Description of Current Situation of TCM for Cancer Care. This review has comprehensively identified and summarized

cancer case series for the first time, and 1,217 reports were found in the area of TCM for cancer from the year 1958 to 2011. This brings us an overview and also can provide information for further research and clinical application.

The number of publications per year increased from 1970s with the peak in 2008, which is consistent with findings in a review of case reports in cancer care [2]. During the literature search and study selection, after evaluating full texts most reports were excluded as non-case-series, especially for reporting "control" or "randomized." This might indicate that researchers have paid more attention to higher-level evidence from 2008. Another possibility is publication lag in different Chinese databases for the year 2009 and 2010, thus an update searching should be conducted in the future to check whether there are more publications identified in the more recent time.

Cancer types treated by TCM therapies in case series covered 10 categories. Either calculated by number of publications or patients, the most frequently reported cancer types were generally consistent with the most common types of cancer (lung, stomach, liver, breast, and esophageal cancer) causing death in Asia and in China [14]. Leukemia, the most frequently reported cancer type in a review of case reports in cancer care [2], was the 4th or 5th most frequently reported cancer type treated by TCM in this review. Leukopenia induced by chemo/radiotherapy was a common type of conditions treated by TCM. These findings might indicate that TCM therapies might have potential advantages for treating hematologic disease.

4.2. Recommendations for Structured Reporting. From a methodological point of view, we found the reporting of current TCM case series is in need of improvement. Though almost all the 1,217 reports structurally reported, they were lack of some important sections or contents, or they reported two or more sections in one section. Most case series reported in Chinese journals were reported in structure of information of participants, treatment regimens, results, and discussion, while case series reported in foreign countries were based on clinical trial reporting format [15]. Based on the findings, we recommend that when reporting a TCM case series, the following is necessary.

(1) Objectives. All the 1,217 reports were retrospective without a section for objectives, which could show the researchers' clinical questions to be studied. We recommend that all the case series, both prospective and retrospective, should present clear objectives, scientific background, and explanation of rationale in the beginning of the reports.

(2) Diagnostic Criteria. A majority of case series reported clinical diagnostic criteria, but just more than half reported gold diagnostic standard and syndrome differentiation based on TCM theory, which should be reported to show the eligibility criteria of patients.

(3) Treatment Regimens. Most of the case series did not report the completed information of treatment. Detailed description of ingredients of herbal medicine, regimens, dosage, and course should be reported for clinical application.

(4) Outcome Measures. Symptom relief was the most frequently reported outcome in this review. We recommend that the researchers in the future pay more attention to terminal outcomes (survival, relapse, or metastasis). For quality of life (QOL), just more than half of the reports mentioned the Karnofsky performance status scale. We recommend that in future studies the international standardized measurement should be applied.

(5) Results. Most of the results reported as composite outcome, which could provide very limited information for clinical application and research. We recommend reporting result according to specific outcome measures.

(6) Conclusion and Discussion. Only a small part of the case series reported the authors' recommendation for clinical application. We recommend that the researchers in the future pay more attention to generate suggestions for clinical application and further research.

A recommendation for the full format of the reporting case series is that it should involve abstract, introduction, objectives, material and methods (including participants, treatment regimens, and outcome measures), results, discussion, and/or conclusion.

4.3. Potential for Further Studies. Since the reports involved in this review were all retrospective case series, we could just provide an overview of TCM for cancer treatment without any recommendation of specific treatment for clinical application. Therefore, we encourage that higher-level prospective studies (controlled clinical trials or randomized controlled trials) with scientific hypothesis could be established to assess the efficacy and safety of TCM for cancer.

Based on TCM therapies used in case series for cancer, we suggest that further studies can focus on the most frequently applied TCM therapies, Chinese herbal medicine, especially formula based on syndrome differentiation.

Our findings also revealed the most common types of cancer treated by TCM in case series, which indicated the potential benefit of TCM therapies for those types of cancer. Therefore, we recommend that further studies should focus on the most common types of cancer, namely, lung cancer, liver cancer, stomach cancer, leukemia, and esophageal cancer on TCM therapy or integrative therapy.

Conflict of Interests

The authors declare no conflict of interests.

Acknowledgments

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Research Article

Development and Validation of an Instrument for Measuring Attitudes and Beliefs about Complementary and Alternative Medicine (CAM) Use among Cancer Patients

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Despite cancer patients' extensive use of complementary and alternative medicine (CAM), validated instruments to measure attitudes, and beliefs predictive of CAM use are lacking. We aimed at developing and validating an instrument, attitudes and beliefs about CAM (ABCAM). The 15-item instrument was developed using the theory of planned behavior (TPB) as a framework. The literature review, qualitative interviews, expert content review, and cognitive interviews were used to develop the instrument, which was then administered to 317 outpatient oncology patients. The ABCAM was best represented as a 3-factor structure: expected benefits, perceived barriers, and subjective norms related to CAM use by cancer patients. These domains had Eigenvalues of 4.79, 2.37, and 1.43, and together explained over 57.2% of the variance. The 4-item expected benefits, 7-item perceived barriers, and 4-item subjective norms domain scores, each had an acceptable internal consistency (Cronbach's alpha) of 0.91, 0.76, and 0.75, respectively. As expected, CAM users had higher expected benefits, lower perceived barriers, and more positive subjective norms (all $P < 0.001$) than those who did not use CAM. Our study provides the initial evidence that the ABCAM instrument produced reliable and valid scores that measured attitudes and beliefs related to CAM use among cancer patients.

1. Introduction

The use of complementary and alternative medicine (CAM) is extensive among cancer patients [1–3]. Many cancer patients turn to CAM therapies in addition to their conventional treatments to deal with ongoing health issues and increased symptom burden such as recurring pain and psychological distress [4–6]. Population-based studies have demonstrated that cancer patients are more likely to use CAM than the general population [7, 8]; thus, it is important to understand the attitudes and beliefs related to CAM use among cancer patients in order to create a more personalized integrative health system to tailor therapies to individual beliefs and decision factors [9].

Why individuals use CAM is complex, personal, and driven by multiple factors. Sociodemographic factors such as female sex, younger age, higher education and income, and white race have been associated with CAM use in epidemiology studies [1, 10–17]. Research has also found that individuals use CAM to improve their physical and emotional health, enhance quality of life, strengthen the immune system, minimize the side effects of conventional medical treatments, and exert positive effects on cancer [11, 12, 18–22]. Other psychological or culture factors relate to CAM use may include being open to new experiences, preferring natural/holistic approaches to treatment, and the desire to exert a sense of personal control over their illness [13, 20, 23, 24].

Several qualitative studies have provided unique insight into the decision making process utilized by individuals regarding CAM use. Verhoef and White interviewed 31 individuals who used CAM instead of conventional cancer treatments and found several themes related to this decision making process: the family's/friend's experiences with conventional cancer treatment, their own experience with cancer care and physician communication, and patients' beliefs and need for control [25]. Balneaves et al. interviewed breast cancer patients about CAM use and developed the "bridging the gap" model in categorizing individuals into three distinct decision making style: taking one step at a time, playing it safe, and bringing it all together [26]. These kinds of distinctive pathways have also been explored by Caspi et al. among patients with chronic rheumatological disorders [27].

Despite this emerging data, few studies have used a theory-driven, well-developed instrument to guide the inquiry into why individuals use CAM, especially in cancer patients. In a recent systematic review of the research using theoretical models to understand why individuals use CAM, Lorenc et al. found that only 22 studies used a theoretical model to predict CAM use, the majority of which were among noncancer populations [28]. The most commonly used model was the health care utilization model, Andersen's sociobehavioral model [28, 29]. Existing research based on this model predominantly evaluates social demographic factors and symptoms without incorporating a comprehensive assessment of facilitators, barriers, and behavioral predictors of CAM use [30–33]. Only one study focused on understanding the psychological and behavioral factors influencing the use of CAM in cancer patients; however, the study was conducted in Japan, limiting the generalizability of the study findings to other nations [34].

To further understand why cancer patients use CAM, we can view CAM use as a set of health behaviors. Doing so, we can draw upon the years of rigorous research in health behaviors to understand the beliefs and attitudes underlying CAM use. In particular, research has shown that applying a theoretical model will both increase the ability to predict health behaviors as well as lead to development of interventions to change behaviors [35]. A critical step in beginning to incorporate health behavior methodology in CAM research is the development and validation of an instrument that can measure the attitudes and beliefs predictive of CAM use among cancer patients.

We chose the theory of planned behavior (TPB) [36] as a conceptual framework to guide the development of the instrument. TBP posits that intentions to use CAM are an important precursor of health behaviors and are influenced by factors such as attitudes, subjective norms, and perceived behavioral control. The TBP has been applied in hundreds of health behavior and health service research studies and has been found to be predictive of health behaviors as well as to inform effective behavioral change interventions [37, 38]. We also chose the TPB because it is conceptually simple and may help point out the major constructs that influence CAM use; as such, it can serve as a starting point for further research and inform intervention development to affect appropriate integration of CAM into cancer care.

Thus, this study aims to develop and validate attitudes and beliefs about complementary and alternative medicine (ABCAM), an instrument capable of reliably measuring the behavioral predictors of CAM use among cancer patients. We hypothesize the factor structure of the instrument to be consistent with that of the TPB domains and that the score of the instrument will be reliable and valid.

2. Methods

2.1. Instrument Development. We developed the items for this instrument through a systematic and critical review of the existing literature on decision making about CAM use in cancer and in the general population to identify relevant conceptual models, instruments, and concepts. Additional items were informed basing on qualitative interviews and modified-grounded theory analysis conducted among 25 breast cancer survivors between 2008 and 2010 [39]. The qualitative interviews were conducted using TPB as a theoretical framework. Informed by our qualitative research and literature search, initial instrument items were drafted to evaluate the specific behavioral predictions of CAM use.

The initial items were reviewed by members ($N = 27$) of the Penn Integrative Oncology Working Group for face validity (March 2010). These members consisted of physicians, nurses/nurse practitioners, psychosocial support staff (e.g., psychologists, social workers, and nutritionists), CAM practitioners (e.g., massage therapists, Reiki practitioners, acupuncturists, and yoga instructors), and patient representatives. The conceptual model and items of the questionnaire were revised based on feedback from the content experts and stakeholders. Next, cognitive interviews were conducted among patients with different types of cancer. Participants were encouraged to share their thoughts about the items with the researcher as they responded to them to provide feedback about the draft instrument, which included content, clarity, and burden. Items were then revised again in discussion with key collaborators (JM, KD, and KA). The initial scale consisted of 25 items (see appendix). Items assessed agreement with statements concerning perceived benefits, barriers, and subjective norms surrounding CAM use on a 5-point Likert scale ("strongly disagree" to "strongly agree").

