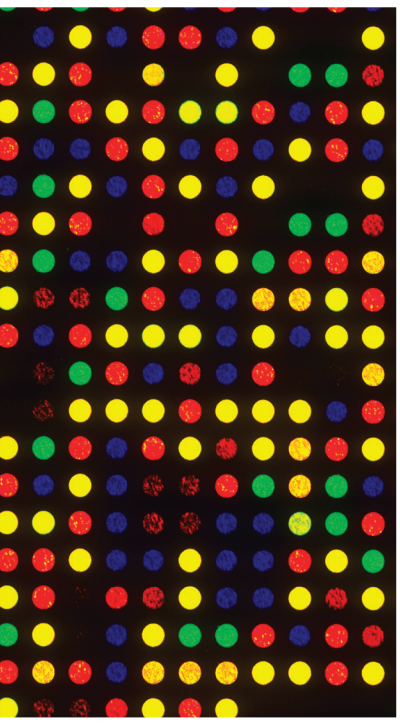
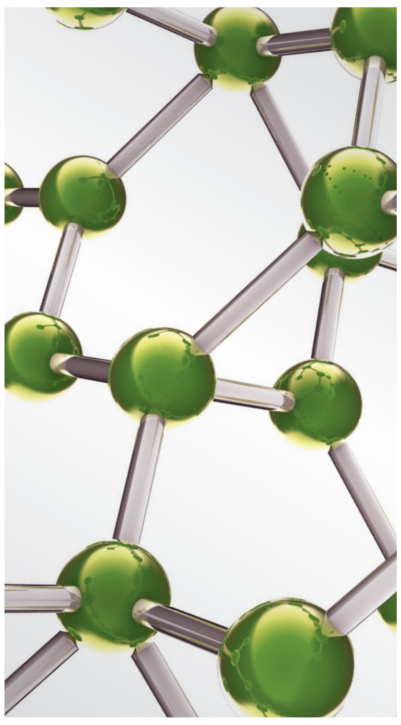
eCAM
Evidence-Based Complementary and Alternative Medicine

Complementary and Integrative Oncology in the Cross-Cultural Region of the Middle East and South Asia

Guest Editors: Eran Ben-Arye, Barrie Cassileth, Peter Heusser, Fatma Afifi, Bashar Saad, and Senthamil R. Selvan






Complementary and Integrative Oncology in the Cross-Cultural Region of the Middle East and South Asia

Evidence-Based Complementary
and Alternative Medicine

Complementary and Integrative Oncology in the Cross-Cultural Region of the Middle East and South Asia

Guest Editors: Eran Ben-Arye, Barrie Cassileth, Peter Heusser, Fatma Afifi, Bashar Saad, and Senthamil R. Selvan

Editorial Board

Contents

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 940961, 3 pages
doi:10.1155/2012/940961

Editorial

Complementary and Integrative Oncology in the Cross-Cultural Region of the Middle East and South Asia

Eran Ben-Arye,[1,2] Barrie Cassileth,[3] Peter Heusser,[4] Fatma Afifi,[5] Bashar Saad,[6,7] and Senthamil R. Selvan[8]

[1] *Integrative Oncology Program, The Oncology Service and Lin Medical Center, Clalit Health Services, Haifa 35152, Israel*
[2] *Complementary and Traditional Medicine Unit, Department of Family Medicine, Technion-Israel Institute of Technology, Haifa 32000, Israel*
[3] *Integrative Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA*
[4] *Department of Medicine, Center for Integrative Medicine, Faculty of Health, University of Witten/Herdecke, 58313 Herdecke, Germany*
[5] *Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Jordan, Amman 11942, Jordan*
[6] *Qasemi Research Center, Al-Qasemi Academic College, Baga Algharbiya 30100, Israel*
[7] *Department of Biology and Biotechnology, Arab American University, Jenin, Palestine*
[8] *Department of Medical Oncology, Thomas Jefferson University, 1015 Walnut Street, Suite 1008, College Bldg Philadelphia, PA 19107, USA*

Correspondence should be addressed to Eran Ben-Arye, eranben@netvision.net.il

Received 21 February 2012; Accepted 21 February 2012

The integration of traditional, complementary, and integrative medicine (CIM) in contemporary cancer care is an emergent field of clinical practice and research throughout the world. The use of herbs, nutrition, mind-body, and spiritual practices is deeply rooted in the cross-cultural mosaic of Middle Eastern and South Asian nations. The concept of integrative oncology has emerged in the last decade to signify the need to amalgamate traditional and complementary medicine practices with evidence-based research aiming to improve supportive cancer care. The integration of ancient *roots* with contemporary scientific *sprouts* is not merely a metaphor but a significant tool for promoting holistic patient-centered care that emphasizes patients' well-being rather than focusing merely on cancer cells and disease-centered terminology. Indeed, the remarkable achievements in contemporary integrative oncology only emphasize the need for a patient-tailored strategy of care attuned to the individual's biophysical, psychological, social, cultural, and spiritual needs and concerns. The integrative challenge is how to provide an evidence-based consultation and supportive treatment to patients who confront fear at the moment of breaking the bad news of cancer diagnosis; how to improve their well-being during chemotherapy, radiation, surgical, or palliative treatment; and how to support patients and their care providers along the survivorship pathway or across the threshold of life. In daily practice, integrative oncology may be employed to reduce nausea and vomiting (e.g., use of the traditional Ayurvedic and Chinese herb *Zingiber officinale* known as ginger [1]), to alleviate pain (e.g., acupuncture [2]), and to improve fatigue (e.g., exercise, relaxation and body awareness training combined with massage [3]), mood disturbances (manual modalities [4]), and many other disease symptoms and chemotherapy side effects. Integrative oncology is also challenged by the need to obtain CIM safety (e.g., awareness of the risks of herbal-chemotherapy interactions) and high-quality standards of CIM supplements as well as professional training of integrative practitioners. Last but not least, these fundamental elements need to be enhanced by open communication channels between CIM practitioners, oncologists, and other health care providers in order to conclude a comprehensive integrative approach based on vibrant multidisciplinary discourse. Hence, the concept of *integrative oncology* goes far beyond *traditional*, *alternative*, or *complementary* practice, signifying a call for

holistic practice, a whole that is larger than the sum of its scientific, clinical, and humanistic parts.

The paper by H. Zaid et al. featured in this special issue reviews the concept of traditional Islamic medicine with regard to herbs with potential anticancer activity. This paper illuminates the importance of bridging ancient knowledge rooted in Greco-Arabic medicine and contemporary research. But, in addition to the extensive review presented by H. Zaid et al., this paper is also distinctive thanks to the contribution of the two other authors in this collaborative Israeli-Palestinian paper. Notable is the contribution of M. Silbermann, the director of the US National Cancer Institute-affiliated Middle-East Cancer Consortium (MECC), who has succeeded over the last 15 years in promoting supportive care collaborations that have included joint integrative oncology projects between MECC (Egypt, Israel, Palestinian Authority, Jordan, Turkey, and Cyprus) and other Middle-Eastern countries [5, 6].

The paper by E. Ben-Arye presents an integrative oncology program operated within conventional oncology services in northern Israel aimed at improving patients' quality of life during chemotherapy and advanced cancer. The authors address barriers to integration of traditional and complementary medicine in supportive care of Arab patients and propose six practical recommendations aimed at improving patients' access to integrative supportive care as well as compliance with treatments. This paper emphasizes the need to base integrative oncology on a sensitive cross-cultural approach that takes into consideration social, cultural, and spiritual elements.

The paper by M. Schaltz et al. intensifies this cross-cultural theme by reflecting on palliative care from the perspective of Jewish and Islamic traditions. The collaboration in this paper between M. Schultz and K. Baddarni, two scholars in spiritual supportive care in northern Israel, highlights the richness of therapeutic dialogue between Muslim and Jewish health care providers who share faith in the role of the integrative dialogue. This paper summarizes ethical, religious, and spiritual insights gleaned in the management of patients in the community-centered Al-Taj organization and in the oncology department in Rambam health care campus, which is named for the renowned Jewish physician Maimonides.

The paper authored by I. Cantarero-Villanueva et al. from Granada presents the flavor of the ancient cities of southern Spain, the backdrop for the Golden Age of collaborative Muslim and Jewish physicians, including Maimonides and the followers of Ibn-Sina, the most prominent Islamic medicine scholar. In this paper, the authors evaluated, in a randomized controlled trial, the effects of a multimodal exercise and massage program on the well-being of breast cancer survivors. The reduced fatigue, tension, depression, and improved vigor and muscle strength after intervention and 6 months after discharge are remarkable and support the need for other rigorous trials in the integrative oncology field.

Moving from West to East across the Mediterranean and West Asia, the paper by P. Puataweeponge et al. presents the notion of complementary medicine in Bangkok, Thailand. The authors present a study regarding CAM use by a large cohort of cancer patients attending outpatient radiotherapy treatment in Thailand. The high prevalence of CAM use of more than 60% is notable in light of the patient-oncologist communication gap illustrated by the high prevalence (58.3%) of patients who did not disclose CAM use to their doctors. This communication aspect should raise concern when 9.4% of patients in this study reported side effects of CAM treatments. Moreover, this study emphasizes the need for a paradigm shift from CAM (with emphasis on *alternative*) to CIM (with emphasis on *integrative*) that will enable patients and physicians to discuss complementary use in an open nonjudgmental context.

Two papers in this issue present the fundamental *in vitro* research elements needed to base any clinical integrative oncology activity. Zhang et al. from China report. the anticancer effects of the photochemical Zerumbone, isolated from the plant *Zingiber zerumbet* Smith. Although additional rigorous studies are warranted, the promising apoptosis induction effect of this plant on pancreatic carcinoma cell lines may suggest that ginger and related plants may have anticancer properties in addition to their beneficial effect in chemotherapy-related nausea and vomiting. In the paper by Y. H. Liu et al. from neighboring Taiwan, they studied Abrin, a protein purified from the seeds of *Abrus precatorius*, and reported that prohibitin, a tumor-suppressing protein, plays a role in abrin-induced apoptosis. These findings join the growing number of promising studies in integrative oncology that may support development of new and, in some cases, traditional medicine-based, therapeutic agents and modalities for the benefit of patients with cancer across the globe.

Acknowledgments

We would like to deeply thank and acknowledge the extensive editorial work that was invested by the coeditors and reviewers of this special issue. This unique group of five coeditors active in integrative oncology research and practice in three continents has inspired us to recognize and realize that, despite cultural and political challenges, we share a sense of grace, for the benefit and well-being of patients confronting cancer.

Eran Ben-Arye
Barrie Cassileth
Peter Heusser
Fatma Afifi
Bashar Saad
Senthamil R. Selvan

References

[1] A. K. Pillai, K. K. Sharma, Y. K. Gupta, and S. Bakhshi, "Anti-emetic effect of ginger powder versus placebo as an add-on therapy in children and young adults receiving high emetogenic chemotherapy," *Pediatric Blood and Cancer*, vol. 56, no. 2, pp. 234–238, 2011.

[2] D. G. Pfister, B. R. Cassileth, G. E. Deng et al., "Acupuncture for pain and dysfunction after neck dissection: results of a randomized controlled trial," *Journal of Clinical Oncology*, vol. 28, no. 15, pp. 2565–2570, 2010.

[3] L. Adamsen, M. Quist, C. Andersen et al., "Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial," *BMJ*, vol. 339, no. 7726, Article ID b3410, pp. 895–898, 2009.

[4] M. Listing, A. Reißhauer, M. Krohn et al., "Massage therapy reduces physical discomfort and improves mood disturbances in women with breast cancer," *Psycho-Oncology*, vol. 18, no. 12, pp. 1290–1299, 2009.

[5] E. Ben-Arye, E. Schiff, E. Hassan et al., "Integrative oncology in the Middle East: from traditional herbal knowledge to contemporary cancer care," *Annals of Oncology*, vol. 23, no. 1, pp. 211–221, 2012.

[6] E. Ben-Arye, M. S. Ali-Shtayeh, M. Nejmi et al., "Integrative oncology research in the Middle East: weaving traditional and complementary medicine in supportive care," *Supportive Care in Cancer*, vol. 20, no. 3, pp. 557–564, 2012.

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 670408, 6 pages
doi:10.1155/2012/670408

Research Article

A Survey of Complementary and Alternative Medicine Use in Cancer Patients Treated with Radiotherapy in Thailand

Putipun Puataweepong,[1] Nongnuj Sutheechet,[2] and Panjachat Ratanamongkol[3]

[1] *Radiotherapy and Oncology Unit, Department of Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Rajtawee, Bangkok 10400, Thailand*
[2] *Department of Anesthesiology, Nopparat Ratchthani Hospital, Kannayao, Bangkok 10230, Thailand*
[3] *Department of Paediatrics, Bhumibol Adulyadej Hospital, Saimai, Bangkok 10220, Thailand*

Correspondence should be addressed to Putipun Puataweepong, rapptw@mahidol.ac.th

Received 15 August 2011; Revised 16 December 2011; Accepted 19 December 2011

Academic Editor: Fatma U. Afifi

Introduction. Use of complementary and alternative medicine (CAM) in cancer patients is increasingly acceptable worldwide, but most of the studies were surveyed from developed countries. In this study, we evaluated the first and large cohort of cancer patients with CAM use in Thailand. *Materials and Methods*. A self-administered questionnaire was completed by 248 cancer patients attending outpatient radiotherapy unit at Ramathibodi Hospital. *Results*. The prevalence of CAM use was 60.9%. The most frequently used CAM were dietary/vitamin supplements (56.9%). Independent predictors of CAM use were high income ($P < 0.001$) and cancer type ($P = 0.019$). About half of the patients (51%) reported positive effects from CAM use. Nevertheless, 9.4% of the patient also reported side effects. The majority of patients (58.3%) did not disclose their use of CAM to their doctors because they felt that it was not necessary for doctors to know (65.9%). The average spending for CAM use was 200 USD/month (range, 10–1,000). *Conclusion*. Although the cost for CAM is relatively expensive, the prevalence of CAM use in cancer patients in Thailand is high particularly, in patients with higher income. Therefore, all clinical oncologists should be concerned about the use of CAM during evaluation of the cancer patients.

1. Introduction

Cancer is the major cause of death in most countries throughout the world. The main standard or conventional therapies such as surgery, chemotherapy, radiotherapy, and hormone therapy usually cause many adverse effects. Complementary and alternative medical (CAM) practices have become increasingly popular worldwide and many cancer patients have turned to CAM with hope of finding a cure to their illness, as well as to make them feel better. The National Center for Complementary and Alternative Medicine (NCCAM) defines CAM as a group of diverse medical and healthcare systems, practices, and products that are not considered to be part of conventional medicine [1]. The prevalence of CAM use in cancer patients is frequently high and estimated to be from 30% to 90% [2–7]. The update systematic review [3] was the surveyed studies published from 18 countries in Australia, Canada, Europe, New Zealand, and the United States. From this study, the combined prevalence for current use of CAM in cancer patients was 40%. The highest was in the United States and the lowest in Italy and the Netherlands. This metaanalysis also suggested an increase in CAM use from an estimated 25% in the 1970s and 1980s to more than 32% in the 1990s and to 49% after 2000. Nevertheless, most of studies for CAM use in cancer patients usually came from western and developed countries. So far, very few studies have described the use of CAM in developing countries. To date in South East Asia including Thailand, the rate of CAM use among cancer patients is unknown. The use of traditional herbs and remedies in our country is, however, well known and relatively common. We evaluated the first and large cohort of cancer patients with CAM use in Thailand. Understanding CAM use among cancer patients may provide insight into the motivations behind such use and, therefore, the degree to which conventional medical care has not met the needs of cancer

patients. Thus, the aims of this study were to determine the prevalence and pattern of CAM use, reason for using CAM, the perceived effectiveness as well as their communication with doctors about its use.

2. Materials and Methods

The study design was a descriptive cross-sectional study conducted at the radiotherapy outpatient clinic at Ramathibodi Hospital, Bangkok, Thailand. It was approved by the Ethics Committee on Human Experimentation of the hospital.

2.1. The Questionnaire. The questionnaire used in this study was the newly developed self-administering questionnaire, because currently there is no related and proper questionnaire developed in Thailand. After an extensive literature reviews on CAM in cancer patients, the 21-item questionnaire was developed on the basis of the standard questionnaire development (see the appendix).

2.2. Study Subjects. All cancer patients attending the radiotherapy outpatient clinic of Ramathibodi Hospital from 1 June to 30 July 2011 were recruited into the study. The inclusion criteria were all of 18-year and older patients with diagnosis of cancer within 3 years, writing ability in Thai, and willingness to participate in this study.

2.3. Data Collection. All patients who met the inclusion criteria during study period were invited to participate. Information about the research was given verbally to each patient; those who gave consent then filled in the questionnaires. The participants used 10–15 minutes to complete the questionnaire while they were waiting at the outpatient clinic to be seen by their physicians. Physicians who were in any way involved in the treatment of each patient were not present during the administration of the questionnaire. On completion, the patients either put the questionnaire in a box or handed it to the researcher assistant.

2.4. Statistical Analysis. The demographic characteristic data were calculated by descriptive statistics. Categorical data were described with frequency and percentage and compared by using chi-square. Continuous data were reported with mean and range and compared by using student's t-test. All analyses were performed using SPSS software version 16.0.

3. Results

There were 248 cancer patients participating in this study. One hundred and fifty-one (60.9%) of the total participants reported having used at least one CAM since their diagnosis of cancer. Table 1 shows the demographic characteristics of CAM users and non-CAM users. There were no significant differences in the proportion of CAM users by gender, age, marital status, religion, education level, occupation, cancer type, or cancer staging. There were, however, significant differences in the proportion of cancer patients using CAM by income achievement ($P = 0.001$) and by the cancer type ($P = 0.019$). The patients with a higher income were more likely to use CAM than those with a lower income. With regard to the cancer type, the highest prevalence rate of CAM use was by those with malignant brain tumor, followed by those with lung cancer, and those with genitourinary cancer. The lowest rates of CAM use were observed in gastrointestinal cancer patients. The CAM products/therapies that were used are shown in Table 2. The most common CAM was dietary/vitamin supplement followed by dietary adjustment, meditation, herbal medicine, and massage, respectively.

Table 1: Patient characteristic of CAM users and non-CAM users.

Characteristics	CAM users (%) 151 (60.9)	Non-CAM user (%) 113 (39.1)	P value
Sex			0.254
Male	47 (56)	37 (44)	
Female	104 (63.4)	60 (36.4)	
Mean age	53.7 yrs	54.3 yrs	0.728
Marital status			0.155
Single	21 (63.6)	12 (36.4)	
Married	100 (57.1)	75 (42.9)	
Widowed/divorced	28 (73.7)	10 (26.3)	
Education status			0.327
Primary school or lower	61 (55.4)	49 (44.6)	
Secondary/vocational school	43 (65.2)	23 (34.8)	
Bachelor or higher	46 (66.7)	23 (33.3)	
Occupation			0.374
Unemployed/retired/housewife	61 (55.4)	49 (44.6)	
Employee	28 (71.8)	11 (28.2)	
Government official	25 (71.4)	10 (28.6)	
Business owner	18 (58.1)	13 (41.9)	
Agriculturist	17 (56.7)	13 (43.3)	
Income (USD/month)			0.001*
Less than 166	38 (46.3)	44 (53.7)	
167–333	32 (60.4)	21 (39.6)	
334–666	40 (71.4)	16 (28.6)	
More than 666	41 (71.9)	16 (28.1)	
Cancer type			0.019*
Breast	38 (61.29)	24 (38.71)	
Genitourinary	36 (67.9)	17 (32.1)	
Head and neck	31 (60.8)	20 (39.2)	
Gastrointestinal	8 (34.8)	15 (65.2)	
Lung	11 (78.6)	3 (21.4)	
Brain	13 (86.7)	2 (13.3)	
Others	7 (41.2)	10 (58.8)	
Not know/uncertain	7 (53.8)	6 (46.2)	
Cancer stage			0.761
Stage I	33 (58.9)	23 (41.1)	
Stage II	40 (58.8)	28 (41.2)	
Stage III	29 (51.8)	27 (48.2)	
Stage IV	12 (50)	12 (50)	
Do not know/uncertain	32 (86.5)	5 (13.5)	

Table 2: Types of complementary and alternative medicine used by patients ($n = 151$).

Type	Frequency (%)
Diet & nutrition	
Food/vitamin supplement	86 (56.9)
Dietary adjustment	75 (49.7)
Vegetarian food	25 (16.6)
High dose vitamin C	14 (9.3)
Physical body/relaxation	
Massage	34 (22.5)
Aromatherapy	23 (15.2)
Detoxification	20 (13.3)
Electromagnetic therapy	4 (2.6)
Acupuncture	3 (2.0)
Mind-body	
Meditation	64 (42.4)
Yoga	8 (5.3)
Tai chi	6 (4.0)
Yorae	5 (3.3)
Herbal medicine	47 (31.1)
Spiritual therapies	17 (11.3)

Most patients were using CAM because as they wanted to counteract suffering symptoms from the cancer or medical treatment (33.1%), to directly fight the disease or decrease the tumor (31.1%), to assist conventional treatment (25.2%), to improve physical well-being (17.2%), to improve emotional well-being or provide hope (11.3%), and as well as to do everything possible to fight the disease (3.3%).

About half of the patients reported positive effects from CAM use including good effect (20%) and moderate effect (31.0%), while 10.3% of patients reported no effect from CAM use. Nevertheless, 38.6% of patients were uncertain about their effect. Fourteen patients (9.4%) reported side effects from the CAM therapy they had used, most of which seemed to be related to ingesting herbs or minerals and massage. These side effects included decrease in appetite (5 cases), diarrhea (3 cases), exhaustion (3 cases), nausea-vomiting (2 cases), gastric discomfort (2 cases), constipation (1 case), abnormal menstruation (1 case), and muscle sprain (1 case). Moreover, two patients complained about the cost of their CAM use.

The majority of CAM users (58.2%) did not disclose the use of CAM to their medical doctors, the most common reasons were that it was not necessary for the doctors to know (65.9%), or the doctors never asked (40.9%) or the doctors would disapprove of it (33.0%). Sixty-three patients (41.7%) had told their doctors that they were using CAM. 39.7% of doctors responded favorably, 33.3% of doctors were against it, and 27% of doctors did not offer any opinion about CAM uses. Reasons for disclosure of CAM use to their doctors were "the doctor asked" (37.1%), "the doctor should know" (20.5%), and "wanted to know doctor's opinion about CAM use" (2.0%).

Patients were asked how much on average they spent on CAM in one month. Only 58 out of 151 patients reported expenses (38.4%). The average spending was 200 USD/month, (with the range of 10–1,000). However, 3 patients reported that they used herbal medicine which they planted for their own use; therefore, they had no expenditure for CAM. Likewise, one patient had relatives massage for him and had no expenditure.

4. Discussion

To our knowledge, this is the first study of the use of CAM by patients with a variety of cancers in Thailand, and it is one of the few representative studies available about the use of CAM in cancer patient in Asia. The use of CAM by cancer patients is very common and varies widely among populations. The update systematic review from Horneber et al. [3] that surveyed a total of 152 studies from 18 countries in the western world such as Australia, Canada, Europe, New Zealand, and the United States reported that the prevalence for current use of CAM across all studies was 40%. Regarding the prevalence of CAM use in Asian countries, there is very few study reports, but the prevalence of CAM use seems to be higher than that from the western countries. For the example, the prevalence of CAM use ranged from 54% to 61% in Turkey [4, 8], 64% in Malaysia [5], 60.9% in Palestine [9], 55% in Singapore [10], and 93.4% in China [11]. The rate of 60.9% that we found in this study is quite similar with the papers from Asian countries but higher than that of the study from Western countries. The higher prevalence rate in our study and in Asian countries may be explained by multiple factors such as traditional culture, religious beliefs, the cost of conventional treatment or the methodology, and the instrument used to collect the data. Sociodemographic factors that appear to be related to CAM use are younger age, higher education, higher income, married status, involvement in a support group, and health insurance [12]. In the present study, it was found that people from higher income used CAM more frequently. It was also interesting to see the prevalence rates of CAM use among different cancer types and stages. Despite suggestions from the literature that CAM applications were significantly higher in the group with advanced diseases and recurrent diseases [13], the present study showed that brain and lung cancer patients used CAM therapies significantly more often than any other cancer types. The possibility of the higher prevalence in both cancer types might be because both of these diagnostic categories are characterised by poor prognosis and a rapid physical decline, often with metastasis present, and such patients may have little hope from conventional treatments, thus turning to CAM as an additional intervention to improve their lives. The role of CAM may be important, not only because it increases hope and optimism, but also improves quality of life and helps manage symptoms, especially in terminal illness; however relevant data in cancer patients are almost nonexistent to date. However, some of the results in this subgroup analysis should be viewed with caution, as only a small number of patients participated in some of the diagnostic categories.

There are many types of CAM use worldwide. The most popular CAM uses were dietary supplements, herbs and botanicals, and relaxation techniques/meditation [2, 12, 14, 15]. In our surveyed population, the most frequently used CAM was dietary and vitamin supplement, followed by dietary adjustment. The choice of the specific CAM treatment used is based primarily on individual patient complaints and problems, which may explain the discrepancies among the studies. Furthermore, the stage of the cancer and the approval of the patient's physician may contribute to determining the type of CAM preferred by the patient. In cases of advanced cancer, spiritual or relaxation therapies may be the most appropriate complementary treatments, whereas homeopathy or acupuncture may be the more popular treatments of choice in earlier stages of cancer or in other chronic diseases. Additional parameters that may affect treatment choice are different cultural norms, backgrounds, and religious beliefs.

The major expectation of the patients in this study was "counteract suffering symptoms from the disease or medical treatment." Since many of these therapies used are "complementary" in nature (such as aromatherapy, massage, meditation, and others), we may not need to prove their effectiveness before using them. As patients are demanding such therapies, they are low-risk therapies and patients feel good after their use. Such therapies may have a great role to play, especially in the palliative care setting, where the goal is not cure but rather improvement in quality of life. Patient satisfaction can be an appropriate end point outcome for evaluation in this setting rather than clinical outcome.

For the positive and negative effects from its use, half of the patients seemed to be satisfied with the use of CAM, for they reported good or moderate benefit from it. A wide range of reasons may contribute to the use of CAM, and perhaps the concept of "hope" is fundamental in each one of these reasons. More than 30% of the patients used CAM therapies to directly fight the cancer or to decrease the tumor burden. It is interesting to see that <5% of the patients used CAM following the recommendation of their physician. These findings coincide with findings from the other previous studies [5–7, 16–19] and perhaps are reflecting the disapproval of CAM therapies by the medical community or the lack of information within the medical community about available and effective CAM therapies. Most patients reported no adverse reactions to CAM. However, the potential for harmful drug: CAM product interactions exists. There was a report showing that the use of CAM is also associated with a significant delay in cancer treatment [20].

Almost 60% of cancer patients who used CAM since the diagnosis of cancer did not disclose the use of their CAM therapies to their doctors. The main reasons for nondisclosure were: "It was not necessary for the doctor to know," 41% of patients reported that "their doctors did not ask," and one-third of the patients feared disapproval from their doctors. These findings are consistent with those of other investigators [5–7, 16–19].

In our survey, when patients consulted their doctors, almost 40% of them were told that they were free to continue using CAM but one-third of the patients were told to stop. These figures were also similar to the results in a previous study of clinical oncologists [21]. It appears that a difficult situation for many oncologists emerges because of their lack of scientific information on CAM. However, physicians should acknowledge that 40.9% of patients did not inform their physicians of their CAM use because their doctors did not ask them. These results indicate that better patient-physician communication and more reliable information on CAM products are needed.

It has been suggested that poor communication between physicians and cancer patients might lead to patients' dissatisfaction. Thus, these patients are more likely to seek alternative methods for their treatment outside the conventional treatment. In other words, it is argued that if patients could better communicate with their care physicians, then it would be possible to receive enough information on the progress of their disease and treatment, and therefore there would not be a ground for seeking alternative methods, or if they still felt it were necessary, they would consult with their physicians about the risks and benefits of complementary therapies.

5. Conclusion

CAM use is common among cancer patients on treatment with radiation therapy in Thailand. The patients with a higher income were more likely to use CAM than those with a lower income. However, the expense of CAM use is relatively expensive when compared to their income. Most of the patients expect to be improved from suffering symptoms of cancer and medical treatment, but only half of the patients experienced the benefit of CAM. The majority of patients did not disclose their use of CAM to their doctors because they felt that it was not necessary for doctors to know. This finding might suggest that there were some communication gaps between the clinicians and their patients. We recommend that all clinical oncologists should be concerned and ask every patient about the use of CAM as a routine practice.

Appendix

I.D.....

Please indicate your answers in the spaces provide below.
(If you do not want to answer a question, please leave it blank)

(1) Diagnosis

- ☐ Liver cancer
- ☐ Lung cancer
- ☐ Skin cancer
- ☐ Lymphoma
- ☐ Brain cancer
- ☐ Breast cancer
- ☐ Gastric cancer
- ☐ Esophageal cancer
- ☐ Colorectal cancer
- ☐ Uterine cancer
- ☐ Cervical cancer
- ☐ Prostate cancer
- ☐ Head and neck cancer
- ☐ Nasopharyngeal cancer
- ☐ Laryngeal cancer

☐ Bladder cancer
☐ Bone cancer
☐ I do not know
☐ Other (please specify)……..

(2) Stage of cancer
☐ (1)
☐ (2)
☐ (3)
☐ (4)
☐ (5) I don't know

(3) Age, yr.....

(4) Sex
☐ (1) Male
☐ (2) Female

(5) Highest level of education completed
☐ (1) None
☐ (2) Primary school
☐ (3) High school
☐ (4) College
☐ (5) Professional degree
☐ (6) Other (please specify).....

(6) What is your religion?
☐ (1) Bhudism
☐ (2) Muslim
☐ (3) Christian
☐ (4) Other (please specify)……

(7) Marital status
☐ (1) Single
☐ (2) Married
☐ (3) Widowed/divorced

(8) Employment status
☐ (1) Employed (full time)
☐ (2) Employed (part time)
☐ (3) Employed but on medical leave/disability
☐ (4) Self-employed
☐ (5) Other (please specify).....

(9) What is your monthly income?
☐ (1) No income
☐ (2) Less than 1,500 USD
☐ (3) 1500–3500 USD
☐ (4) 3500–7000 USD
☐ (5) 7000–10000 USD
☐ (6) 10000 USD

(10) What treatment have you had for your cancer?
☐ (1) Chemotherapy
☐ (2) Radiation therapy
☐ (3) Surgery
☐ (4) Biological or targeted therapy

(11) Do you currently use any supplements or alternative therapies or have you used these in the past
☐ (1) Yes (then proceed to question 12)
☐ (2) No

(12) Please check all that you currently use or have you used these in the past (please check all that apply)
☐ (1) Food/vitamin supplement
☐ (2) Dietary adjustment
☐ (3) High dose vitamin C
☐ (4) Vegetarian diet
☐ (5) Detoxification
☐ (6) Acupuncture
☐ (7) Massage
☐ (8) Aromatherapy
☐ (9) Electromagnetic therapy
☐ (10) Spiritual therapies
☐ (11) Herbal medicine
☐ (12) Meditation
☐ (13) Tai chi
☐ (14) Yoga
☐ (15) Yorae
☐ (16) Other (please specify).....

(13) How did you learn about these supplements or alternative therapy? (check all apply)
☐ (1) Family members
☐ (2) Friends
☐ (3) Personal knowledge
☐ (4) Doctor
☐ (5) Books/Magazines/TV/Radio
☐ (6) Other cancer patients
☐ (7) Other (please specify).....

(14) When using these supplements or alternative therapies, have they benefited you?
☐ (1) No effect
☐ (2) Good effect
☐ (3) Moderate effect
☐ (4) Uncertain

(15) When using these supplements or alternative therapies, have you experienced unpleasant side effects?
☐ (1) Yes, specify.....
☐ (2) No
☐ (3) Uncertain

(16) About how much money have you spent on supplements or alternative therapies?.....USD/month

(17) Have you told your doctor about these supplements or alternative therapies?
☐ (1) Yes because
☐ (1.1) Doctor asked
☐ (1.2) Doctor should know
☐ (1.3) Wanted to know the doctor's opinion
☐ (1.4) Other (please specify).....
☐ (2) No because
☐ (2.1) Doctor did not ask
☐ (2.2) It was not necessary for doctor to know
☐ (2.3) Doctor would disapprove
☐ (2.4) Other (please specify).....

(18) If you told your doctor, what was his/her reaction? (check all apply)
☐ (1) Doctor in favor
☐ (2) Doctor opposed
☐ (3) Doctor do not offer opinion
☐ (4) Other (please specify).....

.....

Thank you

References

[1] http://nccam.nih.gov/health/whatiscam/.
[2] N. Klafke, J. A. Eliott, G. A. Wittert et al., "Prevalence and predictors of complementary and alternative medicine (CAM)

use by men in Australian cancer outpatient services," *Annals of Oncology*, vol. 5, pp. 1–8, 2011.

[3] M. Horneber, G. Bueschel, G. Dennert et al., "How many cancer patients use complementary and alternative medicine: a systematic review and metaanalysi," *Integrative Cancer Therapies*. In press.

[4] A. D. Akyol and B. Oz, "The use of complementary and alternative medicine by patients with cancer: in Turkey," *Complementary Therapies in Clinical Practice*, vol. 17, no. 4, pp. 230–234, 2011.

[5] S. H. Shaharudin, S. Sulaiman, N. A. Emran et al., "The use of complementary and alternative medicine among Malay breast cancer survivors," *Alternative Therapies In Health And Medicine*, vol. 17, no. 1, pp. 50–56, 2011.

[6] A. Naing, S. K. Stephen, M. Frenkel et al., "Prevalence of complementary medicine use in a phase 1 clinical trials program: the MD anderson cancer center experience," *Cancer*, vol. 117, no. 22, pp. 5142–5150, 2011.

[7] M. J. Sewitch, M. Yaffe, J. Maisonneuve et al., "Use of complementary and alternative medicine by cancer patients at a montreal hospital," *Integrative Cancer Therapies*. In press.

[8] L. A. Algier, Z. Hanoglu, G. Ozden, and F. Kara, "The use of complementary and alternative (non-conventional) medicine in cancer patients in Turkey," *European Journal of Oncology Nursing*, vol. 9, no. 2, pp. 138–146, 2005.

[9] M. S. Ali-Shtayeh, R. M. Jamous, and R. M. Jamous, "Herbal preparation use by patients suffering from cancer in Palestine," *Complementary Therapies in Clinical Practice*, vol. 17, no. 4, pp. 235–240, 2011.

[10] W. H. Chow, P. Chang, S. C. Lee, A. Wong, H. M. Shen, and H. M. Verkooijen, "Complementary and alternative medicine among Singapore cancer patients," *Annals of the Academy of Medicine Singapore*, vol. 39, no. 2, pp. 129–135, 2010.

[11] L. Teng, K. Jin, K. He et al., "Use of complementary and alternative medicine by cancer patients at zhejiang university teaching hospital zhuji hospital, China," *African Journal of Traditional, Complementary and Alternative Medicines*, vol. 7, no. 4, pp. 322–330, 2010.

[12] A. Wanchai, J. M. Armer, and B. R. Stewart, "Complementary and alternative medicine use among women with breast cancer: a systematic review," *Clinical Journal of Oncology Nursing*, vol. 14, no. 4, pp. E45–E55, 2010.

[13] O. Tarhan, A. Alacacioglu, I. Somali et al., "Complementary-alternative medicine among cancer patients in the western region of Turkey," *Journal of B.U.ON.*, vol. 14, no. 2, pp. 265–269, 2009.

[14] S. Butler, A. Owen-Smith, C. Diiorio, M. Goodman, J. Liff, and K. Steenland, "Use of complementary and alternative medicine among men with prostate cancer in a rural setting," *Journal of Community Health*, vol. 36, no. 6, pp. 1004–1010, 2011.

[15] J. A. Brauer, A. El Sehamy, J. M. Metz, and J. J. Mao, "Complementary and alternative medicine and supportive care at leading cancer centers: a systematic analysis of websites," *Journal of Alternative and Complementary Medicine*, vol. 16, no. 2, pp. 183–186, 2010.

[16] C. L. McDermott, D. K. Blough, C. R. Fedorenko et al., "Complementary and alternative medicine use among newly diagnosed prostate cancer patients," *Supportive Care in Cancer*, vol. 20, no. 1, pp. 65–73, 2012.

[17] R. Mercurio and J. A. Eliott, "Trick or treat? Australian newspaper portrayal of complementary and alternative medicine for the treatment of cancer," *Supportive Care in Cancer*, vol. 19, no. 1, pp. 67–80, 2011.

[18] B. Oh, P. Butow, B. Mullan et al., "Patient-doctor communication: use of complementary and alternative medicine by adult patients with cancer," *Journal of the Society for Integrative Oncology*, vol. 8, no. 2, pp. 56–64, 2010.

[19] G. A. Saxe, L. Madlensky, S. Kealey, D. P. H. Wu, K. L. Freeman, and J. P. Pierce, "Disclosure to physicians of CAM use by breast cancer patients: findings from the women's healthy eating and living study," *Integrative Cancer Therapies*, vol. 7, no. 3, pp. 122–129, 2008.

[20] G. E. Davis, C. L. Bryson, B. Yueh, M. B. McDonell, M. A. Micek, and S. D. Fihn, "Treatment delay associated with alternative medicine use among veterans with head and neck cancer," *Head and Neck*, vol. 28, no. 10, pp. 926–931, 2006.

[21] D. M. Eisenberg, R. B. Davis, S. L. Ettner et al., "Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey," *Journal of the American Medical Association*, vol. 280, no. 18, pp. 1569–1575, 1998.

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 936030, 8 pages
doi:10.1155/2012/936030

Research Article

Zerumbone, a Southeast Asian Ginger Sesquiterpene, Induced Apoptosis of Pancreatic Carcinoma Cells through p53 Signaling Pathway

Songyan Zhang,[1] Qiaojing Liu,[2] Yanju Liu,[1] Hong Qiao,[3] and Yu Liu[2]

[1] *Department of Hepatopancreatobiliary Surgery, The Third Affiliated Hospital of Harbin Medical University, Harbin 150040, China*
[2] *Department of Laboratory Medicine, The Fourth Affiliated Hospital of Harbin Medical University, Harbin 150001, China*
[3] *Department of Endocrinology, The Second Affiliated Hospital of Harbin Medical University, Harbin 150086, China*

Correspondence should be addressed to Hong Qiao, qiaohonghmu@gmail.com and Yu Liu, liuy.doctor@gmail.com

Received 28 August 2011; Revised 13 October 2011; Accepted 17 October 2011

Academic Editor: Senthamil R. Selvan

Pancreatic carcinoma is one common cancer with gradually increasing incidence during the past several decades. However, currently the candidate drugs to suppress pancreatic cancer remain lacking. This research was carried out to investigate if zerumbone, a natural cyclic sesquiterpene isolated from Zingiber zerumbet Smith, will produce the anticancer effects on pancreatic carcinoma cell lines. The results showed that zerumbone concentration, and time, dependently produced inhibitory actions on cell viability of PANC-1 cells. In addition, Hoechst 33342, AO/EB, TUNEL staining, and caspase-3 activity assay further showed that zerumbone induced apoptosis of PANC-1 cells. The expression of p53 protein was markedly upregulated, and the p21 level was also obviously elevated in zerumbone-treated PANC-1 cells. Moreover, ROS production was increased by about 149% in PANC-1 cells treated by zerumbone 30 μM. Zerumbone also produced the same antitumor activity in pancreatic carcinoma cell lines SW1990 and AsPC-1. In summary, we found that zerumbone was able to induce apoptosis of pancreatic carcinoma cell lines, indicating to be a promising treatment for pancreatic cancer.

1. Introduction

As a crucial part of the digestive system, the incidence of pancreatic cancer is gradually increasing during the past decades all over the world. It was reported that approximately 37,000 individuals were diagnosed with pancreatic cancer in the United States [1]. The 5-year survival rate of patients with pancreatic cancer is less than 10%, and more than 30,000 people die from this cancer every year [2]. Pancreatic cancer remains one of the four or five most common causes of cancer mortality in developed countries. Currently, the therapeutic drugs for pancreatic cancers are lacking, and were hampered by their toxic actions on normal organs. Particularly, pancreatic cancer is seldom diagnosed during its early stages in clinics [2, 3]. Accordingly, developing the new drug and strategy to prevent or treat pancreatic cancer is an important mission.

Zingiber zerumbet Smith is one kind of plant growing mainly in Southeast Asia, which has been demonstrated to possess antinociceptive, anti-inflammatory, antiulcer, antihyperglycemic, and antiplatelet activities [4–7]. As a major compound extract, zerumbone is currently explored for its potential broad use on cancers, leukemia, as well as virus infection (Figure 1) [8–10]. Recently, several studies have shown that zerumbone also produced a variety of pharmacological effects, including antioxidants, antivirus, anti-inflammatory, hepatoprotection, antiplatelet aggregation, and antibacterial [8–13]. Recently, the increasing attention was paid to the anticancer actions of zerumbone. It was reported that zerumbone exhibited a strong ability to treat liver cancer, lung carcinogenesis, and leukemia through increasing the apoptosis and inhibiting the invasion [8, 12–15]. But, whether zerumbone played the inhibitory roles in pancreatic cancer cells remains unknown. The present study

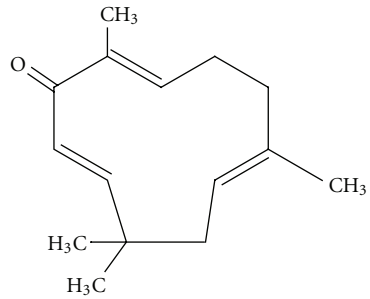


Figure 1: The chemical structure of zerumbone, a Southeast Asian ginger sesquiterpene.

was undergone aiming to determine the antitumor role of zerumbone in pancreatic cancers.