2.2. Instrument Validation. We administered ABCAM among a convenience sample at three oncology practices of the Abramson Cancer Center of the University of Pennsylvania Health System (Philadelphia, PA, USA) between May and August 2010. Eligible participants were patients aged 18 or older who had a primary diagnosis of cancer and a Karnofsky performance status of 60 or greater (i.e., ambulatory). Additional inclusion criteria included the approval of the patient's oncologist and the patient's ability to understand and provide informed consent in English. Trained research assistants screened medical records and approached potential study subjects in the waiting area of the oncology clinics. After discussing any concerns, and signing the informed consent, each participant was

given a self-report survey. The study was approved by the Institutional Review Board of the University of Pennsylvania.

To assess criterion validity, we used the CAM Beliefs Inventory (CAMBI), an instrument developed among British health consumers. The CAMBI is a 15-item scale measuring three aspects of CAM-related treatment beliefs: belief in natural treatment, belief in participation in treatment, and belief in holistic health [40]. A higher score on the CAMBI indicates more positive beliefs about CAM treatments. The subscales had evidence of satisfactory reliability and correlated with CAM use [40]. While the CAMBI was not validated in cancer populations, the constructs have some degree of face validity to cancer patients. We hypothesized that those who hold more holistic views about their health would be likely to have greater expected benefit from CAM therapies; thus offering some evidence of criterion validity.

To measure CAM use, we modified questions from the National Health Interview Survey (NHIS) by asking individuals: "have you used other sources of support or treatment since your cancer diagnosis?" Response options included common CAM items such as natural products (herbs), megavitamins, relaxation techniques (deep breathing and meditation), massage, chiropractic care, acupuncture, yoga, qi gong, and tai chi [7] as well as therapies commonly used in cancer patient populations such as expressive art therapies and energy therapy [9]. Patients answered each option with a dichotomous response (yes; no). We previously used a similar measure in several survey studies and generated the prevalence of CAM use data reflecting that of the national data [41, 42]. Although commonly reported by patients, prayer was not included because findings suggest that factors associated with its use are substantially different from use of nonprayer CAM [7]. Use of any type of CAM was then dichotomized (yes; no).

2.3. Analyses. We first performed descriptive analyses to examine missing data and item distribution. We performed a series of principal component factor (PCF) analyses and item reductions to identify the core factor structure of the instrument. The PCF analysis was used because the primary purpose was to identify and compute composite scores for the factors underlying ABCAM. The number of factors was determined by examination of Eigenvalues ≥ 1.00 and Scree plot [43, 44]. We removed items that cross-loaded greater than 0.3 and retained items that had a loading of 0.5 or greater on the primary factor in an iterative process [45, 46]. Final Varimax-rotated loadings for individual items ranged from 0.5 to 0.9. Oblique rotation was chosen to simplify interpretation of factors, but summation scores rather than factor scores were ultimately examined to avoid overfitting. Cronbach's alpha statistics were calculated to determine the internal consistency of the scale. Coefficients of 0.70 or greater are considered to be acceptable for an instrument developed to evaluate differences in group means [47]. To evaluate construct validity, we used the Student's t-test to compare the scores in each domain between CAM users and nonusers. We hypothesize that greater perceived benefit, lesser perceived barriers, and perceived positive subjective norms are associated with CAM use behaviors. To investigate criterion validity, we correlated ABCAM subscales with the CAMBI [40]. It was expected that perceived benefits and social norms would be positively correlated to domains of CAMBI and that perceived barriers would be negatively correlated to the domains in CAMBI. Data analysis was performed using SPSS 19.0 for Windows (IBM SPSS Statistics 19.0). All statistical tests were two-sided with $P < 0.05$ indicating significance. We chose a sample size of at least 300 to allow adequate power to estimate reliability of the instrument [48].

3. Results

Among the 317 participants (83% response rate), the mean age was 58.4 with a standard deviation (SD) of 12.1; 244 (77.2%) were Caucasian; 56 (17.7%) were African American; 7 (2.2%) were Asian; 6 (1.9%) were Hispanic; 3 (0.9%) identified themselves as other. While 88 (27.9%) reported an education status of high school or less, 79 (25.1%) had some graduate or professional education. Overall, 103 (32.5%) of the participants were diagnosed with lung cancer, 88 (27.8%) with breast cancer, 79 (24.9%) with gastrointestinal cancer, and 47 (14.8%) with another type of cancer.

3.1. Factor Analysis. Of the 25 items included in the initial instrument, one item, "reduce stress," had missing data greater than 5% and was excluded from analysis. The remaining 24 items had missing data ranging from 1.5% to 4.4% with no apparent ceiling or flooring effects. Through iterative factor analysis, we removed items that cross-loaded to multiple domains as well as items that had low correlation coefficients to the intended domains. For example, "boost my immune system," "my family encourages me to use CAM," and "my friend asks me to try CAM" cross-loaded to both expected benefits and social norms. Our final scale consisted of 15 items with a 3-factor structure: expected benefits, perceived barriers, and subjective norms (see Table 1). These three domains had Eigenvalues of 4.79, 2.37, and 1.43, and, together, explained over 57.2% of the variance in items. The component scores were then calculated by summing the individual items and normalizing to a value between 0 and 100 for each of the domains (see Table 2 and Figure 1 for distribution of domain scores).

3.2. Reliability. The 4-item expected benefits, 7-item perceived barriers, and 4-item subjective norms domain scales each had an acceptable internal consistency (Cronbach's alpha coefficient) of 0.91, 0.76, and 0.75, respectively, (Table 2).

3.3. Construct Validity. Among the participants, 192 (60.6%) of participants had used at least one type of CAM therapy since cancer diagnosis. The most common approaches were vitamin supplements (120, 34.0%), relaxation techniques (77, 24.4%), herbs (75, 23.8%), special diet (64, 20.5%), and massage therapy (55, 17.4%). As hypothesized, CAM users had higher expected benefits (65.2 versus 52.1, $t = -5.79$, $P < 0.001$), lower perceived barriers (43.9 versus 50.7,

Table 1: Factor loadings and communalities based on a principal components analysis*.

	Components		
	Expected benefits	Perceived barriers	Social norms
I expect using CAM will decrease my emotional distress	**.88**	−.15	.20
I expect using CAM will reduce symptoms such as pain or fatigue related to cancer and its treatment	**.86**	−.14	.25
I expect using CAM will prevent future development of health problems	**.75**	−.09	.28
I expect using CAM will help me cope with the experience of having cancer	**.91**	−.11	.17
I am unlikely or hesitant about using CAM because it may interfere with the conventional cancer treatment	−.29	**.66**	−.07
I am unlikely or hesitant about using CAM because treatments may have side effects	−.19	**.74**	−.05
I am unlikely or hesitant about using CAM because treatments cost too much money	.05	**.59**	.02
I am unlikely or hesitant about using CAM because it is hard to find good practitioners	.17	**.69**	.02
I am unlikely or hesitant about using CAM because I do not have time to go to CAM treatments	−.14	**.63**	−.11
I am unlikely or hesitant about using CAM because I do not have knowledge about CAM treatments	−.13	**.56**	−.24
I am unlikely or hesitant about using CAM because I do not have transportation to CAM treatments	−.12	**.50**	.05
My health care providers (e.g., doctors, nurses, etc.) encourage me to use CAM	.17	−.10	**.74**
My health care providers (e.g., doctors, nurses, etc.) are open to my use of CAM	.18	−.18	**.76**
Other cancer patients think I should use CAM	.15	−.02	**.77**
My online support group encourages me to try CAM	.23	.09	**.68**

Extraction method: principal component analysis.
Rotation method: Varimax with Kaiser normalization.
*Rotation converged in 5 iterations.

Table 2: Descriptive statistics for the ABCAM sub-scales.

	No. of items	*M* (SD)	Skewness	Kurtosis	Cronbach's α
Expected benefits	4	60.68 (19.49)	−0.09	3.85	.91
Perceived barriers	7	46.10 (13.43)	−0.74	4.29	.76
Social norms	4	49.58 (14.79)	−0.26	4.46	.75

$t = 3.62$, $P < 0.001$), and more positive subjective norms (52.3 versus 45.2, $t = -4.96$, $P < 0.001$) associated with CAM than those who did not use CAM (see Figure 2).

3.4. Criterion Validity. To provide a preliminary examination of the ABCAM scale's criterion validity, Pearson's correlations were calculated between ABCAM scale scores and CAMBI scores (see Table 3). The expected benefit score was positively correlated to both preference for natural therapies and a holistic view of health. The perceived barrier score was negatively correlated to belief in participation in treatment decision and holistic health. The positive social norm score was also positively correlated to belief in holistic health. Interestingly, correlations between domain scores in ABCAM and CAMBI were small-to-moderate suggesting that our instrument is measuring different constructs from the CAMBI.

4. Discussion

This study sought to develop and validate the ABCAM instrument to measure the decision factors related to the use of CAM among cancer patients. The conceptual model of ABCAM was guided by TPB. It was developed through the literature review, qualitative research, expert review, pilot testing, and quantitative psychometric analysis. The final instrument consists of 15 items measuring three domains related to the attitudes and beliefs predictive of CAM use: expected benefits, perceived barriers, and subjective norms. The scores appear to be reliable and valid in our study population. As hypothesized, CAM users reported higher expected benefits, lower perceived barriers, and more positive subjective norms associated with CAM than those who did not use CAM.

In comparison to existing questionnaires [13, 34, 49–51], the ABCAM is the only one we know that has gone through

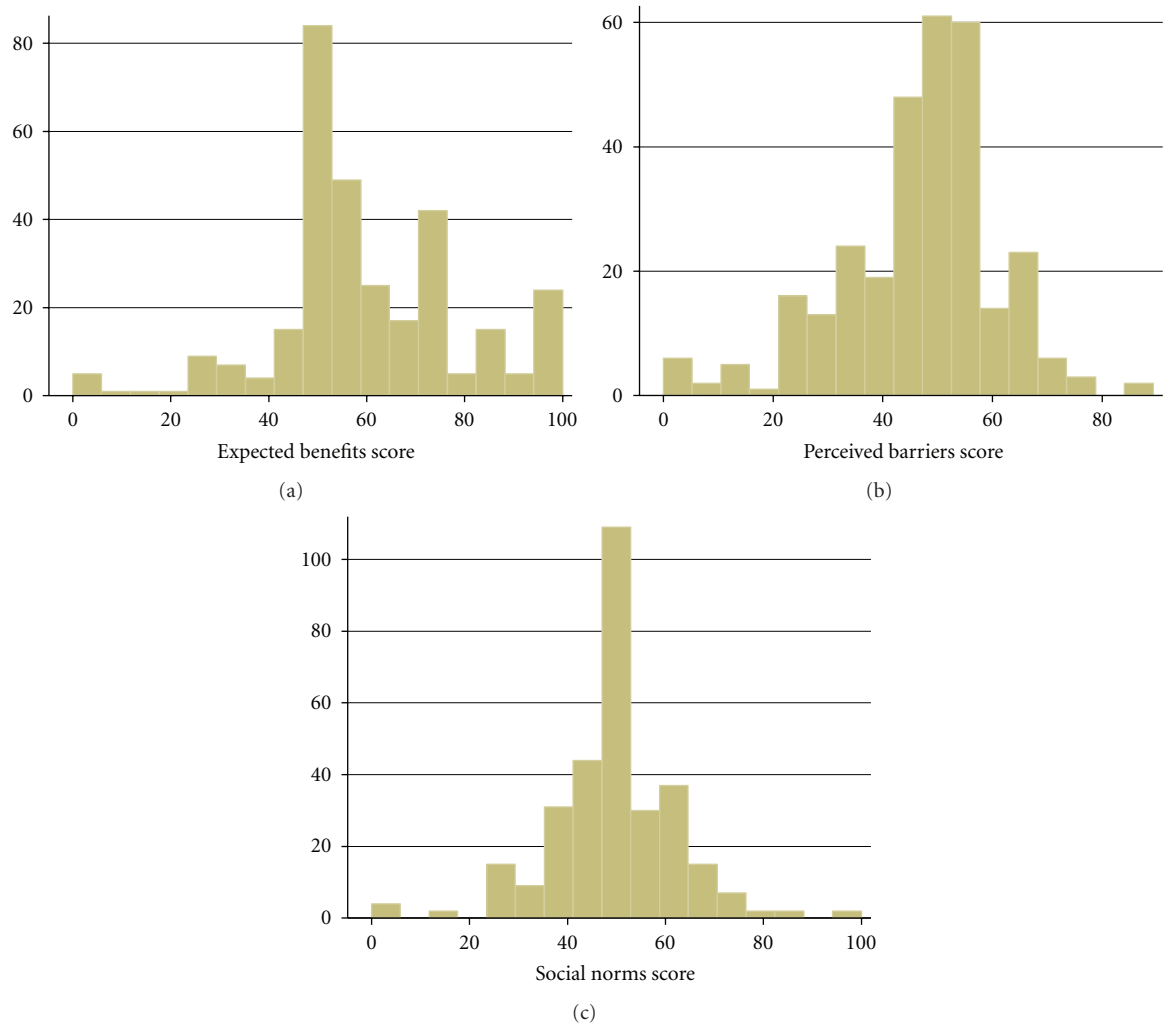

Figure 1: Distribution of domain scores of the ABCAM.

the process from development to validation in cancer patients. The theoretical model and content of our scale had similarities to the scale developed by Hirai et al., however, the perceived negative outcomes of CAM as measured by Hirai et al. did not include the barriers related to CAM use, which our instrument improves upon. Additionally, all three domains of the ABCAM instrument, including perceived benefits, perceived barriers, and subjective norms, demonstrated higher internal consistency than those reported by Hirai et al. [34].

Our study showed that higher scores of perceived benefits were associated with CAM use among cancer patients. Previous research has shown that cancer patients often use CAM because perceiving it will improve their physical and emotional health, enhance their quality of life, strengthen their immune system, reduce symptoms, and have a positive effect on cancer [10–12, 19–21]. Perceived positive outcomes of CAM use were associated with higher CAM use among a sample of Japanese cancer patients in a prior study [34]. It is important to note that while immune enhancement was a response endorsed by participants, this item cross-loaded to social norm which did not get retained in our final shortened instrument because it did not contribute to the unique factor structure of the instrument. This further suggests the belief that CAM improving one's immune system appears to be socially constructed.

The literature suggests that some of the barriers toward the use of CAM include lack of knowledge, perceived ineffectiveness, cost, time constraint, access to the provider, and perceived side effects of CAM therapies [10, 18, 52–54]. As expected, our study showed that cancer patients who used CAM demonstrated lower perceived barriers as compared to non-CAM users. The domain of perceived barriers represents the construct of perceived behavioral control in the TPB. It is important to note that some of barriers listed are experienced by individuals but they are probably structural barriers (e.g., cost, and access) as well. Therefore, these barriers may be beyond the control of many individuals and will require policy change, insurance coverage, and design of an integrative health care delivery system to ultimately influence change.

Prior studies found that CAM users were more likely to be of female sex, younger age, higher socioeconomic status

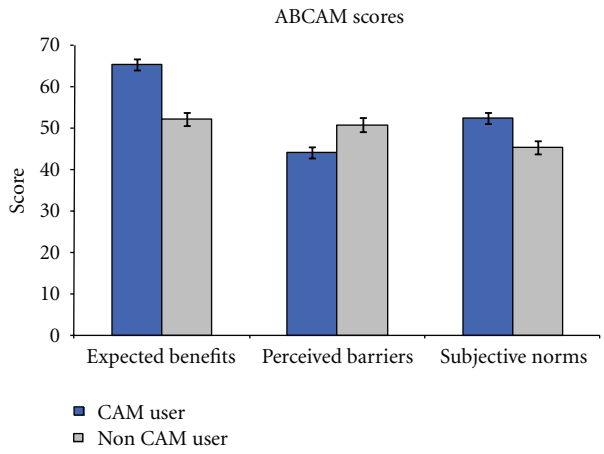

Figure 2: ABCAM domain scores by CAM users versus non-CAM users.

(e.g., education, and income), and white race [1, 10–13]. Our barrier domain may help understand what specific barriers are experienced among different sociodemographic groups. As evidence accumulates regarding the potential efficacy of some of the CAM therapies in cancer symptom management, this understanding may help reduce the potential disparity in CAM integration. Using our instrument may help quantify the level and significance of these barriers and to guide interventions to target them.

Subjective norms play an important role in patients' intended and actual health behaviors. Patients are more likely to use CAM if it is recommended by their family/friends and/or their health care providers [34, 52]. Our study revealed that CAM users had more positive subjective norms than non-CAM users. This suggests that social approval or disapproval may play an important role in influencing patients' use of CAM therapies; however, our items of family/friend influence cross-loaded between expected benefits and social norm and thus were removed from the final instrument. Consistent with prior qualitative research [25, 55], our data further strengthens the evidence that family/friends' opinions help shape an individual's expected benefit of CAM use; thus, its social normative effect cannot be separated from patients' expected benefits derived from the therapy. Another possible explanation is that cancer patients often consider the opinion of their treating specialist as most important and follow their advice [56–59]. As our instrument is investigated in future research, we can tease out how sources of social influence may shape expectations of therapeutic benefits as well as decisions to use a particular therapy.

The limitations to this study need to be acknowledged. First, our qualitative interviews were conducted with breast cancer patients in the context of decision making about acupuncture; the content of the instrument may not be complete. However, our questionnaire items were also supplemented from the existing literature and then discussed among content experts and patients with other cancers during cognitive interviews. Second, our instrument was guided by TPB as a conceptual framework and well captured the domains in TPB, but like any conceptual model, it may not fully capture other important constructs such as preferences for natural therapies, holistic health view, and finding hope [39, 40, 60]. Additionally, we created a brief instrument that can be incorporated into future cancer epidemiology and health service research; thus, the format of ABCAM is not a traditional TPB instrument. Third, our CAM use was based on self-report and may not capture all of the CAM therapies used by individuals; however, 60.9% use is in the range of what is reported in existing literature [3]. Forth, nonparticipation bias is always a concern in an epidemiology study. Our 83% participation rate is acceptable in survey research, but cannot rule out the potential for selection bias. Lastly, our study was conducted in a large academic cancer center, and future research, including community cancer practices, is needed to increase the generalizability of this study.

Table 3: Relationship between domains in ABCAM and CAMBI*.

	Natural	Participation	Holistic
Expected benefits	0.23 $P < 0.001$	0.079 $P = 0.17$	0.48 $P < 0.001$
Perceived barriers	0.033 $P = 0.57$	−0.18 $P = 0.002$	−0.28 $P < 0.001$
Social norms	0.10 $P = 0.077$	0.011 $P = 0.84$	0.28 $P < 0.001$

*Pearson's correlation.

In conclusion, this study provided the initial evidence that the ABCAM produced a reliable and valid score for measuring the behavioral predictors of CAM use. Future research is needed to demonstrate additional aspects of reliability and validity (e.g., confirmatory factor analysis; test-retest reliability; sensitivity to change). In addition, prospective research is needed to determine whether these attitudes and beliefs—expected benefits, perceived barriers, and subjective norms—predict both intended and actual use of CAM among cancer patients. Ultimately, this instrument will help elucidate how demographic, socioeconomic, and cultural issues may relate to these attitudes and beliefs, thereby influencing CAM use in the context of cancer care. Such understanding is necessary to guide the appropriate integration of CAM into the conventional health system to improve the health and wellbeing of diverse populations of cancer patients.

Appendix

See Supplementary Material available online at doi:10.1155/2012/798098.

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Research Article

Prescription Pattern of Chinese Herbal Products for Breast Cancer in Taiwan: A Population-Based Study

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Background. Chinese herbal products (CHPs) given as a therapy for symptom relief have gained widespread popularity among women with breast cancer. The aim of this study was to analyze the utilization of CHP among women with breast cancer in Taiwan. *Methods*. The usage, frequency of services, and CHP prescribed for breast cancer among women with breast cancer were evaluated, recruited from a randomly sampled cohort of 1,000,000 beneficiaries from the National Health Insurance Research Database. The logistic regression method was employed to estimate the odds ratios (ORs) for utilization of CHP. *Results*. 81.5 percent ($N = 2,236$) of women with breast cancer utilized traditional Chinese medicine (TCM) and 18% of them sought TCM with the intent of treating their breast cancer. Jia-wei-xiao-yao-san (*Augmented Rambling Powder*) was the most frequently prescribed formula for treating breast cancer. Among the top 10 most frequently prescribed CHP for treating breast cancer, seven contained dang qui (*Angelica sinensis-radix*) and six contained ren shen (*Panax ginseng-radix*), which are reported to have potential beneficial synergistic effects on breast cancer cells. *Conclusion*. CHP containing dang qui (*Angelica sinensis-radix*) or ren shen (*Panax ginseng-radix*) are the most frequently prescribed for breast cancer and their effects should be taken into account by healthcare providers.