2. Materials and Methods

2.1. Cell Culture. Human pancreatic carcinoma cell lines PANC-1 and SW1990 were cultured in Dulbecco's modified Eagle's medium (DMEM) containing penicillin (100 units/mL), streptomycin (100 μg/mL), and L-glutamine (300 μg/mL) supplemented with 10% fetal bovine serum (FBS). AsPC-1 cells were cultured in RPMI-1640 medium supplemented with 10% FBS. The culture condition for these cell lines was at 37°C in a humidified atmosphere of 5% CO_2 and 95% air in a plastic flask. All cultured medium was changed twice every week.

2.2. Reagents. Zerumbone, DMSO, MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyl Tetrazolium Bromide) kit, and other reagents, if not otherwise specified, were purchased from Sigma-Aldrich, St. Louis, MO, USA. Hoechst 33342 dye and Trizol were obtained from Invitrogen, Carlsbad, CA. In Situ Cell Death Detection Kit was bought from Roche, Penzberg, Germany (Catalog no. 11684795910). Caspase-3 activity colorimetric kit was purchased from R&D Systems Inc. (Biovision, Mountain View, USA). PA Lysis Buffer was obtained from Beyotime, Shanghai. The p53, p21 monoclonal, and PUMA polyclonal antibody were bought from Santa Cruz Biotechnology (Santa Cruz, CA). RNeasy Mini Kit and RNase-free DNase Set were obtained from Qiagen, Valencia, CA. TaqMan Reverse Transcription Reagents were purchased from Applied Biosystems, Foster City, CA. For all experiments of this study, DMSO was used to dissolve zerumbone. In order to avoid possible effects to these cells by DMSO, the volume of DMSO should not exceed 0.1% of the total volume (v/v).

2.3. Cell Proliferation Assay. The cellular viability of pancreatic cancer cells was determined by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyl Tetrazolium Bromide) assay. Briefly, the cells were collected and seeded in 96-well plates to attach overnight in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS). Human pancreatic cancer cells were rendered quiescent by incubation in serum-free media for 24 h. Then pancreatic cancer cells were incubated with zerumbone 3, 10, 30, and 100 μM for 24 h or were cultured for 24, 48, and 72 h in the presence of 30 μM, respectively. Then, the culture media were washed out and the fresh media containing 5 mg/mL MTT were added. The cells were continuously incubated at 37°C for an additional four hours. After this time, the media were washed out, and reduced MTT product (blue formazan product) was solubilized by adding 100 μM DMSO to each wells. After agitation of these plates for 15 min, the optical density of the solubilized formazan product in each well was measured using a microplate reader at 570 nm with background subtraction at 650 nm. The experiment to observe different concentration of zerumbone on cellular viability of pancreatic cancer cells was carried out six times, and the experiment to study different incubation times of zerumbone on cellular viability was performed five times.

2.4. Acridine Orange/Ethidium Bromide (AO/EB) Staining. Morphological signs of apoptosis were detected by using acridine orange-ethidium bromide (AO/EB) staining in pancreatic cancer cells. The cells were incubated with zerumbone for 24 h. The procedure to perform AO/EB staining is just as described below. In order to staining the apoptotic cells, 10 μL prepared AO/EB working solution (100 μg/mL AO and 100 μg/mL EB in PBS) was added to each well for 5 min. Then the pancreatic cancer cells were harvested and the apoptotic cells were counted under an inverted fluorescence microscope (Eclipse TE300, Nikon, Japan).

2.5. Hoechst 33342 Dye Staining. Morphological changes of apoptotic pancreatic cancer cells were evaluated by Hoechst 33342 staining. In brief, the cultured cells were planted in 6-well plates and then exposed to zerumbone treatment for 24 h. After being washed with PBS, the cancer cells were fixed in 4% paraformaldehyde for 30 min at room temperature. After being washed again with PBS, the fixed cells were stained with 20 μg/mL Hoechst 33342 for 15 min at room temperature. The cells were imaged with fluorescence microscope.

2.6. Terminal Deoxynucleotidyl Transferase-Mediated dUTP Nick End Labeling (TUNEL) Assay. TUNEL assay was used to identify the apoptosis of pancreatic cancer cells. The cells were seeded in dishes, grown overnight, and subjected to zerumbone 3, 10, 30, and 100 μM for 24 h. The staining of apoptotic cells was carried out using an In Situ Cell Death Detection Kit. In brief, after being washed twice with PBS, human pancreatic cancer cells were then fixed with 4% paraformaldehyde in PBS (pH 7.4) for 1 h at room temperature. The fixed cancer cells were permeabilised by incubation with 0.1% Triton X-100 in 0.1% sodium citrate for 2 min on ice. The cells were rinsed again with PBS and incubated with TUNEL reaction mixture for 1 h at 37°C in the dark. TUNEL staining of apoptotic cells was viewed under a fluorescence microscopy (Olympus, Tokyo, Japan).

2.7. Measurement of Reactive Oxygen Species (ROS). To quantify intracellular ROS level, we used 2,7-dichlorodihydrofluorescein diacetate (H_2DCF-DA) probe. The procedure

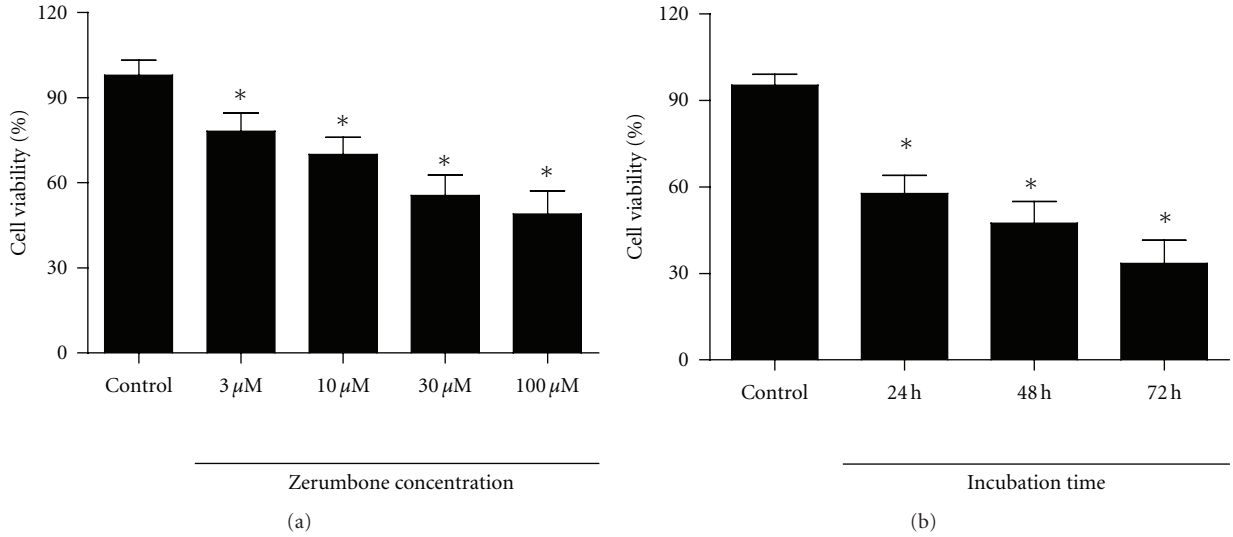


Figure 2: Effects of zerumbone on the cellular viability of PANC-1 cells. (a) The cellular viability of PANC-1 was significantly reduced by zerumbone 3, 10, 30, and 100 μM after 24 h incubation. $n = 6$ independent experiments. (b) Zerumbone obviously decreased the cellular viability of PANC-1 cells in a time-dependent manner. $n = 5$ independent experiments, $^*P < 0.05$ versus Control.

for ROS measurement is as previously described [16]. Briefly, the cells were seeded and then were incubated with different concentration of zerumbone for 24 h. In order to detect the production of ROS, the pancreatic cancer cells were collected, washed twice with PBS, and loaded with H_2DCF-DA 10 μM by incubation for 30 min at 37°C. Fluorescence was measured by flow cytometry. The experiment with ROS assay was repeated four times.

2.8. Caspase-3 Activity Assay. To evaluate the caspase-3 activity, the cancer cells lysates were prepared after their respective treatment with zerumbone. The caspase-3 activity was determined by colorimetric kit. Then, assays were performed by incubating 20 mg of cell lysates with 200 mM chromogenic substrate (DEVD-pNA) in 100 mL reaction buffer. The cell lysate was incubated at 37°C for 2 h. Thereafter, the absorbance at 450 nm was measured to represent the release of chromophore p-nitroanilide (pNA). The experiment with caspase-3 assay was repeated three times.

2.9. Western Blot Analysis. For immunolabeling, the lysates were prepared after the cancer cells were subjected to their respective treatment with zerumbone. One hundred micrograms of each lysate were resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDSPAGE). After electrophoresis, the proteins were transferred onto a nitrocellulose membrane. After blocking with 5% nonfat dried milk and 0.05% Tween 20 in Tris-buffered saline (10 mM Tris, pH 8.0, 135 mM NaCl), the membranes were incubated overnight with the relevant primary antibody followed by the incubation with horseradish peroxidase-conjugated immunoglobulin G (IgG). The blots were then visualized by using Odyssey v1.2 software. The experiments were repeated three times.

2.10. Quantitative Real-Time PCR Analysis. According to the guideline of the manufacturer, the total RNA from pancreatic cancer cells was isolated by Trizol and purified by RNeasy Mini Kit and RNase-free DNase Set. Total RNA from pancreatic cancer cells was subjected to first-strand cDNA synthesis using TaqMan Reverse Transcription Reagents. The method to determine miR-34 mRNA level in cancer cells is just as described previously [17]. Relative mRNA for miR-34 was calculated by the comparative CT method (DDCT) using U6 as an endogenous control and untreated samples as the calibrator.

2.11. Statistical Analysis. All data was presented as mean ± S.E.M. Statistical analysis was performed to determine the significance of differences among groups using ANOVA. All statistical analysis was performed using the SPSS 13.0 software for Windows. Statistical significance was initially set at $P < 0.05$.

3. Results

3.1. Zerumbone Reduced Cellular Viability of PANC-1 Cells. The effects of zerumbone on the proliferation of PANC-1 cells were measured by the MTT assay. As displayed in Figure 2(a), the exposure of PANC-1 cells to zerumbone 3 μM, 10 μM, 30 μM, and 100 μM for 24 h resulted in a significant reduction of cellular viability, compared with untreated cells ($P < 0.05$). Zerumbone 3 μM, 10 μM, 30 μM, and 100 μM decreased the viability of PANC-1 cells from 97.9 ± 5.3 to 78.2 ± 6.4, 70.1 ± 6.0, 55.6 ± 7.2, and 49.1 ± 8.1, respectively, ($P < 0.05$). Figure 2(b) showed that cellular viability of PANC-1 cells after exposure to zerumbone 30 μM for 24 h, 48 h, and 72 h was decreased from 95.3 ± 3.8 to 57.8 ± 6.2, 47.4 ± 7.5, and 33.6 ± 7.9. The results suggest

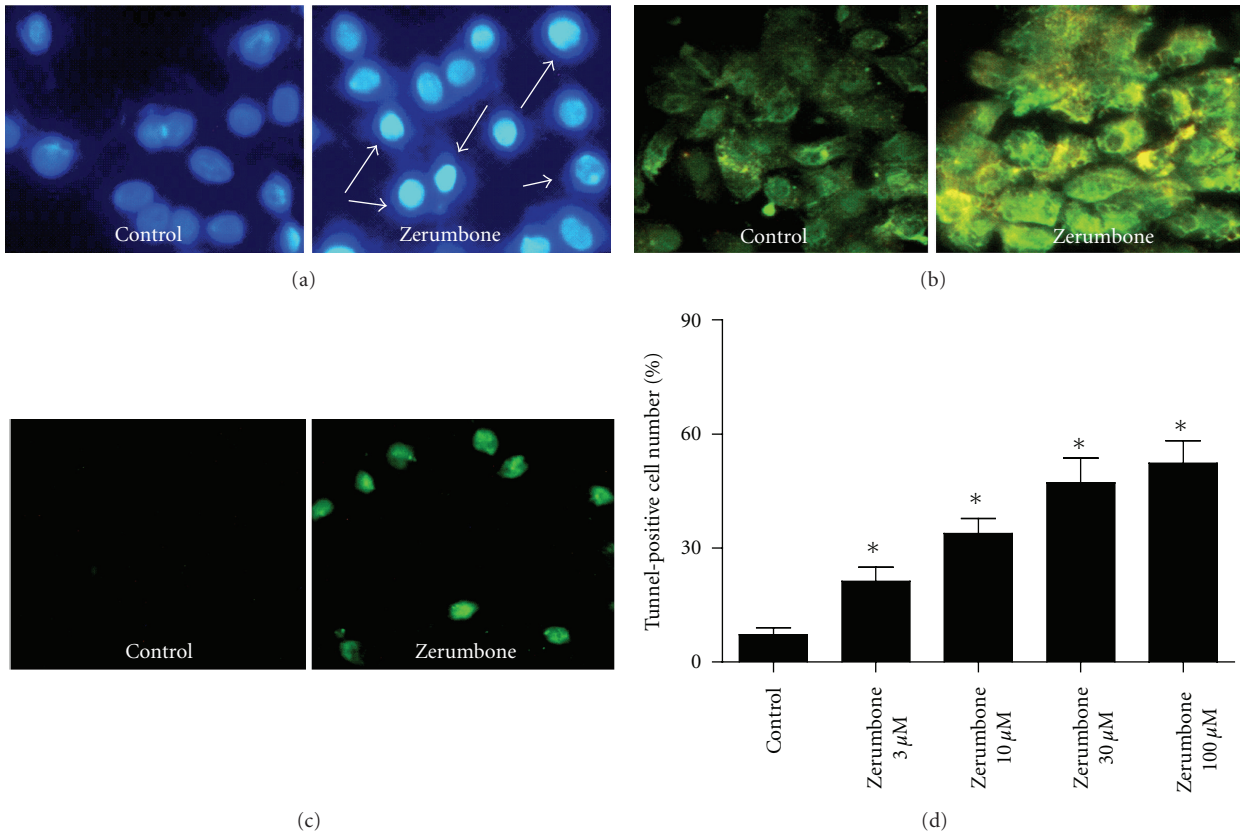


Figure 3: Effects of zerumbone on apoptosis of PANC-1 cells. (a) Hoechst 33342 staining of the apoptosis of PANC-1 in the presence of zerumbone 30 μM. (b) Effects of zerumbone 30 μM on apoptosis of PANC-1 cells were identified by AO/EB staining. (c) and (d) TUNEL-positive cells were viewed in the presence of zerumbone 30 μM. $n = 3$ independent experiments, $^*P < 0.05$ versus Control.

that zerumbone reduces the proliferation of PANC-1 in a concentration- and time-dependent manner ($P < 0.05$).

3.2. Apoptosis of PANC-1 Cells Was Induced by Exposure to Zerumbone. We further used Hoechst 33342 and AO/EB staining to determine the effects of zerumbone on the apoptosis of PANC-1 cells. As demonstrated in Figures 3(a) and 3(b), zerumbone-treated PANC-1 cells exhibited obvious apoptotic morphological changes in the nuclear chromatin, such as cell shrinkage, chromatin condensation, and cell nuclear fragmentation. By contrast, PANC-1 cells without zerumbone treatment presented the intact nuclear architecture (Figure 3(b)). As shown in Figure 3(c), TUNEL-positive staining could be detected more significantly in PANC-1 cells pretreated by zerumbone than in untreated PANC-1 cells. Zerumbone 3 μM, 10 μM, 30 μM, and 100 μM significantly increased the number of TUNEL-positive PANC-1 cells from $7.1 \pm 1.9\%$ to 21.3 ± 3.6, 33.8 ± 4.0, 47.1 ± 6.6 and 52.3 ± 5.9 after 24 h incubation ($P < 0.05$).

3.3. Zerumbone Increased the Activity of Caspase-3 and ROS in PNAC-1 Cells. The effect of zerumbone on the activity of caspase-3 in PANC-1 cells was further investigated. As illuminated in Figure 4(a), the exposure of PANC-1 cells to zerumbone 3 μM, 10 μM, 30 μM, and 100 μM markedly increased the activity of caspase-3 by approximately 56%, 147%, 149%, and 197%, respectively, ($P < 0.05$). These results further confirmed that zerumbone induced apoptosis of PANC-1 cells. Then, we explored the influences of zerumbone on the production of ROS. PANC-1 cells were exposed to zerumbone 3 μM, 10 μM, 30 μM, and 100 μM for 24 h and analyzed for the production of ROS by fluorescence microscopy. Figure 4(b) demonstrated the fluorescence image of ROS in the absence and presence of zerumbone in PANC-1 cells. The generation of ROS was increased by zerumbone in a concentration-dependent manner ($P < 0.05$).

3.4. Effects of Zerumbone on the Expression of p53 and miR-34. We further investigate whether zerumbone plays a regulatory role in the expression of p53 and miR-34. As displayed in Figure 5(a), pretreatment with zerumbone 30 μM significantly increased the expression of p53 protein in PANC-1 cells ($P < 0.05$). In agreement, miR-34 level was also augmented in zerumbone-treated PANC-1 cells ($P < 0.05$) (Figure 5(b)). These results imply that p53 signal pathway is involved in the apoptosis of PANC-1 cells induced by zerumbone. Moreover, the effects of zerumbone on p21 and PUMA protein were investigated and the results showed that PUMA was not affected but p21 was significantly upregulated, indicating that p53 and p21 signal pathway was activated after treatment with zerumbone

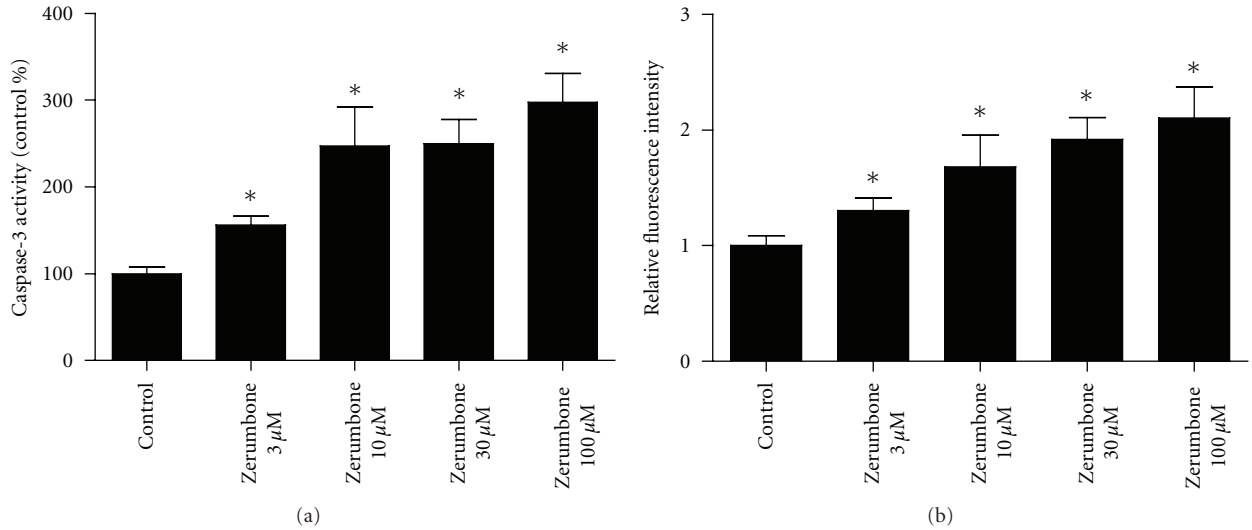


FIGURE 4: Effects of zerumbone on the caspase-3 activity and the generation of ROS production of PNAC-1 cells. (a) Zerumbone increased the caspase-3 activity of PANC-1 cells. $n = 3$ independent experiments. (b) Zerumbone 30 μM increased the fluorescence density of ROS. Zerumbone increased the ROS generation in a concentration-dependent manner. $n = 4$ independent experiments, $^*P < 0.05$ versus Control.

(Figure 5(a)) ($P < 0.05$). We further investigate the effects of the p53-specific inhibitor pifithrin-α on zerumbone-induced decrease of cellular viability in PANC-1 (Figure 5(c)). The results showed that pifithrin-α 20 μM reversed the inhibitory role of zerumbone 30 μM in cellular viability of PANC-1, indicating that zerumbone exerts antitumor effects through p53-dependent manner.

3.5. Zerumbone Induced Apoptosis in SW1990 and AsPC-1 Cells. We also studied the antitumor effects of zerumbone on another two pancreatic cancer cell lines SW1990 and AsPC-1. Figures 6(a) and 6(b) showed that zerumbone 30 μM markedly inhibited cellular viability of SW1990 and AsPC-1 after 24 h incubation ($P < 0.05$). Furthermore, Hoechst 33342 staining displayed that the exposure to zerumbone 30 μM for 24 h induced obvious apoptotic morphological changes in the nuclear chromatin in SW1990 and AsPC-1 (Figure 6(c)). Figures 6(d) and 6(e) showed that zerumbone 30 μM increased the caspase-3 activity in both SW1990 and AsPC-1. These findings suggest the antitumor role of zerumbone in SW1990 and AsPC-1 cell lines.

4. Discussion

It was demonstrated in this study that exposure to zerumbone resulted in apoptosis of PANC-1 cells through p53 signal pathway. The present research offers us a new understanding about the molecular mechanisms of antitumor actions of zerumbone on pancreatic cancer.

A large body of evidence demonstrated that apoptosis is a normal component of the development and health of multicellular organisms and also is a key way to clear the unnecessary cells [18, 19]. Notably, apoptosis is more important in understanding cancer, because cancer cells have developed a way to avoid apoptosis [20]. Thus, cancer is often characterized by too little apoptosis and too much proliferation of cells. To promote apoptosis and inhibit proliferation of cancer cells has been suggested as a therapeutic approach.

Zerumbone is a sesquiterpene phytochemical from a type of edible ginger known as "Zingiber zerumbet Smith" grown in Southeast Asia or "Zingiber aromaticum" [4–9]. In several studies, zerumbone has been showed to play an antitumor role in liver cancer, leukemia, and lung carcinogenesis, which was considered as a promising therapeutic drug for cancers [8–15]. For example, zerumbone was reported to induce G2/M cell cycle arrest and apoptosis in leukemia cells through a Fas- and mitochondria-mediated pathway [12]. In addition, zerumbone also could effectively suppress mouse colon and lung carcinogenesis through multiple modulatory mechanisms of growth, apoptosis, inflammation, and expression of NFkappaB and HO-1 after dietary administration [13]. Zerumbone was shown to strongly inhibit the proliferation of liver cancer cells and enhance the apoptosis [15]. However, the information about the therapeutic effects of zerumbone on pancreatic cancer cells is unavailable. In this study, we uncover for the first time that zerumbone-treated pancreatic cancer cells exhibited a decreased proliferation and increased apoptosis, which is characterized by the formation of apoptotic bodies, condensed nuclei, and the increased activity of caspase-3. The present study therefore offered a new possible application of zerumbone in the treatment of pancreatic cancer.

It is well documented that p53 plays an important role in the control of cell cycle and apoptosis [20]. As a tumor suppressor, p53 plays a more crucial role in preventing tumor development [21]. It is considered responsible for a range of potentially oncogenic stresses by activating antitumor mechanisms, most notably cell cycle arrest and apoptosis. The present study displayed that p53 was significantly increased in zerumbone-treated PANC-1 cells. It suggests

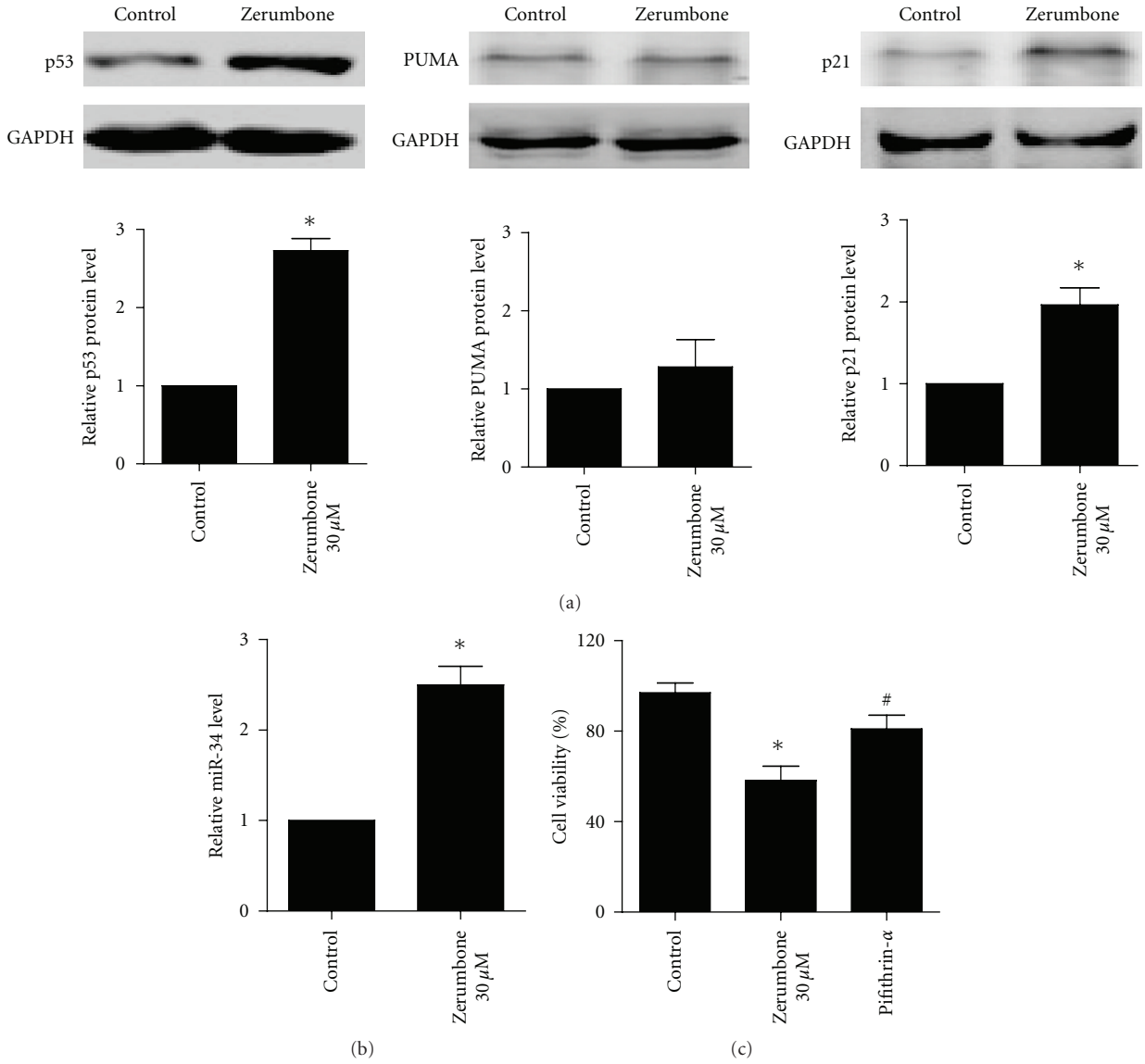


Figure 5: Effects of zerumbone on the expression of p53 and miR-34. (a) Zerumbone 30 μM markedly inhibited the p53, p21, and PUMA protein expression. (b) Zerumbone 30 μM decreased the miR-34 level. (c) The p53 specific inhibitor pifithrin α reversed the inhibitory influences of zerumbone on cellular viability. $n = 3$ independent experiments, $^{*}P < 0.05$ versus Control, $^{\#}P < 0.05$ versus Zerumbone.

that p53 may contribute to the inhibition of the apoptosis of pancreatic cancer cells by zerumbone.

A new component of p53 signaling pathway was recently uncovered, and it was showed that the activation of endogenous p53 induced the upregulation of miR-34 expression and p21, suggesting that miR-34 is a direct target of p53 [22]. Furthermore, it was previously reported that the overexpression of miR-34a led to the growth arrest and apoptosis in neuroblastoma cells by silencing the expression of E2f3 [23]. We found that miR-34 and p21 were obviously increased in zerumbone-treated PANC-1 cells, indicating that p53 signal pathway is activated by zerumbone.

Reactive oxygen species (ROS) are a variety of molecules and free radicals derived from molecular oxygen, which was constantly generated and eliminated in the biological system, and have important roles in cell signaling and homeostasis [24]. Excessive amounts of ROS can cause oxidative damage to lipids, proteins, and DNA leading to tumorigenesis or cell death. Although the use of antioxidants in humans for cancer prevention remains controversial, increasing evidence supported that the increase of ROS generation contributed to the treatment of cancer cells. Reactive oxygen species are suggested as downstream mediators of p53-dependent apoptosis [25, 26]. The cells sensitive to p53-mediated apoptosis promoted the generation of ROS, whereas cells resistant to p53 failed to produce ROS [25]. We found that zerumbone exerted a facilitated role in the production of ROS in a concentration-dependent manner, which is at least in part responsible for its pharmacological actions on PANC-1 cell lines.

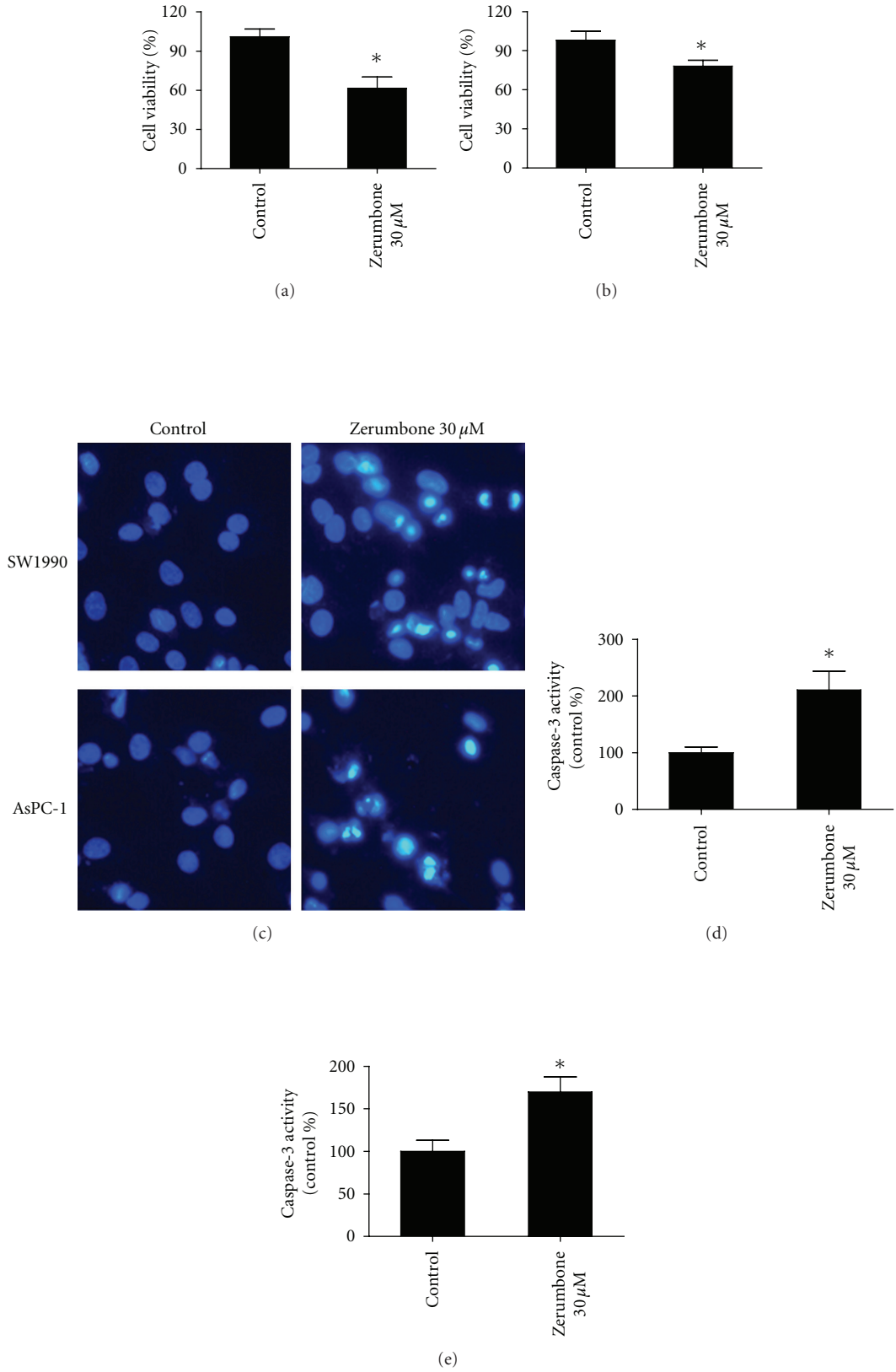


Figure 6: Zerumbone induced apoptosis in SW1990 and AsPC-1 cells. (a) Zerumbone 30 μM significantly decreased the cellular viability of SW1990 after 24 h incubation. (b) The cell viability of AsPC-1 cells was also strongly inhibited in the present of Zerumbone 30 μM. (c) Hoechst 33342 staining of SW1990 and AsPC-1 cells in the absence and presence of zerumbone 30 μM. (d) Zerumbone 30 μM increased the caspase-3 activity in SW1990 cells. (e) Zerumbone 30 μM also enhanced the caspase-3 activity in AsPC-1 cells. $n = 3$ independent experiments, $^*P < 0.05$ versus Control.

In summary, it was uncovered in our study that zerumbone induced apoptosis in pancreatic carcinoma cells through p53 signal pathway. This finding indicates zerumbone, a sesquiterpene in subtropical ginger, as a new therapeutic candidate for pancreatic cancer.

Conflict of Interests

There is no conflict of interest declared by the authors.

Acknowledgments

This work was supported by Science and Technology Fund of Heilongjiang Education Bureau (no. 11511228) and Heilongjiang Health Department (2010-160).

References

[1] R. Pannala, J. B. Leirness, W. R. Bamlet, A. Basu, G. M. Petersen, and S. T. Chari, "Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus," *Gastroenterology*, vol. 134, no. 4, pp. 981–987, 2008.

[2] T. S. Riall, J. L. Cameron, K. D. Lillemoe et al., "Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma—part 3: update on 5-year survival," *Journal of Gastrointestinal Surgery*, vol. 9, no. 9, pp. 1191–1204, 2005.

[3] H. G. Beger, F. Gansauge, M. W. Büchler, and K. H. Link, "Intraarterial adjuvant chemotherapy after pancreaticoduodenectomy for pancreatic cancer: significant reduction in occurrence of liver metastasis," *World Journal of Surgery*, vol. 23, no. 9, pp. 946–949, 1999.

[4] N. J. Yob, S. M. Jofrry, M. M. R. M. M. Affandi, L. K. Teh, M. Z. Salleh, and Z. A. Zakaria, "Zingiber zerumbet (L.) Smith: a review of its ethnomedicinal, chemical, and pharmacological uses," *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 543216, 12 pages, 2011.

[5] M. R. Sulaiman, T. A. S. T. Mohamad, W. M. S. Mossadeq et al., "Antinociceptive activity of the essential oil of zingiber zerumbet," *Planta Medica*, vol. 76, no. 2, pp. 107–112, 2010.

[6] S. J. Dae, A. R. Han, G. Park, G. J. Jhon, and E. K. Seo, "Flavonoids and aromatic compounds from the rhizomes of Zingiber zerumbet," *Archives of Pharmacal Research*, vol. 27, no. 4, pp. 386–389, 2004.

[7] I. M. Chung, M. Y. Kim, W. H. Park, and H. I. Moon, "Histone deacetylase inhibitors from the rhizomes of Zingiber zerumbet," *Pharmazie*, vol. 63, no. 10, pp. 774–776, 2008.

[8] J. R. Dai, J. H. Cardellina, J. B. McMahon, and M. R. Boyd, "Zerumbone, an HIV-inhibitory and cytotoxic sesquiterpene of Zingiber aromaticum and Z. zerumbet," *Natural Product Letters*, vol. 10, no. 2, pp. 115–118, 1997.

[9] C. Kirana, G. H. McIntosh, I. R. Record, and G. P. Jones, "Antitumor activity of extract of Zingiber aromaticum and its bioactive sesquiterpenoid zerumbone," *Nutrition and Cancer*, vol. 45, no. 2, pp. 218–225, 2003.

[10] G. C. Huang, T. Y. Chien, L. G. Chen, and C. C. Wang, "Antitumor effects of zerumbone from Zingiber zerumbet in P-388D1 cells in vitro and in vivo," *Planta Medica*, vol. 71, no. 3, pp. 219–224, 2005.

[11] S. Vimala, A. W. Norhanom, and M. Yadav, "Anti-tumour promoter activity in Malaysian ginger rhizobia used in traditional medicine," *British Journal of Cancer*, vol. 80, no. 1-2, pp. 110–116, 1999.

[12] M. Xian, K. Ito, T. Nakazato et al., "Zerumbone, a bioactive sesquiterpene, induces G2/M cell cycle arrest and apoptosis in leukemia cells via a Fas- and mitochondria-mediated pathway," *Cancer Science*, vol. 98, no. 1, pp. 118–126, 2007.

[13] M. Kim, S. Miyamoto, Y. Yasui, T. Oyama, A. Murakami, and T. Tanaka, "Zerumbone, a tropical ginger sesquiterpene, inhibits colon and lung carcinogenesis in mice," *International Journal of Cancer*, vol. 124, no. 2, pp. 264–271, 2009.

[14] B. Sung, S. Jhurani, S. A. Kwang et al., "Zerumbone down-regulates chemokine receptor CXCR4 expression leading to inhibition of CXCL12-induced invasion of breast and pancreatic tumor cells," *Cancer Research*, vol. 68, no. 21, pp. 8938–8944, 2008.

[15] S. A. S. Sakinah, S. T. Handayani, and L. P. A. Hawariah, "Zerumbone induced apoptosis in liver cancer cells via modulation of Bax/ Bcl-2 ratio," *Cancer Cell International*, vol. 7, no. 4, 2007.

[16] J. D. Song, S. K. Lee, K. M. Kim et al., "Molecular mechanism of diallyl disulfide in cell cycle arrest and apoptosis in HCT-116 colon cancer cells," *Journal of Biochemical and Molecular Toxicology*, vol. 23, no. 1, pp. 71–79, 2009.

[17] T. Zenz, J. Mohr, E. Eldering et al., "miR-34a as part of the resistance network in chronic lymphocytic leukemia," *Blood*, vol. 113, no. 16, pp. 3801–3808, 2009.

[18] J. M. Lee and A. Bernstein, "Apoptosis, cancer and the p53 tumour suppressor gene," *Cancer and Metastasis Reviews*, vol. 14, no. 2, pp. 149–161, 1995.

[19] D. C. Corney, A. Flesken-Nikitin, A. K. Godwin, W. Wang, and A. Y. Nikitin, "MicroRNA-34b and MicroRNA-34c are targets of p53 and cooperate in control of cell proliferation and adhesion-independent growth," *Cancer Research*, vol. 67, no. 18, pp. 8433–8438, 2007.

[20] J. F. R. Kerr, C. M. Winterford, and B. V. Harmon, "Apoptosis: its significance in cancer and cancer therapy," *Cancer*, vol. 73, no. 8, pp. 2013–2026, 1994.

[21] K. Somasundaram, "Tumor suppressor p53: regulation and function," *Frontiers in Bioscience*, vol. 5, pp. D424–437, 2000.

[22] L. He, X. He, L. P. Lim et al., "A microRNA component of the p53 tumour suppressor network," *Nature*, vol. 447, no. 7148, pp. 1130–1134, 2007.

[23] C. Welch, Y. Chen, and R. L. Stallings, "MicroRNA-34a functions as a potential tumor suppressor by inducing apoptosis in neuroblastoma cells," *Oncogene*, vol. 26, no. 34, pp. 5017–5022, 2007.

[24] J. M. Matés and F. M. Sánchez-Jiménez, "Role of reactive oxygen species in apoptosis: implications for cancer therapy," *International Journal of Biochemistry and Cell Biology*, vol. 32, no. 2, pp. 157–170, 2000.

[25] T. M. Johnson, Z. X. Yu, V. J. Ferrans, R. A. Lowenstein, and T. Finkel, "Reactive oxygen species are downstream mediators of p53-dependent apoptosis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 21, pp. 11848–11852, 1996.

[26] J. Bai and A. I. Cederbaum, "Catalase protects HepG2 cells from apoptosis induced by DNA-damaging agents by accelerating the degradation of p53," *Journal of Biological Chemistry*, vol. 278, no. 7, pp. 4660–4667, 2003.

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 401867, 9 pages
doi:10.1155/2012/401867

Research Article

Barriers to Integration of Traditional and Complementary Medicine in Supportive Cancer Care of Arab Patients in Northern Israel

Eran Ben-Arye,[1,2] Mariana Steiner,[1,3] Khaled Karkabi,[2] Tamar Shalom,[1,4] Levava Levy,[1] Ariela Popper-Giveon,[5] and Elad Schiff[6]

[1] *Integrative Oncology Program, The Oncology Service and Lin Medical Center, Clalit Health Services, Haifa and Western Galilee District, Haifa 35152, Israel*
[2] *Complementary and Traditional Medicine Unit, Department of Family Medicine, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa 32000, Israel*
[3] *The Carmel Medical Center, Clalit Health Services, Haifa 34362, Israel*
[4] *School of Public Health, Faculty of Social Welfare & Health Sciences, University of Haifa, Haifa 31905, Israel*
[5] *David Yellin Academic College of Education, Jerusalem 91035, Israel*
[6] *Department of Internal Medicine and Complementary and Integrative Surgery Service, Bnai Zion Medical Center, Haifa 33394, Israel*

Correspondence should be addressed to Eran Ben-Arye, eranben@netvision.net.il

Received 31 August 2011; Revised 6 October 2011; Accepted 14 October 2011

Academic Editor: Barrie Cassileth

In 2008, an Integrative Oncology Program (IOP), aiming to improve patients' quality of life during chemotherapy and advanced cancer, was launched within the Clalit Health Organization's oncology service at the Lin Medical Center, Haifa, Israel. The IOP clinical activity is documented using a research-based registry protocol. In this study, we present an analysis of the registry protocol of 15 Arab patients with cancer who were referred to the IOP. Analysis of patients' reported outcomes using the Edmonton Symptom Assessment Scale suggests that integrative medicine care improves fatigue ($P = 0.024$), nausea ($P = 0.043$), depression ($P = 0.012$), anxiety ($P = 0.044$), appetite ($P = 0.012$), and general well-being ($P = 0.031$). Barriers to integration of traditional and complementary medicine in supportive care of Arab patients are discussed followed by six practical recommendations aimed at improving accessibility of patients to integrative supportive care, as well as compliance with treatments.