1. Introduction

Despite the lack of solid evidence supporting their therapeutic benefit, the reported incidence of use of complementary and alternative medicines (CAMs) among women with breast cancer ranges from 66.7 to 97% [1–3]. An increased perception of breast cancer recurrence and of breast cancer-related death [4] may be the reasons why patients use a wide range of CAM including herbs, vitamins, homeopathic remedies, and Chinese herbal products (CHPs) [5–8]. The expectations of CAM use vary among individuals. Some just hope to strengthen their immune system, some expect to decrease the treatment-associated toxicity, and some want to alleviate the cancer-derived symptoms [9]. However, there is no compelling evidence supporting the effectiveness of CAM use in breast cancer patients [5, 10]. In view of such and without further knowledge on how effective CAM is, it is not easy for oncologists or CAM practitioners to provide an appropriate recommendation that can meet the expectations of women with breast cancer.

Traditional Chinese medicine (TCM) has been growing in popularity and has offered an important alternative or complement to health care in many countries. The most common type of CAM used by Chinese women with breast cancer is CHP [11]. Previous studies have disclosed the potential beneficial synergistic effects of the usage of *dang qui* (*Angelica sinensis-radix*) [12–14] or *ren shen* (*Panax ginseng-radix*) [15–17] among women with breast cancer. Although a previous four-year survey [11] indicated that over 50% of breast cancer patients considered CHP effective in treating cancer, the utilization of individual CHP has rarely been reported. In Taiwan, CHPs have been an important part of health care for hundreds of years and are fully reimbursed under the current National Health Insurance (NHI) system.

Accordingly, the claims database provides a platform for understanding the utilization of CHP prescribed by licensed TCM doctors. The aim of our study is to analyze a random sample of this comprehensive database and to determine the CHP utilization patterns for women with newly diagnosed breast cancer in Taiwan. Results of this study may provide valuable information for physicians, enabling them to respond to patients' use of CHP in an informed way and strengthening the patient-physician relationship in breast cancer care.

2. Materials and Methods

2.1. Data Resources and Study Sample. This study was conducted after approval by the review board of the Committee on Chinese Medicine and Pharmacy (CCMP), Department of Health, Taiwan. It was designed as a population-based study to analyze a sample of 1 million subjects selected at random from the 22 million beneficiaries of the National Health Insurance scheme of Taiwan and to determine the prevalence of prescribed CHP in women with breast cancer between January 1, 1997, and December 31, 2008. All data were obtained from the National Health Insurance Research Database (NHIRD), which included all the reimbursement data of the NHI with identification numbers of all individuals encrypted, transformed, and maintained by the National Health Research Institutes of Taiwan [18]. The NHIRD database contained patient's gender and date of birth, all records of clinical visits and hospitalization, prescribed drugs and dosages, including CHP, and three major diagnoses coded in the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) format [19].

The selection of study subjects from the random sample of one million individuals was performed as follows (Figure 1). First, we excluded all male beneficiaries ($n = 495,835$) or those with missing information concerning gender ($n = 3$). Second, female beneficiaries without breast cancer ($n = 500,809$) were excluded. Third, the prevalent cases of other cancers ($n = 125$) and breast cancer ($n = 486$) diagnosed before the end of 1998 were also excluded to make sure that all the subjects included were newly diagnosed with invasive breast cancer and the diagnosis was verified by the NHI registry of catastrophic illnesses during 1998–2008. All patients who are registered to have a catastrophic illness are exempted from all copayments. To be registered as such, patients must have the diagnosis of invasive breast cancer (*ICD-9* code 174) validated by tissue pathology. Finally, 2,742 female subjects were included in the cohort.

2.2. Traditional Chinese Medicine. TCM treatments include CHP, acupuncture and manipulative therapies for trauma, all of which are reimbursed by the NHI of Taiwan. CHPs composed of one or more herbs (formula) are most widely adopted by patients in Taiwan [20]. To study the utilization of prescribed CHP in the present study, we downloaded the detailed herbal contents for all kinds of reimbursed CHP from the website of the CCMP, including the name of each CHP, the proportion of each constituent, the date and period of approval as drug, the code, and the name of manufacturer. For simplicity, all CHPs with the same CCMP standard formulas are classified under the same categories, regardless of slight variations among products of different pharmaceutical companies [21].

2.3. Study Variables. To determine the key independent variables for the utilization of CHP among women with breast cancer, we selected the demographic factors according to previous studies [22]. Ages were categorized into seven groups: ≤29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥ 80 years. Geographic areas of Taiwan were classified into the following six regions: Taipei city, Kaohsiung city, Northern, Central, Eastern, and Southern regions. We split the monthly wage into four levels: New Taiwan Dollars (NT$) 0, 1–19,999, 20,000–39,999, and ≥40,000.

2.4. Statistical Analysis. Data analysis was performed by descriptive statistics, including the prescription rates of CHP users stratified by patient's age, indications for the prescription of CHP, and the most frequently prescribed herbal formulas for treating breast cancer. Primary indications were classified according to the ICD-9. The diagnoses were coded according to the ICD-9 and grouped into different broader disease categories. For example, ICD-9 codes 460–519 were classified as diseases of the respiratory system, codes 780–799 were grouped as symptoms, signs, and ill-defined conditions, and codes 520–579 were classified as diseases of the digestive system. Multiple logistic regression was conducted to evaluate factors that correlated with CHP use. A significance level of $\alpha = 0.05$ was selected. The statistical software SAS 9.13 was used for data management and analyses.

3. Results

The database of outpatient claims contained information on 2,742 women with breast cancer from 1999 to 2008. Among them, 2,236 (81.5%) breast cancer patients used TCM outpatient services. Most TCM users (95.8%) also received cancer treatment (Table 1). The mean age of TCM nonusers was significantly higher than that of TCM users. There were more TCM users than TCM nonusers with income level of NT$ 1–19,999 or residing in Central and Southern Taiwan. There was no significant difference in cancer treatment modalities between TCM users and non-TCM users.

Adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) obtained by multiple logistic regression are summarized in Table 1. Compared with the age group of 30–39 years (aOR = 1.00), there were no significant differences in ages between TCM users and TCM nonusers except those aged 80 years and above who were more likely to be non-TCM users. There was also no significant difference or trend among women in different income groups.

Chinese herbal medicines were prescribed in 22,755 (76.8%) of visits made by women to TCM doctors, with acupuncture and manipulative therapies for trauma prescribed for the rest. Analysis of the major disease categories for 2,236 TCM users (Table 2) showed that breast cancer was the most common reason for using CHP (21.7%, $n = 6,442$), followed by "symptoms, signs, and ill-defined conditions"

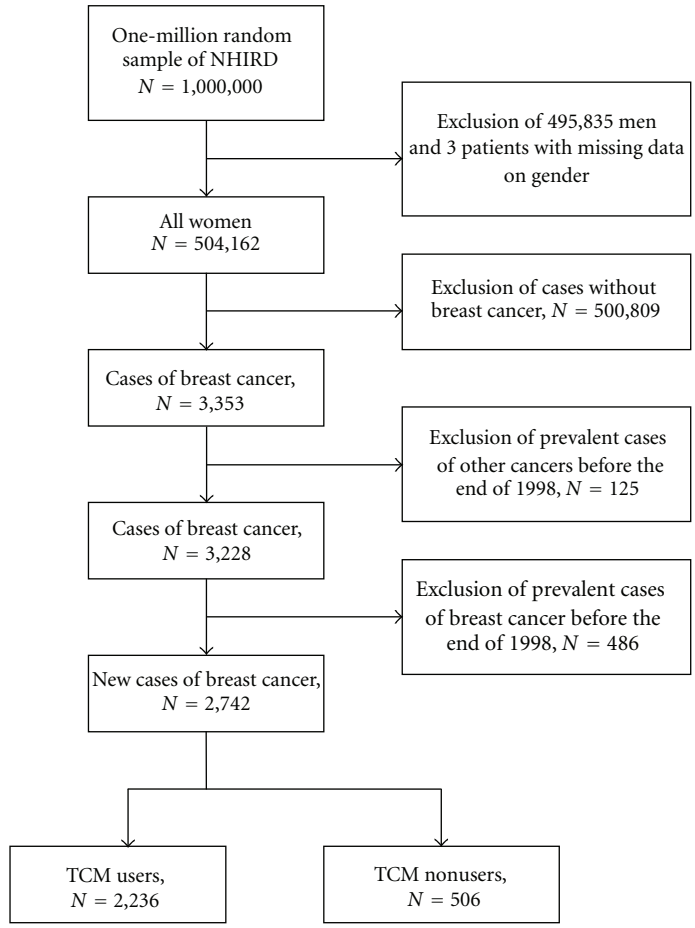

Figure 1: Flowchart of recruitment of subjects from the 1-million random sample of the National Health Insurance Research Database (NHIRD) from 1999 to 2008 in Taiwan.

(17.5%, $n = 5,177$), and "diseases of the respiratory system" (11.0%, $n = 3,253$), as summarized in Table 2.

Details on the most frequently prescribed CHP for treating breast cancer by TCM doctors are provided in Table 3. As can be seen, *Jia-wei-xiao-yao-san* (*Augmented Rambling Powder*) is the most frequently prescribed CHP, followed by *Xiang-sha-liu-jun-zi-tang* (*Vladimiria and Amomum Combination*) and *Gui-pi-tang* (*Ginseng and Longan Combination*). Among the top 10 most frequently prescribed CHPs, seven containing *dang qui* (*Angelica sinensis-radix*) and six containing *ren shen* (*Panax ginseng-radix*) of various doses were identified.

Although over 81% ($n = 2,236$) of women with breast cancer had used TCM and CHP as the major method of treatment from 1999 to 2008, only about 18% ($n = 466$) of them sought TCM with the intent of either treating their breast cancer or relieving the treatment-related side effects. CHP was prescribed in addition to surgery, radiation therapy, and/or chemotherapy and appeared to be used as an adjunct to conventional treatments for cancer, rather than as alternatives. The top three formulas most frequently prescribed by TCM doctors for treating breast cancer were *Jia-wei-xiao-yao-san* (*Augmented Rambling Powder*), *Xiang-sha-liu-jun-zi-tang* (*Vladimiria and Amomum Combination*), and *Gui-pi-tang* (*Ginseng and Longan Combination*).

4. Discussion

The increasing trend of TCM utilization among women with breast cancer in Taiwan is in line with trends reported from China [1]. However, the prevalence of CHP use to treat breast cancer among Taiwanese women is far below the proportions in other countries [2, 3, 6]. Previous studies reported that approximately 43–80% of breast cancer patients used CAM as part of the treatment for their breast cancer [1–3, 6]. Possibly fear of cancer recurrence and cancer-related death is motivation for women to use CAM therapies. The difference in results between the present study and those previously reported was probably due to the disparities in definition of breast cancer treatment between patients and licensed TCM doctors. Previous studies [1–3, 6] collected the information of breast cancer treatment via self-reported questionnaire, which represented the patients' own perception and expectation of the prescribed treatment. On the

Table 1: Demographic characteristics and results of multiple logistic regression showing the adjusted odds ratio (aOR) and 95% CI (confidence interval) of women with newly diagnosed breast cancer from the 1-million random sample of the National Health Insurance Research Database (NHIRD) from 1999 to 2008 in Taiwan.

Characteristics	TCM[a] nonusers	TCM users	aOR[b] (95% CI[c])
No. of cases	506	2,236	
CHP[d] for breast cancer	—	503	
Age at diagnosis (years)			
≤29	8	26	0.63 (0.26–1.52)
30–39	51	283	1
40–49	165	771	0.84 (0.59–1.19)
50–59	146	617	0.78 (0.54–1.11)
60–69	75	356	0.86 (0.57–1.28)
70–79	40	146	0.75 (0.46–1.22)
≥80	21	37	0.35 (0.18–0.68)
Insured salaries (NT$[e]/month)			
0[+]	120	416	1
1–19999	234	1178	1.24 (0.93–1.64)
20000–39999	96	432	1.02 (0.73–1.43)
>40000	56	210	0.96 (0.65–1.42)
Insured region			
Taipei city	171	555	1
Kaohsiung city	34	148	1.33 (0.88–2.02)
Northern Taiwan	159	644	1.27 (0.98–1.63)
Middle Taiwan	49	380	2.66 (1.86–3.79)
Southern Taiwan	80	431	1.83 (1.33–2.52)
Eastern Taiwan	10	59	2.25 (0.98–5.14)
Cancer treatment modalities			
No treatment	26	93	0.86 (0.49–1.51)
Surgery only	46	207	1
Chemotherapy only	7	29	0.98 (0.39–2.47)
Hormone therapy only	21	98	1.07 (0.60–1.91)
Surgery and chemotherapy	74	305	0.82 (0.54–1.25)
Surgery and hormone therapy	113	508	1.10 (0.74–1.63)
Surgery, chemotherapy, and hormone therapy	193	885	1.00 (0.69–1.44)
Others	26	111	0.99 (0.60–1.63)

[a]TCM refers to traditional Chinese medicine; [b]OR refers to odds ratio; [c]CI refers to confidence interval; [d]CHP refers to Chinese herbal products;[e] NT$ refers to new Taiwan dollars, of which 1 US$ = 30 NT$.

contrary, the perspective of TCM doctors concerning the treatment prescribed must be in line with the requirement of the NHI in Taiwan. They had to follow the standard diagnoses using the *ICD-9-CM* [20] coding system when claiming reimbursement, and women with breast cancer are exempted from all copayments once TCM doctors coded their diagnoses as ICD-9 code 174 (malignant neoplasm of female breast) to the NHI bureau. Another possible explanation is that the present study demonstrated only the utilization of CHP, which is the modern form of Chinese herbal remedies, of which a single herb and herbal formulas are concentrated into granulated compounds and made available like over-the-counter dietary supplements in the United States [23]. Decoctions and Chinese herbal remedies purchased directly from TCM herbal pharmacies, which were classified as Chinese herbal medications, were not included in the present study. Although the present findings cannot be generalized to the comprehensive usage of various types of CAM, the present study using a random national-level sample revealed the prevalence in use of CHP prescribed by licensed TCM doctors for treating breast cancer.

Although TCM as a unique traditional therapy for various ailments has been used in Taiwan for over hundreds of years, more than 95% of CHP users continued to receive standard breast cancer treatment during the 10-year study period. Moreover, regardless of the experiences caused by receiving different types of moderately toxic cancer treatments, the choice of major medical options among women

Table 2: Frequency distribution of traditional Chinese medicine (TCM) visits by major disease categories (according to 9th ICD codes) in women with breast cancer from 1999 to 2008 in Taiwan.

Major disease category	*ICD-9-CM codes*	No. of visits *N* (%)		
		Chinese herbal remedies	Acupuncture and manipulative therapies	Total of TCM
Infectious and parasitic diseases	001–139	44 (0.1)	3 (0.0)	47 (0.2)
Neoplasms	140–239	6,672 (22.5)	1,165 (3.9)	7,837 (26.5)
Breast cancer	174	6,442 (21.7)	1,145 (3.9)	7,587 (25.6)
Other cancers (remainder of neoplasms)		230 (0.8)	20 (0.1)	250 (0.8)
Endocrine, nutritional and metabolic diseases, and immunity disorders	240–279	262 (0.9)	1 (0.0)	263 (0.9)
Mental disorders	290–319	127 (0.4)	9 (0.0)	136 (0.5)
Diseases of the nervous system and sense organs	320–389	446 (1.5)	69 (0.2)	515 (1.7)
Diseases of the circulatory system	390–459	310 (1.0)	17 (0.1)	327 (1.1)
Diseases of the respiratory system	460–519	3,253 (11.0)	64 (0.2)	3,317 (11.2)
Diseases of the digestive system	520–579	2,222 (7.5)	72 (0.2)	2,294 (7.7)
Diseases of the genitourinary system	580–629	1,294 (4.4)	74 (0.2)	1,368 (4.6)
Diseases of the skin and subcutaneous tissue	680–709	366 (1.2)	12 (0.0)	378 (1.3)
Diseases of the musculoskeletal system and connective tissue	710–739	1,681 (5.7)	2,461 (8.3)	4,142 (14.0)
Symptoms, signs, and ill-defined conditions	780–799	5,177 (17.5)	108 (0.4)	5,285 (17.8)
Injury and poisoning	800–999	640 (2.2)	2,736 (9.2)	3,376 (11.4)
Supplementary classification[d]	V01–V82, E800–E999	41 (0.1)	59 (0.2)	100 (0.3)
Others*		220 (0.7)	23 (0.1)	243 (0.8)
Total		22,755 (76.8)	6,873 (23.2)	29,628 (100)

*Others include ICD-9-CM codes 280–289, *630–677, 740–759,* 760–779 and missing/error data.
[d]Supplementary classification of factors influencing health status and contact with health service, external causes of injury and poisoning.

with breast cancer was not associated with the use of CHP. Hence, we inferred that CHP for women with breast cancer in Taiwan was generally used as adjuncts to cancer treatment, rather than as replacements for it.

Previous clinical trials have demonstrated that *Jia-wei-xiao-yao-san* (*Augmented Rambling Powder*), which is the most frequently prescribed formula for treating breast cancer in Taiwan, may be an efficacious therapy for reducing psychological (anxiety and depression) symptoms in postmenopausal women [24]. Among the top 10 most frequently prescribed formulas for treating breast cancer, *Gui-pi-tang* (*Ginseng and Longan Combination*), *Tian-wang-bu-xin-dan* (*Ginseng and Zizyphus Combination*), and *Suan-zao-ren-tang* (*Zizyphus Combination*), which all have a long history of use, are said to nourish the blood and calm the nerves and are very often prescribed by TCM doctors to alleviate sleep disturbance [25]. Other commonly prescribed formulas are often for relieving gastrointestinal discomfort (*Ban-xia-xie-xin-tang*, *or Pinellia Combination*), poor appetite (*Xiang-sha-liu-jun-zi-tang, or Vladimiria and Amomum Combination*), fatigue (*Bu-zhong-yi-qi-tang*, *or Ginseng and Astragalus Combination*), palpitation (*Ren-shen-yang-rong-tang*, *or Ginseng Nutritive Combination*), or swelling of lymph nodes (*San-zhong-kui-jian-tang*, *or Forsythia and Laminaria Combination*). It is apparent from this study that TCM doctors in Taiwan prescribed herbal therapies mainly for reducing psychosocial distress and symptomatic discomfort. However, it remains to be clarified whether frequently prescribed CHPs containing *ren shen* (*Panax ginseng-radix*) and *dang qui* (*Angelica sinensis-radix*) for cancer treatment are intended by TCM doctors to decrease the treatment-associated toxicity or to alleviate the cancer-derived symptoms. Notably, there is yet insufficient evidence for reaching a conclusion regarding the cost-effectiveness of the simultaneous administration of cancer treatment with *dang qui* (*Angelica sinensis-radix*) or *ren shen* (*Panax ginseng Radix*) [26]. Further studies are warranted to assess *dang qui* (*Angelica sinensis-radix*) or *ren shen* (*Panax ginseng Radix*) as an add-on treatment for women receiving conventional breast cancer treatments.

Previous studies revealed that CHP users among women with breast cancer were more likely to have higher income or be of younger age [1]. However, the present data

Table 3: Top 10 herbal formulas prescribed by TCM doctors for treating breast cancer among 503 breast cancer women from 1999 to 2008 in Taiwan.