1. Introduction

The Middle East is represented by a rich spectrum of indigenous traditional schools of medicine modeled on a mosaic of social, religious, and spiritual perspectives. Testaments to the amalgam of indigenous roots of medical knowledge can be found in current ethno botanical surveys which document the use of herbs for cancer care in the regions of Israel [1], Syria [2], and the Palestinian Authority [3]. In a survey of Islamic and Jewish traditional medicine historical texts, scholars from Israel, Egypt, and Turkey identified 44 herbs associated with cancer care [4]. In a subsequent international study, a multidisciplinary team of researchers from Israel, the Palestinian Authority, Jordan, Egypt, Morocco and Turkey identified 143 articles on traditional/complementary medicine and cancer care that had been published on medline in 12 Middle Eastern countries [5].

Several studies documented the significant use of complementary medicine (CM) by patients in the Middle East during chemotherapy (Israel, 49%) [6] and radiotherapy (Turkey, 44%) [7] and in subsets of patients with cancer: pediatric (Lebanon, 15%; Turkey, 77%; Israel, 61%) [8–10], gynecological (Turkey, 38%; Israel, 63%) [11, 12], and breast cancer (Israel, 44%) [12].

In Israel, the concept of CM integration within conventional care has been significantly studied among the Arab population in northern Israel. Ben-Arye and his colleagues [13] have studied the prevalence of CM use and attitudes

toward its integration among 3840 patients in 7 primary care clinics operated by Clalit Health Service (CHS) and found that respondents in both groups significantly supported CM integration within primary care clinics.

Following this study, the Haifa and Western Galilee District of CHS initiated a study in 2007 to examine the possibility of CM integration within its oncology service (OS). In 2008, an Integrative Oncology Program (IOP) was launched as a free-of-charge clinical service aiming to improve patients' QOL during chemotherapy and advanced disease state. The IOP is based on a multidisciplinary team that includes physicians and practitioners that are dual trained in conventional care as well as CM. The IOP team provides a wide spectrum of traditional and CM modalities which include nutritional counseling (diet and supplements), herbal medicine, mind-body and touch therapies, acupuncture, anthroposophic medicine, homeopathy and spiritual care. In this paper, we present data regarding Arab patients receiving integrative treatment offered by the IOP during the years 2009–2011. We examine the needs and concerns of Arab patients who were referred to the IOP and explore difficulties and barriers to the provision of CM to this group of patients in integrative setting. Based on these observations, we advocate practical recommendations that may facilitate a cross-culturally sensitive approach that will resonate with Arab patients' expectations and needs in similar integrative health settings.

2. Materials and Methods

2.1. Registry Protocol Data Collection. The IOP clinical activities are documented in a research-based registry protocol (RP) approved by the IRB of the Carmel Medical Center, Haifa, Israel. The RP monitors patients' needs and concerns, symptom and QOL assessment, and prospective evaluation of clinical outcomes. In addition, the RP documents referral patterns, CM practitioner-patient-oncologist communication aspects, and assessment of the patient's, oncologist's, and the integrative physician's perspectives regarding the impact of the integrative intervention on the patient's well-being.

Figure 1 illustrates the flowchart beginning with the patient's referral to the IOP and concluding with follow-up assessments of the integrative process. Referral to the IOP may be initiated by the patient's oncologist, oncology nurse, or social worker and is limited to patients treated within the oncology service during chemotherapy and/or advanced cancer. Following the referral, an initial integrative medical intake interview is scheduled for one hour with an integrative physician (IP) who assesses the patient's expectations regarding CM, previous experience with traditional, alternative or CM, as well as the patient's narrative and outlook regarding diagnosis, treatment, coping, and well-being. The severity of symptoms, concerns, and expectations are evaluated by the IP using the Edmonton Symptom Assessment Scale (ESAS) and Measure Yourself Concerns and Wellbeing (MYCAW) questionnaires and a detailed bio-psychospiritual assessment. The session is typically concluded with outlining of the treatment goals that are shared by the patient and IP, followed by construction of a preliminary treatment plan tailored to the patient's outlook (concerns, symptoms, willingness to experience CM modalities, etc.) and level of evidence (efficacy, safety, possible interactions with chemotherapy, etc.). Each visit is recorded by the IP in the patient's medical file, and a clinical summary is distributed to the patient's healthcare providers (oncologist, nurse, family practitioner, social worker, etc.). Patients are typically scheduled for therapeutic integrative medicine (IM) sessions that may include a variety of CM modalities (e.g., nutritional and herbal counseling, acupuncture, mind-body, and manual therapies) provided from once every week to once every 2-3 weeks. Prior to therapeutic sessions, additional clinical assessment is conducted, aimed to modify, if necessary, the treatment goals and plan. Following 2–4 months of treatment, a concluding clinical assessment is performed with the use of ESAS and MYCAW questionnaires. More therapeutic sessions are provided, if deemed necessary, for patients with advanced cancer or for those receiving adjuvant chemotherapy. Such sessions are also regularly monitored. Figure 1 illustrates supplemental evaluation documented within the registry protocol regarding themes of patients' expectations and communication with healthcare providers. Follow-up evaluations include a self-administered questionnaire completed by the IP at the conclusion of the first medical intake, semistructured telephone interviews with patients conducted by a researcher following the first intake and after the concluding clinical evaluation and a questionnaire administered to the patient's oncologist following the concluding evaluation. In this evaluation process, the patient's and clinician's perspectives are independently compared regarding expectations, satisfaction with treatment and communication, as well as needs that were not fully addressed.

2.2. Assessment Methods. Assessment questionnaires include the following.

(a) MYCAW is an individualized questionnaire constructed and validated by Paterson et al. [14] for evaluating outcomes in cancer support care that includes complementary therapies [15]. Participants were asked to enumerate one or two concerns and, using a seven-point scale, to score these concerns and their general feeling of well being. The follow-up questionnaire also includes the following open question: "Reflecting on your time with this Centre, what were the most important aspects for you?"

(b) ESAS is a questionnaire developed for assessing the symptoms of patients receiving palliative care [16], as well as for assessing outcomes in an integrative oncology context [17]. It consists of an 11-point numerical rating scale for self-reporting of nine common symptoms of cancer, with a 10th scale for assessing the feeling of well-being. Both MYCAW and ESAS questionnaires were linguistically validated to Hebrew using bidirectional translation from their English origin to Hebrew and vice versa.

(c) Questionnaires administered to the IP and/or oncologist and/or patients were developed by the authors following a comprehensive literature review of patients' needs, concerns, and expectations regarding CM in the oncology setting and interviews with 24 patients in different phases

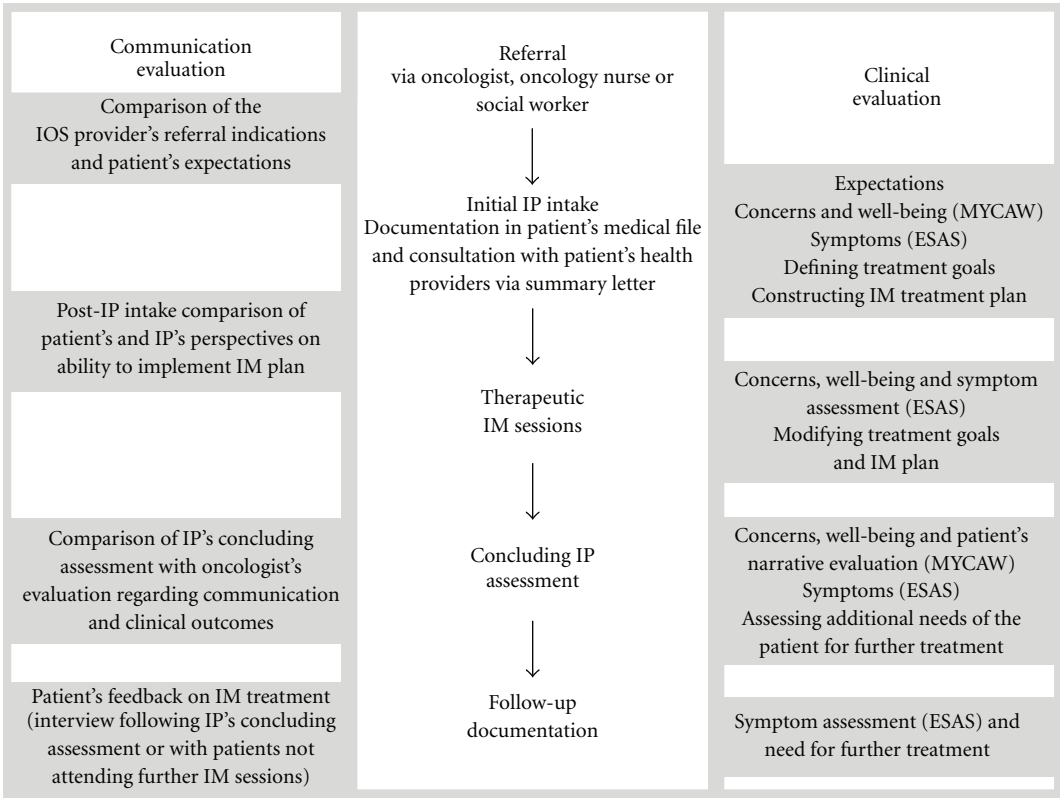


Figure 1: Flowchart of clinical and communicational evaluation along the sequence of integrative sessions within the Integrative Oncology Program (IOS: integrative oncology service; IP: integrative physician; IM: integrative medicine).

of oncology treatment and with 61 health care providers (HCPs) and CM practitioners. Afterwards, a focus group, composed of 5 patients in different phases of cancer treatment, was used to refine the questionnaire and improve its comprehensibility. The focus group participants varied in age, sex, education, health status and CM use. Based on their feedback, the questionnaire was revised and sent for reappraisal to 7 of the HCPs. The final version of the 20-question questionnaire was administered by the IP following initial consultations. The questionnaire consists of 9 limited-choice questions (yes, no, other, or not relevant), 4 multiple-choice questions, one open question, and 6 questions that use a Likert-like scale. Independent researchers interviewed patients, following the IP's initial and concluding assessment, using a similar form of the questionnaire filled in by the IP. In addition, a researcher typically phoned to interview patients no longer attending the IM sessions. Another questionnaire was administered to the patient's oncologist following the IP's concluding assessment. This shortened questionnaire format consists of 4 questions including 3 that utilize a Likert-like scale.

Data was evaluated using the SPSS software program (version 18; SPSS Inc., Chicago, Ill). Wilcoxon Signed Ranks Test and paired t-test were used to detect differences before and after the treatment scores in MYCAW and ESAS questionnaires.

3. Results and Discussion

Participation in the registry protocol-based IOP research was limited to patients in the CHS Haifa and Western Galilee OS during chemotherapy or advanced active disease. The total number of new patients referred to the OS ranges from 800 to 1000 per year. Data regarding the cultural and religious characterization of this newly referred population was not available, nor was data related to the population of patients who theoretically meet the inclusion criteria for referral to the IOP. The best culture-related data available was obtained from analysis of nurse oncology intakes (NOI) which were performed prior to beginning chemotherapy in patients receiving intravenous adjuvant, neoadjuvant, or palliative chemotherapy for the first time in their life. The NOI-based data was collected and analyzed starting from 14/7/2009 (parallel to the launching of the registry protocol) and up to 14/7/2011.

Based on the patient's self-report of spoken language during the NOI, we divided patients into two groups: Arabs (patients speaking Arabic solely or in addition to Hebrew or other languages) or non-Arabs (patients speaking Hebrew or other languages but not Arabic). In cases not determined by the language criterion, we assigned the patient to one of these groups according to the father's name. Five hundred thirty-one patients were thus grouped based on the NOI

data during the two-year study, of whom 103 were Arabs (19.4%) and 428 non-Arabs (80.6%). This data may not reflect the entire population of patients who could have been referred potentially by the OS health providers to the IOP, for the following reasons: (a) patients with recurrent disease treated with chemotherapy initiated prior to July 2009 (about 42.4% of patients in the OS are receiving chemotherapy for recurrent disease); (b) patients receiving oral chemotherapy, biological or hormonal therapy; (c) patients receiving palliative care with no chemotherapy initiated after July 2007.

During this two-year period, 230 of the 531 patients (recorded in NOI data) were referred to the IOP by the OS oncologists, oncology nurses, or OS social workers. Of these referrals, 224 met the inclusion criteria for IOP admission and enrollment in the registry protocol-based research. Of the 224 patients invited for IOP assessment, 203 (response rate 90.6%) participated in the IP's initial intake and provided written consent to participate in the research protocol study. Of the 203 study subjects, who were monitored in the registry protocol, 15 were Arabs (7.39%) and 188 were non-Arabs (92.61%). Figure 2 illustrates an algorithm of the study's recruitment and illustrates the proportion of Arab versus non-Arab patients along the funnel leading to the registry protocol tracking.

Of the 21 patients who were referred to the IOP but did not attend the IP's intake, 4 were Arabs and 17 non-Arabs. The main reason for nonattendance was difficulty in scheduling appointments during progressive treatment.

3.1. Registry Protocol Demographics of Arab Patients. The demographic characteristics of Arab patients enrolled in the integrative registry protocol within the OS are presented in Table 1. This population is characterized by female predominance (11/15, 73.3%), mean age of 52.4 years (range 22–77), and variety of religions (6 Muslim, 5 Christian, and 4 Druze). Most patients reside in cities (9 urban, 4 rural, and 2 semiurban) which are often very far from the OS located in Haifa (4 patients live in zone 1 (Haifa), 1 patient in zone 2 (up to 20 km from Haifa), and 10 in zone 3 (>20 km from Haifa)). Of the 15 patients, 9 were diagnosed with localized disease and were receiving adjuvant chemotherapy following surgery and 6 had advanced disease and were receiving palliative chemotherapy. Patients' cancer sites included the following: breast (6), colon (3), stomach (1), lung (1), bladder (1), testicles (1), mesothelioma (1), and an undiagnosed site (1).

3.2. Assessment of Referral, Expectations, and Communication during and following IP Intake. Referral to IOP was performed via health care practitioners' (HCPs) structured referral letters that specify the indications for referral to the integrative treatment. Of the 15 referrals, 9 were administered by oncology nurses, 4 by oncologists, and 3 by the OS social workers (one referral was administered by both nurse and social worker).

Nine of the 15 patients (60%) reported previous use of traditional/CM in the context of cancer care. Although the IP specifically inquired about cancer-related CM use at the beginning of the medical intake, the majority of patients disclosed CM use only when asked for the second or third time towards the end of the interview. In these cases, disclosure was often related to the patient becoming aware that the definition of cancer-related CM also includes QOL improvement and symptom management rather than curing cancer.

General expectation to reduce chemotherapy side effects was the leading referral indication (6 referrals), followed by more specific expectations concerning symptoms such as anxiety (5), fatigue (3), and vomiting (2). Compared to indications for referrals, patients expressed additional expectations from the IP: what to eat and which herbs to use (4), how to alleviate fatigue and strengthen their condition (4), and how to improve management of pain (3), emotional state (2), and other symptoms. Expectation analysis of each of the 15 referrer-patient couples revealed that matching of expectations was largely evident in only four pairs for specific symptoms that need to be addressed by the IP (e.g., improving urination, bitter taste, stomatitis, and other gastrointestinal symptoms). Compared to HCPs, patients expressed more concrete expectations from the IP (e.g., specific symptom improvement versus general reduction of side effects) and in some cases anticipated outcomes beyond QOL improvement such as cancer cure and recurrence prevention.

Assessment of HCP-IP communication following the IP's initial intake revealed that the IP addressed a medical letter to all 15 patients' oncologists and to 14 nurses, 14 social workers, and 9 family physicians. Typically, these letters were referred to 3-4 of the patient's HCPs and often responded to by at least two HCPs.

Patient's and IP's evaluation were based on questionnaires completed by the IP following the initial visits and semistructured interviews with patients that were conducted by an independent researcher. Of the 15 patients interviewed, 5 anticipated difficulty in implementing the therapeutic plan as presented by the IP in the first visit. In contrast, the IP expected difficulty in 12 of the patients, mainly due to limited accessibility to the clinic and an impression that these patients doubted the benefits of the treatment. In 12 out of 15 patients there was incongruence between the patient and IP regarding perceived difficulty in implementing the treatment plan. This patient-IP mismatch is also evident in 9 patients regarding satisfaction following the initial visit. Compared to patient evaluations, IP scores were higher in 7 of these 9 pairs.

3.3. Clinical Assessment in Initial IP Intakes. Evaluation of the severity of patients' two main concerns was performed both in the initial IP intake and the concluding session that followed several therapeutic sessions. This evaluation was based on the MYCAW questionnaire which followed symptom assessment based on the ESAS questionnaire and an open interview with the IP. Leading concerns consisted of gastrointestinal symptoms (9) including nausea/vomiting, digestion, bitter taste, and other mouth symptoms; emotional distress

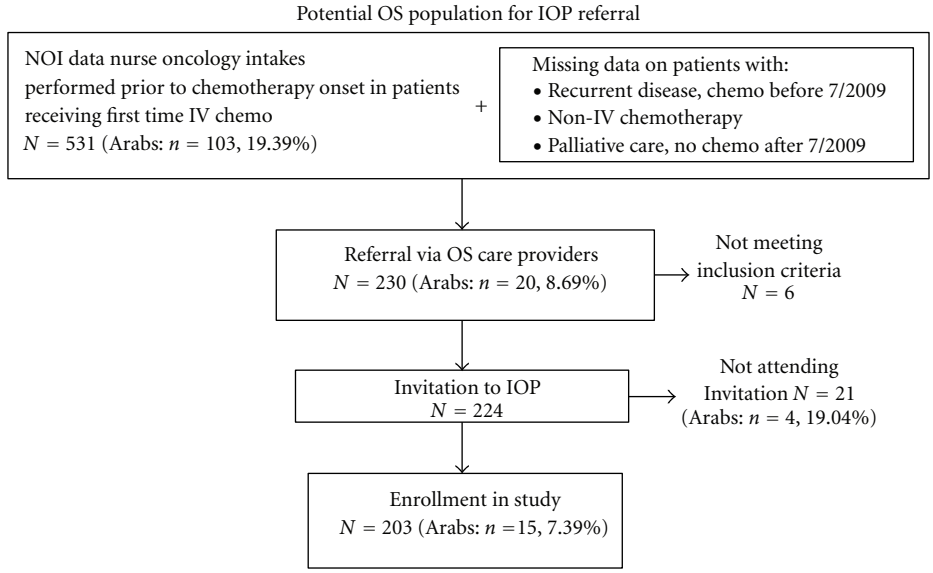


Figure 2: Algorithm of study recruitment (in brackets the proportion of Arab patients).

Table 1: Demographic characteristics of Arab patients enrolled in the integrative registry protocol within the oncology service (OS) in the Lin Medical Center, Haifa.

Patient's code	Age	Gender	Religion	Settlement type and zone*	Cancer site	Oncology status (and chemotherapy setting)
1	59	F	Christian	Urban 1	Breast	Localized (adjuvant)
2	44	F	Muslim	Urban 3	Breast	Localized (adjuvant)
3	62	F	Christian	Urban 3	Breast	Advanced (palliative)
4	47	M	Druze	Rural 3	Mesothelioma	Advanced (palliative)
5	46	F	Druze	Rural 3	Stomach	Localized (adjuvant)
6	45	F	Druze	Rural 3	Breast	Localized (adjuvant)
7	44	F	Druze	Semiurban 3	Unknown	Advanced (palliative)
8	62	F	Christian	Urban 3	Breast	Localized (adjuvant)
9	38	F	Muslim	Urban 3	Breast	Localized (adjuvant)
10	22	M	Muslim	Rural 3	Testicular	Localized (adjuvant)
11	65	F	Muslim	Urban 3	Bladder	Localized (adjuvant)
12	67	M	Muslim	Urban 1	Colon	Localized (adjuvant)
13	67	F	Muslim	Semiurban 2	Lung	Advanced (palliative)
14	42	F	Christian	Urban 1	Colon	Advanced (palliative)
15	77	M	Christian	Urban 1	Colon	Advanced (palliative)

* Distance from the oncology service in Haifa is classified according to zones as follows: zone 1: city of Haifa; zone 2: up to 20 kilometers from Haifa; zone 3: more than 20 kilometers from Haifa.

(5); fatigue (5); pain/neuropathy (3); other symptoms. The average degree of concern on a 7-point scale (from 0: *not bothering me at all* to 6: *bothers me greatly*) is 5.16.

At the conclusion of every initial intake, the IP and the patient defined the integrative medicine treatment goals together. This shared decision-making was regarded by the IP as the climax of the meeting that determined which objectives were both acknowledged and accepted by the patient and could be fully regarded in the formulation of the treatment plan that followed. Common treatment goals accepted by both the patient and the IP in the 15 intakes are as follows: fatigue (12), pain (12—including neuropathy and headache), emotional distress (8—including also the caregiver's well-being), nausea/vomiting (8) and other gastrointestinal symptoms (constipation-3, taste alteration (3), mouth sores (1), diarrhea (1), and heartburn (1)), appetite loss (5), difficulty in breathing (4), sleep (4), and others (miscellaneous).

3.4. Clinical Outcome Assessment. The number of integrative medicine sessions that followed the initial IP intake up to the concluding session varied from 1 (two patients participated only in IP intakes and did not attend further sessions) to 39 (mean 9.06, median 8). In total, 136 integrative medicine

sessions have been recorded in the registry protocol for these patients. Typically, various CM modalities were integrated in each of the sessions and were coded according to the main CM modality and its specific technique within this modality (e.g., guided imagery is regarded as *CM code* within mind-body modality). Altogether, 383 CM codes were recorded during the 136 sessions. CM modalities that were practiced include acupuncture (in 13 patients), herbal medicine mainly traditional Arab herbs (12), manual and touch therapies (10 including acupressure, Reiki, and shiatsu), nutritional counseling with traditional Arab medicine orientation (9), mind-body-spiritual practices (7 including breathing exercises, guided imagery, and spiritual counseling and meditation), nutritional supplements (5), homeopathy (2), exercise counseling (2), and anthroposophic medicine (1).

Clinical outcome assessment was mainly based on IP's and patient's evaluation performed during the concluding session. Following this session, the IP asked the oncologist to assess the integrative treatment role in the patient's care, thus adding a third perspective to the concluding evaluation. The extent to which clinical assessment was achieved was graded on three levels: *comprehensive*—in 8 of 15 patients a 3-way perspective (IP's, patient's, and oncologist's) evaluation was obtained; *partial*—for 3 patients, evaluation was available from 2 of the 3 assessors; *deficient*—4 patients had no, or almost no, evaluation at all. These three levels of assessment comprehensiveness was often correlated with the IP's evaluation of patient's compliance (high, moderate, and low).

Analysis of pre- and posttreatment outcomes was performed by comparing baseline and concluding session scores on the MYCAW and ESAS questionnaires. MYCAW scores which reflect patients' leading concerns, improved from 5.15 ± 0.933 to 2.05 ± 1.504 ($P < 0.0001$) (mean ± SD on a 7-point scale ranging from 0: *not bothering me at all* to 6: *bothers me greatly*). MYCAW's well being score improved from 4 ± 1.155 to 1.9 ± 1.853 ($P = 0.015$). In addition, the following symptoms improved as reflected by comparing pre- and post-ESAS scores (11-point scale ranging from 0 to 10): fatigue (6.1 ± 2.514 versus 2.9 ± 2.47, $P = 0.024$), nausea (3.9 ± 2.998 versus 1.7 ± 2.669, $P = 0.043$), depression (4.4 ± 2.951 versus 1.1 ± 1.595, $P = 0.012$), anxiety (3.6 ± 3.893 versus 1.3 ± 2.058, $P = 0.044$), appetite (4.7 ± 3.466 versus 0.9 ± 1.729, $P = 0.012$), and feeling of well-being (5.9 ± 2.601 versus 3.3 ± 2.869, $P = 0.031$). No significant statistical differences were noted regarding the ESAS subscales for pain, drowsiness, shortness of breath, and sleep quality.

Within the group of 8 patients (coded in Table 1 as patients 4–6, 8-9, 11-12, 15) with comprehensive assessment and high compliance, MYCAW scores reflected improvement in regard to nausea/vomiting (4 patients), fatigue (3), and emotional distress (3). Improvement in ESAS scores was more evident for pain (6), fatigue (6), nausea (5), anxiety (5), and depression (4). Patients' narrative evaluation as obtained in the MYCAW questionnaire administered in the concluding session emphasized the following themes: (a) improved acceptance of natural remedies (e.g., patient 4: "I feel better with natural remedies"); (b) a sense of well-being and empowerment (e.g., patient 5: "Following acupuncture I feel stronger"; patient 11: "Treatment with needles and breathing exercises gave me more strength… more energy"); (c) increased symptom control (reported by all 8 patients); (d) calming effect of the treatment (e.g., patient 6: "Acupuncture relieved pain and calmed me"; patient 12: "Acupuncture releases the body and reduces agitation").

Within the group with deficient assessment and low compliance (4 patients coded as 1, 2, 7, and 14), two of the patients attended only one session (IP intake), whereas the other two attended 2 to 3 sessions. The information regarding the noncompliance of this group of patients is indirect and based on either a telephone interview with the independent researcher following the initial IP intake (patient 4 reporting reluctance towards needle insertion) or interviews with the patients' oncology nurse (e.g., patient 7: "Although the patient had faith in CM, she was frustrated by the dramatic deterioration in her health and felt that neither chemotherapy nor CM improved her condition"; patient 14: "The patient ignored the severity of her illness. It seems that QOL is not the most important theme for her; she just wished to "taste" CM but not make full use of it").

Last but not least, the group of 3 patients with partial assessment and moderate to high compliance (patients coded as 3, 10, and 13) may add insight to the perceptions of the other two groups. The number of integrative sessions in this group ranged from 8 to 16 per patient. In contrast to the deficient assessment group, evaluation was available but incomplete. With two of the patients, clinical improvement was either implicit (patient 3 reporting sleep improvement following acupuncture) or explicit (patient 13 reporting that "following needling I felt better in breathing and returned a different person"). In contrast, clinical evaluation of patient 10 is contradictory, as evident in the simultaneous improvement and worsening in MYCAW and ESAS symptoms and the low score in the oncologist's evaluation.

3.5. Discussion. In this study, we present our experience with Arab patients referred to the IOP with the aim of improving their well-being during chemotherapy for either localized or advanced cancer. The main question we encounter daily is how optimal our communicational and clinical approach is in meeting the needs of Arab patients with cancer who are being treated in the IOP. Our intention was not to compare such aspects between Arab and Jewish patients but rather to understand and acknowledge cross-cultural barriers that potentially hamper optimal integrative care. The hypothesis that potential barriers do exist in provision of complementary therapies among the Arab population was recently supported by Keshet and Ben-Arye who surveyed 58 HMO-related complementary medicine clinics in north Israel [18].

In our study, we cautiously suggest that a disturbing gap exists between the percentage of Arab patients referred to nurse oncology intakes (19.4%) and those referred ultimately to the IOP (only 7.4% were finally enrolled in the registry protocol), as compared to non-Arab patients.

Table 2: Potential barriers to CM integration in supportive cancer care of Arab patients in northern Israel and recommendations for bridging the barriers.

Potential Barrier	Recommendation	Practical implications
Geographical factor: 68% of the Arab patients receiving chemotherapy reside >20 km from the IOP in Haifa OS	Opening a second site of IOP activity in Haifa periphery (zone 2 or 3)	Minimizing distance-bias may help patients to overcome initial hesitations regarding the first IP visit and enable them to attend weekly CM sessions
Not having an Arab CM practitioner in the IOP staff	Inclusion of an Arab CM practitioner (preferably a dual practitioner) in the IOP	Improving verbal communication with patients, enhancing the IOP attentiveness to their needs, and concerns and promoting development of traditional Arab-oriented therapies
Gap between patients' expectations and IOP objectives and CM repertoire	Increasing IP awareness of patients' expectations; developing integrative modalities that will resonate more with traditional Arab medicine	Matching patients' expectations with IP goals of treatment is essential and should be continuously monitored, especially with regard to QOL-oriented care rather than "attacking" cancer cells
Suboptimal matching of CM modalities to patients' cultural and religious codes and beliefs	Raising the IP's and CM practitioner's awareness of cultural and religious codes within the Arab society	The IOP staff need to consider cultural appropriateness of certain CM modalities (e.g., touch), reluctance concerning unfamiliar treatments (e.g., acupuncture, guided imagery), and gender issues (patient treated by a CM practitioner of the opposite sex, presence of another person in the room, etc.)
Suboptimal communication between the IOP and the other OS sectors	Improving IP-oncologist-nurse-social worker communication in order to enhance coordinated comprehensive care	Closer monitoring of patient compliance may also reveal the patient's difficulties and barriers to seeking integrative care
Lack of communication with the patient's family physician (FP)	Initiating a structured form of communication with the patient's FP via summary letter e-mailed from the patient's medical file	The FP often operates within the cultural milieu of the patients, care givers, and the extended family circle Integrative care-oriented medical education courses are needed to familiarize FPs with the IOP activity

Although the NOI data includes only i.v. chemotherapy-naive patients and does not necessarily reflect patients treated with oral chemotherapy or for recurrent disease or in a palliative context, the gap between the 103 Arab patients admitted to NOI in the 2-year period and the small group of 15 patients actually enrolled in the registry protocol necessitates further contemplation. What are the reasons for this referral bias? Although further studies are needed to answer this query, four explanatory factors may be hypothesized: (1) patient-related factors (e.g., lack of patient's interest or belief that CM is beneficial during chemotherapy); (2) culturally-dependent factors (e.g., health-belief model that views cancer treatment in the context of "cure" and survival extension, rather than focusing on QOL aspects); (3) HCP-related factors (e.g., OS health providers speculating that CM may be less appropriate for Arab patients); (4) HMO-related factors (e.g., limited access of Arab patients that live in zone 3, far from Haifa, to the IOP; lack of Arab HCPs within the OS and the IOP staff, which limits communication and complicates matching expectations regarding CM).

The question of barriers in providing integrative care to Arab patients is multifaceted (Table 2). We initiated the registry protocol and gained a preliminary unsatisfactory experience with the first 3 Arab patients (coded 1–3). As we gained more experience, we acknowledged that goodwill, openness, and sympathy to the needs of the Arab patient are not sufficient to catalyze a breakthrough. The tipping point was established when we understood that a cross-cultural dialogue needs at least two partners to embark on a journey. We understood that the IP-patient interaction mirrors a more complex cultural interaction between individual- and collective-oriented perspectives. On a practical level, we learned that patients may view CM modalities not only by an efficacy-safety scale (e.g., Does it work? Is it safe?) but also as metaphors and gestures (e.g., the invasiveness of the acupuncture needle or the calmness and feeling of contentment induced by touch). Thus, our experience has taught us that we need our patients to discover their needs alongside our own bias. Furthermore, we learned how patient-tailored treatment necessitates both skill and modesty to determine the appropriateness and sequence of treatment with herbs, touch, breathing, or needles. The establishment of trust between the patient and the IP/CM practitioner is the key element in modeling the therapeutic plan. Barriers such as the patient's reluctance to experience unfamiliar CM modalities (e.g., acupuncture, massage, and guided imagery) should not be ruled out in advance but perhaps could determine the sequence of CM modalities suggested along the course of treatment. As we gained more experience with Arab patients, we learned that herbal and nutritional counseling should typically be prioritized as the first CM modality of choice, which then can facilitate trust and openness towards additional modalities. Moreover, within each CM modality we were able to identify a scale of techniques ranging from "acceptable" to "odd" (e.g., within the mind-body modality, we typically started with a breathing

exercise, moving gradually, in following sessions, to suggest closing the eyes, guided imagery, deeper meditation, etc.). Gender is another trust-dependent factor that may hamper patients' willingness to experience CM, which includes the following considerations: a mismatch of patient's and IP/CM practitioner's gender (typically female patient and male IP), the presence of another person in the room from the same or opposite sex (such as the patient's spouse, relative or another CM practitioner), and immodesty as a challenge determined either by the CM procedure (e.g., acupuncture in the knee area) or the patient's cultural/religious values, or both. As our clinical and communicational skills developed, we learned to acknowledge the complex of cultural considerations, discover our own limitations in understanding "the other" and "ourselves" in the cross-cultural equation, and become increasingly committed to the needs, concerns, and hopes of our patients who speak Arabic, Hebrew, and the many other languages spoken in our region's contemporary "Tower of Babel".

3.6. Recommendations and Practice Implications. We support the following recommendations (see Table 2) aimed at improving accessibility and motivation of Arab patients to seek integrative supportive care in our oncology service. We believe that these recommendations may also be beneficial in other integrative settings in the West that provide supportive cancer care to patients from cultural minorities.

(1) Location and accessibility of the integrative oncology center is a pivotal aspect, and therefore, IOP should be operated geographically within the minority population.

(2) The integrative medicine staff should include a CM practitioner from the cultural minority in order to identify patients' cultural-related expectations, concerns, and barriers, with the aim of bridging the gap between traditional, complementary, and conventional agendas regarding cancer supportive care.

(3) Developing integrative modalities that will resonate more with traditional medicine especially regarding the use of herbs and nutrition in relieving chemotherapy side effects and improving QOL.

(4) Raising IPs' and CM practitioners' awareness of the patient's cultural and religious codes and beliefs (e.g., appropriateness of applying manual therapies (including massage and acupuncture) that may be interpreted by patients as immodest).

(5) Close monitoring of the patient's compliance by improving IP-oncologist-nurse-social worker communication regarding the patient's difficulties and barriers to receiving thorough integrative care.

(6) Initiating structured communication with the patient's family physician, who often operates within the cultural milieu of the patients, care givers, and the extended family circle.

3.7. Study Limitations and Recommendations for Following Studies. This study is limited by several considerations that may restrict the generalization of our findings to other societies and clinical settings. The group of 15 Arab patients in our registry protocol is small and lacks a control group not receiving integrative care. Thus, clinical outcomes reported in this paper may not strictly reflect the specific effects of CM intervention but also the complex interactions among the following factors: natural history of the disease and treatment-related effects (improvement as well as deterioration caused by chemotherapy) on patients' quality of life, clinical natural history (e.g., improvement of surgery-related symptoms along the course of time, disease progression causing QOL worsening, etc.), anxiety relief following the patient's adjustment to treatment, and nonspecific effects of his/her interaction with the IP and CM practitioners (e.g., attention, empathy, professionalism, etc.). However, taking this limitation into account, the comprehensiveness of our methodology provides us with a perspective of real-life patient-tailored settings and the ability to interpret social, cultural, and clinical findings in a broad and complex context, though the researcher's subjectivity should be kept in mind as potential bias. Another limitation is the lack of data regarding Arab patients with recurrent disease or during palliative care who potentially could have been referred to the IOP. Missing data is also a limiting aspect concerning the registry protocol patients with low compliance. The current study lacks sufficient qualitative research that could shed light on the motives of those Arab patients who discontinue treatment or, on the other hand, those who were highly compliant. Finally, this study is limited to the local features of the Arab community in northern Israel and the local characteristics of the CHS oncology service in Haifa, and the Integrative Oncology Program operated within the OS.

4. Conclusions

Barriers to integration of CM in the supportive care of Arab patients in northern Israel are multifaceted and include cross-cultural and institutional factors that influence referral and contribute to compliance and clinical outcomes. Bridging cultural gaps and traditional values with regard to CM can assuage patients' concerns and, ultimately, facilitate an enhanced integrative approach to symptom control resulting in improved quality of life.

Acknowledgments

The authors thank Professor Efraim Lev, Dr. Ibrahim Hogerat, and Clalit Health Services Research Institute for their contribution in constructing an integrative agenda oriented toward the Arab population. They also thank the following health care providers and medical directors for their contribution to the development of the IOP: Dr. Roni Amar, Professor Ofer Lavie, Dr. Chen Shapira, Ms. Michelle Katz, Ms. Judith Tapiro, Ms. Haya Vintal, Ms. Olga Agour, Ms. Michal Pereg, Ms. Haviva Kol, Ms. Avital Stanger, and Ms. Dikla Krieger, and Ms. Marianne Steinmetz for editing the paper.

References

[1] O. Said, K. Khalil, S. Fulder, and H. Azaizeh, "Ethnopharmacological survey of medicinal herbs in Israel, the Golan Heights and the West Bank region," *Journal of Ethnopharmacology*, vol. 83, no. 3, pp. 251–265, 2002.

[2] A. Alachkar, A. Jaddouh, M. S. Elsheikh, A. R. Bilia, and F. F. Vincieri, "Traditional medicine in Syria: folk medicine in aleppo governorate," *Natural Product Communications*, vol. 6, no. 1, pp. 79–84, 2011.

[3] M. S. Ali-Shtayeh, Z. Yaniv, and J. Mahajna, "Ethnobotanical survey in the Palestinian area: a classification of the healing potential of medicinal plants," *Journal of Ethnopharmacology*, vol. 73, no. 1-2, pp. 221–232, 2000.

[4] E. Ben-Arye, E. Schiff, E. Hassan et al., "Integrative oncology in the Middle East: from traditional herbal knowledge to contemporary cancer care," *Annals of Oncology*. In press.

[5] E. Ben-Arye, M. S. Ali-Shtayeh, M. Nejmi et al., "Integrative oncology research in the Middle East: weaving traditional and complementary medicine in supportive care," *Supportive Care in Cancer*. In press.

[6] E. Ben-Arye, G. Bar-Sela, M. Frenkel, A. Kuten, and D. Hermoni, "Is a biopsychosocial-spiritual approach relevant to cancer treatment? A study of patients and oncology staff members on issues of complementary medicine and spirituality," *Supportive Care in Cancer*, vol. 14, no. 2, pp. 147–152, 2006.

[7] M. G. Aksu, H. S. Bozcuk, and A. F. Korcum, "Effect of complementary and alternative medicine during radiotherapy on radiation toxicity," *Supportive Care in Cancer*, vol. 16, no. 4, pp. 415–419, 2008.

[8] F. Naja, M. Alameddine, M. Abboud, D. Bustami, and R. Al Halaby, "Complementary and alternative medicine use among pediatric patients with leukemia: the case of Lebanon," *Integrative Cancer Therapies*, vol. 10, no. 1, pp. 38–46, 2011.

[9] R. E. Genc, S. Senol, A. S. Turgay, and M. Kantar, "Complementary and alternative medicine used by pediatric patients with cancer in western Turkey," *Oncology nursing forum*, vol. 36, no. 3, pp. E159–E164, 2009.

[10] M. W. Ben Arush, H. Geva, R. Ofir, T. Mashiach, R. Uziel, and Z. Dashkovsky, "Prevalence and characteristics of complementary medicine used by pediatric cancer patients in a mixed western and middle-eastern population," *Journal of Pediatric Hematology/Oncology*, vol. 28, no. 3, pp. 141–146, 2006.

[11] Y. Yildirim, S. Tinar, S. Yorgun et al., "The use of complementary and alternative medicine (CAM) therapies by Turkish women with gynecological cancer," *European Journal of Gynaecological Oncology*, vol. 27, no. 1, pp. 81–85, 2006.

[12] E. Ben-Arye, E. Schiff, M. Steiner, Y. Keshet, and O. Lavie, "Attitudes of patients with gynecological and breast cancer toward integration of complementary medicine in cancer care," *International Journal of Gynecological Cancer*. In press.

[13] E. Ben-Arye, K. Karkabi, S. Karkabi, Y. Keshet, M. Haddad, and M. Frenkel, "Attitudes of Arab and Jewish patients toward integration of complementary medicine in primary care clinics in Israel: a cross-cultural study," *Social Science and Medicine*, vol. 68, no. 1, pp. 177–182, 2009.

[14] C. Paterson, K. Thomas, A. Manasse, H. Cooke, and G. Peace, "Measure Yourself Concerns and Wellbeing (MYCaW): an individualised questionnaire for evaluating outcome in cancer support care that includes complementary therapies," *Complementary Therapies in Medicine*, vol. 15, no. 1, pp. 38–45, 2007.

[15] M. Frenkel, L. Cohen, N. Peterson, J. L. Palmer, K. Swint, and E. Bruera, "Integrative medicine consultation service in a comprehensive cancer center: findings and outcomes," *Integrative Cancer Therapies*, vol. 9, no. 3, pp. 276–283, 2010.

[16] V. T. Chang, S. S. Hwang, and M. Feuerman, "Validation of the Edmonton Symptom Assessment Scale," *Cancer*, vol. 88, no. 9, pp. 2164–2171, 2000.

[17] K. L. Tsang, L. E. Carlson, and K. Olson, "Pilot crossover trial of Reiki versus rest for treating cancer-related fatigue," *Integrative Cancer Therapies*, vol. 6, no. 1, pp. 25–35, 2007.

[18] Y. Keshet and E. Ben-Arye, "Which complementary and alternative medicine modalities are integrated within Israeli healthcare organizations and do they match the public's preferences?" *Harefuah*, vol. 150, no. 8, pp. 635–638, 2011.