Herbal formulas	English name	Frequency of prescriptions $N = 6{,}442$ (%)	Average daily dose (g)	Average duration for prescriptions (day)
Jia-wei-xiao-yao-san†	Augmented Rambling Powder	1,045 (16.2)	5.1	12.8
Xiang-sha-liu-jun-zi-tang‡	*Vladimiria* and *Amomum* Combination	450 (7.0)	5.5	11.5
Gui-pi-tang†‡	*Ginseng* and *Longan* Combination	414 (6.4)	5.0	12.1
San-zhong-kui-jian-tang†	*Forsythia* and *Laminaria* Combination	367 (5.7)	6.3	10.2
Bu-zhong-yi-qi-tang†‡	*Ginseng* and *Astragalus* Combination	347 (5.4)	5.2	12.3
Tian-wang-bu-xin-dan†‡	*Ginseng* and *Zizyphus* Combination	302 (4.7)	4.7	13.8
Ban-xia-xie-xin-tang‡	*Pinellia* Combination	289 (4.5)	5.0	11.6
Suan-zao-ren-tang	*Zizyphus* Combination	276 (4.3)	4.5	13.4
Ren-shen-yang-rong-tang†‡	*Ginseng* Nutritive Combination	272 (4.2)	5.1	10.3
Xue-fu-zhu-yu-tang†	*Persica* and *Achyranthes* Combination	254 (3.9)	3.8	12.2

†Chinese herbal products containing *dang qui (Angelica sinensis-radix)*.
‡Chinese herbal products containing *ren shen (Panax ginseng-radix)*.

demonstrated no significant difference in these two variables, possibly, because the NHI system has a comprehensive coverage and the copayment for CHP is universally NT$50 (approximately US$1.5), which provides an affordable health access for all age groups and different income levels. Symptoms, signs, and ill-defined conditions and diseases of the respiratory system were the two most frequent diagnoses in disease category for TCM visits with prescription of CHP, after breast cancer. The results indicate that, besides breast cancer care, health care providers should pay more attention to the general health conditions of patients suffering from symptoms, signs, and ill-defined conditions as well as respiratory discomfort and provide proactive recommendations for these medical needs.

The present study has two limitations. First, because the identities of the patients were encrypted and thus not available in the NHI reimbursement database, we were unable to obtain any histopathology reports to verify the diagnoses. However, because the registration of breast cancer as a catastrophic illness is approved on the basis of pathology and/or cytology evidence and is followed by a full waiver of copayment, such a diagnosis is made only after very serious review and is generally accurate. The diagnostic accuracy of breast cancer among the NHI data is corroborated by the significant agreement between the incidence rate calculated herein and that determined by the National Cancer Registry of Taiwan, in which 95% of the breast cancers are accompanied by histopathologic validation. Second, this study did not include Chinese herbal remedies purchased directly from TCM herbal pharmacies, nor did we include health food containing herbs. Thus, the frequency of CHP utilization might be underestimated. However, because the NHI system has a comprehensive coverage for TCM prescriptions, which is generally less than the cost of herbs sold in Taiwan markets, the likelihood that subjects purchased lots of other herbs outside the NHI database is not high.

5. Conclusions

It is apparent that our findings may have implications for physicians attending to women with breast cancer. Our results suggest that, under the coexistence of the conventional medical treatments and TCM, most breast cancer patients consumed herbal therapies with the intention of relieving their treatment-induced symptoms, rather than rejecting standard cancer treatments. Recognizing the use of TCM, exploring potential interactions and adverse effects, and integrating both technologies may be more beneficial to the overall health, or survival and quality of life, of breast cancer patients. Thus, health care providers had better proactively explore a personalized optimal treatment for breast cancer, as well as attend to the patients' psychosocial and physical needs.

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Research Article

Massage for Children Undergoing Hematopoietic Cell Transplantation: A Qualitative Report

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Background. No in-depth qualitative research exists about the effects of therapeutic massage with children hospitalized to undergo hematopoietic cell transplantation (HCT). The objective of this study is to describe parent caregivers' experience of the effects of massage/acupressure for their children undergoing HCT. *Methods*. We conducted a qualitative analysis of open-ended interviews with 15 parents of children in the intervention arm of a massage/acupressure trial. Children received both practitioner and parent-provided massage/acupressure. *Results*. Parents reported that their child experienced relief from pain and nausea, relaxation, and greater ease falling asleep. They also reported increased caregiver competence and closeness with their child as a result of learning and performing massage/acupressure. Parents supported a semistandardized massage protocol. *Conclusion*. Massage/acupressure may support symptom relief and promote relaxation and sleep among pediatric HCT patients if administered with attention to individual patients' needs and hospital routines and may relieve stress among parents, improve caregiver competence, and enhance the sense of connection between parent and child.

1. Introduction

Therapeutic massage, a term that encompasses a wide variety of techniques of touch and tissue manipulation, has deep roots in the world's oldest medical practices, including both traditional Chinese medicine and Western medicine. In the late 19th century, a rift between massage and Western medical practice grew with the rise of scientific medicine, and physicians relinquished massage as a routine clinical practice. By the second half of the 20th century, massage had become professionalized and was increasingly associated with the alternative medicine movement [1].

More recently, a growing body of scientific literature on therapeutic massage—bolstered by its widespread popular use—has led to the reintroduction of various forms of massage as an adjunct to biomedical therapies. This shift is situated in growing popular and scientific interest in nonpharmacologic approaches to symptom management [2].

Research on therapeutic massage has shown benefits in managing adult and pediatric patients' distress related to cancer and cancer treatment [3–7], and hematopoietic cell transplantation (HCT) [8, 9], although results are not consistent [10]. Acupressure massage has shown benefits for

chemotherapy-related nausea [8, 11, 12], anxiety [13], and fatigue [8, 14]. In addition, performing massage on a family member with cancer has been shown to reduce anxiety and fatigue [9, 15] among caregivers, and to increase their sense of well being and confidence in managing their family member's symptoms [16–18].

To date, most studies on therapeutic massage have measured predefined patient outcomes, usually medical and psychological symptoms. This growing body of research can be complemented by more in-depth investigations of patients' and caregivers' lived experiences of receiving and performing massage. Qualitative research has demonstrated, for example, that massage practices contribute to improvements in patient-caregiver relations [19] and to the "meaningful relief" of suffering among cancer patients [20]. Through open-ended interviews and close attention to the perceptions and interactions of participants, clinicians, and researchers, qualitative methods can examine aspects of massage practices that may go undetected by quantitative methods. This study focuses primarily on the perceptions and experiences of parent caregivers of pediatric HCT patients at an academic hospital. Parents living with and caring for a pediatric HCT patient typically spend weeks and even months in an isolated hospital room with filtered air and limited access to visitors. Parents are neither patient nor clinician; they are witness to their child's pain, suffering and confinement, as well as healing and resilience.

This study is one component of a mixed-method, randomized controlled pilot study introducing a combined Swedish and acupressure massage intervention in a pediatric HCT hospital unit. The overall aim of the pilot study was to assess whether conducting a study of such an intervention is feasible in the HCT unit, whether massage/acupressure alleviates patients' and parent-caregivers' distress and discomfort associated with HCT and accompanying chemotherapy, and to explore the effects of caregivers' experiences performing massage. Quantitative outcome measures of this feasibility study are reported separately [21]. The study described here examined caregivers' experiences learning to perform massage for their child and observing their child receive massage from a professional massage practitioner. Building on recent, more quantitatively oriented research assessing the effects of massage for pediatric HCT patients [6, 9], this study offers important new findings through the most in-depth, descriptive analysis to date of parent- and practitioner-provided massage for children undergoing HCT.

2. Methods

The massage intervention provided (1) practical, hands-on training for parents to provide massage/acupressure for their child; (2) professional practitioner-performed massages and acupressure treatments for children undergoing HCT. Professional massage practitioners provided up to three massages/acupressure sessions per week to the children during their entire hospital stay (days of hospitalization: median 37, range 23–110). They demonstrated massage/acupressure techniques to the parents for additional parent-provided massages for approximately ten minutes whenever the parent was present and amenable to it and provided a detailed handout with locations of and indications for specific acupressure points. The massage practitioners received training in several sessions with the research team (EAL, WEM) and received additional consultation from Traditional Chinese Medicine practitioners at the academic medical center. The massage intervention was a semistandardized integration of Swedish massage (gentle to moderately firm strokes, light pressure, holding touch to the back, shoulder girdle, hands, and legs) and acupressure based on traditional Chinese medicine using points on the feet, lower legs, wrist, and chest that are commonly used for nausea, pain and distress (9 points: PC6, ST36, LI4, LV3, BL62, KI6, SP6, HE7, CV17) [22]. Massage practitioners had more than ten years of experience each with Swedish massage and acupressure in a hospital setting. Variations in pressure, strokes, and massaged body areas were permitted within the frame of the intervention manual according to the child's needs and response. Symptom-specific acupressure points were selected according to patient needs and the massage protocol instructions. Foot massage (Swedish and acupressure) was routinely given for relaxation. In what follows, we will use the shorter term "massage" for the combination of Swedish massage elements, including foot massage, with acupressure as it was applied in this study. Massage duration was typically 10 to 30 minutes. Children wore hospital gowns during massage. Massage practitioners produced written reports on the type and duration of each massage, their impression of the child's response to the massage, and how they adapted their technique to accommodate this response.

We decided to interview parents and massage practitioners exclusively in order to reduce the burden of research participation on the children. Data collection was restricted to the intervention arm using interviews with parents after hospital discharge, detailed hand-written notes by massage practitioners about each massage session, and interviews with two massage practitioners.

Semistructured interviews with twelve mothers and three fathers were conducted by telephone approximately one week after hospital discharge. Each interview lasted approximately 30 minutes. Semistructured interviews with two massage practitioners were conducted by phone and lasted approximately 45 minutes. Interviews were conducted by two authors (ED and SA) who were not directly involved with the study intervention or the medical and nursing care on the unit. Practitioner interviews asked massage practitioners open-ended questions about their experiences performing massage for study participants, and their impressions of the children's experiences receiving massage and parents' experiences performing massage. The questions asked in the parent interviews were as follows.

> "Can you tell us in a few words how it was for you to learn some massage and to massage your child?"
>
> "What was the best thing about the massage experience for you?"
>
> "Was it possible for you to give massages?"

(*If yes:*) "How did that go for you and your child?"

(*If no:*) "What was the biggest barrier for giving a massage?"

"What was the best thing for you when you were giving your child a massage?"

"What do you think was the best thing about the massage experience for your child?"

"Was it the same with the practitioner and with you?"

"What do you think was the hardest thing about the massage experience for your child?"

"What was the hardest thing about the massage experience for you?"

"What was the hardest thing about the massage study?"

2.1. Participants/Context. English-speaking children, 5 to 18 years of age, and their parents were invited to participate in the randomized controlled trial (RCT) as they were consecutively admitted to the transplant unit over a twelve month period (November 2008 to December 2009, patient characteristics in Table 1; additional details in [21]). Participation in the RCT was offered to child and parent during their preadmission consenting visit with a nurse manager and attending physician. No children over age 5 were excluded. Twenty-three children and their parents (rooming in with the child in the same hospital room) signed informed consent, enrolled and were randomized 2 : 1 to intervention versus control. The RCT was registered with clinicaltrials.gov NCT00843180. The qualitative study reported here included 15 of the 16 parents in the intervention arm. No payment was offered to participants in this group. Both the RCT and the qualitative study were approved by the university's Human Subjects Review boards.

Children under age twelve signed assent forms, children twelve years and older signed consent forms, and parents signed consent for their own participation and their children under age 18. Seven child-parent dyads were assigned to the control arm, sixteen child-parent dyads to the intervention. One child subsequently declined all massages. The remaining 15 dyads are the subjects of this qualitative study (Table 1): eight were mother-son or father-daughter and seven were mother-daughter or father-son. Children in the intervention arm underwent autologous or allogeneic HCT for treatment of malignancies and other diseases listed in Table 1. Participants remained on the unit in their individual hospital rooms, behind double doors with high-level infection precautions. Massage group participants received 8.5 professional massages (median) during their hospitalization, at an average of 1.6 massages per week.

2.2. Analysis. Qualitative data analysis was conducted collaboratively by three of the authors (SA, EAL, WEM). The interpretive process was iterative and multistaged and included coding and thematic development [23, 24]. Data included transcripts of audio-recorded interviews, massage practitioners' written reports on massage sessions and study activities. First, interview recordings were listened to, and interview transcripts and massage therapists' report cards were read repeatedly, in order to form an overall impression of participants' and practitioners' experiences. Recurrent themes and patterns were identified in the data—particularly in terms of massage's effects on patients' and caretakers' experiences at the intersection of cognitive, affective, and physical states. Descriptive categories, or codes, were then developed for each emerging theme, and data fragments were systematically assigned codes. After the data were organized by code, key concepts were reworked through further discussion and analysis. This process included linking data extracts back to their original narrative context and conceptually situating ambivalent and contradictory statements.

Table 1: Patient characteristics.

N	15
Demographics:	
Age (mean) [Range 5–18]	11.3
Sex	
Female	7
Male	8
Ethnicity	
White	8
Asian	3
Hispanic	3
Other	1
Diagnoses:	
Congenital or acquired bone marrow failure	5
Hematologic malignancy	5
Congenital immune deficiency	3
Solid tumor	2
Hemoglobinopathy	0
Transplant type:	
Autologous	3
Allogeneic	12

3. Results

Three major themes were developed: (1) perceived benefits of massage for patients; (2) massage's effects on parents and family dynamics; and (3) impact of the timing and duration of massage therapy over the period of hospitalization. Each theme, along with related subthemes and examples, is described below. The voices of participants (parents of patients), massage practitioners, and researchers are included; their words are reported verbatim, revealing differing levels of English fluency among participants. Quotes are identified as follows:

P = parent of pediatric HCT patient,

R = research assistant/interviewer,

M = massage practitioner.

4. Parent-Perceived Benefits of Massage for Patients

Without exception, parents said that massage brought relief, comfort, and even pleasure to their children, although the effectiveness of massage in relieving specific treatment-related symptoms was variable among patients. The particular strength of the massage intervention appeared to be in promoting pleasurable sensations and a state of relaxation, with many children dozing off near the end of massage sessions. Most parents reported that their child looked forward to massages performed by parents and/or practitioners, and several parents continued to perform massage on their child after completion of the study. According to a massage practitioner, nurses on the transplant floor also described children's eagerness for the massage visits.

4.1. Symptom Relief. Parent caregivers reported that massage—performed by the professional massage therapist and/or a parent—provided relief from or support with symptoms, including nausea, pain, and inflammation.

4.1.1. Pain.

> *(P6) We still use the pressure points. She loves the foot pressure points for the pain. She enjoys it.*
>
> *(P17) I think it was very beneficial to have massage during the time when he was in a lot of pain and very uncomfortable. It was a good distraction and comforting.*

4.1.2. Nausea.

> *(P1) It was amazing, especially with the nausea points. It worked.*
>
> *(P20) Even though she's got headache or even though she's got vomiting, she wanted to have massage.*

4.1.3. Inflammation.

> *(P21) When he had the joint inflammation, they were able to relieve–to help him through that.*

However, according to parents, not all patients found consistent symptom relief through massage.

> *(P6) For pain it did not work as well, but the nausea—it really did, at times, alleviate all the nauseous feeling.*
>
> *(P17) I cannot say that, you know, when I press on a certain area that it really made it [nausea] go away.*

4.2. Positive Feelings, Relaxation, and Sleep. Although relief from acute physical symptoms was reported by parents to be variable among patients, massage was uniformly associated with relaxation, comfort, positive physical sensation, and greater ease falling asleep. Whereas physical contact is often associated with uncomfortable treatments and procedures for children on the transplant unit, massage offered more pleasurable, calming sensations, which was seen by the massage providers as a way for children to "be in their bodies" instead of dissociating from them. A massage practitioner reported, for example, that a patient told her he felt like he was "floating on air" after massage.

> *(P12)* [Massage] *make her more comfortable. At least make her have a better sleep.*
>
> *(P7) The best thing about the whole experience was knowing that it helped him to relax.*
>
> *(P14) Best thing is that it was making him relax, feel calm, and then he went to sleep.*
>
> *(P21) He was really in a lot of pain, and for him to fall asleep during that 15 to 20 minutes was amazing… so that's–I took pictures [laughs].*
>
> *(M) Some of the kids were trying not to be in their bodies because the whole thing was so unpleasant. The massage was a way for them to be in their bodies in a way that was pleasurable.*

4.3. Special Treatment. Parent caregivers often experienced massage as a practice situated outside of the transplant unit's routine activities, and as a kind of nonmedical therapy—or gift—that attended to the patient as a complex, feeling person, in contrast to the biomedical emphasis on treating disease as an entity belonging to the body and distinct from the person.

> *(P21) It really is one of the few things outside of medicine that I saw work. You know, right before your eyes you can see the results.*
>
> *(P20) I learned that giving a massage to my daughter was kind of changing atmosphere. It made more comfortable and safe…that was not the kind of giving medicine, but giving a kind of touch. There is big difference between medicine and massage.*
>
> *(P13) When the therapist came in…she [the daughter] was getting the royal treatment… It was a person that was bringing peace to her versus an injection or taking blood from her. [The massage therapist] was not taking from her, but giving…I think it's just good for their soul…*

4.4. A Heightened Sense of Control. Hospital patients are subject to frequent and unannounced invasions of their privacy and bodies, and they often experience a sense of loss of control. This may be particularly true of pediatric patients, for whom cooperative decision making is limited. Massage sessions offered through this study, in contrast, took place only with patients' consent. Participation gave patients the opportunity to say "yes" or "no" and to shape the course of therapy, in a context in which their control over their environment and bodies is greatly diminished.

> *(P12) Sometimes she do not want anybody to bother her…and I'm not bother her…only when she want it [massage] and she needs it.*

(P22) Sometimes she did not want to be touched, so I would just leave her alone.

(M) Massage is the one thing in the hospital regimen that is voluntary, where the kids have the power to say "no." It is the one time where how they feel is the most important thing. I think this made them feel empowered.

4.5. Tailoring the Massage Protocol. Not only were patients able to choose whether to undergo a massage when a session was offered to them, at each session the patient was asked by the massage practitioner to describe in detail how he or she was feeling. Following a semistandardized protocol with specific instructions on how to choose acupressure points, practitioners would tailor the massage based on the patient's self-reported key symptoms, making adjustments throughout the session according to the patients' response. This process of tailoring within a given frame of techniques and specific acupressure points was described as essential to massage's efficacy by practitioners. Although parents were not asked directly about adapting massage techniques to their child's current physical and emotional state, their use of this approach was implicit in interview narratives.

(M) Mom said they'd used the P6 point when she was feeling nausea earlier in the day and it had helped. Mom said she wished she would move around more so I showed them some gentle stretches she could do in bed-knees pulled up to belly and knees going to either side… so she could do ST36 point herself.

(M) I think it is really important…that the massage therapist be able to determine what the patient needs at the moment because their needs do change.

(P4) On last Sunday when he feel his body ached, so I just rub him. Most of the time he do not feel like getting massage.

5. Massage's Effects on Parents and Family Dynamics

5.1. Performing Massage Improved Parents' Confidence as Caregivers. Most parents reported that they were able to learn massage techniques, and that they performed massage for their child intermittently or regularly—particularly parents of younger patients. Feelings of helplessness and anxiety are common among parents with hospitalized children, and parents expressed satisfaction and pride at being able to offer comfort and symptom relief to their children.

(P21) It was great. It was one of the few things I could do to help him through everything he was going through.

(P23) It felt good because I was able to put her at peace, relax, help her to go to sleep, help her with the pain.

(P13) For me it was, as a parent, taking control of her pain and just providing the peace that she needs. So just creating an environment of peace that you normally do not find in a hospital…I was reassuring her that…it was going to be all right.

5.2. The Social Effects of Massage. Parents reported that performing massage contributed to a heightened sense of intimacy and connection with their child.

(P10) When I give her massage, I just feel closer to her. I feel we're like one.

(P13) When you massage someone, you're touching them, and you're loving them at the same time…it gives you the desire to love your child, to touch them, to let them know that you are there for them.

(R) What was the best thing for you when you were giving your child a massage?

(P3) Well, that bond that occurs between two people when there's comforting happening.

(P22) To be able to talk to her and touch her at the same time, and just talk about how she was feeling.

At least two parents, however, reported that they did not readily learn or perform massage for their child, either due to the parent's perceived lack of competence or a missed opportunity for instruction in massage because she welcomed the opportunity for respite outside the hospital room when the massage practitioner arrived.

(P6) It helped when the massage therapist would show me and do it on my child, and then I would do it with her there. After she left, I kind of forgot where those [pressure points] were.

(M) She seemed amenable to learning the points and doing massage, but in practice she wasn't often there when I came… Some of the parents used the time when I came as respite time to leave the room.

Indeed, practitioner-provided massage offered parents a respite from caretaking and worry about their child, particularly since individual massage therapists became known and trusted by patients and parents over the course of the intervention. The knowledge that their children were experiencing comfort or pleasure provided stress relief for the parent and an opportunity to relax and take a break from the confines of the hospital room.

(P4) Sometime when she's give him massage, I was like out for a walk. Sometime when the therapist come in, I was like tired and fall asleep and nap.

(P7) It was actually relaxing. Knowing that it was helping him to relax, then it also helps me to relax.

(M) It gave the kids a sense of nurturing when their parents were absent or too overwhelmed or exhausted to provide physical touch.