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 693092, 8 pages
doi:10.1155/2012/693092

Review Article

Reflections on Palliative Care from the Jewish and Islamic Tradition

Michael Schultz,[1] Kassim Baddarni,[2] and Gil Bar-Sela[1]

[1] *Division of Oncology, Rambam Health Care Campus, Faculty of Medicine, Technion Israel Institute of Technology, P.O. Box 9602, Haifa 31096, Israel*
[2] *Al-Taj for Health and Heritage Organization, Arraba 30812, Israel*

Correspondence should be addressed to Michael Schultz, m_schultz@rambam.health.gov.il

Received 21 September 2011; Accepted 24 October 2011

Academic Editor: Peter Heusser

Spiritual care is a vital part of holistic patient care. Awareness of common patient beliefs will facilitate discussions about spirituality. Such conversations are inherently good for the patient, deepen the caring staff-patient-family relationship, and enhance understanding of how beliefs influence care decisions. All healthcare providers are likely to encounter Muslim patients, yet many lack basic knowledge of the Muslim faith and of the applications of Islamic teachings to palliative care. Similarly, some of the concepts underlying positive Jewish approaches to palliative care are not well known. We outline Jewish and Islamic attitudes toward suffering, treatment, and the end of life. We discuss our religions' approaches to treatments deemed unnecessary by medical staff, and consider some of the cultural reasons that patients and family members might object to palliative care, concluding with specific suggestions for the medical team.

1. Introduction

Holistic patient care must relate to the spiritual aspect of patients' experience and concerns. This is especially clear in an area such as the Middle East, where religious beliefs are strong and widespread, but holds true anywhere, since spirituality is a universal part of the human experience [1]. A truly integrative, holistic approach is one that addresses all aspects of the patient experience—the biopsychosocial-spiritual model [2, 3]. Religion and spirituality are important for a majority of our patients, yet their spiritual needs are not supported by the medical team most of the time [4]. The integration of spiritual care into the team approach can pay significant dividends, as spiritual care in particular and spiritual wellbeing in general are correlated with higher patient quality of life [4, 5], reduced anxiety [6, 7], reduced end-of-life despair and depression [8, 9], and shorter hospital stays [6, 7]. Even and especially at the end of life, the spiritual dimension is a very significant part of the lived experience: "As physical health wanes, spiritual health may increasingly play a central role in determining patient well-being" [4]. Religious struggle, on the other hand, can have a negative impact on well-being or even on mortality [10]. Faith is also significant for medical decision making [4, 11].

What role can the medical team play in addressing patient spirituality? Aside from the focused spiritual care provided by the chaplains, all team members have a crucial role to play in engaging patients around this part of their experience of illness. By asking patients directly about their spirituality and religious beliefs, staff better understand patients as a whole person, deepen the caring relationship, build trust, and can potentially uncover spiritual distress or spiritual beliefs that will impact on decision making [12, 13]. McCord et al. found that a large majority of patients wanted staff to discuss spiritual matters with them, and the primary reason for that desire was in order to increase patient-staff understanding [14]. Yet many doctors and nurses feel hesitant to bring up spirituality with patients. One of the factors leading to this reluctance may be unfamiliarity with specific religions' beliefs relating to illness, treatment, and death.

In Israel, the two predominant religions are Judaism and Islam, both of which are well represented in the rest of

the world as well. Over 19 million Muslims have made their homes in the West. These communities are heterogeneous in many aspects—in terms of dress, diet, language, and ethnic origin [15]. Consequently, more and more doctors and nurses will come across Muslim patients in the course of their work. Building on the existing literature [15–24], this review of the Muslim approach to illness and death and the beliefs and needs of the Muslim patient will open the door to fruitful communication between Muslim patients and their health care professionals with respect to their spiritual beliefs and needs. The outcome will ensure improvement of care and mutual respect while preventing embarrassment and confrontation. Cultural competence of Muslim spiritual and religious beliefs constitutes a critical component of total care. Though there is of course a range of beliefs and religiosity in Islam, as in all religions, strong adherence to the approaches and beliefs outlined here is widespread in our country.

Judaism, perhaps more so than Islam, has a wide range of perspectives on almost every issue. Rather than focusing on legal issues, as other recent excellent works have done [25–27], we will discuss some of the range of beliefs in Judaism regarding questions of illness, treatment, and the end of life. In so doing, we hope to provide the medical practitioner with a deeper understanding of the religious thinking that may underlie a patient or family member's response to the medical situation, and ease that practitioner's entry into a conversation about spirituality with the patient or their family, thereby deepening the caring relationship and better understanding the patient as a whole person. Additionally, and perhaps most importantly, we see in our work on a daily basis that just speaking about spirituality is a way for patients to reconnect to and "touch" their own spirituality, and that alone provides a great deal of comfort and strength.

It may even be that in specific cases of spiritual struggle, where a patient or family member is having a hard time reconciling their desire for a more palliative approach to care with their self-perception that Judaism does not allow them to do so, that the perspectives offered in this article will help enable staff to share the perspective with them that such a contradiction might not exist. In general, the principles of palliative care are largely in accord with Jewish, as well as Islamic, tradition [26]. In Israel in particular, the power of traditional beliefs is strong for a considerable majority of the population, many more than those who preserve traditional practices, and of course belief only strengthens in the face of serious illness.

We will draw on our experience in the field of Israeli professional spiritual care, a young field that has developed in the last decade and ongoing research has documented its progress [28, 29].

In this discussion, our goal is not to consider the religious dimensions of end-of-life questions, such as disconnection from a ventilator. Rather, our focus will be on examining Judaism's and Islam's attitudes toward illness and the end of life, since these are essential to considering a palliative approach. In that vein, we will consider cultural concerns that arise around end-of-life care, and will examine some approaches to thinking about treatment decisions when medical hope for a cure greatly diminishes.

2. Attitudes toward Suffering and Treatment

One of the crucial foundations of the palliative approach is the understanding that treatment of serious illness is not only about the tension between life and death, but also includes reducing suffering and improving the patient's quality of life. In Judaism, the Biblical commandment "and you shall return it (a lost object) to him (its owner)" (Deuteronomy 22 : 4) is the source for the doctors' obligation to heal their patients. If a doctor has it in his power to "return" to the patient that which he has lost, namely, his health, then he must do so. However, there is no reason why this need be limited to his health only. As the medieval scholar Maimonides writes, this commandment broadly obtains to returning "his body, his money, and his mental health." (translations are the authors' [30]). In this vein, the obligation to provide healing includes returning to a patient his lost quality of life and returning to him the previous form of life that he had enjoyed—life that was not full of suffering.

In Islamic belief, suffering plays an important role in life. For the Muslim, sickness and suffering are a part of life: a matter of coincidence, an attack of the evil eye, or a spiritual test from the creator. Emotional and physical suffering caused by illness is regarded as a test of faith in God, expunging the sins of the Muslim [31]. Sickness should wake people up from heedlessness, guide them to give up their sins, make them think about the hereafter, and lead them to pious foundations. It should make people more thankful to Allah and teach them the necessity of taking better care of their health and making better use of their life—something they may not have realized before. Illness should teach them to understand other sick and pained people better, to feel sorry for them, and to help them. Going through suffering also raises their ranks and degrees higher in the hereafter. According to the Islamic philosophy of life, there is a transcendental dimension to pain and suffering. Pain is a form of test or trial, to confirm a believer's spiritual station [32]. Suffering is considered a part of life, and forbearance of hardship is greatly rewarded in Islam. In particular, forbearance of an illness leads to expiation of sins in Islam [33]. The Quran tells us that those who claim to believe in Allah will not be left alone after a proclamation of their belief and asserts that believers will be put to the test in various ways: "Be sure that we shall test you with something of fear and hunger, some loss in goods or lives or the fruits of your toil, but give glad tidings to those who patiently preserve" [34] (2 : 155). Islam teaches that pain and suffering delete sins: "And bear in patience whatever (ill) may befall you: this, behold, is something to set one's heart upon" [34] (31 : 17). The Prophet (peace be upon him) said that "When the believer is afflicted with pain, even that of a prick of a thorn or more, God forgives his sins, and his wrongdoings are discarded as a tree sheds off its leaves."

At the same time, treatment to reduce pain and suffering is mandated in Islam. The Islamic teaching encourages Muslims to seek treatment when they fall sick [31], "Seek treatment, because Allah did not send down a sickness but has sent down a medication for it, except for death." The majority of traditional scholars viewed medical treatment

as permissible in cases of chronic illness and an obligation in cases of emergency in which loss of life would occur if the person was not treated [15]. Pain relief by analgesic, including morphine, to prevent suffering is allowed and recommended, even if it hastens death, since actions are judged by their intention. The Muslim believes that pain expunges sins, but pain must be treated because God opposes human suffering; (see Jotkowitz and Zivotofsky [25] for an extended discussion of the varying, though similar, Jewish approaches to pain relief).

3. Thinking about Death

A second foundational aspect of the palliative approach is that death is not the enemy. In Islam, death is inevitable and occurs only with a command from God: "Every soul shall have a taste of death: in the end to Us shall you be brought back" [34] (29 : 57). It also states, "Wherever you are, death will find you out, even if you are in towers built up strong and high" [34] (4 : 78). "From it (the earth) did We create you, and into it shall We return you, and from it shall We make you appear once again" [34] (20 : 55), referring to life after death. Death should not be resisted or fought against, but rather it is something to be accepted as part of the overall divine plan [35]. "It is God who creates you and takes your souls at death" [34] (16 : 70). When death is approaching, believers should pronounce the Faith of Testimony (*Shahada*): "There is no god but Allah, and Muhammad is the messenger of Allah." This short, important ritual consolidates the dying person's expectation that death is not the end, and that he or she is now entering the world of the divine with the proper attitude. Death is the will of God: "It is not possible for a soul to die except with the permission of God at a term set down on record" [34] (3 : 139). The only guarantee that comes along with birth is death. "To God we belong and to Him is our return" [34] (2 : 156). Death is unpredictable and can happen at any time and as such Muslims should always be prepared for the inevitable and for what is about to occur. "When their time comes they cannot delay it for a single hour nor can they bring it forward by a single hour" [34] (16 : 61). Death is but a gateway from this short but mortal existence to a life of immortality in the afterlife. The Quran always affirms the unlimited mercy and forgiveness of God, but links future life to performance in the present life, from birth to death [36]. The earth is described as a resting place for the purpose of worshipping God and doing good deeds [34] (2 : 20-21).

In Judaism, there are sharply contrasting views of how to think about death. Very common is the belief articulated well by Rabbi Lord Immanuel Jacobovits, the late chief rabbi of England and founder of the modern study of Jewish medical ethics, who writes that the parallelism in Deuteronomy 30 : 15—"behold, I set before you this day life and good and death and evil"—indicates that death is evil. Without discounting that prevalent view, we would like to round out the picture by examining two sources from the Jewish tradition that endorse the belief that death is not the enemy. Rather, in this view, life is a wonderful gift. It is an opportunity to serve the Creator and, for this reason, we do our best to preserve life. "And G-d saw all that He had made, and behold it was very good" (Genesis 1). In the teachings of Rabbi Meir they found written: "And behold it was very good"—behold how good is death." (*Midrash Genesis Rabbah* 9 : 5). The beginning of Genesis describes the creation on each of the first five days; at the end of each day, God looks at what He has created and declares that "it was good." Yet at the end of the sixth day of Creation, the text is slightly but significantly different—God declares that "it was very good." What is the significance of the extra word, very? Rabbi Meir teaches that there is something additional, not explicitly mentioned in the text, which is also good. Perhaps, surprisingly, he teaches that this "hidden" final good element of creation is death itself. Another source explains, in greater detail, how it is it that the fact of death's existence is actually something positive: "(The angels) said to the Master of the Universe, "It is better for you to give the Torah to the heavens, since we are holy and pure, and the Torah is holy and pure, and we live (eternally), and the Torah is the tree of life, it's better that it should be given to us!" He said to them, "It cannot be fulfilled in the heavens, as it is written, "It is not found in the land of [eternal] life" (Job 28). Rabbi Nehemia said in the name of Rabbi Yehuda, "Draw a parable to a man who had a son who lacked one finger, and he took him to learn the arts. There was one art which requires all the fingers. After some time his father came to see him and found that he had not learned that art. He asked his teacher, "Why have not you taught him this art?!" He replied, "This art requires all the fingers. Your son is lacking one finger, and you are asking for him to learn this art?" So too God said to the angels, "You cannot fulfill the Torah, for you do not reproduce, you do not have impurity or death or sickness, rather you are all holy!" (*Midrash Psalms 8*). Let us closely examine this text. The Torah is the collective body of God's teachings in general, often used to mean the Five Books of Moses in particular. This text teaches that man is able to fulfill God's commands better than the angels, immortal and perfectly pure, ever could. The very fact of our mortality and our experience with impurity enhances mankind's ability to serve God. In Judaism, impurity is generally a function of contact with the world of the souls (contact with a dead body, giving birth, the unfertilized life ending in menstruation) or, in effect, of contact with death. The angels, who live forever, are actually in this sense lesser beings than mankind, who have contact with death, because one grows as a person as a result of living with the reality of death. This takes shape in numerous different ways. The reality of death provides us with the fundamental attitude of gratitude for our very lives. The fact that our time might run out at any moment provides us with motivation to live our lives well, every single day. Many of our patients report how the experience of illness has taught them valuable lessons, such as self-respect and the willingness to admit that we are not in complete control, and helped them to grow as a person. The same can hold true for friends or family members of someone who is ill. In this view, the creation of death as a part of our world is, in fact, "very good."

4. Challenges in Accepting Palliative Care

Cultural factors can pose difficulties in successfully suggesting palliative care to a patient and his family. Many Muslims believe that palliative care does not preserve life but delays death and postpones one's fate. There are those who will feel discriminated against as a minority or as a result of inferior insurance, or because they believe that decisions were made to free up space for another patient [33]. Palliative care, and especially deescalation of care, is seen as "giving up" or shirking one's duty to heal. Furthermore, immigrant or minority Muslims may feel that inferior care is being given because of their religion or ethnicity or level of insurance, or that the physician is lying to the family, exaggerating a poor prognosis to end care sooner and make way for other patients [33].

In Judaism, some patients or their families might refuse palliative care because they see it as a prohibited form of "giving up" on healing. In particular, they might feel that it demonstrates a less than perfect faith that God will heal. The husband of one of our patients refused palliative care for her because he was worried that doing so would show a deficiency of faith for which his wife would be punished by God. There are, of course, a great variety of approaches in Judaism, and it is never helpful to challenge or "correct" a patient or his/her spouse's view, only to learn what their approach is and work within it.

We would like to present one perspective within the Jewish tradition that may be helpful to those looking to find a Jewish viewpoint more in keeping with the palliative approach. The son of one of our patients asked us, "Do you believe in the Maimonidean or the Nachmanidean approach to doing our part to bring about a miracle?" What he was asking, by referring to the positions of two illustrious rabbis of the Middle Ages, was whether or not it was acceptable for them to take a palliative approach in their father's care while maintaining hope for his miraculous healing, or whether they needed to pursue curative oncology treatments as a way of partnering with God in bringing about the miraculous healing. The debate, in philosophical terms, is whether God simply does the miracles or whether we first need to do our part, futile though we know our efforts will be in bringing about the miracle without God's help, and then God will meet us halfway. But the question, in human, pastoral terms, asks whether we must "do everything" or is it permissible, from the perspective of proper faith, to maintain hope for healing while at the same time focusing on palliation.

An important Jewish source for this discussion is the commentary of Rabbi Shmuel ben Meir on the Babylonian Talmud. The Talmud states, "Rav Amram said in the name of Rav, From three sins a man has no escape every day: from sinful (lustful) thoughts, *iyyun tefilla*, and harmful speech" (Babylonian Talmud, Bava Batra 164b). What could be the meaning of the sin of *iyyun tefila*, literally "close examination of prayer," that people violate every day? Rabbi Shmuel ben Meir explains as follows: "Some explain that after he prays he thinks in his heart that God will reward him and do what he needs and fulfill his request because he prayed with proper intent (*kavana*)." In other words, one must not be so arrogant as to think that God is somehow required to provide what one asks for. Even if we behave perfectly, or pray perfectly, God does not have to do what we say. We can extend this from prayer to faith. Maintaining perfect faith that He will heal will not necessarily lead God to heal our beloved. And not having perfect faith in their healing will not bring about someone's death. We must preserve perfect faith that God can heal, but we need not act as if we are 100% confident that God will heal. Rather, we must do what is best for the moment, given a realistic understanding of the situation, and maintain hope that things will change for the better. Otherwise, we could end up causing a lot more pain and suffering to the patient, our beloved family member, and that is not what Judaism requires.

To return to the philosophical question of whether or not there is a need to "do everything" in order to partner with God in bringing about a miracle, we would suggest that undergoing all the treatment options recommended by the medical team is already a sufficient means of partnership and that, when palliative care is indicated, it is fine to focus on treating the pain and suffering.

5. Avoiding Unnecessary Treatments That Increase or Extend Suffering

Another principle of palliative care is to avoid treatments that add to the amount of suffering without a medical expectation of curing the condition or improving quality of life. What do Islam and Judaism have to say?

When death approaches and is unavoidable, Islam directs that the patient be allowed to die without heroic measures or supreme efforts [37]. Medications and medical technology should be used to enhance the patient's quality of life during his life. At the same time, Islam forbids acts that expedite death. Withdrawing care is permissible in two circumstances in Islam. The first is when a diagnosis of brain death has been made. The second is when the current treatment, be it curative or palliative, is no longer curing or palliating suffering but merely prolonging a natural and inevitable death [33]. The Prophet is quoted as saying "None of you should wish for death because of a calamity befalling him; but if he has to wish for death he should say: O Allah! Keep me alive as long as life is better for me and let me die if death is better for me."

In Judaism, the belief cited earlier, that death is evil, dovetails with many Jews' desire to "do everything" to try for a cure. Even if the goal is not a cure, one common approach is to do whatever is possible to extend life, since one moment of life in this world is more valuable than all the world to come. In contrast to those views, we will bring two recent voices from among the many great Jewish thinkers. Rabbi Moshe Feinstein, a leading American Jewish legal thinker of the 20th century, in response to a question regarding care of a patient for whom no cure is possible, wrote: "If physicians have no means of healing such a patient or of reducing his suffering, but do know a treatment to keep him alive for a limited time at the current level of suffering, then they should not give him this treatment . . . . Even great medical experts, if

they do not know how to heal the patient, then they should not give treatments that do not cure, relieve suffering, or give him the strength to endure his suffering, but if it will calm the patient's soul by giving him something, then it must be given" [38] (2 : 74.1). Rabbi Feinstein grounds his ruling in the Talmudic story (Ketubot 104a) of the death of Rabbi Yehuda the Prince, the leader of the Jewish people. Rabbi Yehuda the Prince was very ill and in a lot of pain and the prayers of all his students and the greatest leaders of the age were only effective enough to preserve his life, but not to reduce his suffering. When his handmaid saw how much pain he was in every time he went to the bathroom, she went up to the roof of the building where the rabbis were praying and threw down a jar. When it shattered, they were momentarily distracted from their prayers and Rabbi Yehuda passed away. The handmaid's action is praised—this was a situation where nothing more could be done for him, neither to cure him of illness nor to relieve his suffering, and she stopped the treatment from being given.

Rabbi Shlomo Zalman Auerbach, a leading Israeli Jewish legal thinker of the 20th century, in discussing the case of a dying patient at the end of his life, wrote: "Some are of the opinion that just as the Sabbath must be violated to preserve even temporary life, so it is similarly obligatory to force the patient [to be treated], because he does not own himself so that he [has the right to] relinquish even a moment of life. However, it is reasonable that if the patient is suffering a lot of physical pain, or even if he is in great psychological pain, (although) I believe it is mandatory give him food and oxygen for breathing even against his will, it is permissible to withhold treatment that causes suffering if he requests it. However, if the patient is God fearing and is not mentally confused, it is extremely desirable to explain to him that a single hour of repentance in this world is more valuable than all of the world-to-come, as (it is written) that it is a "privilege" to suffer seven years rather than to die immediately [39] (1 : 91.24)".

Thus, we see that very significant rabbinic writers do not automatically endorse continuing with treatments, and either indicate that it would be better not to give the treatment unless the patient specifically requests it or at least conclude that it is up to the patient to decide (see Bleich's alternative application of these rulings [40] and Brody's rebuttal [41]). At the same time, elsewhere, they rule that treatments to reduce pain and suffering must be obtained wherever possible [42]. What conceptual analysis underlies their rulings? For Rabbi Feinstein, at least, it seems that the duty to seek and provide healing only applies to treatments that actually help, either by potentially leading to a cure or by improving the patient's condition [25]. If pain and suffering cannot be reduced, and attempts to cure have failed, then these treatments are not in fact helpful. However, if the patient actively wants the treatment, or if it helps him psychologically or spiritually, then an otherwise unhelpful treatment turns into a beneficial one, and as such it should be pursued.

In the cases generally addressed by palliative care, we can consider a second approach, even though it would not have pertained to the cases that Rabbis Feinstein and Auerbach were discussing. They ruled regarding a situation where additional treatment could extend life slightly, but could not reduce suffering. Even in such a case, they said that Jewish ethics did not mandate such treatment. In palliative care cases, however, palliative care can actually reduce suffering. Furthermore, it is important to note that we have no medical reason to expect that continuing treatments will actually extend life as opposed to a purely palliative approach. Treatments given against doctors' advice in the hope of extending life just as often lead to complications that shorten life. In addition, pain and suffering themselves can shorten life (as noted by Jewish thinkers, as well. See Rabbi Waldenberg citing the statement in the Babylonian Talmud, Tractate Ketuvot 62b, "A groan breaks half a person's body" [43]). In one recent study among several showing this same result, patients with nonsmall-cell lung cancer who received early palliative care lived longer than patients receiving standard care, even though fewer patients in the palliative care group received aggressive end-of-life care [44]. Not all studies have shown such a benefit from palliative care, but many have, so at best the question of which approach extends life more is, at this point, a factual tossup. In addition to a longer life, the palliative care group also enjoyed more productive time at a higher quality of life. Thus, in applying the "extending life" approach, we cannot be sure which approach is better, and the decision can then be left to the patient (Jotkowitz and Zivotovsky [25] cite the opinion of Rabbi Waldenberg, mandating treatment in the same case discussed by Rabbis Feinstein and Auerbach above. However, their position is predicated on the assumption that we are discussing a case where additional treatment will extend life. In our cases, where that assumption may well not be valid, he might not disagree).

In addition to these two conceptual approaches, we would like to suggest and endorse a third possibility [45]. In Judaism, Jews have an obligation to make the most of their lives in terms of serving God, fulfilling the commandments, and growing religiously and spiritually. We have to maximize our ability to achieve in these areas, and not only maximize the amount of time that we live. Once we refocus the conversation on the religious goals of life, we realize that palliative care can sometimes be more conducive to fulfilling these tasks than continued treatments that involve difficult side effects. For example, the palliative approach can leave the patient with more strength for doing good deeds, while the aggressive approach might mean that all one's energy is devoted just to getting through the treatment. As Rabbi Auerbach noted, the conversation with patients should revolve around how best to fulfill one's religious duties during the life that remains. With that guiding principle, the decision regarding undergoing aggressive treatment can be left to the patient because he is often best placed to know for himself which approach will best enable him to serve God.

6. Psychological and Spiritual Care

Palliative care also mandates caring for the psychological and spiritual needs of the patient. As we have noted, in Judaism, the command to heal implied in the verse, "and you shall

return it to him," means that whatever is in the palliative care team's power to help restore to the patient, we must try to do so. This can include peace of mind and a sense of hope and meaning. Fear is often one of the overwhelming parts of the experience of the seriously ill patient. Judaism puts treatment of such a patient's fears on the same level as their medical needs. In the Talmud (Shabbat 128b), we read that if a blind woman giving birth on the Sabbath asks that a lamp be lit, in violation of the Sabbath, we light the lamp, in keeping with the well-established principle that we violate the Sabbath in order to save a life. In the Talmud, every teaching comes to teach something we would not have known otherwise. We need to understand what exactly is the case being discussed and what new lesson it is teaching about saving a life on the Sabbath. If the midwife herself needed a lamp for the delivery, then she could light it herself, without the pregnant woman requesting it, since in that case the light is needed to safely deliver the woman's baby. However, we already know that law and so the Talmud would not need to include this statement. Additionally, the innovation of this statement cannot be that the need of the woman giving birth for light is sufficient reason to light it on the Sabbath, since this woman is blind and cannot make use of the light. Where, the Talmud asks, is the new threat to life that motivates the addition of this permissive ruling? The Talmud explains that this will calm her fears that there is not enough light for the others to see her needs and respond to them quickly. Thus, fear alone is considered a life and death condition in the context of medical treatments. The palliative care team can be very helpful in addressing patients' fears, and in this additional way even help to "save a life." By listening to patients' fears, acknowledging and accepting them, the strength of the fears can be diminished. In addition, by engaging patients in a life review, thinking about the good things that they have already enjoyed in life, the fear for the future can take its place in the larger picture of thinking about one's life in its entirety.

A common spiritual need our patients face is despair, or the lack of hope. Very sick patients might despair not only for their physical health, but they might also despair of their life having any meaning anymore. The palliative care team can help in the process of finding meaning even at this stage. As we noted in our examination of the *Midrash* from Psalms, the encounter with death can actually help facilitate spiritual growth. This can be a time for even greater connectedness with God. It is also worth remembering and reminding patients that even at this point in life, religious good deeds (*mitzvot)* can still be done, and every second of faith or prayer or good deeds is invaluable.

Spiritual care is a vital part of care for the Muslim patient. The spiritual aspect of the Muslim patient is very important in preserving calmness and general wellbeing: disruption to the balance causes illness or worsens existing illness. Abu-Bakr Al-Razi was among the first to present the subject in his book "Spiritual Medicine" (*Al-Tib Al-Ruhani*) [46]. The reading of special verses from the Quran constitutes the cornerstone of spiritual healing. The first to present the subject was Abu-Zaid Al-Balkhi (b. 850, d. 934), who wrote the book "Sustenance for Body and Soul" (*Masalih al-Abdan wa al-Anfus*), in which he stressed the importance of the combined treatment of body and soul. He criticized the doctors who, in his opinion, were interested only in findings about the body when treating illnesses and neglected the emotional and spiritual aspects of the patient. Al-Balkhi stressed the importance of treatment by means of looking at beautiful pictures (guided imagery) and listening to beautiful music (music therapy). Muslims find the greatest solace and comfort in the remembrance of God. During illness, the Muslim patient should set for himself these spiritual goals.

(1) Muslims are expected to seek God's help with patience and prayer, increase the remembrance of God to obtain peace, ask for forgiveness, give more in charity, and read or listen to more of the Quran.

(2) Muslims repeat the saying "To God we belong and to Him is our return" to ease the shock of death.

(3) Atonement (*Tauba*): this is done by experiencing a genuine sense of remorse for one's transgressions and a removal of the unhealthy effects of that state by turning to God and seeking divine grace through prayer, charity, and a sincere resolution not to return to the destructive patterns of the past.

Patients need to make peace with God through religious duties in order to meet God free of sins, and also to make peace with relatives and friends. When a Muslim individual is dying, several things may be comforting to the patient and the family: (a) turning the patient on his/her right side to face Mecca; (b) letting those visiting the patient recite the prayer of allegiance to Allah, and encouraging the dying person to recite it also, if possible. If the patient is unable, another Muslim should recite it; (c) having friends and loved ones pray that mercy, forgiveness, and the blessing of Allah be given to the deceased; (d) reading specific verses from the Quran; (e) helping the dying person overcome the fear of death [47].

7. Conclusion—Doctors' Duties

The medical team should keep a number of things in mind in working with a Muslim patient. Health care should inform the patient of diagnosis and prognosis, but should not give a specific estimated life expectancy at any point, since life is in the hands of God, not in the physicians' hands. The patient needs to make peace with God through religious duties, so as to meet God free of sin, and with relatives and friends. This will enable the patient to finish the "unfinished business."

Truth telling: telling lies is considered a great sin according to the Islamic faith. The Prophet (peace be upon him) said "the signs of a hypocrite are three: whenever he speaks, he tells a lie; whenever he promises, he breaks it; and if you trust him, he proves to be dishonest" [31]. In addition, doctors need to be sensitive to patients' fears that the suggestion of palliative care is a form of discrimination, pushing the patient aside to make room for other patients.

Health care professionals should adopt cultural competence and sensible awareness when caring for Muslim patients and family. A holistic approach to health care demands

staff understanding of Islamic belief, religious practice, spiritual beliefs, cultural mores, and social background. With the open borders strategy and population shift from East to West, it is crucial that physicians and nurses be transcultural with sensitivity to spiritual needs of their patients. The spiritual treatment of the Muslim patient in general and the terminally ill patient in particular is essential in easing the patient's pain and suffering. The patient must be listened to and the differences in his values and faith must be accepted, reflecting sensitivity and mutual respect and avoiding judging and engaging in prejudice. Improving communication and mutual respect is the basis of achieving the best medical treatment with conflict and stress reduction with the patient and family, and a more satisfied and rewarding practice for the caregiver. Spiritual history and assessment are vital to implementing holistic care, preventing confrontations and embarrassment, and finally ensuring a better quality of life of the acute or terminally ill Muslim patient and family.

In working with the Jewish patient, one must always remember the very diverse set of beliefs and practices to be found among Jews and listen closely to understand the set of beliefs out of which a particular patient or family is operating. Palliative care itself, whether or not it is pursued along with standard care, and regardless of how one thinks of its philosophical underpinnings, is mandated in much if not all of Judaism and should certainly be brought up in conversations with the patient or his/her family in an appropriately sensitive manner. Psychological and spiritual care are a crucial part of the care that needs to be provided, in consonance with the patient's needs and wishes, which may be more or less "religious."

References

[1] C. Puchalski, B. Ferrell, R. Virani et al., "Improving the quality of spiritual care as a dimension of palliative care: the report of the consensus conference," *Journal of Palliative Medicine*, vol. 12, no. 10, pp. 885–904, 2009.

[2] D. P. Sulmasy, "A biopsychosocial-spiritual model for the care of patients at the end of life," *Gerontologist*, vol. 42, no. 3, pp. 24–33, 2002.

[3] D. D. McKee and J. N. Chappel, "Spirituality and medical practice," *Journal of Family Practice*, vol. 35, no. 2, pp. 201–208, 1992.

[4] T. A. Balboni, L. C. Vanderwerker, S. D. Block et al., "Religiousness and spiritual support among advanced cancer patients and associations with end-of-life treatment preferences and quality of life," *Journal of Clinical Oncology*, vol. 25, no. 5, pp. 555–560, 2007.

[5] S. R. Cohen, B. M. Mount, J. J. Tomas, and L. F. Mount, "Existential well-being is an important determinant of quality of life: evidence from the McGill Quality of Life Questionnaire," *Cancer*, vol. 77, no. 3, pp. 576–586, 1996.

[6] J. Florell, "Crisisintervention in orthopedic surgery—empirical evidence of the effectiveness of a chaplain working with surgery patients," *Bulletin of the American Protestant Hospital Association*, vol. 37, no. 2, pp. 29–36, 1973.

[7] W. Iler, D. Obenshain, and M. Camac, "The impact of daily visits from chaplains on patients with chronic obstructive pulmonary disease (COPD): a pilot study," *Chaplaincy Today*, vol. 17, no. 1, pp. 5–11, 2011.

[8] C. S. McClain, B. Rosenfeld, and W. Breitbart, "Effect of spiritual well-being on end-of-life despair in terminally-ill cancer patients," *Lancet*, vol. 361, no. 9369, pp. 1603–1607, 2003.

[9] C. J. Nelson, B. Rosenfeld, W. Breitbart, and M. Galietta, "Spirituality, religion, and depression in the terminally ill," *Psychosomatics*, vol. 43, no. 3, pp. 213–220, 2002.

[10] K. I. Pargament, H. G. Koenig, N. Tarakeshwar, and J. Hahn, "Religious struggle as a predictor of mortality among medically ill elderly patients: a 2-Year longitudinal study," *Archives of Internal Medicine*, vol. 161, no. 15, pp. 1881–1885, 2001.

[11] G. A. Silvestri, S. Knittig, J. S. Zoller, and P. J. Nietert, "Importance of faith on medical decisions regarding cancer care," *Journal of Clinical Oncology*, vol. 21, no. 7, pp. 1379–1382, 2003.

[12] G. D. Sherwood, "The power of nurse-client encounters. Interpreting spiritual themes," *Journal of Holistic Nursing*, vol. 18, no. 2, pp. 159–175, 2000.

[13] C. Puchalski and A. L. Romer, "Taking a spiritual history allows clinicians to understand patients more fully," *Journal of Palliative Medicine*, vol. 3, no. 1, pp. 129–137, 2000.

[14] G. McCord, V. J. Gilchrist, S. D. Grossman et al., "Discussing spirituality with patients: a rational and ethical approach," *Annals of Family Medicine*, vol. 2, no. 4, pp. 356–361, 2004.

[15] A. Sheikh and R. Gatrad, *Caring for Muslim Patients*, Radcliffe Publishing, Oxford, UK, 2007.

[16] Z. Al-Shahri, N. Fadul, and A. Elsayem, "Death, dying and burial rites in Islam," *European Journal of Palliative Care*, vol. 13, no. 4, pp. 164–167, 2007.

[17] M. Asadi-Lari, Z. Madjd, and S. Goushegir, "Gaps in the provision of spiritual care for terminally ill patients in Islamic societies— a systematic review," *Advances in Palliative Medicine*, vol. 7, no. 2, pp. 73–80, 2008.

[18] N. Dessing, *Rituals of Birth, Circumcision, Marriage, and Death Among Muslims in the Netherlands*, Uitgeverij Peeters, Brussels, Belgium, 2001.

[19] A. R. Gatrad, "Muslim customs surrounding death, bereavement, postmortem examinations, and organ transplants," *British Medical Journal*, vol. 309, no. 6953, pp. 521–523, 1994.

[20] N. Ghouri, "Health fair in a mosque: putting policy into practice," *Public Health*, vol. 119, no. 3, pp. 197–201, 2005.

[21] J. Green and M. Green, "Islam," in *Dealing with Death—A Handbook of Practices, Procedures and Law*, pp. 272–278, Jessica Kingsley Publishers, Philadelphia, Pa, USA, 2nd edition, 2006.

[22] H. Gulam, "Care of the Muslim patient," *Australian Defense Forces—ADF*, vol. 4, pp. 81–83, 2003.

[23] J. Neuberger, *Caring for Dying people of Different Faiths*, Radcliffe Medical Press, UK, 2005.

[24] C. Parkes, P. Laungani, and B. Young, *Death and Bereavement Across Cultures*, Brunner-Routlege, New York, NY, USA, 2000.

[25] A. Jotkowitz and A. Z. Zivotofsky, ""Love your neighbor like yourself": a Jewish ethical approach to the use of pain medication with potentially dangerous side effects," *Journal of Palliative Medicine*, vol. 13, no. 1, pp. 67–71, 2010.

[26] B. Kinzbrunner, "Jewish medical ethics and end-of-life care," *Journal of Palliative Medicine*, vol. 7, no. 4, pp. 558–573, 2004.

[27] J. Loike, M. Gillick, S. Mayer et al., "The critical role of religion: caring for the dying patient from an orthodox Jewish perspective," *Journal of Palliative Medicine*, vol. 13, no. 10, pp. 1267–1271, 2010.

[28] N. Bentur and S. Resnizky, "Challenges and achievements in the development of spiritual-care training and implementation in Israel," *Palliative Medicine*, vol. 24, no. 8, pp. 771–776, 2010.
[29] N. Bentur, S. Resnitzky, and A. Sterne, "Attitudes of stakeholders and policymakers in the healthcare system towards the provision of spiritual care in Israel," *Health Policy*, vol. 96, no. 1, pp. 13–19, 2010.
[30] Maimonides. Commentary on the Mishna, Tractate Nedarim 4:4, s.v., "Hamudar hanaa mechaveiro," Fes, Morocco: 1168.
[31] M. Al-Shahri and A. Al-Khenaizan, "Palliative care for Muslim patients," *Journal of Supportive Oncology*, vol. 3, no. 6, pp. 432–436, 2005.
[32] F. Zahedi and B. Larijani, "Cancer ethics from the Islamic point of view," *Iranian Journal of Allergy, Asthma and Immunology*, vol. 6, no. 5, pp. 17–24, 2007.
[33] K. Hedayat, "When the spirit leaves—childhood death, grieving, and bereavement in Islam," *Journal of Palliative Medicine*, vol. 9, no. 6, pp. 1282–1291, 2006.
[34] Quran—The Islamic Holy Book.
[35] A. Sheikh, "Death and dying—a Muslim perspective," *Journal of the Royal Society of Medicine*, vol. 91, no. 3, pp. 138–140, 1998.
[36] N. Sarhill, S. LeGrand, R. Islambouli, M. P. Davis, and D. Walsh, "The terminally ill Muslim: death and dying from the Muslim perspective," *American Journal of Hospice and Palliative Care*, vol. 18, no. 4, pp. 251–255, 2001.
[37] A. Sachedina, "End-of-life: the Islamic view," *Lancet*, vol. 366, no. 9487, pp. 774–779, 2005.
[38] M. Feinstein, *Responsa Igrot Moshe, Choshen Mishpat*, vol. 2, Noble Book Press, New York, NY, USA, 1985.
[39] S. Z. Auerbach, *Responsa Minchat Shlomo*, vol. I, Jerusalem, Israel, 1986.
[40] J. D. Bleich, "Treatment of the terminally Ill," in *Jewish Ethics and the Care of End-of-Life Patients*, P. Hurwitz, J. Picard, and A. Steinberg, Eds., Ktav, New Jersey, NJ, USA, 2006.
[41] B. Brody, *Taking Issue: Pluralism and Casuistry in Bioethics*, Georgetown University Press, 2003.
[42] S. Z. Auerbach, *Responsa Minchat Shlomo Tanina*, vol. 2-3, Jerusalem, Israel, 1976.
[43] E. Waldenberg, *Responsa Tzitz Eliezer*, Jerusalem, Israel, 1977.
[44] J. S. Temel, J. A. Greer, A. Muzikansky et al., "Early palliative care for patients with metastatic non-small-cell lung cancer," *New England Journal of Medicine*, vol. 363, no. 8, pp. 733–742, 2010.
[45] M. Schultz and G. Bar-Sela, "Curative vs. palliative care in Jewish bioethics: duties of the medical staff when there seems to be no hope for a cure," *Palliative Medicine*. In press.
[46] I. Syed, "Spiritual medicine in the history of Islamic medicine," *Journal of International Society for the History of Islamic Medicine—JISHAM*, vol. 2, pp. 45–49, 2003.
[47] B. Ott, J. Al-Khadhuri, and S. Al-Junaibi, "Preventing ethical dilemmas: understanding Islamic health care practices," *Pediatric Nursing*, vol. 29, no. 3, pp. 227–230, 2003.

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 349040, 13 pages
doi:10.1155/2012/349040

Review Article

Greco-Arab and Islamic Herbal-Derived Anticancer Modalities: From Tradition to Molecular Mechanisms

Hilal Zaid,[1,2] Michael Silbermann,[3] Eran Ben-Arye,[4,5] and Bashar Saad[1,2]

[1] *Qasemi Research Center, Al-Qasemi Academy, P.O. Box 124, Baqa El-Gharbia 30100, Israel*
[2] *Faculty of Arts and Sciences, Arab American University Jenin, P.O. Box 240, Jenin, Palestine*
[3] *Technion—Israel Institute of Technology, Middle East Cancer Consortium, Haifa, Israel*
[4] *Integrative Oncology Program, The Oncology Service, Lin Medical Center, Clalit Health Services, Western Galilee District, Haifa, Israel*
[5] *Complementary and Traditional Medicine Unit, Department of Family Medicine, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel and Clalit Health Services, Western Galilee District, Haifa, Israel*

Correspondence should be addressed to Bashar Saad, bsaad@netvision.net.il

Received 17 July 2011; Accepted 26 September 2011

Academic Editor: Fatma U. Afifi

The incidence of cancer is increasing in the developed countries and even more so in developing countries parallel to the increase in life expectancy. In recent years, clinicians and researchers advocate the need to include supportive and palliative care since the establishment of the diagnosis and throughout the duration of treatment, with the goal of improving patients' quality of life. This patient-centered approach in supportive care is also shared by various traditional and complementary medicine approaches. Traditional Arab-Islamic medicine offers a variety of therapeutic modalities that include herbal, nutritional, and spiritual approaches. Physicians and scholars, such as Avicenna (980–1037), Rhazes (965–915), Al Zahrawi (936–1013), and Ibn al Nafis (1218–1288) referred to cancer etiology in various medicinal texts and suggested both preventive and therapeutic remedies to alleviate suffering. This review presents research data related to the anticancer activities of herbs used in Arab-Islamic medicine and allude to their potential role in improving the quality of life of cancer patients.

1. Introduction

In recent years, traditional Arab-Islamic herbal medicine has been gaining interest in the scientific community, and more specifically, regarding cancer treatment [1–3]. This school of medicine, often referred to as Greco-Arab medicine, is still influential in Arab and Islamic societies, especially throughout the Mediterranean region. Throughout Muslim history, Greco-Arab and Islamic herbal medicine were the first choice of treatment for ailments involving infertility, epilepsy, cancer, psychosomatic troubles, and depression. Arab and Muslim physicians were among the first to use scientific methods in the field of medicine, including the introduction of quantity measurements, animal testing, and clinical trials. Hospitals in the Arab-Islamic world featured drug tests, drug purity regulations, and competency tests for physicians. The earliest known tests related to public health were carried out by Rhazes (865–925), searching for the most hygienic place to build a hospital. To that purpose, he placed pieces of meat throughout Baghdad and subsequently built a hospital at the site where the meat decomposition was the least. In his *Comprehensive Book of Medicine*, Rhazes documented his own clinical cases and provided very useful documentation of various diseases. He also introduced urinalysis and stool tests. Avicenna (980–1037), who introduced quantity measurements in experimental medicine, discovered the contagious nature of diseases, introduced clinical trials, risk factor analysis, and the idea of a syndrome in the diagnosis of complex clinical entities. His book, *The Canon of Medicine*, was the first to deal with evidence-based medicine, randomized controlled trials, and efficacy tests.

Concerning medical documentation, the first documented evidence for a peer review publication was published by Ishaq bin Ali al-Rahwi (854–931). In his work, *the Ethics of the Physician,* he stated that a physician must always

document in duplicate the patient's records. When the patient was healed or died, the physician's records were examined by a local medical council, comprising of other physicians, in order to decide as to whether the treatment met the required standards of medical care.

Cancer is a leading cause of mortality, and it strikes more than one-third of the world's population and it's the cause of more than 20% of all deaths [4]. Among the causes for cancer are tobacco smoke, viral infection, chemicals, radiation, environmental factors, and dietary factors. Contemporary physicians and biomedical researchers advocate the need for a comprehensive cancer treatment including supportive and palliative care. This patient-centered approach is based, in part, on the increased awareness of the role of traditional and complementary medicine in supportive care aimed at improving patients' quality of life. This review aims at elucidating Arab and Islamic medicines and their involvement in approaching issues associated with cancer diagnosis and treatment, while reviewing the potential role of herbs in contemporary cancer care.

2. Relevance of Arab and Islamic Medicine on Cancer Care in the Middle East

In early 2011, Ben-Arye and his colleagues from six Middle-Eastern countries identified 143 articles on complementary and traditional medicine that had been published in 12 Middle-Eastern countries in relation to cancer care [5]. In studies performed in Turkey and Israel, about half of the patients diagnosed with cancer reported use of complementary and alternative medicine (CAM) [6], even during chemotherapy treatment [7]. These findings are comparable with other reports in the West [8]. Herbal medicine is the leading modality used by patients with cancer in the Middle East (e.g., 35% of cancer patients using CAM in Jordan) [9] along with spiritual practices that are also prevalent (e.g., 75% of CAM users in Iranian study) [10]. CAM use is also popular among patients with pediatric [11], gynecological [12], and hematological [13] malignancies and among patients with an advanced disease [14]. Ben-Arye and colleagues reported on 59 articles published in the Middle East in relation to cancer-related herbal research including ethnobotanical surveys and reviews (7 articles), *in vitro* studies (33 articles), animal studies (8 articles), and clinical studies (11 articles) [15].

3. Cancer in Greco-Arab and Islamic Medicine

Roman physicians, for example, Galen (129–199), were already acquainted with tumors as clinical entities while adopting Hippocrates' (470–370 BC) basic theory of cancer being an excess of black bile. In the golden Islamic-Arab era, classic texts, including those of Galen, were translated into Arabic and thereby influenced physicians in the Arab-Islamic world. During the Golden Arab-Islamic civilization (7th to 14th century), Arab and Muslim physicians studied cancer and applied various medicines and surgical means for its treatment. In the medicinal texts of Rhazes, Avicenna, and Abulcasis, the authors distinguish clearly between the varieties of cancer types in relation to specific organs such as, eye, nasal, tongue, stomach (gastric), liver, bladder, kidney, testis, breast, spleen, and nerve tumors. Kidney cancer was first mentioned by Al Zahrawi (Abulcasis 936–1013) who was the first to differentiate between acute inflammation of the kidney and kidney cancer. Both Rhazes and Avicenna described cancer as a disease which is difficult to treat.

Rhazes, Abulcasis, and Avicenna all realized that the prospects of curing cancer are prognostically improved if the cancer is detected at an early stage [16, 17]. Hence, the first goal of treatment would be controlling the tumor's growth. They recommended surgical removal if the tumor was small and accessible, and not close to vital organs. Avicenna (980–1037), the most influential of all Islamic philosopher scientists, suggested "*When cancer starts, it may be possible to keep it as it is, so that it will not increase and keep it non-ulcerated. It may happen sometimes that the stating cancer may be cured. But when it is advanced, verily will not*" [16, 17]. In his book, *Canon*, Avicenna described four ways to treat cancer: (a) total arrest, which was regarded as difficult; (b) preventing progress; (c) preventing ulceration; (d) treatment of the ulceration. He empathized that medications per se would not be of great value since strong medications increase "cancer evil". In addition, "*one should avoid irritant medications. And for this, good medications are: pure minerals like washed pure tutty mixed with oils like rose oil and the oil of yellow gillyflower mixed with it*" [16]. Avicenna also described one of the very early surgical approaches for cancer treatment, as he noted "*the excision should be radical and that all diseased tissue should be removed, which included the use of amputation or the removal of veins running in the direction of the tumor . . . so that nothing of these will be left*" [16, 17]. He also recommended the "*use of cauterization for the area being treated if necessary.*" One mode of treatment which he discovered was the "Hindiba" (The plant *Chicorium intybus*), which Ibn al-Baitar later on identified as having anticancer properties and which could also be used for other tumors and neoplastic disorders [2, 18–20]. Avicenna had also stated that *"it (cancer) can be reached by controlling the material, improving the diet and reinforcing the involved organ by the known effective medicines, and by using mineral smears like those containing millstone dust and whet-stone dust and from smears taken from a mixture between the stone pounder for aromatics and black head stone moisturized with rose oil and coriander water. . . ".*

4. Cancer Prevention and Treatment in Greco-Arab and Islamic Medicine

Based on recommendations of Rhazes and Avicenna, patients in general were treated through a scheme starting with physiotherapy and diet; if this failed, drugs were used. Rhazes treatment scheme started with diet therapy, he noted that "*if the physician is able to treat with foodstuffs, not medication, then he has succeeded. If, however, he must use medications, then it should be simple remedies and not compound ones*". Drugs were divided into simple and compound drugs.

Physicians were aware of the interaction between drugs, thus, they used simple drugs first. If these failed, compound drugs consisting of two or more compounds were used. If these conservative measures failed, surgery was undertaken.

4.1. Diet-Based Prevention and Therapy. Food was a substantial part of pre-Islamic medicine as well as in other traditional medicines, for example, Greek, Persian, Ayurvedic, and Chinese. Diet is a matter of faith in Islam and plays an important role in maintaining a healthy body, soul, and spirit. Muslims are commanded to follow a set of dietary laws outlined in the Holy Qur'an, where almost everything is permitted, except what Allah specifically prohibited. Later on, when the Islamic empire covered all of Arabia, half of Byzantine Asia, all of Persia, Egypt, the Maghreb (North Africa), and Spain, Arabs and Muslims not only conquered new lands, but also became exposed to foreign and multinational culinary heritages. Great developments in scientific fields, the establishment of "modern" hospitals, and growing socioeconomic conditions of Islamic empire increased the awareness of the relationship between food and health. During this period a type of Islamic food therapy was developed that was a blend of Qur'anic teaching and Greek medicine.

According to a Hadith (saying) of the Prophet, Peace Be Upon Him (PBUH) "*The stomach is the central basin of the body, and the veins are connected to it. When the stomach is healthy, it passes on its condition to veins, and in turn the veins will circulate the same and when the stomach is putrescence, the veins will absorb such putrescence and issue the same*". Indeed, the Prophet used to recommend food for ailments even more than he prescribed herbs or medicines. The impact of diet and herbs for the well being of people was also acknowledged in the Holy Qur'an which mentioned beneficial effects of several plants and animal products on nutritional health. Among these are grapes, citrus, melon, squash, figs, dates, honey, olive oil, and black seeds. For example, figs (*Ficus carica*) are mentioned by the Prophet (PBUH) who state that "*If I had to mention a fruit that descended from paradise I would say this is it because the paradisiacal fruits do not have pits…eat from these fruits for they prevent hemorrhoids, prevent piles and help gout*." [21]. Indeed, ethnobotanical research suggests that figs are used to treat malignant and inflammatory diseases [22]. The Prophet (PBUH) also recommended the use of olive oil, by stating "*Eat olive oil and massage it over your bodies since it is a holy (Mubarak) tree*". Dates were mentioned in twenty places in the Qur'an, as the Prophet (PBUH) was reported to have said: "*if anyone of you is fasting, let him break his fast with dates. In case he does not have them, then with water. Verily water is a purifier*" [21].

Greco-Arab and Islamic scholars, such as Avicenna, Rhazes, and Abulcasis discussed the effect of diet on cancer development and progression. While alluding to cancer prevention Avicenna quoted "*As to preventing its (cancer) progress, it can be achieved by … improving the diet and reinforcing the involved organ by the known effective medications.*" This ancient attribution of the role of nutrition in cancer has been acknowledged extensively in the scientific literature involving carcinogenesis [23] and the interrelation between cancer incidence and recurrence and nutrition and lifestyle (e.g., obesity as a cancer risk factor [24, 25]).

4.2. Mediterranean Diet. During the last half century, epidemiological studies have consistently shown that there are clear significant positive associations between intake of fruits and vegetables and reduced rate of heart diseases mortality, common cancers, and other degenerative diseases as well as ageing. This is attributed to the fact that these foods may provide an optimal mix of dietary fiber, natural antioxidants, and other biotic compounds. Various substances in the food can control the physiological functions of the body and modulating immune responses. Immune functions are indispensable for defending the body against attack by pathogens or cancer cells and thus play a pivotal role in the maintenance of health. However, the immune functions are disturbed by malnutrition, aging, physical and mental stress, or undesirable lifestyle. Therefore, the ingestion of foods with immune-modulating activities is considered an efficient way to prevent immune functions from declining and reduce the risk of infection or cancer.

Traditional Mediterranean diet includes a significantly large amount and variety of plant foods, for example, fruits, vegetables, wild edible plants, breads, seeds, nuts, and olive oil. Therefore, it guarantees an adequate intake of carotenoids, vitamin C, tocopherols, α-linolenic acid, various important minerals, and several possibly beneficial nonnutrient substances such as polyphenols and anthocyanins and dietary fiber [26, 27].

4.3. Edible Wild Plants. Wild edible plants are commonly consumed in the eastern region of the Mediterranean. Wild edible herbs have always been a main part of traditional diets and were known for their health qualities among local communities and indigenous people long before their nutritious, protective, and therapeutic effects were proved by scientific research. A high percentage of individuals collect wild edible plants and consume them as part of traditional food habits. Traditional food habits have been characterized by dietary diversity and have been associated with low health risks. Wild edible plants have been identified as main components of these diets and as important contributors to their health-protective properties. Many wild species are collected from the surrounding environment and consumed as part of local diets, especially in times of shortage. Various wild greens contain high nutritional values with relatively low energy. Compared with commonly eaten vegetables, they provide the diet with greater amounts of minerals. Additionally, their antioxidant property, mainly from phytochemicals, was found to be two to three times higher than that of common vegetables [26].

4.4. Herbal-Based Prevention and Therapy. There is compelling evidence from epidemiological and experimental studies that highlight the importance of phytochemicals isolated from traditional medicinal plants to prevent/reduce some types of cancer and inhibit the development and spread of tumors in test animals. The term phytochemical refers to any herbal-based molecule, but in the field of diet and cancer

Table 1: Effects of food and herbal-derived compounds in cancer chemoprevention.

Active principle(s)	Sources	Apoptosis induction	Anti angiogenesis	Anti metastasis effect	Anti inflammatory/ Antioxidant properties	References
Citral	*Aloysia citrodora* Palau, *Cymbopogon* sp. *Melissa officinalis* L.	+				[43]
Crocetin	*Crocus sativus* L.	+	+	+	+	[44, 45]
Curcumin	*Curcuma longa* L.	+	+		+	[46, 47]
Diallyl sulfide	*Allium sativum* L.	+	+		+	[48, 49]
Fibers, Lignans, isoflavones, and phenolic acids	*Triticum aestivum* L.	+				[50–52]
Several flavonoids	*Ficus carica* L.			+	+	[53, 54]
Inulin-type fructans beta(2,1) fructans	*Cichorium intybus* L.		+	+	+	[55]
Oleuropein	*Olea europea* L.	+	+	+	+	[39, 40, 56]
Several polyphenols	*Punica granatum* L.	+	+	+	+	[57, 58]
Quercetin	*Allium cepa* L.	+	+		+	[59, 60]
Silymarin	*Silybum marianum* L. Gaertn.	+	+		+	[61–63]
Thymoquinone	*Nigella sativa* L.	+	+	+	+	[64–66]
Several active compounds	*Arum palaestinum* L.	+			+	[2, 30, 67]
Several active compounds	Honey			+	+	[68–70]

this term is usually applied to nutritive and nonnutritive compounds that occur naturally in fruits and vegetables. More than 25% of drugs used during the last 20 years are directly derived from plants, while the other 25% are chemically altered natural products. Still, only 5–15% of the approximately 260,000 higher plants have ever been investigated for bioactive compounds. The advantage of using such compounds for cancer treatment is their relatively low/non-toxic nature [28, 29]. An ideal phytochemical is one that possesses antitumor properties with minimal side effects and has a defined mechanism of action. Some phytochemicals are likely to possess anticancer effects (Table 1). According to recent surveys, many cancer patients use complementary and alternative medicines, including phytochemicals in addition to, or following the failure of standard cancer therapy. A diet rich in fruits and vegetables has long been suggested to correlate with reduced risk of certain epithelial malignancies, including cancers in the lung, colon, prostate, oral cavity, and breast [28, 30]. Also, the cancer prevention potential of Mediterranean diets based mainly on olive tree products is known. As discussed below, the major active ingredient of the leaves and oil of *Olea europaea* is oleuropein and the majority of polyphenols found in olive oil or table olives are derived from its hydrolysis. Oleuropein is a novel, naturally occurring antioxidant compound, which may possibly be used to prevent cancer and cardiotoxicity induced by doxorubicin. Searching for medicinal benefits from edible or inedible plants is not a novel idea since numerous modern medicines have plant origins. Given that the ingestion of some plant foods results in reduced risk for cancer, researchers are delving into the identification of phytochemicals with cancer preventive ability in studies *in vitro, in vivo,* and those in humans. Phytochemicals can be roughly classified into four groups based on their mechanisms of chemopreventive and therapeutic properties, as shown in Table 1.

In the following paragraphs, we will focus on nine widely used herbs that are commonly used in the context of cancer by patients in the Middle East: Olive, black seeds, saffron, pomegranate, nettle, Garlic, onion, Palestinian arum, and grapes [2, 3, 5, 31–33]. Other commonly used medicinal plants and wild edible plants are described in Table 1 and [30].

4.5. Olea Europea (Olive). *O. europaea* (the olive) is a species of the family Oleaceae. The olive tree is an evergreen tree or shrub native to the Mediterranean, Asia, and the Maghreb region. Olive leaf and olive leaf extracts are now marketed as antioxidants, antiaging, immunostimulators, and even antibiotics. Clinical evidence has proven the antidiabetes and antihypertension effects of leaf extracts. In addition, several studies support its antibacterial, antifungal, and anti-inflammatory properties [34–36].

Epidemiological studies provide convincing evidence for a protective effect of the Mediterranean diet against cardiovascular disease and cancer [37, 38]. These findings

prompted scientists to search for Mediterranean flora as a rich source of bioactive phytochemicals with a potential to evolve into preventive and possibly therapeutic agents. Much epidemiological evidence suggests that people who consume an olive oil rich diet have a lower incidence of certain cancers, including breast, skin, and colon [34]. The lower incidence of certain cancers is most likely associated with the antioxidant activity of active ingredients of the olive oil. Oxidative stress has been shown to contribute to cancer development, and antioxidants are believed to reduce the risk of mutagenesis and carcinogenesis. Hydroxytyrosol was found to be capable of protecting cells from hydrogen peroxide damage and DNA from peroxynitrite-induced damage, blocking cell cycle progression at the G1 phase, and inducing apoptosis [39]. *In vivo* and *in vitro* studies on the activity of oleuropein have found that, in addition to antioxidant properties, it has antiangiogenic action and inhibits cell growth, motility, and invasiveness. Oleuropein was also found to cause cell rounding, which disrupts the cell actin cytoskeleton. Oleuropein also affects and disrupts purified actin filaments, providing direct antitumor effects due to cell disruption. In *in vivo* animal studies, rapid tumor regression was observed when mice were given one percent oleuropein in drinking water [40]. Saturated animal fats and polyunsaturated plant fats in the diet have been implicated in colon, breast, prostate, and ovarian cancers. The vast usage of olive oil in the Mediterranean diet may explain its apparent cancer-protective effect, rather than the amount of fat consumed. Furthermore, in a recent study evaluating the antioxidant and antiproliferative activity of water and methanol olive leaves extracts in cancer and endothelial cells, olive leaf crude extracts were found to inhibit proliferation of cell from a human breast adenocarcinoma, cells from human urinary bladder carcinoma (T-24), and cells from bovine brain capillary endothelial (BBCE) [39, 41, 42].

4.6. Nigella Sativa (Black Seeds). *N. sativa* of the Ranunculaceae family is one of the most commonly used medicinal plants throughout the Middle East. *N. sativa* seeds have been used for centuries as a spice and food preservative, as well as a protective and curative remedy for numerous diseases. The seeds are known to have many medicinal properties and are widely used in Greco-Arab and Islamic medicine. The plant is found wild in North Africa, the Mediterranean region, Asia Minor, and in Southern Europe. *N. sativa* is one the most referenced medicinal seeds in history. In many civilizations the herbal spice *N. sativa* was referred to as Habbat-el-barakah (literally seeds of blessing in Arabic), Kalonji (Hindi), Kezah (Hebrew), Sijah Daneh (Persian) and Black Caraway in English. The famous Greek physician dioscorides [40–42, 44, 45, 57, 59, 71–114] used black seeds to treat headaches and toothaches. *N. sativa* seeds and oil extracts have been widely used for centuries to treat disorders in the respiratory system, stomach, kidney and liver function, and circulatory, immune system as well as cancer. In Islam, it was regarded as one of the greatest forms of healing medicine available [71]. Prophet Mohammad (PBUH) stated "*The black seed can heal every disease, except death*" [21]. Avicenna referred to black seed in his "Canon of Medicine" as the seed that stimulates the body's energy and helps recovery from fatigue and dispiritedness. In the Unani Tibb system which is still practiced in central Asia and India seeds are regarded as a valuable remedy for a number of diseases. The seed's oil was used to treat skin conditions such as eczema and burns and to treat cold symptoms.

Modern research studies showed that *N. sativa* seeds ethanol extract possesses antitumor activity in mice implanted with tumor primary cells [72]. *N. sativa* seed extracts contain amino acids, proteins, carbohydrates, alkaloids, saponins, fixed, and volatile oils.

Thymoquinone has been found to be the main compound responsible for the pharmacological properties of the volatile oil of *N. sativa*. The biological activities and therapeutic potential of thymoquinone are discussed in details by Salem [73]. In brief, thymoquinone was found to possess potent anticancer and antioxidant abilities in animal models and cell culture systems. It acts as an antioxidant and inhibited iron-dependent microsomal lipid peroxidation, cardiotoxicity induced by doxorubin in rats, and inhibited ifosfamide-induced damage in kidney. It also prevented liver injury induced with carbon tetrachloride, lowered drug-induced toxicity and causes amelioration in the drug's anticancer activity. There are studies reporting that the anticancer potential of thymoquinone is related to its pro-oxidant activities. In human colon cancer cell cultures and in isolated rat liver mitochondria, thymoquinone induced a significant release of reactive oxygen species and inhibited the activity of aconitase, an enzyme sensitive to superoxide anion generation. One of the most promising effects of thymoquinone is its high cancer specificity and low toxicity to normal cells. This has been observed in prostate cancer, colon cancer, canine osteosarcoma, and skin cancer [74, 75]. Many multi-drug-resistant variants of human pancreatic adenocarcinoma, uterine sarcoma, and leukemia were found to be sensitive to thymoquinone [76]. These findings provide further support to the great potential of developing synthetic derivatives of thymoquinone as anticancer agents. Thymoquinone induces apoptosis through modulation of multiple targets and hence is a promising phytochemical agent that could be used for killing many types of cancer cells, such as prostate cancer cells. Thymoquinone blocked angiogenesis *in vivo*, prevented tumor angiogenesis in a xenograft human prostate cancer model in mouse, and inhibited human prostate tumor growth with almost no side effects. *In vivo*, thymoquinone inhibited the growth of prostate and colon tumors implanted in nude mice with no noticeable side effects. In colon xenografts, growth inhibition by thymoquinone was not due to decreased proliferation but rather to the significant induction of apoptosis. However, in androgen-independent prostate tumor xenografts, the suppression of tumor growth was associated with a massive apoptosis [77]. These results indicate that the antitumor activity or cell growth inhibition could in part be due to the effect of thymoquinone on cell cycle [75].

Although *N. sativa* seeds and oil are recognized safe, only a few studies have addressed its potential toxicity. In

one study, serum gamma-glutamyl transferase and alanine aminotransferase concentrations were significantly increased after water extracted black seeds were administered orally to rats for 14 days. However, no evident pathological changes were reported [78]. Black seeds oil toxicity was tested in another study in mice and rats through examination of possible biochemical, hematological, and histopathological changes. LD_{50} was 28.8 mL/kg body for single (acute) oral determination dose and 2.06 mL/kg for intraperitoneal administration [79].

Chronic toxicity was studied in rats treated with an oral dose of 2 mL/kg daily for 12 weeks. No changes were reported neither in key hepatic enzymes levels (i.e., ALT, AST, and GSH), nor in histopathological modifications (heart, liver, kidneys, and pancreas). Nevertheless, serum cholesterol, triglyceride, and glucose levels as well as the count of leukocytes and platelets decreased significantly and slowing of body weight gain was reported. Some other studies had reported black seeds and thymoquinone toxicity in rats and mice when exposed to high doses [79–81]. Taken together, a degree of caution is necessary with larger amounts of *Nigella sativa* due to the presence of thymoquinone and other active ingredients.

4.7. Crocus Sativus (Saffron). Saffron has a long history as part of traditional healing. Modern medicine has also discovered saffron as having anticarcinogenic, antimutagenic, immunomodulating, and antioxodant-like properties [82]. Saffron contains several active compounds including, but not limited to, flavonoids, tannins, carotenoids, anthocyanins, alkaloids, and saponins. A number of *in vitro* and *in vivo* studies have reported an antitumor properties of saffron [44, 82–85]. Pretreatment with saffron prevented oxidative stress induced by DMBA (7,12-dimethylbenz[α]anthracene), known to generate DNA-reactive species and skin carcinoma in mice [83]. These effects are contributed to an active compound, crocetin [86, 87], that exhibited antitumor activity in a lung cancer animal model by scavenging free radicals and drug metabolizing enzymes [88]. It also inhibited pancreatic cancer cell proliferation and tumor progression in a xenograft mouse model and downregulated growth and proliferation stimulated apoptosis and resulted in significant growth regression in pancreatic tumors. However, it is not known whether the effect of crocetin on pancreatic cancer regression is its own receptor-dependent or receptor-independent mechanisms [89].

Crocetins antitumor activity was evaluated in several cancer cell lines [86, 87]. For instance, crocetin inhibited MCF-7 and MDA-MB-231 breast cancer cell lines proliferation [82, 84, 90] via downregulation of matrix metalloproteinases [45]. Crocetin and carotenoids, in general, showed cytotoxic effects on a range of tumors and malignant cells [82]. It had interfered with DNA transcription as well as DNA, RNA, and protein synthesis through suppression of the activity of DNA-dependent RNA polymerase II [44]. Crocetins LD_{50} is relatively high (2 g/kg) [82, 84, 90] raising the possibility that it could be relatively nontoxic with a potential to exert an antitumor effect.

4.8. Punica Granatum (Pomegranate). Pomegranates have been used for a long time in traditional Greco-Arab and Islamic medicine for the treatment of a variety of ailments, including sort throat, inflammation, and rheumatism. It was also used for treating bladder disturbances, strengthening gums, and soothing mouth ulcers. Pomegranates feature prominently in all religions: Islam, Judaism, Christianity, Buddhism, and Zoroastrianism. According to the Qur'an pomegranates grow in the gardens of paradise. Among the small number of fruits and vegetables mentioned in the Qur'an, (including date, olive, grape, banana, fig, cucumber, garlic, lentil, and onion), pomegranate was mentioned three times, indicating its significance in Muslims life. This fruit was consumed as fresh or in the form of juice. Pomegranate is known as an antioxidant agent and is used to treat several diseases including cancer, inflammation, cardiovascular disease, diabetes, bacterial infections and antibiotic resistance, and ultraviolet radiation-induced skin damage [91–93]. Yet, for the most part, research is focused on its antioxidant, anti-inflammatory, and anticarcinogenic properties.

4.9. Pomegranate Juice. Pomegranate Juice is a rich source of antioxidant tannins, flavonoids (quercetin), and some other antitumor compounds. Recent research has shown that pomegranate juice selectively inhibited the growth of breast, colon, and lung cancer cells in culture, decreased proliferation and induced apoptosis of DU-145 prostate cancer cells and suppressed invasive potential of PC-3 cells. These effects may be associated with the plant-based anti-inflammatory effects [94, 95]. Pomegranate juice was also effective in inhibition of inflammatory cell signaling in colon cancer [96]. In preclinical animal studies, oral consumption of pomegranate extract inhibited growth of lung, skin, colon, and prostate tumors [95, 96]. Pomegranate fruit extract was also effective in inhibition of lung tumorigenesis in mice [97]. Thus, pomegranates consumption could potentially help in reducing the growth and spread of prostate and lung cancer cells or even prevent cancer from developing. Pomegranate juice has also shown an initial promise in a phase II clinical trial against prostate cancer [98]. Pomegranate juice given to men with rising prostate specific antigen (PSA) following surgery or radiation offered positive and beneficially significant effects on PSA parameters, suggesting a potential of pomegranate-derived products for prevention of human prostate cancer [91].

4.10. Pomegranate Seeds. Up to 20% of the pomegranate seed weight is oil especially fatty acids (manly is triacylglycerols) [99]. Pomegranate seeds matrix includes also lignines and some of its derivates possess antioxidant activity [100]. The seeds oil had beneficial outcome in inflammation downregulation and thus cancer preventive effects. For instance, it had inhibited PC-3 prostate cancer cell line phospholipase A2 expression [94] and upregulated MAPK-APK2 in DU-145 prostate cancer cells [57]. In mouse model, 1 μg/mL seed oil suppressed tumor occurrence almost completely in mammary organ culture [101] and colon carcinogenesis induced by azoxymethane [102]. External treatment with 5% seeds oil produced significant decreases in mouse skin tumor

incidence and multiplicity [103]. The oil also downregulated proangiogenic vascular endothelial growth factor (VEGF) in MCF-7 breast cancer cells and induced apoptosis in human breast cancer cells [104].

4.11. Pomegranate Peel. Traditionally, pomegranate peels are dried, decocted in water, and employed both internally and externally to heal aphthae and diarrhea. Pomegranate peel has been shown to possess anticancer activities, including interference with tumor cell proliferation, cell cycle, invasion, and angiogenesis [101]. Pomegranate peel extract delays the proliferation of human breast and prostate cancer cell lines [105]. Pomegranate peel and juice contain several active compounds (i.e., catechins, epicatechins, proanthocyanidins, anthocyanidins, quercetin) known to be principal for cell cycle arrest, proliferation prevention, and apoptosis initiation [106].

More specifically, catechins and epicatechins possess antiangiogenic, antioxidant, and anticarcinogenic activities [107]. They also inhibited cyclooxygenase activity, nitric oxide production, and the epidermal growth factor receptor [108].

Quercetin is well known for its anticancer activity. It had inhibited lung cancer cell growth via cell cycle arrest and apoptosis induction [109]. More recently, Park and Min showed that quercetin induces downregulation of phospholipase D1 and thus inhibited proliferation and invasion in glioma (U87) cells [110]. Quercetin anticancer beneficial effects were also evaluated in animal models [111] and in clinical trials [59]. The anticarcinogenic effects of the other isolated fractions and compounds of the pomegranate were described elsewhere [92, 112].

4.12. Urtica Dioica (Nettle). The origin of its Latin name, Urtica, means "I burn", indicative of the stings caused by glandular hairs on the leaves that contain formic acid and histamine, two agents known to cause the stinging and skin irritation after contact. *U. dioica* leaf has a long history as an herbal remedy and nutritious addition to the diet. Nettle leaves are a rich source of essential amino acids, ascorbic acid, several mineral element, and vitamins, such as iron, provitamin A, and vitamin C [113]. Nettle extracts can be used to treat arthritis, hay fever, kidney problems, pain, and anemia. Nettle extracts possess hypoglycaemic properties and improve glucose tolerance [35]. *U. dioica* is believed to be antioxidant, immunesuppressive, antirheumatoid, antiulcer, anti-inflammatory, and anticarcinogenic [14]. Indeed, its leaf [114] and roots [115] extracts were effective against prostate cancer proliferation.

4.13. Allium Sativum L. and Allium Cepa (Garlic and Onion). Prophet Mohammad (PBUH) said "*although onion and garlic have a bad smell, they are cures for 70 different illnesses that cannot be cured by any other means*". Onion (*A. cepa*) and garlic (*A. sativa*) are closely related vegetables that belong to the Allium class of bulb-shaped plants, which also includes chives, leeks, and scallions. Garlic is used for flavoring in cooking and is unique due to its high sulfur content, along with arginine, oligosaccharides, flavonoids, and selenium, all of which might promote health [116].

The association between the consumption of *Allium* vegetables and the risk for cancer was assessed in several epidemiologic studies, showing the protective effect of garlic and onion on cancer. In China, high consumption of *Allium* vegetables was associated with lower incidence of gastric cancer [117, 118]. Additional studies in the Netherlands suggested an inverse correlation between the risk of colorectal, breast, and lung cancers and the consumption of onion and garlic [119].

Steinmetz et al. [120] studied the association between garlic consumption and the risk of colon cancer and found that women who consumed high amounts of garlic had a 50 percent lower incidence of distal colon cancer compared with women who consumed less garlic [120]. The risk of breast cancer was also found to be reduced in women consuming greater amounts of fiber garlic and onions [31], as well as that of esophageal and stomach cancers [121]. Similar findings were noted with reference to the risk of prostate cancer [122, 123], pancreatic cancer [33], and other known cancer types [124]. The amount of garlic consumed in the above studies varied from 2 to 20 g daily (The World Health Organization (WHO) guidelines for general health promotion for adults recommend a daily dose of 2 to 5 g of fresh garlic). It was noted that although garlic had been used safely in cooking, excessive consumption can cause some side effects, in addition to those of strong breath and body odors [125]. The protective effect of *Allium* vegetables against tumor progression and against angiogenesis were attributed to its organosulfur compounds especially allicin (an active compound in garlic) and diallyl disulfide [126]. Such compounds are able to block the formation of cancer-causing substances [127], halt the activation of cancer-causing substances [128, 129], enhance DNA repair [130], reduce cell proliferation, or induce apoptosis-programmed cell death (Table 1 and [126, 131]).

The protective effects of onion and garlic organosulfur compounds against carcinogenesis were also studied in animal models and *in vitro*. When administrating the above compounds to mice 2–4 days prior to a carcinogen challenge, these compounds inhibited the development of pulmonary adenoma [132]. Intravenous administration of the garlic active compound (diallyl trisulfide) significantly retarded the growth of orthotopically transplanted hepatoma in BALB/c nude mice [133]. These compounds had also halted the proliferation of cancer cell lines, including human lung, skin and colon tumor cell lines, human neuroblastoma cells, human and murine melanoma cells, and human prostatic carcinoma cells [134–137].

4.14. Arum Palaestinum (Palestinian Arum). Arum is edible plant and is widely used in the Middle-East cooking, especially in the Palestinian kitchen. According to a survey conducted in 2008, Palestinian Arum was found to be one of the most potent anticancerous (especially colon cancer) plant in Palestine [3]. Moreover, *A. palaestinum* is also effective against internal bacterial infections, poisoning, and disturbances of the circulatory system. Care should be taken

especially when using *A. palaestinum* to treat tumor since it may cause negative side effects. For instance, flavonoid isoorientin (6-C glucoside of luteolin), isolated from *A. palaestinum* possesses myolytic activity on rat and guinea pig smooth muscle [138]. However, the action mechanism of Palestinian Arum awaits further studies.

4.15. Vitis Vinifera (Grapes). Grapes exert several health benefits, including, but not limited to, anti-inflammatory and anticancer effects and prevent lipid oxidation and platelet aggregation. The main active compound in grapes is the polyphenol compound resveratrol. Resveratrol is believed to decrease circulating LDL (low-density lipoprotein) and cholesterol and thus reduce the risk of cardiovascular diseases [139]. Grapes, as many other fruits and vegetables, are rich in antioxidant compounds called flavonoids. They are among the plant chemicals that have shown a potential benefit against heart disease. Flavanoids as well as the whole black grape (including seeds) were shown to inhibit key enzymes in tumor cell, thereby inducing apoptosis and or blocking their growth [140, 141]. In rats, grape seeds extracts (proanthocyanidins) reduced the progress of ulcerative colitis thereby decreasing the risk of colorectal cancer [142].

5. Discussion

During the Arab-Islamic Golden Age, collaborative works of physicians and scientists from different nations and ethnic groups raised the dignity and caliber of the medical profession. Disease was seen by Arabs and Muslim physicians as a problem that can be challenged. The Prophet (PBUH) was credited with many statements on health care problems and their treatments. For instance, "*The one who sent down the disease sent down the remedy.*" and "*For every disease, God has given a cure.*" He was also credited with articulating several specific medical treatments, including the use of honey, olive oil, figs, and cupping. Regarding cancer, Avicenna, Rhazes, and Al-Zahrawi have influenced the field of oncology, by establishing clinical approach and therapeutic means (i.e., surgery) which inspired medical research for five centuries. Contemporary research supports the potential of herbs used in Islamic medicine for patients with cancer. More research is warranted regarding the potential benefit of traditional Islamic herbs in alleviation of chemotherapy side effects and improved patients' quality of life. This line of research may bridge past wisdom with present needs and future perspectives, thus fostering comprehensive cancer treatment attuned to the social and religious concerns of patients allover the Middle-East.

Despite the rapidly increasing understanding of the molecular and cellular processes, the morbidity of cancer is still on the rise. Cancer epidemiology has revealed that certain cancers are more common among people of different cultures and ethnicities, such as cancer of the lung, colon, prostate, and breast, which are very common in western societies, while they are not as prevalent in eastern societies. The prevalence of cancer in the developing countries is increasing, and the global burden of cancer is estimated to approximately double between 2008 and 2030 from 12.4 million new cases per year to around 26.4 million. A majority of this increase will occur in developing countries where the health services are least able to cope with the challenge. This inequality is highlighted by the markedly lower cancer survival rates in these regions (including Arab-Islamic countries) [143], and the best way to treat cancer is by preventing it and diagnosing it at earlier stages.

Past medical literature is a valuable source of information which entails potential research topics for contemporary scientific work. Several studies have already referred to the biological activities of natural products such as stimulation of the immune system, antibacterial, antiviral, antihepatotoxic, antiulcer, anti-inflammatory, antioxidant, antimutagenic, and anticancer effects [2, 125, 144–146]. A variety of grains, cereals, nuts, soy products, olives, beverages such as tea and coffee, and spices including turmeric, garlic, ginger, black pepper, cumin and caraway confer a protective effect against cancer [31, 33, 125, 145, 147]. Several studies have also documented the relationship between decreased cancer risk and high consumption of vegetables, including cabbage, cauliflower, broccoli, brussels sprout, tomatoes, and fruits such as, apples and grapes [2, 33, 146, 148]. In addition, a number of medicinal plants and herbs have also been reported to reduce the risk of cancer in multiple sites (Table 1 and [149, 150]). With regard to anticancer drugs, various currently used drugs are the derivatives of plant sources including, but not limited to, paclitaxel (taxol), vinblastine, capsaicin, vincristine, the camptothecin derivatives, topotecan, irinotecan, and etoposide (Table 1 and [146, 151–153]). Many commonly used anticancer herbs possess chemopreventive effects within their diverse pharmacological properties. Since cancer evolves over a long period of time, agents that inhibit or retard one or more of its stages could affect the overall course of the disease. Certain micronutrients (like oleuropein and diallyl sulfide compounds found in olives and garlic, resp.) possess potent cancer-preventive capacities.

Acknowledgments

The authors would like to acknowledge the USDA-Agricultural Research Service (ARS) and Al-Qasemi Research Foundation for providing their financial support.

References

[1] B. Saad and O. Said, *Greco-Arab and Islamic Herbal Medicine: Traditional System, Ethics, Safety, Efficacy and Regulatory Issues*, Wiley-Blackwell John Wiley & Sons, 2011.

[2] B. Saad, H. Azaizeh, and O. Said, "Arab herbal medicine," *Botanical Medicine in Clinical Practice*, vol. 4, p. 31, 2008.

[3] M. S. Ali-Shtayeh, R. M. Jamous, J. H. Al-Shafie' et al., "Traditional knowledge of wild edible plants used in Palestine (Northern West Bank): a comparative study," *Journal of Ethnobiology and Ethnomedicine*, vol. 4, article 13, 2008.

[4] I. Toni, E. Flamini, L. Mercatali, E. Sacanna, P. Serra, and D. Amadori, "Pathogenesis of osteoblastic bone metastases from prostate cancer," *Cancer*, vol. 116, no. 6, pp. 1406–1418, 2010.

[5] E. Ben-Arye, M. S. Ali-Shtayeh, M. Nejmi et al., "Integrative oncology research in the Middle East: weaving traditional and complementary medicine in supportive care," *Supportive Care in Cancer*. In press.

[6] F. Tas, Z. Ustuner, G. Can et al., "The prevalence and determinants of the use of complementary and alternative medicine in adult Turkish cancer patients," *Acta Oncologica*, vol. 44, no. 2, pp. 161–167, 2005.

[7] E. Ben-Arye, G. Bar-Sela, M. Frenkel, A. Kuten, and D. Hermoni, "Is a biopsychosocial-spiritual approach relevant to cancer treatment? A study of patients and oncology staff members on issues of complementary medicine and spirituality," *Supportive Care in Cancer*, vol. 14, no. 2, pp. 147–152, 2006.

[8] E. Ernst and B. R. Cassileth, "The prevalence of complementary/alternative medicine in cancer: a systematic review," *Cancer*, vol. 83, no. 4, pp. 777–782, 1998.

[9] F. U. Afifi, M. Wazaify, M. Jabr, and E. Treish, "The use of herbal preparations as complementary and alternative medicine (CAM) in a sample of patients with cancer in Jordan," *Complementary Therapies in Clinical Practice*, vol. 16, no. 4, pp. 208–212, 2010.

[10] A. Montazeri, A. Sajadian, M. Ebrahimi, S. Haghighat, and I. Harirchi, "Factors predicting the use of complementary and alternative therapies among cancer patients in Iran," *European Journal of Cancer Care*, vol. 16, no. 2, pp. 144–149, 2007.

[11] R. E. Genc, S. Senol, A. S. Turgay, and M. Kantar, "Complementary and alternative medicine used by pediatric patients with cancer in western Turkey," *Oncology Nursing Forum*, vol. 36, no. 3, pp. E159–164, 2009.

[12] Y. Yildirim, S. Tinar, S. Yorgun et al., "The use of complementary and alternative medicine (CAM) therapies by Turkish women with gynecological cancer," *European Journal of Gynaecological Oncology*, vol. 27, no. 1, pp. 81–85, 2006.

[13] O. Paltiel, M. Avitzour, T. Peretz et al., "Determinants of the use of complementary therapies by patients with cancer," *Journal of Clinical Oncology*, vol. 19, no. 9, pp. 2439–2448, 2001.

[14] O. Tarhan, A. Alacacioglu, I. Somali et al., "Complementary-alternative medicine among cancer patients in the western region of Turkey," *Journal of B.U.ON.*, vol. 14, no. 2, pp. 265–269, 2009.

[15] E. Ben-Arye, E. Lev, and E. Schiff, "Complementary medicine oncology research in the Middle-East: shifting from traditional to integrative cancer care," *European Journal of Integrative Medicine*, vol. 3, no. 1, pp. 29–37, 2011.

[16] A. H. Avi Senna, *AlKanoon Fi Altib (The Rules of Medicine)*, Iz Aldin Publications, Beirut, Lebanon, 1993.

[17] Rhazes, *AlHawy (The Comprehensive)*, Dar AlKalam Publishing, Beirut, Lebanon, 925.

[18] P. K. Hitti, *History of the Arab*, Mac Millan St. Martin's Press, 1970.

[19] J. O. A. AlTurkimany, *AlMoatamad Fi Aladweah Almofradah, The Source of the Single Pharmaceuticals*, Dar AlKalam Publishing, Beirut, Lebanon, 1993.

[20] D. A. M. Ibn AlBitar, *AlJame Li-Mofradat al Adwiyah wal Aghthiyah (The Collection of Medical and Food Items)*, Dar Sader Publishing, Beirut, Lebanon, 1874.

[21] M. K. D. Al-Turki, *Prophet's Medicine*, vol. 2, Dar Ibn Hazm, 2006.

[22] E. P. Lansky, H. M. Paavilainen, A. D. Pawlus, and R. A. Newman, "Ficus spp. (fig): ethnobotany and potential as anti-cancer and anti-inflammatory agents," *Journal of Ethnopharmacology*, vol. 119, no. 2, pp. 195–213, 2008.

[23] D. Volanis, T. Kadiyska, A. Galanis, D. Delakas, S. Logotheti, and V. Zoumpourlis, "Environmental factors and genetic susceptibility promote urinary bladder cancer," *Toxicology Letters*, vol. 193, no. 2, pp. 131–137, 2010.

[24] K. A. Brown and E. R. Simpson, "Obesity and breast cancer: progress to understanding the relationship," *Cancer Research*, vol. 70, no. 1, pp. 4–7, 2010.