Although most parents reported feeling closer to their child as a result of learning and performing massage, it is important to note that parent-child or broader social dynamics can also be a barrier to massage as a beneficial practice for children undergoing HCT. For example, one child mentioned to the professional massage practitioner that she preferred the professional massage to her father's

massage, but felt uncomfortable communicating this to her father. Once this was revealed, the massage practitioner was able to help the father to improve his technique. Also, two teenage boys in this study declined to receive massage from parents or massage practitioners (all women), which may suggest possible discomfort with touch or embarrassment of female touch.

6. Impact of Timing of Massage and Length of Hospitalization

The timing of massage treatments was an important factor in parents' perception of the efficacy and desirability of massage. The concept of timing includes how a massage session fit into a patient's daily schedule, and whether massage was perceived as more or less beneficial at particular phases of an individual's journey through the transplant process. In addition, participants who remained hospitalized—and therefore enrolled in the study—for a longer period of time often moved from initial skepticism to becoming strong advocates for massage.

6.1. Fitting Massage into the Daily Clinical Routine. Patients on the unit follow a busy schedule of tests and treatments, and the degree to which massage was welcomed by patients and their parents was contingent on how well it was coordinated with clinical routines and family visits. Massage practitioners were attuned to these scheduling issues, and often tried to schedule their visits to the unit during the late afternoon lull in clinical activity.

> *(R) What was the hardest thing about the massage study?*
>
> *(P2) Scheduling. . .when they were ready, [my daughter] wasn't ready sometimes, or when [she] was ready, they were far away.*
>
> *(P12) . . .it's evening, it's nighttime, so they're [massage practitioners] all gone. I would like to call them back [laughs].*

One parent felt that she had to "stand guard" at her child's hospital room door so that her massage would not be interrupted by hospital staff.

> *(P13) . . .[the practitioner] coming in was very important to her. . .and that's when I had to step in and say, "She's getting a massage". . .I had to be the keeper of the door.*

6.2. Massage during Periods of Acute Symptoms. During periods of acute discomfort or nausea, generally during the first week after chemotherapy, children varied in their response to massage, and some did not want it.

> *(P6) I think the hardest thing was just being open to it when she really felt miserable.*
>
> *(P17) . . .As he got more sick and was feeling worse, he wasn't able to have the massage therapist come in. . .So I would say at the beginning it's nice, and maybe at the end as they're getting back into normal life again, it's good. But there in the middle of the transplant, it's not so necessary.*
>
> *(R) And what was the biggest barrier for giving a massage?*
>
> *(P2) Basically, I do not know, if she's in deep pain or if she's not in the mood or she's sick and tired of the whole situation, you know?*

Several parents, however, reported that massage was particularly beneficial for their child during periods of acute discomfort.

> *(P12) I remember one day she said she hardly to sleep. The whole body is miserable and tired. And I have a really gentle massage for her, but it help.*
>
> *(P4) It's only whenever he feels nauseous and, yeah, vomiting, then he agree he want to have physical therapy [massage]. Most of all, he's always like not agree with the physical therapies.*

6.3. Length of Participation in the Study and Being "Won Over". Most parents in the study were new to massage. Some were immediately convinced of the potential benefit of massage while others were initially doubtful about whether massage could be helpful for their child. However, through the course of the study most parents came to value massage as an important component of the healing process.

> *(P21) Well, it's just something that he never really experienced before and was hesitant about in the beginning. But once they started, he looked forward to it every night that it was available.*
>
> *(P13) . . . You tend to be in the hospital and you do not want extra people coming into your room. But once [the practitioner] came in and we realized the benefits that she was getting from it, J. welcome her in. . .*

7. Discussion

HCT has resulted in improved survival rates among children with certain cancers, immune deficiency syndromes, or bone marrow failure, but it can be an agonizing ordeal for patients and their families. Indeed, in 1998 bone marrow transplantation was described as "the most devastating treatment that the human body could be subjected to" [25]. Medical advances in intervening years have resulted in a less punishing regimen, but transplantation still remains arduous and disruptive of the lives of patients and their caregivers. This study contributes to a growing body of research suggesting that massage can help alleviate the distress associated with HCT among both patients and their family caregivers. The qualitative methods employed by this study reveal outcomes that were undetected—and undetectable—by the broader study's quantitative design, including several that have not yet been reported in the literature. New findings include reported benefits for patients

in promoting sleep and providing symptom relief; benefits for parents in an increased sense of competence and respite from caregiving; and increased closeness between parent and child and a demonstrated willingness by parents to perform massage on their child

According to parent caregivers, massage provided varying degrees of relief from pain, nausea, and other symptoms associated with HCT for most, but not all, participants. Nearly all parents reported that massage sessions facilitated a general state of comfort, relaxation, and pleasure for their child. These findings are consistent with a study that reported reduced pain and increased relaxation among pediatric cancer patients who received massage [6], and with the results of a study suggesting that massage for cancer patients promotes positive feelings, relaxation, and a sense of being special and cared for [26]. Whether these benefits are sustained over time is an important question for future research, given the long-term suffering among survivors of childhood cancer and family caregivers described in numerous studies [27–31].

Massage helped children fall asleep. This finding is notable because HCT patients often find sleep elusive in the midst of chronic pain, nausea, and discomfort, yet sleep is rarely mentioned in the literature on massage and symptom management. Moreover, the promotion of comfort and sleep–states not easily reduced to dualistic conceptions of mind or body–suggest that the positive effects of massage are not physical *or* affective, but rather both simultaneously. This result is in line with previous research reporting that massage alleviates physical symptoms while also addressing the "existential suffering" associated with cancer and cancer treatments and improving patients' "quality of life" [20, 32, 33].

It should not be assumed, however, that massage is relaxing and pleasurable for all patients at all times. As demonstrated by our results, patients' request for, and response to, massage varied widely throughout the different stages of HCT, with some patients declining massage during periods of acute pain and nausea, and others requesting massage at precisely these times. Massage enabled children undergoing HCT to become coagents in the therapeutic process, and most children embraced this agency without reserve—electing massage only when it suited them. While most children appeared to appreciate parent massage, one child felt unable to decline her father's massages when she did not want them. Individual patients' needs, and the specific ways in which family dynamics mediate these needs, should be carefully determined and addressed in any pediatric massage intervention so as to avoid coercion and the perception among patients that massage is obligatory.

This study suggests that it is important to adapt a semistandardized massage protocol to the immediate, and always mutable, sensations and perceptions of individual patients; when it offers respite from long periods of tedium and inactivity; and when it does not interfere with treatment schedules and hospital routines. This is not to suggest that a carefully constructed protocol with clear instructions on acupressure and massage techniques for typical HCT-related symptoms is not important. However, a massage protocol that does not allow for flexibility within a semistandardized frame runs counter to the study's findings and may undermine some of massage's reported benefits.

Parents in this study were, for the most part, amenable to learning massage techniques that they could perform for their child, and the resulting interactions tended to have a positive effect on parent-child relations and to mitigate parents' and patients' suffering. These findings are in alignment with a nascent body of research suggesting that learning to perform massage for a family member can alleviate caregivers' anxiety and feelings of helplessness [16, 17], and that caregiver-provided massage for chronically ill family members increases a sense of intimacy and connection between the provider and recipient of massage [19]. More broadly, these results offer support for an understanding of disease and healing as social and material processes that extend beyond the individual, physical body [34].

Moreover, providing parents with a means of actively participating in their child's treatment and recuperation—and children with a sense of control over their bodies—may represent a shift in what one of the study's massage practitioners described as a hospital culture in which "the professionals are taking care of the children and the parents try not to get in the way." Parents felt comforted and strengthened when they were able to alleviate their child's suffering through massage. What are the broader implications, then, of parents playing a more active role in supportive care? Future research on massage and its increasing inclusion in biomedical treatment regimes could help elucidate these processes.

The success of parent-provided massage was dependent not only on parents' desire to help their child, but on the nature of the interaction between patient, parent, and massage practitioner, and on the development of trust and recognition within this triad. Massage is an inherently social practice, and for most of the children participating in the study, who was touching them was as important as which massage techniques were used. For example, in addition to the two teenage boys who decided not to enroll in the study, some older children, particularly boys, declined massage from their parent and/or from a massage practitioner (who were all women). These children's reluctance emerged postintervention in conversations between researchers and massage practitioners, rather than in interviews with participants, so the causes have not been explored in depth. In a study on massage for children with cancer, Post-White et al. reported no gender differences in response to massage, but 8 boys (over 30 percent of enrolled participants) failed to complete the study [6]. It is clear that more research is needed to examine how factors such as the child's age, sex, and ethnicity mediate the perception and experience of massage.

The limitations of this investigation are primarily related to it being a small pilot study without data from direct interviews with patients. There are also limitations in the study's data collection methods. First, conducting interviews by telephone limited the interviewer's ability to establish rapport with participants. In addition, scheduling the interviews after parents and children returned home from the hospital meant that participants' perspectives were restricted to recall.

Future research would be enriched by a series of in-depth, in-person interviews with both caregivers and patients over the course of treatment.

While parent reports indicate that massage may offer some short-term symptom relief, and that teaching massage to a parent may increase her or his sense of self-efficacy in managing a child's symptoms, longer-term benefits for both symptom relief and parent-child relationships were beyond the scope of this study. Questions that could be explored in more detail in follow-up studies include whether massage mitigates long-term, posttreatment suffering associated with HCT among both patients and caregivers, including post-traumatic stress. If massage/acupressure can provide relief from symptoms and even provide pleasurable feelings, it may reduce parental feelings of helplessness in the face of their child's pain and discomfort, a key symptom of posttraumatic stress. [35] Future research could also investigate the extent to which massage influences children's perceptions of their bodies [36] as they struggle with chronic disease and prolonged, invasive treatments for these diseases.

8. Conclusion

This study suggests that parent- and practitioner-provided massage may reduce suffering associated with HCT among pediatric patients and their parent caregivers. According to parent caregivers, massage relieved symptoms associated with HCT, and promoted sleep, relaxation, and comfort for their child. The data suggest that massage also may enhance the experience of intimacy and connection between children and parents; offer relief from prolonged periods of social isolation, boredom, and anxiety that characterize life for families in the pediatric HCT unit; and enable both patients and parents to play a more active role in managing symptoms. As a simultaneously physical and social practice, massage as applied in the context of this study's hospital setting is a therapy whose effectiveness among children requires family support, practitioner flexibility, coordination with clinical routines, and affinity among those who perform and receive it.

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