[25] B. F. Fuemmeler, M. K. Pendzich, and K. P. Tercyak, "Weight, dietary behavior, and physical activity in childhood and adolescence: implications for adult cancer risk," *Obesity Facts*, vol. 2, no. 3, pp. 179–186, 2009.

[26] Z. Jeambey, T. Johns, S. Talhouk, and M. Batal, "Perceived health and medicinal properties of six species of wild edible plants in north-east lebanon," *Public Health Nutrition*, vol. 12, no. 10, pp. 1902–1911, 2009.

[27] L. E. Grivetti and B. M. Ogle, "Value of traditional foods in meeting macro- and micronutrient needs: the wild plant connection," *Nutrition Research Reviews*, vol. 13, no. 1, pp. 31–46, 2000.

[28] T. Oyama, Y. Yasui, S. Sugie, M. Koketsu, K. Watanabe, and T. Tanaka, "Dietary tricin suppresses inflammation-related colon carcinogenesis in male Crj: CD-1 mice," *Cancer Prevention Research*, vol. 2, no. 12, pp. 1031–1038, 2009.

[29] A. Amin, H. Gali-Muhtasib, M. Ocker, and R. Schneider-Stock, "Overview of major classes of plant-derived anticancer drugs," *International Journal of Biomedical Science*, vol. 5, no. 1, pp. 1–11, 2009.

[30] H. Zaid, A. Rayan, O. Said, and B. Saad, "Cancer treatment by Greco-Arab and Islamic herbal medicine," *The Open Nutraceuticals Journal*, vol. 3, pp. 203–213, 2010.

[31] B. Challier, J. M. Perarnau, and J. F. Viel, "Garlic, onion and cereal fibre as protective factors for breast cancer: a French case-control study," *European Journal of Epidemiology*, vol. 14, no. 8, pp. 737–747, 1998.

[32] A. V. Khan, *Avicenna (Ibn Sina): Muslim Physician and Philosopher of the Eleventh Century (Great Muslim Philosophers and Scientists of the Middle Ages)*, The Rosen Publishing Group, 2006.

[33] J. M. Chan, F. Wang, and E. A. Holly, "Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco Bay Area," *Cancer Epidemiology Biomarkers and Prevention*, vol. 14, no. 9, pp. 2093–2097, 2005.

[34] S. H. Omar, "Olive: native of Mediterranean region and Health benefits," *Pharmacognosy Reviews*, vol. 2, no. 3, pp. 135–142, 2008.

[35] O. Said, S. Fulder, K. Khalil, H. Azaizeh, E. Kassis, and B. Saad, "Maintaining a physiological blood glucose level with 'glucolevel', a combination of four anti-diabetes plants used in the traditional Arab herbal medicine," *Evidence-based Complementary and Alternative Medicine*, vol. 5, no. 4, pp. 421–428, 2008.

[36] H. Zaid and B. Saad, "State of the art of diabetes treatment in Greco-Arab and islamic medicine," *Bioactive Foods in Chronic Disease States*. In press.

[37] R. W. Owen, A. Giacosa, W. E. Hull, R. Haubner, B. Spiegelhalder, and H. Bartsch, "The antioxidant/anticancer potential of phenolic compounds isolated from olive oil," *European Journal of Cancer*, vol. 36, no. 10, pp. 1235–1247, 2000.

[38] I. Andreadou, F. Sigala, E. K. Iliodromitis et al., "Acute doxorubicin cardiotoxicity is successfully treated with the

phytochemical oleuropein through suppression of oxidative and nitrosative stress," *Journal of Molecular and Cellular Cardiology*, vol. 42, no. 3, pp. 549–558, 2007.

[39] J. Han, T. P. N. Talorete, P. Yamada, and H. Isoda, "Anti-proliferative and apoptotic effects of oleuropein and hydroxytyrosol on human breast cancer MCF-7 cells," *Cytotechnology*, vol. 59, no. 1, pp. 45–53, 2009.

[40] E. S. R. de Cassia da Silveira and M. de Oliveira Guerra, "Reproductive toxicity of lapachol in adult male wistar rats submitted to short-term treatment," *Phytotherapy Research*, vol. 21, no. 7, pp. 658–662, 2007.

[41] V. Goulas, V. Exarchou, A. N. Troganis et al., "Phytochemicals in olive-leaf extracts and their antiproliferative activity against cancer and endothelial cells," *Molecular Nutrition and Food Research*, vol. 53, no. 5, pp. 600–608, 2009.

[42] R. Fabiani, A. De Bartolomeo, P. Rosignoli et al., "Virgin olive oil phenols inhibit proliferation of human promyelocytic leukemia cells (HL60) by inducing apoptosis and differentiation," *Journal of Nutrition*, vol. 136, no. 3, pp. 614–619, 2006.

[43] N. Dudai, Y. Weinstein, M. Krup, T. Rabinski, and R. Ofir, "Citral is a new inducer of caspase-3 in tumor cell lines," *Planta Medica*, vol. 71, no. 5, pp. 484–488, 2005.

[44] F. I. Abdullaev and J. J. Espinosa-Aguirre, "Biomedical properties of saffron and its potential use in cancer therapy and chemoprevention trials," *Cancer Detection and Prevention*, vol. 28, no. 6, pp. 426–432, 2004.

[45] D. G. Chryssanthi, P. G. Dedes, N. K. Karamanos, P. Cordopatis, and F. N. Lamari, "Crocetin inhibits invasiveness of MDA-MB-231 breast cancer cells via downregulation of matrix metalloproteinases," *Planta Medica*, vol. 77, no. 2, pp. 146–151, 2011.

[46] G. Kuttan, K. B. Hari Kumar, C. Guruvayoorappan, and R. Kuttan, "Antitumor, anti-invasion, and antimetastatic effects of curcumin," *Advances in Experimental Medicine and Biology*, vol. 595, pp. 173–184, 2007.

[47] S. C. Gupta, J. H. Kim, S. Prasad, and B. B. Aggarwal, "Regulation of survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals," *Cancer and Metastasis Reviews*, vol. 29, no. 3, pp. 405–434, 2010.

[48] P. P. Wu, H. W. Chung, K. C. Liu et al., "Diallyl sulfide induces cell cycle arrest and apoptosis in HeLa human cervical cancer cells through the p53, caspase- and mitochondria-dependent pathways," *International Journal of Oncology*, vol. 38, no. 6, pp. 1605–1613, 2011.

[49] B. B. Aggarwal and S. Shishodia, "Molecular targets of dietary agents for prevention and therapy of cancer," *Biochemical Pharmacology*, vol. 71, no. 10, pp. 1397–1421, 2006.

[50] J. L. Slavin, "Mechanisms for the impact of whole grain foods on cancer risk," *Journal of the American College of Nutrition*, vol. 19, no. 3, 2000.

[51] H. Qu, R. L. Madl, D. J. Takemoto, R. C. Baybutt, and W. Wang, "Lignans are involved in the antitumor activity of wheat bran in colon cancer SW480 cells," *Journal of Nutrition*, vol. 135, no. 3, pp. 598–602, 2005.

[52] I. T. Johnson, G. Williamson, and S. R. Musk, "Anticarcinogenic factors in plant foods: a new class of nutrients?" *Nutrition Research Reviews*, vol. 7, pp. 175–204, 1994.

[53] P. N. Simon, A. Chaboud, N. Darbour et al., "Modulation of cancer cell multidrug resistance by an extract of *Ficus citrifolia*," *Anticancer Research*, vol. 21, no. 2, pp. 1023–1028, 2001.

[54] X. M. Yang, W. Yu, Z. P. Ou, H. L. Ma, W. M. Liu, and X. L. Ji, "Antioxidant and immunity activity of water extract and crude polysaccharide from Ficus carica L. fruit," *Plant Foods for Human Nutrition*, vol. 64, no. 2, pp. 167–173, 2009.

[55] B. L. Pool-Zobel, "Inulin-type fructans and reduction in colon cancer risk: review of experimental and human data," *British Journal of Nutrition*, vol. 93, pp. S73–S90, 2005.

[56] J. Anter, Z. Fernández-Bedmar, M. Villatoro-Pulido et al., "A pilot study on the DNA-protective, cytotoxic, and apoptosis-inducing properties of olive-leaf extracts," *Mutation Research*, vol. 723, no. 2, pp. 165–170, 2011.

[57] M. Albrecht, W. Jiang, J. Kumi-Diaka et al., "Pomegranate extracts potently suppress proliferation, xenograft growth, and invasion of human prostate cancer cells," *Journal of Medicinal Food*, vol. 7, no. 3, pp. 274–283, 2004.

[58] V. M. Adhami and H. Mukhtar, "Polyphenols from green tea and pomegranate for prevention of prostate cancer," *Free Radical Research*, vol. 40, no. 10, pp. 1095–1104, 2006.

[59] K. V. Hirpara, P. Aggarwal, A. J. Mukherjee, N. J. Joshi, and A. C. Burman, "Quercetin and its derivatives: synthesis, pharmacological uses with special emphasis on anti-tumor properties and prodrug with enhanced bio-availability," *Anti-Cancer Agents in Medicinal Chemistry*, vol. 9, no. 2, pp. 138–161, 2009.

[60] P. Bulzomi, P. Galluzzo, A. Bolli, S. Leone, F. Acconcia, and M. Marino, "The pro-apoptotic effect of quercetin in cancer cell lines requires ERbeta-dependent signals," *Journal of Cellular Physiology*. In press.

[61] M. K. Shanmugam, R. Kannaiyan, and G. Sethi, "Targeting cell signaling and apoptotic pathways by dietary agents: role in the prevention and treatment of cancer," *Nutrition and Cancer*, vol. 63, no. 2, pp. 161–173, 2011.

[62] W. Li, D. Mu, L. Song et al., "Molecular mechanism of silymarin-induced apoptosis in a highly metastatic lung cancer cell line Anip973," *Cancer Biotherapy and Radiopharmaceuticals*, vol. 26, no. 3, pp. 317–324, 2011.

[63] K. Ravichandran, B. Velmurugan, M. Gu, R. P. Singh, and R. Agarwal, "Inhibitory effect of silibinin against azoxymethane-induced colon tumorigenesis in A/J mice," *Clinical Cancer Research*, vol. 16, no. 18, pp. 4595–4606, 2010.

[64] F. Li, P. Rajendran, and G. Sethi, "Thymoquinone inhibits proliferation, induces apoptosis and chemosensitizes human multiple myeloma cells through suppression of signal transducer and activator of transcription 3 activation pathway," *British Journal of Pharmacology*, vol. 161, no. 3, pp. 541–554, 2010.

[65] A. R. Hussain, M. Ahmed, S. Ahmed et al., "Thymoquinone suppresses growth and induces apoptosis via generation of reactive oxygen species in primary effusion lymphoma," *Free Radical Biology and Medicine*, vol. 50, no. 8, pp. 978–987, 2011.

[66] S. Banerjee, S. Padhye, A. Azmi et al., "Review on molecular and therapeutic potential of thymoquinone in cancer," *Nutrition and Cancer*, vol. 62, no. 7, pp. 938–946, 2010.

[67] S. K. El-Desouky, H. K. Ki, Y. R. Shi, A. F. Eweas, A. M. Gamal-Eldeen, and Y. K. Kim, "A new pyrrole alkaloid isolated from Arum palaestinum Boiss. and its biological activities," *Archives of Pharmacal Research*, vol. 30, no. 8, pp. 927–931, 2007.

[68] E. Pichichero, R. Cicconi, M. Mattei, M. G. Muzi, and A. Canini, "Acacia honey and chrysin reduce proliferation of melanoma cells through alterations in cell cycle progression," *International Journal of Oncology*, vol. 37, no. 4, pp. 973–981, 2010.

[69] M. Mandal and S. K. Jaganathan, "Antiproliferative effects of honey and of its polyphenols: a review," *Journal of*

Biomedicine and Biotechnology, vol. 2009, Article ID 830616, 2009.

[70] K. J. Woo, Y. J. Jeong, J. W. Park, and T. K. Kwon, "Chrysin-induced apoptosis is mediated through caspase activation and Akt inactivation in U937 leukemia cells," *Biochemical and Biophysical Research Communications*, vol. 325, no. 4, pp. 1215–1222, 2004.

[71] D. Zohary and M. Hopf, *Domestication of Plants in the Old World: The Origin and Spread of Cultivated Plants in West Asia, Europe, and the Nile Valley*, Oxford University Press, 3rd edition, 2007.

[72] D. Musa, N. Dilsiz, H. Gumushan, G. Ulakoglu, and M. Bitiren, "Antitumor activity of an ethanol extract of Nigella sativa seeds," *Biologia*, vol. 59, no. 6, pp. 735–740, 2004.

[73] M. L. Salem, "Immunomodulatory and therapeutic properties of the Nigella sativa L. seed," *International Immunopharmacology*, vol. 5, no. 13-14, pp. 1749–1770, 2005.

[74] H. Gali-Muhtasib, M. Diab-Assaf, C. Boltze et al., "Thymoquinone extracted from black seed triggers apoptotic cell death in human colorectal cancer cells via a p53-dependent mechanism," *International Journal of Oncology*, vol. 25, no. 4, pp. 857–866, 2004.

[75] H. U. Gali-Muhtasib, W. G. Abou Kheir, L. A. Kheir, N. Darwiche, and P. A. Crooks, "Molecular pathway for thymoquinone-induced cell-cycle arrest and apoptosis in neoplastic keratinocytes," *Anti-Cancer Drugs*, vol. 15, no. 4, pp. 389–399, 2004.

[76] H. Gali-Muhtasib, A. Roessner, and R. Schneider-Stock, "Thymoquinone: a promising anti-cancer drug from natural sources," *International Journal of Biochemistry and Cell Biology*, vol. 38, no. 8, pp. 1249–1253, 2006.

[77] T. Yi, S. G. Cho, Z. Yi et al., "Thymoquinone inhibits tumor angiogenesis and tumor growth through suppressing AKT and extracellular signal-regulated kinase signaling pathways," *Molecular Cancer Therapeutics*, vol. 7, no. 7, pp. 1789–1796, 2008.

[78] K. H. Tennekoon, S. Jeevathayaparan, A. P. Kurukulasooriya, and E. H. Karunanayake, "Possible hepatotoxicity of Nigella sativa seeds and Drega volubilis leaves," *Journal of Ethnopharmacology*, vol. 31, no. 3, pp. 283–289, 1991.

[79] A. Zaoui, Y. Cherrah, N. Mahassini, K. Alaoui, H. Amarouch, and M. Hassar, "Acute and chronic toxicity of Nigella sativa fixed oil," *Phytomedicine*, vol. 9, no. 1, pp. 69–74, 2002.

[80] E. I. Salim and S. Fukushima, "Chemopreventive potential of volatile oil from black cumin (Nigella sativa L.) seeds against rat colon carcinogenesis," *Nutrition and Cancer*, vol. 45, no. 2, pp. 195–202, 2003.

[81] M. A. Mansour, O. T. Ginawi, T. El-Hadiyah, A. S. El-Khatib, O. A. Al-Shabanah, and H. A. Al-Sawaf, "Effects of volatile oil constituents of Nigella sativa on carbon tetrachloride-induced hepatotoxicity in mice: evidence for antioxidant effects of thymoquinone," *Research Communications in Molecular Pathology and Pharmacology*, vol. 110, no. 3-4, pp. 239–251, 2001.

[82] F. I. Abdullaev, "Cancer chemopreventive and tumoricidal properties of saffron (*Crocus sativus* L.)," *Experimental Biology and Medicine*, vol. 227, no. 1, pp. 20–25, 2002.

[83] I. Das, S. Das, and T. Saha, "Saffron suppresses oxidative stress in DMBA-induced skin carcinoma: a histopathological study," *Acta Histochemica*, vol. 112, no. 4, pp. 317–327, 2010.

[84] S. C. Nair, B. Pannikar, and K. R. Panikkar, "Antitumour activity of saffron (*Crocus sativus*)," *Cancer Letters*, vol. 57, no. 2, pp. 109–114, 1991.

[85] A. Amin, A. A. Hamza, K. Bajbouj, S. S. Ashraf, and S. Daoud, "Saffron: a potential candidate for a novel anticancer drug against hepatocellular carcinoma," *Hepatology*, vol. 54, no. 3, pp. 857–867, 2011.

[86] W. G. Gutheil, G. Reed, A. Ray, and A. Dhar, "Crocetin: an agent derived from saffron for prevention and therapy for cancer," *Current Pharmaceutical Biotechnology*. In press.

[87] R. Yang, K. Vernon, A. Thomas, D. Morrison, N. Qureshi, and C. W. Van Way III, "Crocetin reduces activation of hepatic apoptotic pathways and improves survival in experimental hemorrhagic shock," *Journal of Parenteral and Enteral Nutrition*, vol. 35, no. 1, pp. 107–113, 2011.

[88] V. Magesh, J. P. Vijeya Singh, K. Selvendiran, G. Ekambaram, and D. Sakthisekaran, "Antitumour activity of crocetin in accordance to tumor incidence, antioxidant status, drug metabolizing enzymes and histopathological studies," *Molecular and Cellular Biochemistry*, vol. 287, no. 1-2, pp. 127–135, 2006.

[89] A. Dhar, S. Mehta, G. Dhar et al., "Crocetin inhibits pancreatic cancer cell proliferation and tumor progression in a xenograft mouse model," *Molecular Cancer Therapeutics*, vol. 8, no. 2, pp. 315–323, 2009.

[90] D. G. Chryssanthi, F. N. Lamari, G. Iatrou, A. Pylara, N. K. Karamanos, and P. Cordopatis, "Inhibition of breast cancer cell proliferation by style constituents of different crocus species," *Anticancer Research*, vol. 27, no. 1 A, pp. 357–362, 2007.

[91] A. J. Pantuck, J. T. Leppert, N. Zomorodian et al., "Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer," *Clinical Cancer Research*, vol. 12, no. 13, pp. 4018–4026, 2006.

[92] E. P. Lansky and R. A. Newman, "*Punica granatum* (pomegranate) and its potential for prevention and treatment of inflammation and cancer," *Journal of Ethnopharmacology*, vol. 109, no. 2, pp. 177–206, 2007.

[93] J. Jurenka, "Therapeutic applications of pomegranate (*Punica granatum* L.): a review," *Alternative Medicine Review*, vol. 13, no. 2, pp. 128–144, 2008.

[94] E. P. Lansky, W. Jiang, H. Mo et al., "Possible synergistic prostate cancer suppression by anatomically discrete pomegranate fractions," *Investigational New Drugs*, vol. 23, no. 1, pp. 11–20, 2005.

[95] A. Malik and H. Mukhtar, "Prostate cancer prevention through pomegranate fruit," *Cell Cycle*, vol. 5, no. 4, pp. 371–373, 2006.

[96] L. S. Adams, N. P. Seeram, B. B. Aggarwal, Y. Takada, D. Sand, and D. Heber, "Pomegranate juice, total pomegranate ellagitannins, and punicalagin suppress inflammatory cell signaling in colon cancer cells," *Journal of Agricultural and Food Chemistry*, vol. 54, no. 3, pp. 980–985, 2006.

[97] N. Khan, F. Afaq, M. H. Kweon, K. Kim, and H. Mukhtar, "Oral consumption of pomegranate fruit extract inhibits growth and progression of primary lung tumors in mice," *Cancer Research*, vol. 67, no. 7, pp. 3475–3482, 2007.

[98] V. M. Adhami, N. Khan, and H. Mukhtar, "Cancer chemoprevention by pomegranate: laboratory and clinical evidence," *Nutrition and Cancer*, vol. 61, no. 6, pp. 811–815, 2009.

[99] E. Hornung, C. Pernstich, and I. Feussner, "Formation of conjugated Δ11 Δ13-double bonds by Δ12-linoleic acid (1,4)-acyl-lipid-desaturase in pomegranate seeds," *European Journal of Biochemistry*, vol. 269, no. 19, pp. 4852–4859, 2002.

[100] R. F. Wang, W. D. Xie, Z. Zhang et al., "Bioactive compounds from the seeds of *Punica granatum* (pomegranate)," *Journal of Natural Products*, vol. 67, no. 12, pp. 2096–2098, 2004.

[101] R. Mehta and E. P. Lansky, "Breast cancer chemopreventive properties of pomegranate (*Punica granatum*) fruit extracts in a mouse mammary organ culture," *European Journal of Cancer Prevention*, vol. 13, no. 4, pp. 345–348, 2004.

[102] H. Kohno, R. Suzuki, Y. Yasui, M. Hosokawa, K. Miyashita, and T. Tanaka, "Pomegranate seed oil rich in conjugated linolenic acid suppresses chemically induced colon carcinogenesis in rats," *Cancer Science*, vol. 95, no. 6, pp. 481–486, 2004.

[103] J. J. Hora, E. R. Maydew, E. P. Lansky, and C. Dwivedi, "Chemopreventive effects of pomegranate seed oil on skin tumor development in CD1 mice," *Journal of Medicinal Food*, vol. 6, no. 3, pp. 157–161, 2003.

[104] N. D. Kim, R. Mehta, W. Yu et al., "Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer," *Breast Cancer Research and Treatment*, vol. 71, no. 3, pp. 203–217, 2002.

[105] M. Toi, H. Bando, C. Ramachandran et al., "Preliminary studies on the anti-angiogenic potential of pomegranate fractions in vitro and in vivo," *Angiogenesis*, vol. 6, no. 2, pp. 121–128, 2003.

[106] M. Dikmen, N. Ozturk, and Y. Ozturk, "The antioxidant potency of *Punica granatum* L. fruit peel reduces cell proliferation and induces apoptosis on breast cancer," *Journal of Medicinal Food*. In press.

[107] D. Bagchi, C. K. Sen, M. Bagchi, and M. Atalay, "Anti-angiogenic, antioxidant, and anti-carcinogenic properties of a novel anthocyanin-rich berry extract formula," *Biochemistry (Moscow)*, vol. 69, no. 1, pp. 75–80, 2004.

[108] D. X. Hou, T. Ose, S. Lin et al., "Anthocyanidins induce apoptosis in human promyelocytic leukemia cells: structure-activity relationship and mechanisms involved," *International Journal of Oncology*, vol. 23, no. 3, pp. 705–712, 2003.

[109] J. H. Yang, T. C. Hsia, H. M. Kuo et al., "Inhibition of lung cancer cell growth by quercetin glucuronides via G 2/M arrest and induction of apoptosis," *Drug Metabolism and Disposition*, vol. 34, no. 2, pp. 296–304, 2006.

[110] M. H. Park and D. S. Min, "Quercetin-induced downregulation of phospholipase D1 inhibits proliferation and invasion in U87 glioma cells," *Biochemical and Biophysical Research Communications*, vol. 412, no. 4, pp. 710–715, 2011.

[111] L. Gibellini, M. Pinti, M. Nasi et al., "Quercetin and cancer chemoprevention," *Evidence-based Complementary and Alternative Medicine*, vol. 2011, Article ID 591356, 2011.

[112] D. N. Syed, F. Afaq, and H. Mukhtar, "Pomegranate derived products for cancer chemoprevention," *Seminars in Cancer Biology*, vol. 17, no. 5, pp. 377–385, 2007.

[113] V. Exarchou, Y. C. Fiamegos, T. A. van Beek, C. Nanos, and J. Vervoort, "Hyphenated chromatographic techniques for the rapid screening and identification of antioxidants in methanolic extracts of pharmaceutically used plants," *Journal of Chromatography A*, vol. 1112, no. 1-2, pp. 293–302, 2006.

[114] I. Durak, H. Biri, E. Devrim, S. Sözen, and A. Avci, "Aqueous extract of *Urtica Dioica* makes significant inhibition on adenosine deaminase activity in prostate tissue from patients with prostate cancer," *Cancer Biology and Therapy*, vol. 3, no. 9, pp. 855–857, 2004.

[115] L. Konrad, H. H. Müller, C. Lenz, H. Laubinger, G. Aumüller, and J. J. Lichius, "Antiproliferative effect on human prostate cancer cells by a stinging nettle root (*Urtica dioica*) extract," *Planta Medica*, vol. 66, no. 1, pp. 44–47, 2000.

[116] J. A. Milner, "Garlic: its anticarcinogenic and antitumorigenic properties," *Nutrition Reviews*, vol. 54, no. 11, pp. S82–S86, 1996.

[117] X. Mei, M. C. Wang, H. X. Xu et al., "Garlic and gastric cancer-the effect of garlic on nitrite and nitrate in gastric juice," *Acta Nutrimenta Sinica*, vol. 4, pp. 53–56, 1982.

[118] T. Takezaki, C. M. Gao, J. H. Ding, T. K. Liu, M. S. Li, and K. Tajima, "Comparative study of lifestyles of residents in high and low risk areas for gastric cancer in Jiangsu Province, China; with special reference to allium vegetables," *Journal of Epidemiology*, vol. 9, no. 5, pp. 297–305, 1999.

[119] E. Dorant, P. A. Van den Brandt, R. A. Goldbohm, and F. Sturmans, "Consumption of onions and a reduced risk of stomach carcinoma," *Gastroenterology*, vol. 110, no. 1, pp. 12–20, 1996.

[120] K. A. Steinmetz, L. H. Kushi, R. M. Bostick, A. R. Folsom, and J. D. Potter, "Vegetables, fruit, and colon cancer in the Iowa women's health study," *American Journal of Epidemiology*, vol. 139, no. 1, pp. 1–15, 1994.

[121] C. M. Gao, T. Takezaki, J. H. Ding, M. S. Li, and K. Tajima, "Protective effect of allium vegetables against both esophageal and stomach cancer: a simultaneous case-referent study of a high-epidemic area in Jiangsu Province, China," *Japanese Journal of Cancer Research*, vol. 90, no. 6, pp. 614–621, 1999.

[122] J. L. Colli and C. L. Amling, "Chemoprevention of prostate cancer: what can be recommended to patients?" *Current Urology Reports*, vol. 10, no. 3, pp. 165–171, 2009.

[123] A. W. Hsing, A. P. Chokkalingam, Y. T. Gao et al., "Allium vegetables and risk of prostate cancer: a population-based study," *Journal of the National Cancer Institute*, vol. 94, no. 21, pp. 1648–1651, 2002.

[124] Y. K. Ji and O. Kwon, "Garlic intake and cancer risk: an analysis using the Food and Drug Administration's evidence-based review system for the scientific evaluation of health claims," *American Journal of Clinical Nutrition*, vol. 89, no. 1, pp. 257–264, 2009.

[125] H. Boon and J. Wong, "Botanical medicine and cancer: a review of the safety and efficacy," *Expert Opinion on Pharmacotherapy*, vol. 5, no. 12, pp. 2485–2501, 2004.

[126] I. Arnault and J. Auger, "Seleno-compounds in garlic and onion," *Journal of Chromatography A*, vol. 1112, no. 1-2, pp. 23–30, 2006.

[127] N. R. Shenoy and A. S. U. Choughuley, "Inhibitory effect of diet related sulphydryl compounds on the formation of carcinogenic nitrosamines," *Cancer Letters*, vol. 65, no. 3, pp. 227–232, 1992.

[128] J. A. Milner, "Mechanisms by which garlic and allyl sulfur compounds suppress carcinogen bioactivation: garlic and carcinogenesis," *Advances in Experimental Medicine and Biology*, vol. 492, pp. 69–81, 2001.

[129] A. A. Powolny and S. V. Singh, "Multitargeted prevention and therapy of cancer by diallyl trisulfide and related Allium vegetable-derived organosulfur compounds," *Cancer Letters*, vol. 269, no. 2, pp. 305–314, 2008.

[130] G. N. Lvova and G. D. Zasukhina, "Modification of repair DNA synthesis in mutagen-treated human fibroblasts during adaptive response and the antimutagenic effect of garlic extract," *Genetika*, vol. 38, no. 3, pp. 306–309, 2002.

[131] A. Malki, M. El-Saadani, and A. S. Sultan, "Garlic constituent diallyl trisulfide induced apoptosis in MCF7 human breast cancer cells," *Cancer Biology and Therapy*, vol. 8, no. 22, pp. 2175–2185, 2009.

[132] V. L. Sparnins, G. Barany, and L. W. Wattenberg, "Effects of organosulfur compounds from garlic and onions on benzo[a]pyrene-induced neoplasia and glutathione s-transferase activity in the mouse," *Carcinogenesis*, vol. 9, no. 1, pp. 131–134, 1988.

[133] Z. M. Zhang, X. Y. Yang, S. H. Deng, W. Xu, and H. Q. Gao, "Anti-tumor effects of polybutylcyanoacrylate nanoparticles of diallyl trisulfide on orthotopic transplantation tumor model of hepatocellular carcinoma in BALB/c nude mice," *Chinese Medical Journal*, vol. 120, no. 15, pp. 1336–1342, 2007.

[134] S. G. Sundaram and J. A. Milner, "Diallyl disulfide induces apoptosis of human colon tumor cells," *Carcinogenesis*, vol. 17, no. 4, pp. 669–673, 1996.

[135] K. Sakamoto, L. D. Lawson, and J. A. Milner, "Allyl sulfides from garlic suppress the in vitro proliferation of human A549 lung tumor cells," *Nutrition and Cancer*, vol. 29, no. 2, pp. 152–156, 1997.

[136] C. Welch, L. Wuarin, and N. Sidell, "Antiproliferative effect of the garlic compound S-allyl cysteine on human neuroblastoma cells in vitro," *Cancer Letters*, vol. 63, no. 3, pp. 211–219, 1992.

[137] H. Takeyama, D. S. B. Hoon, R. E. Saxton, D. L. Morton, and R. F. Irie, "Growth inhibition and modulation of cell markers of melanoma by S-allyl cysteine," *Oncology*, vol. 50, no. 1, pp. 63–69, 1993.

[138] F. U. Afifi, E. Khalil, and S. Abdalla, "Effect of isoorientin isolated from Arum palaestinum on uterine smooth muscle of rats and guinea pigs," *Journal of Ethnopharmacology*, vol. 65, no. 2, pp. 173–177, 1999.

[139] V. R. Ramprasath and P. J. H. Jones, "Anti-atherogenic effects of resveratrol," *European Journal of Clinical Nutrition*, vol. 64, no. 7, pp. 660–668, 2010.

[140] I. Durak, R. Çetin, E. Devrim, and I. B. Ergüder, "Effects of black grape extract on activities of dna turn-over enzymes in cancerous and non cancerous human colon tissues," *Life Sciences*, vol. 76, no. 25, pp. 2995–3000, 2005.

[141] J. Y. Jo, E. Gonzalez De Mejia, and M. A. Lila, "Catalytic inhibition of human DNA topoisomerase II by interactions of grape cell culture polyphenols," *Journal of Agricultural and Food Chemistry*, vol. 54, no. 6, pp. 2083–2087, 2006.

[142] X. L. Li, Y. Q. Cai, H. Qin, and Y. J. Wu, "Therapeutic effect and mechanism of proanthocyanidins from grape seeds in rats with TNBS-induced ulcerative colitis," *Canadian Journal of Physiology and Pharmacology*, vol. 86, no. 12, pp. 841–849, 2008.

[143] A. M. Tuncer, *New Hope in Health Foundation, Cancer Report 2010*, Asian Pacific Organization for Cancer Prevention, Ankara, Turkey, 2010.

[144] B. Saad, B. S. Abouatta, W. Basha et al., "Hypericum triquetrifolium—derived factors downregulate the production levels of LPS-induced nitric oxide and tumor necrosis factor-α in THP-1 cells," *Evidence-based Complementary and Alternative Medicine*, vol. 2011, Article ID 586470, 2011.

[145] D. Al-Johar, N. Shinwari, J. Arif et al., "Role of Nigella sativa and a number of its antioxidant constituents towards azoxymethane-induced genotoxic effects and colon cancer in rats," *Phytotherapy Research*, vol. 22, no. 10, pp. 1311–1323, 2008.

[146] G. M. Cragg and D. J. Newman, "Plants as a source of anti-cancer agents," *Journal of Ethnopharmacology*, vol. 100, no. 1-2, pp. 72–79, 2005.

[147] J. L. Clifford and J. DiGiovanni, "The promise of natural products for blocking early events in skin carcinogenesis," *Cancer Prevention Research*, vol. 3, no. 2, pp. 132–135, 2010.

[148] H. Vainio and E. Weiderpass, "Fruit and vegetables in cancer prevention," *Nutrition and Cancer*, vol. 54, no. 1, pp. 111–142, 2006.

[149] E. J. Park and J. M. Pezzuto, "Botanicals in cancer chemoprevention," *Cancer and Metastasis Reviews*, vol. 21, no. 3-4, pp. 231–255, 2002.

[150] D. J. Kroll, H. S. Shaw, and N. H. Oberlies, "Milk thistle nomenclature: why it matters in cancer research and pharmacokinetic studies," *Integrative Cancer Therapies*, vol. 6, no. 2, pp. 110–119, 2007.

[151] M. S. Butler and D. J. Newman, "Mother Nature's gifts to diseases of man: the impact of natural products on anti-infective, anticholestemics and anticancer drug discovery," *Progress in Drug Research*, vol. 65, pp. 2–44, 2008.

[152] G. M. Cragg, P. G. Grothaus, and D. J. Newman, "Impact of natural products on developing new anti-cancer agents," *Chemical Reviews*, vol. 109, no. 7, pp. 3012–3043, 2009.

[153] A. Saklani and S. K. Kutty, "Plant-derived compounds in clinical trials," *Drug Discovery Today*, vol. 13, no. 3-4, pp. 161–171, 2008.

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 605154, 11 pages
doi:10.1155/2012/605154

Research Article

Involvement of Prohibitin Upregulation in Abrin-Triggered Apoptosis

Yu-Huei Liu,[1,2,3] Konan Peck,[4] and Jung-Yaw Lin[1]

[1] *Institute of Biochemistry and Molecular Biology, College of Medicine, National Taiwan University, Taipei 100, Taiwan*
[2] *Graduate Institute of Integrated Medicine of Chinese Medicine, China Medical University, Taichung 404, Taiwan*
[3] *Department of Medical Genetics and Medical Research, China Medical University Hospital, Taichung 404, Taiwan*
[4] *Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan*

Correspondence should be addressed to Jung-Yaw Lin, linjy@ntu.edu.tw

Received 20 May 2011; Accepted 18 July 2011

Academic Editor: Senthamil R. Selvan

Abrin (ABR), a protein purified from the seeds of *Abrus precatorius*, induces apoptosis in various types of cancer cells. However, the detailed mechanism remains largely uncharacterized. By using a cDNA microarray platform, we determined that prohibitin (PHB), a tumor suppressor protein, is significantly upregulated in ABR-triggered apoptosis. ABR-induced upregulation of PHB is mediated by the stress-activated protein kinase/c-Jun NH2-terminal kinase (SAPK/JNK) pathway, as demonstrated by chemical inhibitors. In addition, ABR significantly induced the expression of Bax as well as the activation of caspase-3 and poly(ADP-ribose) polymerase (PARP) in Jurkat T cells, whereas the reduction of PHB by specific RNA interference delayed ABR-triggered apoptosis through the proapoptotic genes examined. Moreover, our results also indicated that nuclear translocation of the PHB-p53 complex may play a role in the transcription of Bax. Collectively, our data show that PHB plays a role in ABR-induced apoptosis, which may be helpful for the development of diagnostic or therapeutic agents.

1. Introduction

Abrin (ABR), purified from the seeds of *Abrus precatorius*, belongs to the family of type II ribosome-inactivating proteins (RIPs) that contain 2 subunits. These include a toxic A chain with RNA *N*-glycosidase activity and a galactose-binding B chain with lectin activity [1]. Like ricin from *Ricinus communis*, the A chain of ABR functions via the inhibition of protein biosynthesis through depurination of a single adenine residue (A^{4324}) of the 28S ribosomal RNA [2, 3]. In contrast, the B chain of ABR functions by interacting with the galactose moiety of glycoproteins or glycolipids on the cell membrane and is internalized into cells through receptor-mediated endocytosis. Several reports have documented that ABR is mitogenic [4], antifertility [5], antitumoral [6, 7], and immunopotentiating [8–12] agent. In addition to its ability to inhibit protein synthesis, ABR is believed to adopt alternative mechanisms to trigger cell apoptosis [13]; despite this, it is relatively less toxic to normal cells than to cancer cells [10, 14]. Our previous studies have implied that apoptosis induced by ABR could be partially independent of its RNA *N*-glycosidase activity and instead be mediated by its binding and the decrease of antioxidant protein-1 (AOP-1), increase of reactive oxygen species production, and release of cytochrome c into the cytosol [15].

Prohibitin (PHB) is localized on the cell membrane, mitochondria, and nucleus; this localization may play a pivotal role in its regulation of cell-cycle progression by the inhibition of DNA replication in multiple cell types [16]. The protumorigenic versus antitumorigenic role of PHB in cancer cells remains controversial. An oncogenic role has been identified for PHB in different kinds of cancer cells, including those of the breast [17], bladder [18], gastric [19], ovary [20], and prostate [21], whereas PHB's role as a tumor suppressor has been demonstrated in esophageal squamous cell carcinoma [22–26]. These opposing effects of PHB in cancer may be due to 2 possible mechanisms. One is a polymorphism in PHB [27]. The other involves its

subcellular localization; increased levels of PHB on the cell membrane facilitates tumorigenesis through its interaction with c-Raf induced by the Ras oncogene [28], whereas increased levels of PHB in the nucleus induces apoptosis by increasing the transcriptional activity of p53 and its translocation to the cytoplasm [29].

In order to understand the genetic basis of the apoptotic signaling exerted by ABR, a microarray platform was used to investigate the expression profiles of genes in Jurkat T cells after ABR exposure. Among the genes identified, PHB was significantly upregulated; however, it has yet to be determined whether PHB plays a role in ABR-triggered apoptosis. Here, we report that overexpression of PHB is involved in ABR-triggered Jurkat T cell apoptosis. Upregulation of PHB through the JNK/SAPK pathway activated the pro-apoptotic gene Bax via the accumulation and translocation of the PHB-p53 complex to the cytoplasm. The elucidation of the changes in gene expression and the cellular mechanisms of the response to ABR exposure may be helpful for the development of diagnostic or therapeutic agents.

2. Materials and Methods

2.1. Isolation of ABR. ABR was isolated from seeds of the red variety of *A. precatorius* using Sepharose 6B affinity column chromatography and purified as described in a previous study [30]. The purity and molecular weight of ABR protein were confirmed by Coomassie blue staining (data not shown). The stock protein solution was diluted with phosphate-buffered saline (PBS, pH 7.2) to a concentration of 100 μM.

2.2. Cells and Culture Conditions. The human Jurkat T leukemia cancer cell line was obtained from American Type Culture Collection and maintained in RPMI-1640 medium supplemented with 10% heat-inactivated fetal bovine serum, 100 U/mL penicillin, and 100 μg/mL streptomycin. Cells were grown in suspension in a 5% CO_2 humidified atmosphere at 37°C.

2.3. Cell Proliferation Assay. Cells were seeded in 96-well plates at a density of 5×10^3 cells per well and were treated with (various doses) or without ABR. At the indicated times, viable cells were analyzed by measuring the conversion of the tetrazolium salt 4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-benzene disulfonate (WST-1) to formazan. The formazan dye produced by metabolically active cells was measured with a scanning multiwell spectrophotometer after 4 h of incubation, according to the manufacturer's instructions.

2.4. The cDNA Microarray System. The gene expression patterns regulated by ABR were analyzed with a previously established cDNA microarray platform (9600 probes) [31]. The mRNA from cells with or without ABR treatment was extracted using an Oligotex-dT column (Qiagen). A 2 mg quantity of each mRNA sample was labeled with biotin or digoxigenin for membrane hybridization, dual-color detection, and image analysis as described previously [31].

2.5. Antibodies and Chemical Inhibitors. An antibody specific to PHB was purchased from Lab Vision Corporation. An antibody specific to p53 was obtained from Santa Cruz Biotechnology. Antibodies specific to cleaved-caspase-3, and cleaved-poly(ADP-ribose) polymerase (PARP) were purchased from Cell Signaling. Antibodies against Bax and actin were obtained from Chemicon. The chemical inhibitors PD 98059, SB 203580, and SP600125 were purchased from Sigma.

2.6. Immunoblotting. Total cell lysates were collected in lysis buffer (50 mM HEPES-KOH, pH 7.5, 1% Triton X-100, 150 mM NaCl, and protease inhibitor cocktail (Roche)). The extracts were centrifuged at 14000 rpm for 20 min, and then the clear supernatant was separated by using 10% SDS-PAGE. After transferred, the separated proteins to a polyvinyldene fluoride (PVDF) membrane (Immunobilon-P, 0.45 mm; Millipore, Billerica, Mass, USA) by using the NA-1512 semi-dry transfer apparatus (NIHON EIDO), the membranes were blocked with 5% skim milk in trisbuffered saline containing 1% Tween 20 (TBST, pH 7.4) at room temperature for 30 min and then incubated overnight at 4°C with primary antibodies. The membranes were washed 4 times with TBST for 10 min each at room temperature and incubated with HRP-conjugated secondary antibodies for 1 h at room temperature. The membranes were then washed 4 times with TBST. The proteins were visualized using the SuperSignal West Femto Chemiluminescent Kit (Thermo Scientific) and exposed to an X-ray film (Kodak). The Image J program (http://rsb.info.nih.gov/) was used for quantization the expression fold. For western blot analysis, the fold increase of the indicated proteins was determined by normalizing to corresponding actin expression. For IP-western analysis, the densitometry readings of the bands were normalized to control.

2.7. Enzyme-Linked Immunosorbent Assay (ELISA) for Phosphor MAPK Detection. Cells were treated with or without ABR after pretreating with the indicated inhibitors or vehicle (DMSO) alone. After the indicated period of time, cells were harvested and lysed as above. The PathScan MAP Kinase Multi-Target Sandwich ELISA kit was used to determine phosphor ERK, -p38, and-JNK/SAPK levels according to manufacturer's instruction (Cell Signaling).

2.8. Short Interfering RNA . Short interfering RNAs (siRNAs) against PHB (sc-37629) and the negative control siRNA (sc-37007) were obtained from Santa Cruz Biotechnology. A total of 2×10^5 cells were plated in a 6-well plate for 24 h, and siRNA transfection was carried out using the Lipofectamine 2000 kit according to the manufacturer's instructions (Invitrogen).

2.9. Terminal Deoxynucleotidyl Transferase-Catalyzed Deoxyuridine Triphosphate (dUTP)-Nick End Labeling (TUNEL) Method [15]. Apoptotic cell death was examined by TUNEL method as manufactory's suggestion (Roche Molecular Biochemicals). Each sample with 1×10^4 events was analyzed with a Becton-Dickinson FACSCalibur, and the distribution of cells was determined.

2.10. Chromatin Immunoprecipitation (ChIP) Assays. Cells treated with or without ABR for the indicated time periods were examined. After fixing the protein-DNA complex using formaldehyde (1% final concentration) at room temperature for 10 min, the reaction was stopped with glycine. After washed and lysed the cells, the lysates were sonicated and centrifuged, and the supernatants were used for immunoprecipitation of Bax with PHB antibody or control IgG. Antibody-bound protein/DNA complexes were precipitated and eluted in 300 μL of elution buffer (1% SDS, 50 mM $NaHCO_3$). Cross-linking was reversed by heating at 65°C for 4 h. The DNA was resuspended in 200 μL of distilled water and treated with 30 μg of proteinase K at 37°C for 1 h, followed by phenol/chloroform extraction and ethanol precipitation. PCR was conducted using 100 ng of DNA as the template. The following PCR primers were used for the Bax promoter: forward primer 5′-CCGGGAATTCCA-GACTGCA-3′ and reverse primer 5′-AGCTCTCCCCAG-CGCAGAA-3′. Each band was quantitatively determined using the Image J program (http://rsb.info.nih.gov/). The densitometry readings of the bands were normalized to the input.

2.11. Statistical Analysis. SPSS 12.0 for Windows (SPSS Inc.) was used to analyze the data. A two-tailed paired-samples Student's t-test was used for statistical analysis of the comparative data from the two groups. P-value <0.05 values were considered statistically significant.

3. Results

3.1. ABR Induces Upregulation of PHB in Human Jurkat T Cells. To evaluate the effect of ABR on leukemia cells in vitro, Jurkat T leukemia cells were exposed to 0.01–100 nM of ABR for 24 h. The cell viability was then determined by WST-1 assay. As shown in Figure 1(a), the growth of Jurkat T cells was reduced by ABR in a dose-dependent manner. The value of the 50% cytotoxic concentration (CC_{50}) for the 24 h treatment was determined for the water fraction to be 0.32 ± 0.06 nM. The data are represented as mean ± SD from 3 independent experiments.

Microarray analysis was used to identify novel candidates that are differentially expressed after 1 nM ABR treatment for 3 h. A total of 128 genes, out of the 9600 probes tested, were significantly altered by >1.5-fold in response to ABR ($P < 0.05$). The top 10 significant up-/down-regulated genes are listed in Table 1, sorted by fold increase or decrease. PHB, a significantly upregulated gene with diverse cellular functions, was selected for further investigation. To explore the potential role of PHB in ABR-treated apoptosis, Jurkat T cells were first treated with ABR (0.1–10 nM). As shown in Figure 1(b), ABR significantly increased the expression of PHB protein after treatment for 9 h. Cells were further treated with 1 nM ABR for different time periods. An initial increase of PHB protein was observed at the 3 h time point and was sustained for up to 18 h after ABR treatment (Figure 1(c)). To determine whether PHB upregulation due to ABR is because of increased transcription or increased RNA stability, the RNA synthesis inhibitor actinomycin D or the protein synthesis inhibitor cyclohexamide was preincubated with cells for 1 h before ABR was added. The results show that not only actinomycin D but also cyclohexamide significantly diminished ABR-induced PHB upregulation (Figure 1(d)). This finding suggests that ABR-induced PHB upregulation requires de novo RNA synthesis.

3.2. ABR Upregulates PHB Expression through the SAPK/JNK Pathway. To explore which of the signaling pathways are required for ABR-induced upregulation of the PHB gene, several specific chemical inhibitors were used. The effect of these inhibitors was examined using an ELISA-based detection system (Figure 2(a)). Jurkat T cells were pretreated with PD98059 (PD, MEK inhibitor; 20 μM), SB203580 (SB, p38 MAPK inhibitor; 20 μM), or SP600125 (SP, JNK/SAPK inhibitor; 30 μM) for 1 h, followed by treatment with ABR for the time indicated; total protein was used to determine PHB expression. SP significantly reduced the ABR-induced PHB expression, whereas the 2 other kinase inhibitors PD and SB rarely affected on the upregulation of PHB (Figure 2(b)). These results suggest the possible involvement of JNK/SAPK, but not of ERK1/2 or p38 MAPK, in the regulation of PHB expression in Jurkat T cells treated with ABR.

3.3. PHB Is Involved in ABR-Induced Cell Apoptosis. Since ABR induced the expression of PHB, a tumor suppressor gene that may induce cell apoptosis by arresting the cell cycle at the G1/S phase, we focused on determining whether PHB participates in the apoptotic signaling triggered by ABR. Apoptosis induced by ABR (0.1 and 1 nM) was investigated using TUNEL method. As shown in Figure 3(a), group 1 and 2, the maximal apoptotic response was achieved 18 h after treating cells with ABR (77.7% apoptosis after 1 nM ABR treatment versus 38.5% apoptosis after 0.1 nM ABR treatment; $P < 0.001$). Although the specific PHB RNA interference (PHB siRNA) did significantly enhance cell apoptosis (PHB siRNA induces 22.8% apoptosis versus control siRNA induces 7.4% apoptosis, $P < 0.001$; Figure 3(a) groups 1 and 3), knockdown PHB reduced ABR-induced apoptosis (PHB siRNA reduced 1 nM ABR-induced apoptosis by 9.7%, $P < 0.001$, and PHB siRNA reduced 0.1 nM ABR-induced apoptosis by 16.6%, $P < 0.001$; Figure 3(a) groups 2 and 4). Apoptosis-related genes including Bax, caspase-3, and PARP were also examined. ABR significantly induced the expression of Bax (6.3-fold; $P < 0.001$) as well as the activation of caspase-3 and PARP in the Jurkat T cells (Figure 3(b), lanes 1 and 2). However, the activation was reduced when the PHB expression reduced (Figure 3(b),

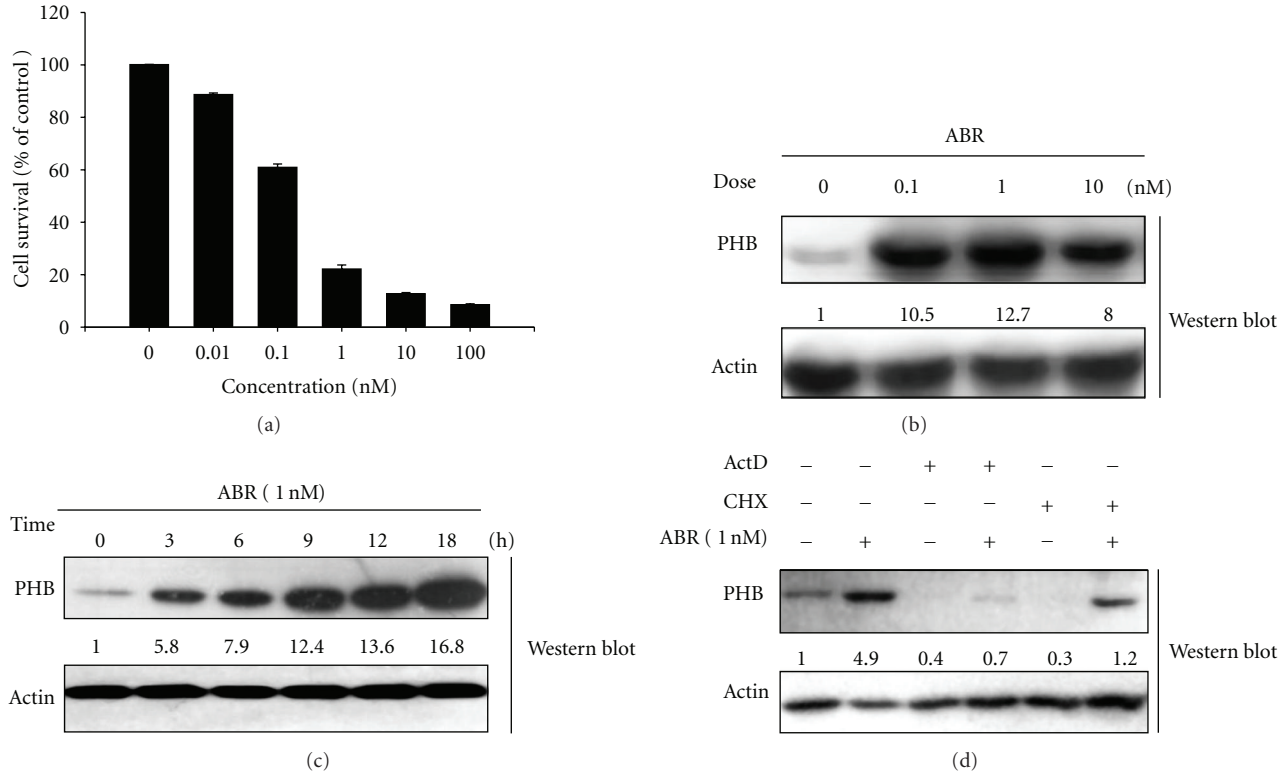


Figure 1: Abrin (ABR) upregulates prohibitin (PHB) expression through transcriptional regulation in Jurkat T cells. (a) ABR-induced cytotoxic activity in a dose-dependent manner in Jurkat T cells after 24 h treatment. The data are represented as mean ± SD from 3 independent experiments. (b) ABR (0.1–10 nM) significantly increased the expression of PHB after treatment for 9 h. (c) ABR (1 nM)-induced upregulation of PHB in a time-dependent manner. (d) ABR-induced PHB upregulation requires de novo RNA synthesis.

lanes 3 and 4). The data showed that PHB is involved in ABR-triggered apoptosis.

3.4. Upregulation of Human Bax Expression through Translocation of the PHB-p53 Complex from the Cytoplasm to the Nucleus. The previously described results raised the possibility that PHB may be involved in the apoptotic processes triggered by ABR. On the other hand, increased levels of PHB in the nucleus may interact with the tumor suppressor protein p53 by which it exerts its apoptotic effect. Therefore, we attempted to determine whether there was an interaction between PHB and p53. As shown in Figure 4(a), PHB was translocated from the cytoplasm to the nucleus after ABR treatment for 6 h. Furthermore, a 1.3-, 1.4-, and 3.2-fold increase in p53 and a 1.1-, 1.3-, and 3.1-fold increase in the interaction with PHB were observed when cells were treated with ABR for 3, 6, and 9 h, respectively (Figure 4(b)). These results indicated that ABR may induce a physical interaction between PHB and p53 in the early stage of ABR-induced cell apoptosis. Since Bax is known to be one of the transcriptional regulation targets for PHB and p53, a ChIP assay was performed by using specific primers to amplify a potential p53-binding region in Bax. As shown in Figure 4(c), p53 was recruited to the promoter regions of Bax in a time-dependent manner. These results suggest that ABR induces the formation of the PHB-p53 complex in the nucleus, which enhances the transcriptional activity of p53 on Bax following apoptosis.

4. Discussion

Studies have shown that some proteins, including ABR, ricin, modeccin, diphtheria toxin, shiga toxin, and pseudomonas toxin, are apoptosis inducers [32–34]. Although ABR has been clearly identified as an inducer of apoptotic cell death by activating caspase-3 in several kinds of cancer cells [15, 35–38], the mechanisms of its involvement in cell apoptosis remain to be investigated. In this study, PHB is shown to be upregulated in a dose-dependent manner during ABR treatment and might play a potent role in ABR-triggered apoptosis by enhancing the activity and expression of p53. To the best of our knowledge, this is the first study to explain and demonstrate the role of PHB in ABR-induced apoptosis in human leukemia cells. The potential clinical applications of ABR may involve the enhancement of drug targeting as well as a decrease in side effects on noncancerous cells.

ABR is a RIP, which induces a shutdown of protein synthesis in target cells [33, 39]. However, previous reports also showed that the apoptosis-related protein Bax can be upregulated by ABR [40, 41]. Our results also indicated an overexpression of PHB and p53. One explanation is

Table 1: Top 10 up-/downregulated genes changing in response to abrin exposure arranged by fold change. Gene common name, description, and gene ontology classification (where known) are listed.

Unigene number	Common name	Description	Fold change	GO biological process	GO molecular function	GO cellular process
				Upregulation		
Hs.326035	EGR1	Early growth response 1	12.9	Transcription, DNA dependent	Transcription activator activity	Nucleus
Hs.502769	SLC3A2	Solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2	3.0	Transmembrane transport	Catalytic activity	Plasma membrane
Hs.2178	HIST2H2BE	Histone cluster 2, H2be	2.5	Nucleosome assembly	Binding to DNA and protein	Nucleus
Hs.82963	GNRH1	Gonadotropin-releasing hormone 1 (luteinizing-releasing hormone)	2.4	Multicellular organismal development	Hormone activity	Extracellular
Hs.467408	TRIM28	Tripartite motif-containing 28	2.3	Transcription, DNA dependent	Transcription coactivator/corepressor activity	Nucleus
Hs.514303	PHB	Prohibitin	2.3	Negative regulation of cell proliferation, gene-specific transcription from RNA polymerase II promoter by competitive promoter binding; regulation of apoptosis; signal transduction	Transcription activator/repressor activity	Cytoplasma, plasma membrane, mitochondria, nucleus
Hs.534404	RPL10	Ribosomal protein L10	2.2	Translation	Structural constituent of ribosome	Cytosol
Hs.5120	DYNLL1	Dynein, light chain, LC8-type 1	2.2	Induction of apoptosis	Motor activity	Cytosol
Hs.226390	RRM2	Ribonucleotide reductase M2	2.1	DNA replication	Oxidoreductase activity	Cytosol
Hs.202207	OSCP1	Organic solute carrier partner 1	2.1	Transport		Plasma membrane
Hs.25524	PTPN23	Protein tyrosine phosphatase, non-receptor type 23	2.1	Cell projection organization	Hydrolase activity	Cytoplasma

Table 1: Continued.

Unigene number	Common name	Description	Fold change	GO biological process	GO molecular function	GO cellular process
				Downregulation		
Hs.725987	TUBA1C	Tubulin, alpha 1c	−1.8	Cellular protein metabolic process	Structural molecule activity	Cytosol
Hs.535192	EEF1A1	Eukaryotic translation elongation factor 1 alpha 1	−1.6	Translation	Translation elongation factor activity	Cytosol
Hs.514581	ACTG1	Actin, gamma 1	−1.6	Cellular component movement	Protein binding	Cytosol
Hs.5662	GNB2L1	Guanine nucleotide-binding protein (G protein), beta polypeptide 2-like 1	−1.5	Positive regulation of apoptosis	Protein binding	Cytosol
Hs.534346	RPS7	Ribosomal protein S7	−1.5	Translation	Structural constituent of ribosome	Cytosol
Hs.433427	RPS17	Ribosomal protein S17	−1.5	Translation	Structural constituent of ribosome	Cytosol
Hs.5662	GNB2L1	Guanine nucleotide-binding protein (G protein), beta polypeptide 2-like 1	−1.5	Negative regulation of cell growth	Protein binding	Nucleus, cytosol
Hs.444467	EEF1G	Eukaryotic translation elongation factor 1 gamma	−1.5	Translational elongation	Translation elongation factor activity	Cytosol
Hs.514581	ACTG1	Actin, gamma 1	−1.5	Cellular component movement	Structural constituent of cytoskeleton	Cytosol
Hs.509736	HSP90AB1	Heat shock protein 90 kDa alpha (cytosolic), class B member 1	−1.5	Regulation of type I interferon-mediated signaling pathway	Unfolded protein binding	Cytosol

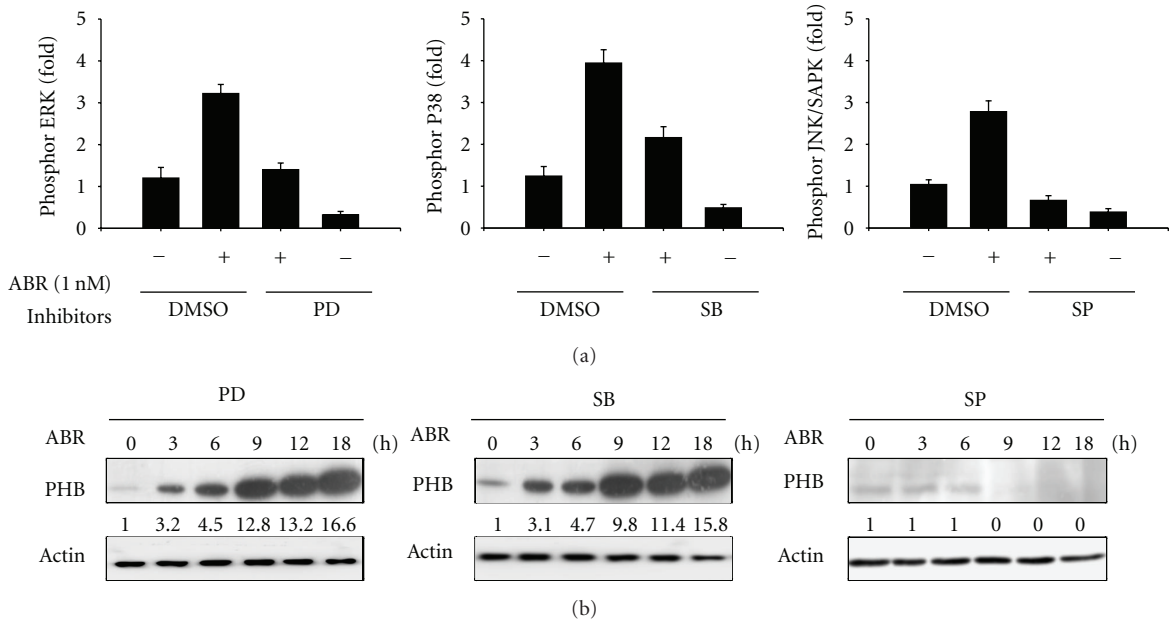


Figure 2: The JNK/SAPK signaling pathway is required for abrin (ABR)-triggered upregulation of prohibitin (PHB). (a) Cells were treated with or without indicated inhibitors for 1 h before ABR treatment. Effects of PD98059 (PD; 20 μM), SB203580 (SB; 20 μM), or SP600125 (SP; 30 μM) on their target signaling molecules were shown. (b) Cells were pretreated with 20 μM PD, 20 μM SB, or 30 μM SP for 1 h before ABR treatment. After the indicated period of time, only SP significantly inhibited the upregulation of PHB by ABR as shown by western blot analysis.

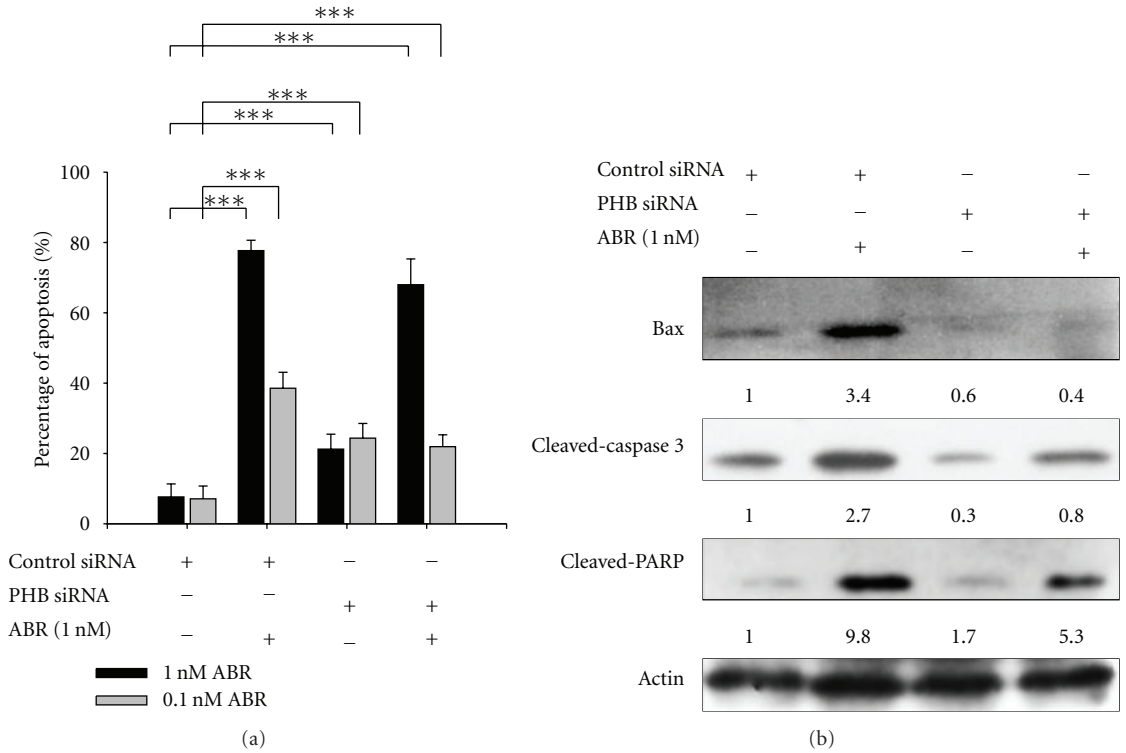


Figure 3: Downregulation of prohibitin (PHB) delays abrin (ABR)-triggered cell apoptosis. (a) Downregulation of PHB expression with siRNA delays ABR-triggered cell apoptosis in Jurkat T cells. The cells were treated with 1 nM ABR for 18 h ($n = 5$). The average ± SD is shown from separate experiments. $^{***}P < 0.001$. (b) Downregulation of PHB inhibits expression of Bax and activation of caspase-3 and poly(ADP-ribose) polymerase (PARP) 9 h after ABR treatment as shown by western blot analysis.

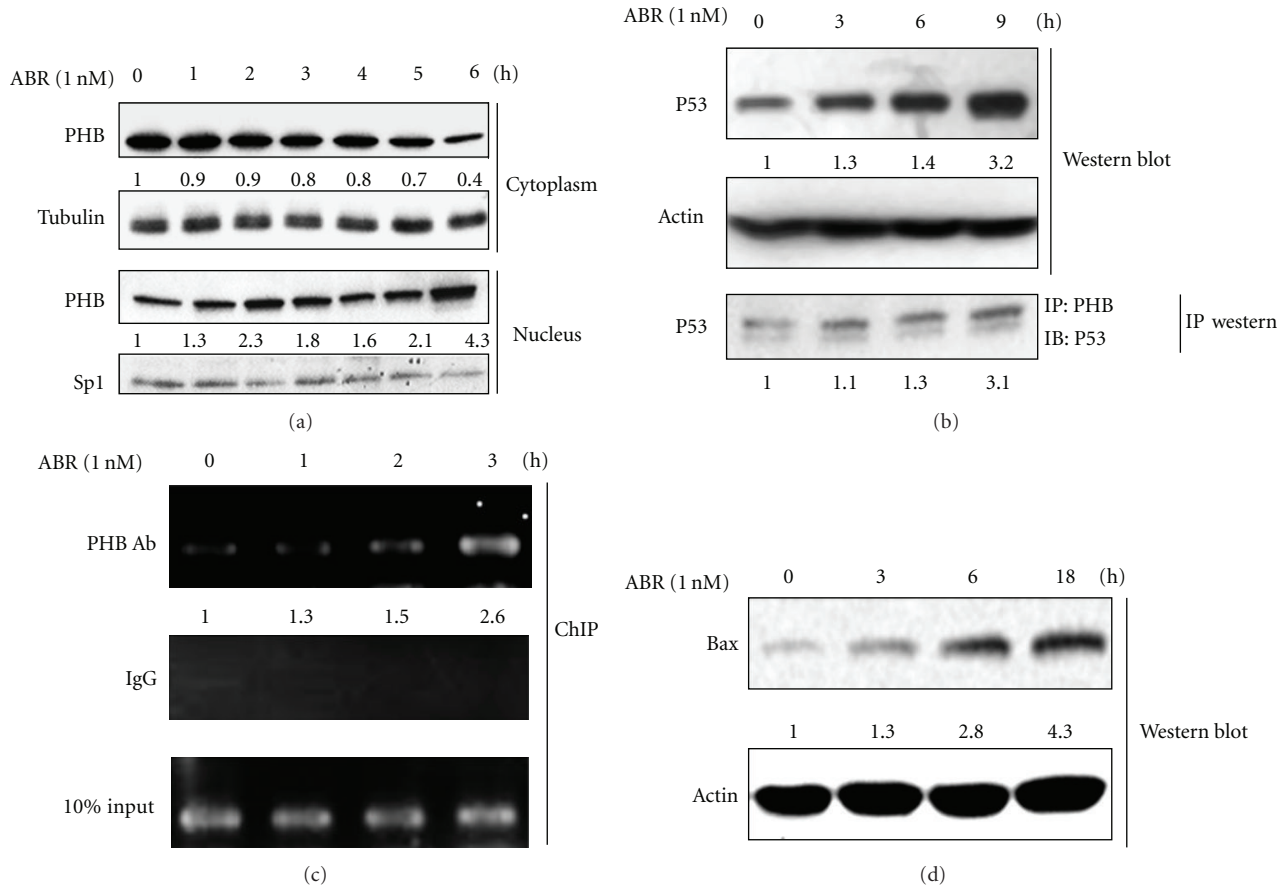


Figure 4: Prohibitin (PHB) induces the transcriptional activity of p53, which promotes expression of Bax. (a) Abrin (ABR)-induced translocation of PHB from cytoplasm to nucleus. (b) ABR upregulates p53 (western blot) and promotes the interaction between PHB and p53 in cells (immunoprecipitated western blot). (c) Association of PHB with the promoter region of the p53-targeted gene Bax.

that cap-independent protein translation occurs in ABR-triggered apoptosis [42]. Hence, although PHB was first defined as a mitochondrial protein stabilizer [43], it was later shown to have diverse functions in a variety of processes including senescence, development, and tumor suppression [44]. In addition, PHB enhances the transcriptional activity of the tumor suppressor p53 via physical interaction [29, 45]. Our results are in agreement with earlier findings that PHB can interact with and upregulate p53 function during apoptosis [29]. It would, therefore, be interesting to determine the involvement of other coactivators in the PHB-p53 transcriptional activator complex upon ABR treatment.

Indeed, ABR may trigger cell apoptosis through its protein synthesis inhibition, ribotoxic stress, mitochondrial stress, PARP-induced NAD^+ depletion, and ROS- and nuclease-induced DNA damage [46]. In addition, others and our previous works showed that ABR-induced apoptosis seems to occur either concomitant with or before the inhibition of protein synthesis [15, 46]. Although we have not yet determined a correlation between the 3 different ABR-induced pathways (including depurination activity, AOP-1 interaction, and prohibitin upregulation), both our current study and previous results indicated that either overexpression of AOP-1 or blockade of PHB expression may significantly reduce apoptosis ($P < 0.05$ for each). ABR upregulates the expression of, but does not interact with, PHB. On the contrary, ABR interacts with AOP-1 without upregulating it (data not shown). Although AOP-1 and PHB are thought to share several conserved domains that are expected to play similar roles in normal cells, the reason why they display distinct functions upon ABR treatment is still unclear; this would be an interesting topic for further studies. In addition, it seems that the interaction of ABR with AOP-1 is independent of depurination activity, and whether the upregulation of PHB depends on depurination is open to further study. Only an efficient cellular transport system for the toxicity-free mutant (ABR A chain E164Q) would be free of intact protein contamination (e.g., the reassociation of the A chain to the B chain).

Moreover, our results here show that early growth response 1 (EGR1), a transcription factor that controls the early growth response and facilitates tissue healing, is significantly upregulated by ABR in leukemia cells. This result is in agreement with the response of lung epithelial cells to ricin [47], which may well serve as one of the markers of RIP-exerted toxicity. Ongoing studies are evaluating the

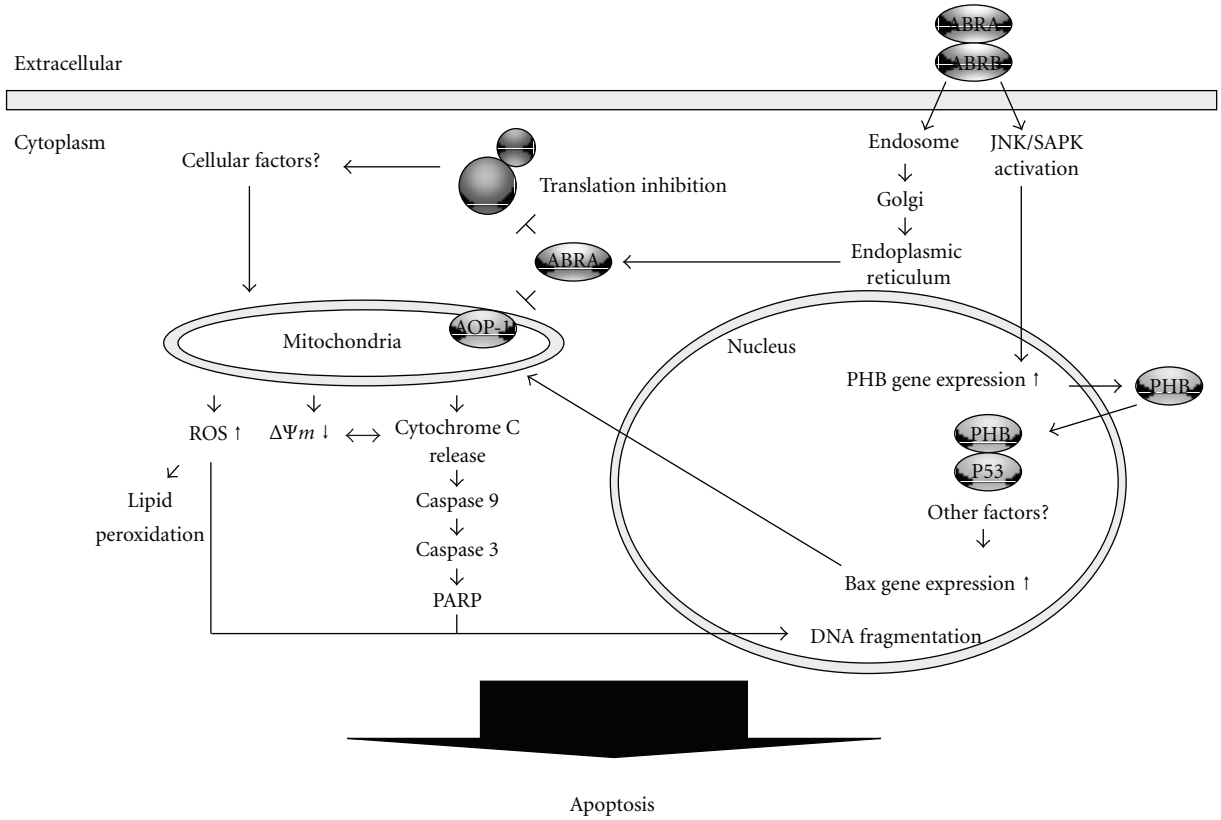


Figure 5: A model of abrin (ABR)-triggered apoptosis. ABR-induced apoptosis may occur through at least 3 pathways: first, inhibition of protein synthesis by its *N*-glycosidase activity; second, modulation of the function of mitochondria by specific interaction with antioxidant protein-1 (AOP-1); and third, interference with the transcription regulated by prohibitin (PHB). Repression of prohibitin attenuates ABR-triggered apoptosis via preventing the expression of BAX, cleaved-caspase 3, and cleaved-poly(ADP-ribose) polymerase (PARP). Once PHB is upregulated by ABR through the JNK/SAPK signaling pathway, the expression of proapoptotic gene Bax is turned on through the nuclear translocation and p53 interaction of PHB, by which activates the caspase cascade, and finally, apoptosis occurs.

potential of these ABR-related genes for clinical intervention. Nevertheless, as *Abrus precatorius* is labeled as a biological weapon which may be fatal if eaten, development of a passive vaccine or an antidote for ABR is necessary but under investigation [48, 49]. More understanding of the molecular mechanisms exerted by RIP family proteins may accelerate their clinical applications.

In conclusion, we propose the model shown in Figure 5. ABR exhibits biological functions involving at least 3 pathways: translational inhibition, mitochondrial dysfunction, and transcriptional interfere through the upregulation of PHB. Since the downregulation of PHB significantly delays apoptosis induced by ABR, PHB could be employed in reducing the toxicity of immunotoxins and, hence, improve the efficiency of cancer chemotherapy.

Acknowledgments

This study was supported by Grants from the Committee on Chinese Medicine and Pharmacy (CCMP-96-RD-203-1) and the Department of Health (DOH97-TD-I-111-TM018, DOH98-TD-I-111-TM020), executive Yuan, Taiwan.

References

[1] J. Y. Lin, K. Y. Tserng, C. C. Chen, L. T. Lin, and T. C. Tung, "Abrin and ricin: new anti-tumour substances," *Nature*, vol. 227, no. 5255, pp. 292–293, 1970.

[2] J. U. Baenziger and D. Fiete, "Structural determinants of Ricinus communis agglutinin and toxin specificity for oligosaccharides," *Journal of Biological Chemistry*, vol. 254, no. 19, pp. 9795–9799, 1979.

[3] F. Stirpe, L. Barbieri, M. G. Battelli, M. Soria, and D. A. Lappi, "Ribosome-inactivating proteins from plants: present status and future prospects," *Nature Biotechnology*, vol. 10, no. 4, pp. 405–412, 1992.

[4] S. J. Kaufman and A. McPherson, "Abrin and hurin: two new lymphocyte mitogens," *Cell*, vol. 4, no. 3, pp. 263–268, 1975.

[5] V. P. Kamboj and B. N. Dhawan, "Research on plants for fertility regulation in India," *Journal of Ethnopharmacology*, vol. 6, no. 2, pp. 191–226, 1982.

[6] J. Y. Lin, T. C. Lee, and T. C. Tung, "Inhibitory effects of four isoabrins on the growth of sarcoma 180 cells," *Cancer Research*, vol. 42, no. 1, pp. 276–279, 1982.

[7] R. Hegde, T. K. Maiti, and S. K. Podder, "Purification and characterization of three toxins and two agglutinins from *Abrus precatorius* seed by using lactamyl-sepharose affinity chromatography," *Analytical Biochemistry*, vol. 194, no. 1, pp. 101–109, 1991.

[8] S. Tripathi and T. K. Maiti, "Stimulation of murine macrophages by native and heat-denatured lectin from *Abrus precatorius*," *International Immunopharmacology*, vol. 3, no. 3, pp. 375–381, 2003.

[9] V. Ramnath, G. Kuttan, and R. Kuttan, "Immunopotentiating activity of abrin, a lectin from *Abrus precatorius* Linn," *Indian Journal of Experimental Biology*, vol. 40, no. 8, pp. 910–913, 2002.

[10] V. Ramnath, G. Kuttan, and R. Kuttan, "Antitumour effect of abrin on transplanted tumours in mice," *Indian Journal of Physiology and Pharmacology*, vol. 46, no. 1, pp. 69–77, 2002.

[11] S. Tripathi and T. K. Maiti, "Immunomodulatory role of native and heat denatured agglutinin from *Abrus precatorius*," *International Journal of Biochemistry and Cell Biology*, vol. 37, no. 2, pp. 451–462, 2005.

[12] A. Tilwari, N. P. Shukla, and U. D. Pathirissery, "Immunomodulatory activity of the aqueous extract of seeds of *Abrus precatorius* Linn (Jequirity) in mice," *Iranian Journal of Immunology*, vol. 8, no. 2, pp. 96–103, 2011.

[13] K. J. Dickers, S. M. Bradberry, P. Rice, G. D. Griffiths, and J. A. Vale, "Abrin poisoning," *Toxicological Reviews*, vol. 22, no. 3, pp. 137–142, 2003.

[14] L. N. L. Chan, J. S. Li, and S. Y. Liu, "Differential effects of abrin on normal and tumor cells," *Journal of Cellular Physiology*, vol. 123, no. 1, pp. 132–138, 1985.

[15] S. F. Shih, Y. H. Wu, C. H. Hung, H. Y. Yang, and J. Y. Lin, "Abrin triggers cell death by inactivating a thiol-specific antioxidant protein," *Journal of Biological Chemistry*, vol. 276, no. 24, pp. 21870–21877, 2001.

[16] W. Rizwani, M. Alexandrow, and S. Chellappan, "Prohibitin physically interacts with MCM proteins and inhibits mammalian DNA replication," *Cell Cycle*, vol. 8, no. 10, pp. 1621–1629, 2009.

[17] S. Manjeshwar, D. E. Branam, M. R. Lerner, D. J. Brackett, and E. R. Jupe, "Tumor suppression by the prohibitin gene 3'untranslated region RNA in human breast cancer," *Cancer Research*, vol. 63, no. 17, pp. 5251–5256, 2003.

[18] T. F. Wu, H. Wu, Y. W. Wang et al., "Prohibitin in the pathogenesis of transitional cell bladder cancer," *Anticancer Research*, vol. 27, no. 2, pp. 895–900, 2007.

[19] X. Kang, L. Zhang, J. Sun et al., "Prohibitin: a potential biomarker for tissue-based detection of gastric cancer," *Journal of Gastroenterology*, vol. 43, no. 8, pp. 618–625, 2008.

[20] R. C. Gregory-Bass, M. Olatinwo, W. Xu et al., "Prohibitin silencing reverses stabilization of mitochondrial integrity and chemoresistance in ovarian cancer cells by increasing their sensitivity to apoptosis," *International Journal of Cancer*, vol. 122, no. 9, pp. 1923–1930, 2008.

[21] R. Ummanni, H. Junker, U. Zimmermann et al., "Prohibitin identified by proteomic analysis of prostate biopsies distinguishes hyperplasia and cancer," *Cancer Letters*, vol. 266, no. 2, pp. 171–185, 2008.

[22] H. Z. Ren, J. S. Wang, G. Q. Pan et al., "Comparative proteomic analysis of β-catenin-mediated malignant progression of esophageal squamous cell carcinoma," *Diseases of the Esophagus*, vol. 23, no. 2, pp. 175–184, 2010.

[23] M. J. Nuell, D. A. Stewart, L. Walker et al., "Prohibitin, an evolutionarily conserved intracellular protein that blocks DNA synthesis in normal fibroblasts and HeLa cells," *Molecular and Cellular Biology*, vol. 11, no. 3, pp. 1372–1381, 1991.

[24] T. Sato, H. Saito, J. Swensen et al., "The human prohibitin gene located on chromosome 17q21 is mutated in sporadic breast cancer," *Cancer Research*, vol. 52, no. 6, pp. 1643–1646, 1992.

[25] R. T. Dell'Orco, J. K. McClung, E. R. Jupe, and X. T. Liu, "Prohibitin and the senescent phenotype," *Experimental Gerontology*, vol. 31, no. 1-2, pp. 245–252, 1996.

[26] E. Ikonen, K. Fiedler, R. G. Parton, and K. Simons, "Prohibitin, an antiproliferative protein, is localized to mitochondria," *FEBS Letters*, vol. 358, no. 3, pp. 273–277, 1995.

[27] E. R. Jupe, X. T. Liu, J. L. Kiehlbauch, J. K. McClung, and R. T. Dell'Orco, "Prohibitin in breast cancer cell lines: loss of antiproliferative activity is linked to 3' untranslated region mutations," *Cell Growth and Differentiation*, vol. 7, no. 7, pp. 871–878, 1996.

[28] K. Rajalingam and T. Rudel, "Ras-Raf signaling needs prohibitin," *Cell Cycle*, vol. 4, no. 11, pp. 1503–1505, 2005.

[29] G. Fusaro, P. Dasgupta, S. Rastogi, B. Joshi, and S. Chellappan, "Prohibitin induces the transcriptional activity of p53 and is exported from the nucleus upon apoptotic signaling," *Journal of Biological Chemistry*, vol. 278, no. 48, pp. 47853–47861, 2003.

[30] P. P. Knowles and P. E. Thorpe, "Purification of immunotoxins containing ricin A-chain and abrin A-chain using blue sepharose CL-6B," *Analytical Biochemistry*, vol. 160, no. 2, pp. 440–443, 1987.

[31] J. J. W. Chen, R. Wu, P. C. Yang et al., "Profiling expression patterns and isolating differentially expressed genes by cDNA microarray system with colorimetry detection," *Genomics*, vol. 51, no. 3, pp. 313–324, 1998.

[32] N. Komatsu, T. Oda, and T. Muramatsu, "Involvement of both caspase-like proteases and serine proteases in apoptotic cell death induced by ricin, modeccin, diphtheria toxin, and pseudomonas toxin," *Journal of Biochemistry*, vol. 124, no. 5, pp. 1038–1044, 1998.

[33] K. Sandvig and B. van Deurs, "Toxin-induced cell lysis: protection by 3-methyladenine and cycloheximide," *Experimental Cell Research*, vol. 200, no. 2, pp. 253–262, 1992.

[34] S. K. Kochi and R. J. Collier, "DNA fragmentation and cytolysis in U937 cells treated with diphtheria toxin or other inhibitors of protein synthesis," *Experimental Cell Research*, vol. 208, no. 1, pp. 296–302, 1993.

[35] S. Narayanan, A. Surolia, and A. A. Karande, "Ribosome-inactivating protein and apoptosis: abrin causes cell death via mitochondrial pathway in Jurkat cells," *Biochemical Journal*, vol. 377, no. 1, pp. 233–240, 2004.

[36] H. Ohba, S. Moriwaki, R. Bakalova, S. Yasuda, and N. Yamasaki, "Plant-derived abrin-a induces apoptosis in cultured leukemic cell lines by different mechanisms," *Toxicology and Applied Pharmacology*, vol. 195, no. 2, pp. 182–193, 2004.

[37] X. Qu and L. Qing, "Abrin induces HeLa cell apoptosis by cytochrome c release and caspase activation," *Journal of Biochemistry and Molecular Biology*, vol. 37, no. 4, pp. 445–453, 2004.

[38] V. Ramnath, P. S. Rekha, G. Kuttan, and R. Kuttan, "Regulation of Caspase-3 and Bcl-2 expression in Dalton's lymphoma ascites cells by abrin," *Evidence-Based Complementary and Alternative Medicine*, vol. 6, no. 2, pp. 233–238, 2009.

[39] G. D. Griffiths, M. D. Leek, and D. J. Gee, "The toxic plant proteins ricin and abrin induce apoptotic changes in mammalian lymphoid tissues and intestine," *Journal of Pathology*, vol. 151, no. 3, pp. 221–229, 1987.

[40] S. K. Bhutia, S. K. Mallick, S. Maiti, D. Mishra, and T. K. Maiti, "*Abrus* abrin derived peptides induce apoptosis by targeting mitochondria in HeLa cells," *Cell Biology International*, vol. 33, no. 7, pp. 720–727, 2009.

[41] S. K. Bhutia, S. K. Mallick, S. Maiti, and T. K. Maiti, "Inhibitory effect of *Abrus* abrin-derived peptide fraction against Dalton's lymphoma ascites model," *Phytomedicine*, vol. 16, no. 4, pp. 377–385, 2009.

[42] T. E. Graber and M. Holcik, "Cap-independent regulation of gene expression in apoptosis," *Molecular Biosystems*, vol. 3, no. 12, pp. 825–834, 2007.

[43] X. Wang, X. Zuo, B. Kucejova, and X. J. Chen, "Reduced cytosolic protein synthesis suppresses mitochondrial degeneration," *Nature Cell Biology*, vol. 10, no. 9, pp. 1090–1097, 2008.

[44] J. K. McClung, E. R. Jupe, X. T. Liu, and R. T. Dell'Orco, "Prohibitin: potential role in senescence, development, and tumor suppression," *Experimental Gerontology*, vol. 30, no. 2, pp. 99–124, 1995.

[45] S. Rastogi, B. Joshi, P. Dasgupta, M. Morris, K. Wright, and S. Chellappan, "Prohibitin facilitates cellular senescence by recruiting specific corepressors to inhibit E2F target genes," *Molecular and Cellular Biology*, vol. 26, no. 11, pp. 4161–4171, 2006.

[46] S. Narayanan, K. Surendranath, N. Bora, A. Surolia, and A. A. Karande, "Ribosome inactivating proteins and apoptosis," *FEBS Letters*, vol. 579, no. 6, pp. 1324–1331, 2005.

[47] L. DaSilva, D. Cote, C. Roy et al., "Pulmonary gene expression profiling of inhaled ricin," *Toxicon*, vol. 41, no. 7, pp. 813–822, 2003.

[48] K. Surendranath and A. A. Karande, "A neutralizing antibody to the A chain of abrin inhibits abrin toxicity both in vitro and in vivo," *Clinical and Vaccine Immunology*, vol. 15, no. 5, pp. 737–743, 2008.

[49] J. Tang, T. Yu, L. Guo, J. Xie, N. Shao, and Z. He, "*In vitro* selection of DNA aptamer against abrin toxin and aptamer-based abrin direct detection," *Biosensors and Bioelectronics*, vol. 22, no. 11, pp. 2456–2463, 2007.

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 620619, 9 pages
doi:10.1155/2012/620619

Research Article

Effectiveness of Core Stability Exercises and Recovery Myofascial Release Massage on Fatigue in Breast Cancer Survivors: A Randomized Controlled Clinical Trial

Irene Cantarero-Villanueva,[1] Carolina Fernández-Lao,[1] Rosario del Moral-Avila,[2] César Fernández-de-las-Peñas,[3] María Belén Feriche-Fernández-Castanys,[4] and Manuel Arroyo-Morales[1]

[1] *Department of Physical Therapy, Health Sciences Faculty, University of Granada, 18071 Granada, Spain*
[2] *Radiotherapy Breast Oncology Unit, University Hospital Virgen de las Nieves, Granada, Spain*
[3] *Department of Physical Therapy, Occupational Therapy, Rehabilitation, and Physical Medicine, King Juan Carlos university, Alcorcón, Spain*
[4] *Physical Education Department, Faculty of Sciences, Physical Activity, and Sports, University of Granada, 18071 Granada, Spain*

Correspondence should be addressed to Manuel Arroyo-Morales, marroyo@ugr.es

Received 31 May 2011; Accepted 6 June 2011

Academic Editor: Bashar Saad

The purpose of the present paper was to evaluate the effects of an 8-week multimodal program focused on core stability exercises and recovery massage with DVD support for a 6-month period in physical and psychological outcomes in breast cancer survivors. A randomized controlled clinical trial was performed. Seventy-eight ($n = 78$) breast cancer survivors were assigned to experimental (core stability exercises plus massage-myofascial release) and control (usual health care) groups. The intervention period was 8 weeks. Mood state, fatigue, trunk curl endurance, and leg strength were determined at baseline, after the last treatment session, and at 6 months of followup. Immediately after treatment and at 6 months, fatigue, mood state, trunk curl endurance, and leg strength exhibited greater improvement within the experimental group compared to placebo group. This paper showed that a multimodal program focused on core stability exercises and massage reduced fatigue, tension, depression, and improved vigor and muscle strength after intervention and 6 months after discharge.

1. Introduction

Almost all breast cancer survivors (BCS) suffer from one or more cancer-related symptoms that impact their quality of life. Multimodal therapeutic programs can ameliorate and reduce the patient's impairments by improving their ability to carry out daily tasks [1]. Nevertheless, health care practitioners feel that their practice is usually affected by the lack of exercise guidance for cancer population suffering from fatigue-related cancer [2].

One principal component of a multimodal program is the therapeutic exercise. Similar levels of physical activity as general people have been recommended in BCS [3]. This recommendation was reviewed by American College Sports Medicine experts in exercise for cancer who suggested the necessity to individualize the programs to cancer populations [4]. A recent meta-analysis concluded that exercise interventions should be multidimensional, including both exercise and behavioral interventions [3].

In fact, there is evidence that exercise and massage can be beneficial when tested as separate interventions for improving physical function in BCS [3]. A recent study has reported psychological and physical improvements after the application of a multimodal physical therapy program including in patients with different types of cancer [5]. Although conventional exercise programs [3] and alternative medicine approachs [6] applied on BCS with cancer-related fatigue have been previously studied, the application of core

stability exercises (CSEs) as the main component of theprogram has not yet been investigated.

CSEs are defined as exercises developing the ability to control the position and motion of the trunk during end-range segment in integrated kinetic chain activities [7]. It is known that BCS exhibit reduction in muscle strength associated with cancer-related symptoms [8], which could be improved with an exercise program including CSEs.

Finally, disturbances of mood state have been reported as a frequent symptom in BCS [9]. Massage, which has been shown to be effective as a psychological resource [10, 11] and a recovery method after exercise [12] could be a main component of recovery process. Therefore, the aim of the current randomized controlled trial was to investigate the effectiveness of an 8-week physical therapy program focused on CSEs and recovery massage in physical (muscle strength) and psychological (mood state) outcomes in BCS.

2. Methods

2.1. Subjects. Participants were recruited from the Breast Oncology Unit of Hospital Virgen de las Nieves, Granada, Spain from December 2008 to June 2010. The patients were approached and enrolled by physicians and nurses from two treatment departments. Participants were eligible if they (1) had a diagnosis of breast cancer (stage I–IIIA), (2) were 25–65 years, (3) finished coadjuvant treatment except hormone therapy, (4) not do have active cancer, and (5) present 4 or 5 of the following physical findings, judged by the oncologist who referred the patient: neck or shoulder pain, reduced range of motion in neck-shoulder region, reduced physical capacity, psychological problems, increased fatigue, sleep disturbances, or any problem in coping with physical and psychosocial functioning. They were excluded if they were receiving chemotherapy or radiotherapy treatment at the time of the study or they had chronic or orthopedic diseases which do not permit following the physical program.

Potential participants were contacted by phone by 2 oncologists of the hospital. Those interested were cited for an appointment, received a complete explanation of the protocol and signed the consent form. The ethical approval for the study was granted by the Ethics Committee of the Hospital Virgen de las Nieves (no. 0890418, Granada, Spain). After inclusion, participants were scheduled for a medical visit including a history, physical examination, and a medical questionnaire. This visit had the goal of discovering conditions which justified any medical exclusion.

2.2. Design, Randomization, and Allocation. A randomized controlled clinical trial was conducted. Eligible participants, after providing written informed consent, were randomly assigned into 2 groups: multimodal exercise group or a control group who received the usual care treatment for breast cancer. For ethical implications, those participants allocated to the control group, who finished the period of 6 months for the current study, were invited to be included into a new multimodal program or received an intervention by multimedia electronic document including exercises of all therapeutic sessions. We allocated patients to a multimodal program or control group in 4 randomization cycles, using computer-generated numbers. The sequence was entered into numbered opaque envelopes by an external member and they were opened after completion of the baseline assessment.

2.3. Treatment: Multimodal Program. Multimodal program consisted of 24 hours of individual physical training and 12 hours of recovery procedures, conducted 3 times/week for 90 min each (Table 1). The intensity of the aerobic training was conducted following ACSM and AHA recommendations [13].

Physical training was followed by 30–40 min of low intensity interventions for improving recovery after exercise. This period included stretching of the muscles used during exercise and massage (myofascial release techniques) which has the ability to improve recovery after exercise [12].

After finish the 8 weeking supervised multimodal program, participants received an instructional DVD with the same exercise program which included aerobic exercise progression, resistance exercise, neck-shoulder mobility exercises, self-massage, and some relaxation techniques. The DVD included safety precautions related to exercise and health advice related to maintain and promote healthy lifestyle.

2.4. Control Condition. Participants followed usual care recommended by the oncologist in relation with healthy lifestyle. A followup of the physical activity during control period was used to control possible bias detected in previous studies on exercise in BCS [3]. For that purpose, we used the Spanish version of Minnesota Leisure Time Physical Activity Questionnaire [14].

2.5. Data Analysis—Outcomes. The primary outcome was fatigue assessed using the fatigue subscale of Profile of Mood State (POMS) questionnaire. The POMS questionnaire (Spanish version) consists of 63 items on mood state. Scores (on a 5-point scale from 0 to 4) are grouped into six subscales: tension-anxiety, depression-dejection, anger-hostility, vigor, fatigue, and confusion. Subscale scores were converted into T-scores for the analysis, and the overall mood disturbance was also calculated. The reliability of the Spanish version of the POMS has been found to be high (Cronbach's α ranging 0.76–0.91) [15]. Assessors, participants, and therapists were blinded to the POMS scores during all the trial.

Secondary outcome measures included the following physical tests.

(1) Trunk Curl Static Endurance Test. This test requires a wedged piece of wood to support the patient at a fixed angle of 60°. The patients maintain both knees and hips flexed at 90°, the arms are folded across the chest and toes are anchored by the tester. The wood is pulled back 10 cm and the subject holds the isometric posture as long as possible. This test has proved to be reliable with coefficients of >0.97 for repeated tests [16].

Table 1: Description of the CUIDATE (intervention) program.

CUIDATE program		
Week 1–4		
Material	Small soft ball, mats, and fit-ball	
Endurance program	Unspecific work during sessions	
Exercise Program	Content	Dosage and progression
	(1) Half squat with arm movement (2) Standing rows with leg semiflexion maintained (3) Wall push-ups (4) Abdominal with lower limb movement (5) All tours with hip and knee movement (6) Abdominal with adductor isometric contraction and armmovement (7) Standing hip circumduction (8) Supine on fit-ball with arm movements (9) Superman on fit-ball (10) Oblique partial sit-up	Week 1: Learning proposal. Assessment maximum load Week 2-3: 75% maximum load Increase 5% per week Continue progression between exercises: 2 sets/30 sec pause Week 4: 75% maximum load. Increase number series (3 sets) Medium velocity execution exercises Increase range of joint motion
Week 5–8		
Materials	Fit-ball, elastic band, mats, and small soft ball	
Endurance program	10–25 min of fast working with arms movement two days per week	
Exercise Program	Content	Dosage and progression
	(1) Chest press on fit-ball with elastic band (2) Squat with elastic band (3) Seated rows on fit-ball with elastic band (4) Isometric abdominal sitting on fit-ball with arm and leg movement (5) Biceps curl on fit-ball with elastic band (6) Biceps curl with elastic band and leg semiflexion maintained (7) Leg curl with fit-ball (8) Sit-up with lower limb movement	Week 5: 10–12 repetitions × 2 sets Week 6: 12–15 repetitions × 2 sets Week 7: 10–12 repetitions × 3 sets Week 8: 10–12 repetitions × 2 sets Increase resistance with elastic band and positions that require more body control

(2) Multiple Sit-to-Stand Test. Participants were asked, while sitting at the front of a chair, to rise until they reached full knee extension and sit back 10 times as fast as they can. This test was used to assess general lower-extremity endurance [17]. This test has been showed reliable in similar age population [18].

All outcomes were completed before the program (pre-), immediately after the 8-week intervention (post-), and 6 months after discharge (followup).

Based on a previous pilot study the sample size was calculated on an 80% power to detect a mean difference of 5 points, with a standard deviation of 4 (7%), on the POMS fatigue subscale, using a type 1 error (α) of 5%, and a type 2 error (β) of 20%. This power calculation resulted in 35 patients on each group. To accommodate expected dropouts before study completion, a total of 78 participants were included.

2.6. Statistics. Statistical analysis was performed using SPSS statistical software, version 19.0, and it was conducted according to intention to treat analysis principle. We used t-tests and Chi-square tests to examine differences in baseline sociodemographic and medical features between included and excluded patients, as well as between participants who completed the study and those who dropped out. A one-way ANOVA was used to compare both groups of BCS with healthy women from Hospital Virgen de las Nieves influence area ($n = 43$, age: 47 ± 12 years).

The main analysis examined whether differences in outcomes (mean differences) among baseline, 8 weeks, and 6 months of followup existed between the groups. A 2×3 repeated-measure ANCOVA with intervention (experimental and control) as between-subjects variable, time (pre-, post-, and 6 months) as within-subjects variable, and age, status, educational level, and clinical features as covariates was used to examine the effects of the intervention on the main outcome.

Intergroup effect sizes were calculated (*Cohen d*). An effect size <0.2 reflects a negligible difference, between ≥0.2 and ≤0.5 a small difference, between ≥0.5 and ≤0.8 a moderate difference, and ≥0.8 a large differences. The Pearson correlation test (r) was used to analyze the association between

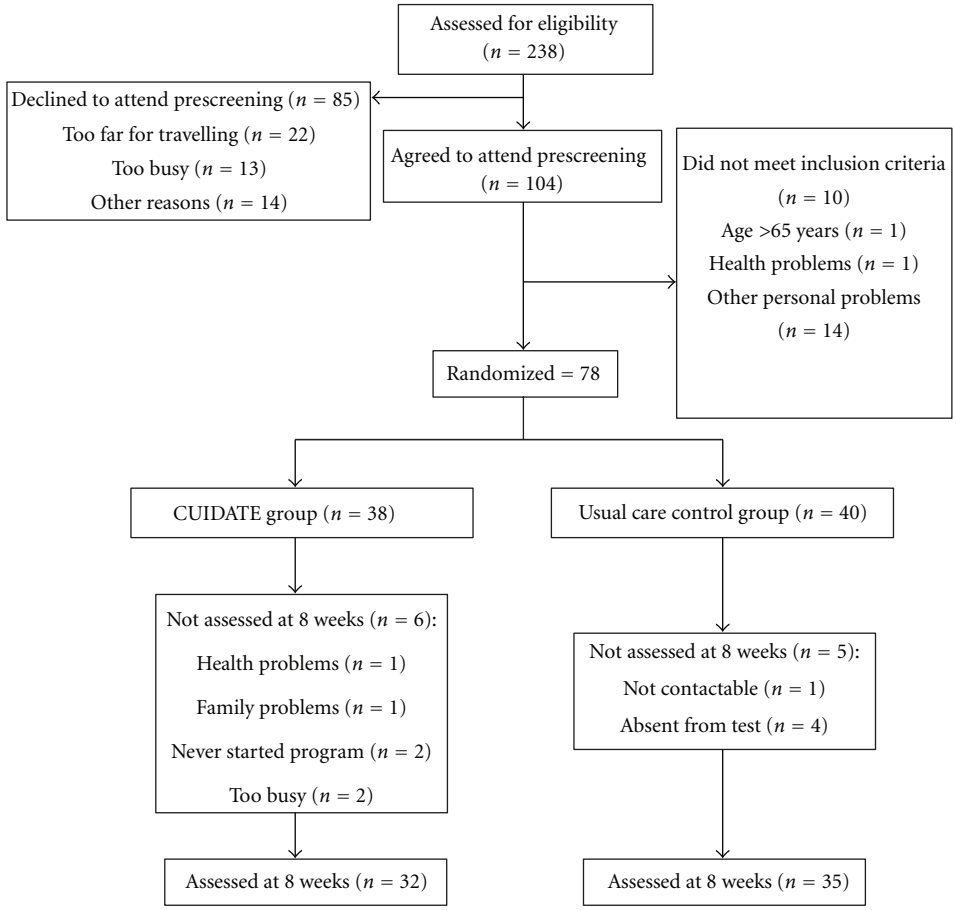


Figure 1: Flow diagram of subject recruitment and retention throughout the course of the study.

changes in mood state (mean differences) and in strength in the multimodal exercise group. A $P < 0.05$ was considered statistically significant.

3. Results

During the study period (from March 2009 to June 2010), 104 patients with cancer were agreed to attend prescreening (Figure 1). No differences in sociodemographic and medical features between the 78 patients (75%) included and the 26 patients (25%) who were excluded or declined to participate were found (Table 2). Participants who completed the study did not show differences in mood at baseline as compared to those who dropped out. The ANOVA revealed that patients in both groups had significantly disturbances of mood state in all subscales of the POMS as compared to healthy women (Table 3).

Patients who finished cancer treatment within the first 6 months before begining the multimodal exercise program completed 79.6% of the 24 physical therapy sessions (mean ± SD: 19 ± 5) whereas patients incorporated >6 months after finishing cancer treatment completed 87.4% of the 24 sessions (mean: 21 ± 6). No adverse effect was reported during the study.

The ANCOVA found significant group × time interaction for the main outcome of the study, fatigue ($F = 4.506$; $P = 0.015$): the multimodal exercise group experienced a greater decrease of fatigue than the control group (Table 4). Intergroup effect sizes were moderate at postintervention (d: 0.52, 95% CI 0.14–0.81) and small at 6-month followup (d: 0.38, 95% CI 0.05–0.66).

Additionally, significant group × time interactions for the remaining domains of the POMS were also found: tension-anxiety ($F = 5.918$, $P = 0.005$); depression-dejection ($F = 5.214$, $P = 0.01$); anger-hostility ($F = 5.082$, $P = 0.010$); vigor ($F = 6.090$, $P = 0.004$), and also for total mood disturbance ($F = 3.512$, $P = 0.037$): the multimodal exercise group experienced a greater decrease of tension-anxiety, depression-dejection, or anger-hostility and a greater increase of vigor compared to the control group (Table 4). Intergroup effect sizes were large for both tension-anxiety (d: 1.05, 95% CI 0.54–1.55) and depression-dejection (d: 0.80, 95% CI 0.29–1.30) domains, and small for total mood disturbance (d: 0.40, 95% CI 0.16–0.65), anger-hostility (d: 0.40, 95% CI 0.16–0.63), and vigor (d: 0.35, 95% CI 0.18–0.67) domains after treatment. Intergroup effect sizes after 6-month followup were moderate for tension-anxiety (d: 0.76, 95% CI 0.20–1.31) and depression-dejection (d: 0.74, 95% CI 0.25–1.35), and small for anger-hostility

Table 2: Patient's characteristics and comparisons between both breast cancer survivor groups.

Variable	Control Group ($n = 35$)	CUIDATE program ($n = 32$)	P value
Age (y), mean (SD)	48 (9)	49 (9)	0.415
Time after treatment, n (%)			
<12 months	29 (82.9)	22 (68.8)	0.176
>12 months	6 (17.1)	10 (31.3)	
Civil status, n (%)			
Married	21 (60.0)	20 (62.5)	0.718
Unmarried	8 (22.9)	5 (15.6)	
Divorced	6 (17.1)	7 (21.9)	
Educational level, n (%)			
Low	13 (37.1)	11 (34.4)	0.481
Medium	6 (17.1)	8 (25.0)	
University level	16 (45.7)	13 (40.6)	
Employment status, n (%)			
Home employed	8 (22.9)	7 (21.9)	0.586
Employed	14 (40.0)	10 (31.3)	
Un employed	13 (37.1)	15 (46.9)	
Tumor stage, n (%)			
I	12 (34.3)	4 (12.5)	0.145
II	16 (45.7)	23 (71.9)	
IIIA	7 (20.0)	5 (15.6)	
Type of surgery, n (%)			
Tumorectomy	21 (60.0)	21 (65.6)	0.596
Mastectomy	14 (40.0)	11 (34.4)	
Type of treatment n (%)			
Radiation	1 (2.9)	1 (3.1)	0.991
Chemotherapy	3 (8.6)	3 (9.4)	
Radiation + chemotherapy	31 (88.6)	28 (87.5)	
Menopause, n (%)			
Yes	20 (57.1)	24 (75.0)	0.197
Not	15 (42.9)	8 (25.0)	
Physical activity (METS/h*day)	7.94 (3.37)	8.63 (3.85)	0.364

* P values for comparisons among group based on Chi-square and analysis of variance tests.

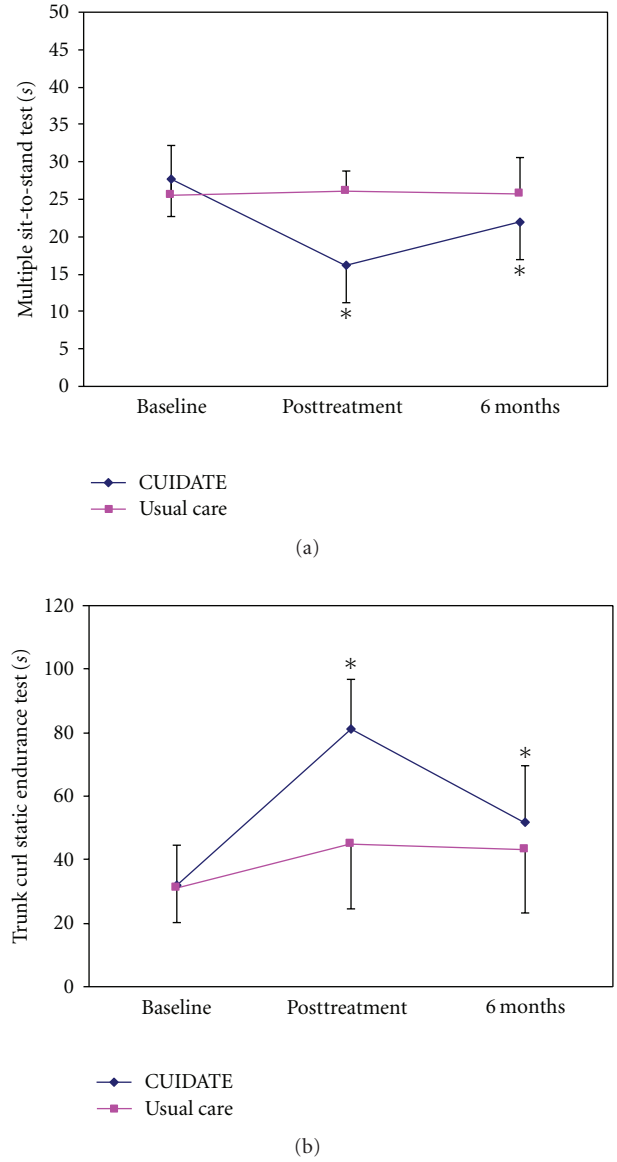


Figure 2: Multiple sit-to-stand test (s) and trunk curl static endurance test (s) changes after postintervention and 6 months followup, * significant changes respect baseline ($P < 0.05$).

(d: 0.39, 95% CI 0.12–0.67), vigor (d: 0.41 95% CI 0.16–0.69) and total mood disturbance (d: 0.32 95% CI 0.05–0.60). No group × time interaction for confusion was found ($F = 0.831$; $P = 0.442$).

A significant group × time interaction for multiple sit-to-stand test ($F = 11.315$; $P < 0.001$) and trunk curl static endurance test ($F = 6.916$; $P = 0.002$) was also found (Figure 2). Intergroup effect sizes were large for multiple sit-to-stand test (d: 0.96, 95% CI 0.71–1.20) and trunk curl static endurance test (d: 0.89, 95% CI 0.71–1.19) at postintervention, but moderate (multiple sit-to-stand test, 0.50 95% CI 0.27–0.90) and small (trunk curl static endurance test, 0.21 95% CI 0.20–0.47) at 6 month followup.

A significant negative association ($r = -0.352$; $P = 0.046$) between changes in the total mood state and in the trunk curl static endurance test was found: the greater the decrease in mood, the higher the increase in muscle strength.

4. Discussion

The current study found that an 8-week supervised multimodal program induced physical and psychological improvements in BCS. We noted a greater decrease on fatigue as compared to usual breast cancer care. The effects over fatigue were maintained at 6 months after discharge using DVD support. We also observed significant effects on other aspects of mood and physical capacity.

Table 3: Comparison of Profile of Mood State (POMS) data among healthy reference women and breast cancer survivors at baseline.

POMS	Healthy women ($n = 43$)	CUIDATE program ($n = 32$)	CONTROL group ($n = 35$)	P CUIDATE versus control
Tension-anxiety[a]	37.93 ± 8.71	49.00 ± 10.44	50.14 ± 10.18	0.65
Depression-dejection[a]	42.56 ± 7.14	52.39 ± 12.14	52.42 ± 11.01	0.99
Anger-hostility[a]	46.66 ± 6.89	55.17 ± 11.99	57.03 ± 14.12	0.53
Vigor[a]	57.43 ± 6.61	48.17 ± 7.08	49.19 ± 6.47	0.52
Fatigue[a]	39.90 ± 5.61	51.48 ± 10.85	54.19 ± 10.09	0.24
Confusion[a]	32.86 ± 4.53	42.35 ± 9.68	44.30 ± 9.70	0.53
Disturbance[a]	−14223 ± 2743	−19942.85 ± 5901.69	−20845.15 ± 5299.82	0.61

[a] $P < 0.001$ for ANOVA analysis among breast cancer survivors at baseline and healthy women.

The effect size of the improvement in fatigue (0.52) suggests a medium clinically important change. Our results are relatively better from the findings of a recent meta-analysis which indicates that the magnitude of the effects from exercise interventions on CRS is small (effect size 0.31, 95% CI 0.22–0.40) [3]. Our study used similar length of treatment (8 weeks) than previous studies investigating exercise in CRF [3, 19, 20], but we extended postural control by including CSEs and combined movement on extremities which could explain our results. The results of the current study also showed that BCS within the first year after treatment exhibit more disturbances of mood state and fatigue than healthy women. At postintervention, mood disturbance improved in BCS within the multimodal program, reaching similar values to healthy women. On the contrary, BCS included in the control group continued exhibiting altered mood state as compared to healthy women.

The POMS has been previously used to assess disturbance of mood state in oncology exercises studies [3]. Current results on mood state confirm the results from a previous pilot study using a similar exercise approach [21], since we found moderate-large effect sizes on several aspects of mood after the application of the multimodal program. Multimodal programs can help to BCS for coping with their cancer-related symptoms. Previous studies have suggested the necessity to apply interventions to better assist BCS for managing cancer related fatigue [19]. The multimodal program had a higher ratio of supervision with 2–4 therapists for 6–8 patients (ratio therapist/patient: 1/3–4). Only 60% of the exercise programs applied to reduce cancer related fatigue had employed therapist supervision [3], and the higher ratio therapist/patient of the multimodal program can promote social and environmental support, and satisfaction to the patients, both aspects which improve the mood state of BCS [22].

We also found significant and clinical improvement in muscle strength, which is consistent with recent studies on exercise [19, 20]. Current exercise guidelines for cancer apply minimal mention to muscle strength in BCS [23]. Our results suggest the necessity of including strength exercises in physical therapy programs for BCS. This may be related to the fact that cancer treatment, particularly chemotherapy, promotes disruption in muscle metabolism (i.e., adenosine triphosphate dysregulation, cytokine dysregulation, deprivation of satellite cells) wasting which may impair the maintenance of muscle mass [24]. CSEs were a major component of our program. Effectiveness of CSEs has been associated with modification of plasma levels of IL-6 and TNF-α by contraction of different muscles [25]. Interestingly, the current multimodal program produced large effect sizes in core-related muscles (trunk curl static endurance test) and also in nonrelated core muscles (leg muscles). These results may be explained because one of the principles of CSE is their ability to proximal muscle activation, providing interactive moments that would allow efficient distal muscle function [6]. Therefore, CSEs employed in our study may be also used for improving function of distal musculature through proximal (core-related) muscles.

One interesting result of our study was the relationship between the decrease in mood disturbance and the increase in strength of abdominal muscles. Cancer related fatigue constitutes a complex process involving both physical and psychosocial aspects [26]. Cancer patients who engage in negative beliefs about their cancer related symptoms (i.e., catastrophizing, fear of recurrence) are more likely to experience more intense symptoms [27]. It is possible that treatment programs combining preferred women's exercises [24] and recovery massage following an integrative oncology approach have a relevant role in mood improvement associated to increased functional state, as reflected in an increase of strength.

One of the most important results of this trial is the maintained effects in mood and strength, although slightly reduced, after 6-month followup using a DVD support. This kind of strategy based on multimedia supporting promote exercise in BCS had shown good results in previous studies [28]. A mixed intervention, including an initial supervised phase focussed on proper learning of the exercise program, promotes high improvements in BCS. Nevertheless, after the program, DVD support is needed for maintaining the improvements during the treatment. Future studies investigating effects of supervised programs with a follow-up period based on telerehabilitation are needed.

Strengths of the current trial include supervised and structured exercise program, multimodal cancer approach, use of validated objective measurements and a validated questionnaire, and intention-to-treat analyses; however, we should recognize that the control group was allowed to freely

Table 4: Preintervention, postintervention, and change scores for mean values of POMS.

Group	CUIDATE program	Control	Between-group differences
	Tension-anxiety		
Preintervention	49.00 ± 10.44	50.14 ± 10.18	
Postintervention	39.33 ± 8.08	49.80 ± 10.32	
6 months followup	43.53 ± 9.62	51.12 ± 11.08	
Within group change scores			
Pre-post intervention	−9.66 (−13.45; −5.83)	−0.34 (−2.95; 2.26)	−9.32 (−13.79; −4.85)*
Pre intervention–6 months follow up	−5.89 (−2.53; −9.54)	−0.28 (−2.76; 6.26)	−6.17 (−1.71; −10.63)
	Depression-dejection		
Preintervention	52.39 ± 12.14	52.42 ± 11.01	
Postintervention	47.15 ± 9.34	52.40 ± 10.91	
6 months followup	48.17 ± 8.94	55.30 ± 12.12	
Within group change scores			
Pre-post intervention	−7.36 (−11.15; −3.57)	−0.02 (−2.84; 2.79)	−7.33 (−11.93; −2.73)*
Pre intervention–6 months follow up	−4.22 (−8.62; −0.87)	2.88 (0.73; 6.50)	−7.00 (−12.64; −0.77)
	Anger-hostility		
Preintervention	55.17 ± 11.99	57.03 ± 14.12	
Postintervention	46.82 ± 9.14	58.34 ± 11.65	
6 months followup	49.25 ± 8.07	58.76 ± 13.17	
Within group change scores			
Pre-post intervention	−7.87 (−12.16; −3.59)	1.31 (−2.05; 4.04)	−9.19 (−14.20; −3.65)*
Pre intervention–6 months follow up	−5.92 (−10.13; −1.72)	1.73 (−1.59; 5.06)	−7.65 (−12.95; −2.36)
	Vigor		
Preintervention	48.17 ± 7.08	49.19 ± 6.47	
Postintervention	53.46 ± 8.02	49.29 ± 7.31	
6 months followup	53.17 ± 8.41	48.00 ± 6.98	
Within group change scores			
Pre-post intervention	5.29 (3.40; 8.29)	0.17 (−2.57; 2.22)	5.12 (2.65; 9.38)*
Pre intervention–6 months follow up	5.00 (2.16; 7.83)	−1.19 (−3.94; 1.56)	6.19 (2.30; 10.06)
	Fatigue		
Preintervention	51.58 ± 10.85	54.19 ± 10.09	
Postintervention	43.93 ± 8.58	52.26 ± 10.09	
6 months followup	45.12 ± 10.31	53.34 ± 9.36	
Within group change scores			
Pre-post intervention	−8.03 (−11.19; −4.86)	−1.93 (−5.06; 0.20)	−6.10 (−9.12; −1.07)*
Pre intervention–6 months followup	−6.45 (−9.50; −3.39)	−0.84 (−3.44; −1.74)	−5.61 (−8.56; −0.35)
	Confusion		
Preintervention	42.35 ± 9.68	44.30 ± 9.70	
Postintervention	37.67 ± 7.08	42.90 ± 8.82	
6 months followup	39.85 ± 9.48	43.70 ± 9.44	
Within group change scores			
Pre-post intervention	−4.68 (−7.71; −1.55)	−1.40 (−4.55; 1.11)	−3.28 (−7.05; 1.22)
Pre intervention–6 months follow up	−2.50 (−5.36; 0.36)	−0.60 (−4.39; 3.19)	−2.91 (−6.42; 2.62)
	Total disturbance mood		
Preintervention	−19942.85 ± 5901.69	−20845.15 ± 5299.82	
Postintervention	−16000.00 ± 3532.28	−20353.84 ± 5888.03	
6 months followup	−17257.14 ± 4528.05	−20884.61 ± 6171.78	
Within group change scores			
Pre-post intervention	3442.85 (1623.71; 5353.11)	491.31 (−905.90; 1608.76)	2951.54 (754.29; 5124.67)*
Pre intervention–6 months follow up	2685.71 (986.08; 4835.34)	38.46 (−1553.29; 1630.21)	2647.25 (454.29; 4854.29)

* Significant group × time interaction (Repeated ANOVA test, $P < 0.05$).

increase physical activity during the study. The possible bias [3] associated to this weakness was controlled since our control group did not show significant increases in physical activity during the study.

5. Conclusions

In conclusion, an 8-week multimodal physical therapy program using CSE and massage recovery was clinically effective for improving physical (muscle strength) and psychological (mood state and fatigue) aspects in BCS as compared to usual treatment care.

Funding

The authors certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated with and, if applicable, the authors certify that all financial and material support for this paper (e.g., NIH or NHS grants) and work are clearly identified in the Acknowledgments section of the paper.

Acknowledgments

The paper was funded by a Research Project Grant (FIS ETES-PI0890418 and 10/02749) from the Health Institute Carlos III and PN I+D+I 2008–2011, Madrid, Spanish Government and a Grant of Andalusian Health Service, Junta de Andalucia (PI-0457-2010).

References

[1] L. S. Gilchrist, M. L. Galantino, M. Wampler, V. G. Marchese, G. S. Morris, and K. K. Ness, "A framework for assessment in oncology rehabilitation," *Physical Therapy*, vol. 89, no. 3, pp. 286–306, 2009.

[2] C. M. Donnelly, A. Lowe-Strong, J. P. Rankin, A. Campbell, J. M. Allen, and J. H. Gracey, "Physiotherapy management of cancer-related fatigue: a survey of UK current practice," *Supportive Care in Cancer*, vol. 18, no. 7, pp. 817–825, 2010.

[3] J. C. Brown, T. B. Huedo-Medina, L. S. Pescatello, S. M. Pescatello, R. A. Ferrer, and B. T. Johnson, "Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis," *Cancer Epidemiology, Biomarkers and Prevention*, vol. 20, pp. 123–133, 2011.

[4] K. H. Schmitz, K. S. Courneya, C. Matthews et al., "American college of sports medicine roundtable on exercise guidelines for cancer survivors," *Medicine and Science in Sports and Exercise*, vol. 42, no. 7, pp. 1409–1426, 2010.

[5] L. Adamsen, M. Quist, C. Andersen et al., "Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial," *The British Medical Journal*, vol. 13, no. 339, p. b3410, 2009.

[6] J. E. Bower, D. Garet, and B. Sternlieb, "Yoga for persistent fatigue in breast cancer survivors: results of a pilot study," *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 623168, 8 pages, 2011.

[7] W. B. Kibler, J. Press, and A. Sciascia, "The role of core stability in athletic function," *Sports Medicine*, vol. 36, no. 3, pp. 189–198, 2006.

[8] K. M. Winters-Stone, J. A. Bennett, L. Nail, and A. Schwartz, "Strength, physical activity, and age predict fatigue in older breast cancer survivors," *Oncology Nursing Forum*, vol. 35, no. 5, pp. 815–821, 2008.

[9] J. E. Bower, "Behavioral symptoms in patients with breast cancer and survivors," *Journal of Clinical Oncology*, vol. 26, no. 5, pp. 768–777, 2008.

[10] J. Imanishi, H. Kuriyama, I. Shigemori et al., "Anxiolytic effect of aromatherapy massage in patients with breast cancer," *Evidence-Based Complementary and Alternative Medicine*, vol. 6, no. 1, pp. 123–128, 2009.

[11] C. A. Moyer, J. Rounds, and J. W. Hannum, "A meta-analysis of massage therapy research," *Psychological Bulletin*, vol. 130, no. 1, pp. 3–18, 2004.

[12] M. Arroyo-Morales, N. Olea, M. M. Martínez, A. Hidalgo-Lozano, C. Ruiz-Rodríguez, and L. Díaz-Rodríguez, "Psychophysiological effects of massage-myofascial release after exercise: a randomized sham-control study," *Journal of Alternative and Complementary Medicine*, vol. 14, no. 10, pp. 1223–1229, 2008.

[13] M. E. Nelson, W. J. Rejeski, S. N. Blair et al., "Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association," *Medicine and Science in Sports and Exercise*, vol. 39, no. 8, pp. 1435–1445, 2007.

[14] R. Elosua, M. Garcia, A. Aguilar, L. Molina, M. I. Covas, and J. Marrugat, "Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish Women. Investigators of the MARATDON Group," *Medicine and Science in Sports and Exercise*, vol. 32, no. 8, pp. 1431–1437, 2000.

[15] E. M. Andrade, C. Arce, and G. Seoane, "Adaptación al español del cuestionario Perfil de los Estados de Ánimo en una muestra de deportistas," *Psicothema*, vol. 14, no. 4, pp. 708–713, 2002.

[16] S. M. McGill, A. Childs, and C. Liebenson, "Endurance times for low back stabilization exercises: clinical targets for testing and training from a normal database," *Archives of Physical Medicine and Rehabilitation*, vol. 80, no. 8, pp. 941–944, 1999.

[17] Y. Netz, M. Ayalon, A. Dunsky, and N. Alexander, "The multiple-sit-to-stand field test for older adults: what does it measure?" *Gerontology*, vol. 50, no. 3, pp. 121–126, 2004.

[18] C. Ritchie, S. G. Trost, W. Brown, and C. Armit, "Reliability and validity of physical fitness field tests for adults aged 55 to 70 years," *Journal of Science and Medicine in Sport*, vol. 8, no. 1, pp. 61–70, 2005.

[19] M. J. Velthuis, S. C. Agasi-Idenburg, G. Aufdemkampe, and H. M. Wittink, "The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomised controlled trials," *Clinical Oncology*, vol. 22, no. 3, pp. 208–221, 2010.

[20] R. M. Speck, K. S. Courneya, L. C. Mâsse, S. Duval, and K. H. Schmitz, "An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis," *Journal of Cancer Survivorship*, vol. 4, no. 2, pp. 87–100, 2010.

[21] K. S. Keays, S. R. Harris, J. M. Lucyshyn, and D. L. MacIntyre, "Effects of pilates exercises on shoulder range of motion, pain, mood, and upper-extremity function in women living with breast cancer: a pilot study," *Physical Therapy*, vol. 88, no. 4, pp. 494–510, 2008.

[22] A. Talley, L. Molix, R. J. Schlegel, and A. Bettencourt, "The influence of breast cancer survivors perceived partner social

support and need satisfaction on depressive symptoms: a longitudinal analysis," *Psychology and Health*, vol. 25, no. 4, pp. 433–449, 2010.

[23] National Comprehensive Cancer Network (NCCN), *Clinical Practice Guidelines in Oncology: Cancer Related-Fatigue*, National Comprehensive Cancer Network, Fort Washington, Pa, USA, 2009.

[24] P. M. Clarkson and S. A. Kaufman, "Should resistance exercise be recommended during breast cancer treatment?" *Medical Hypotheses*, vol. 75, no. 2, pp. 192–195, 2010.

[25] N. Drela, E. Kozdron, and P. Szczypiorski, "Moderate exercise may attenuate some aspects of immunosenescence," *BMC Geriatrics*, vol. 29, pp. 4–8, 2004.

[26] I. Cantarero-Villanueva, C. Férnandez-Lao, C. Fernández-DE-Las-Peñas, L. Díaz-Rodríguez, E. Sanchez-Cantalejo, and M. Arroyo-Morales, "Associations among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment," *The European Journal of Cancer Care*. In press.

[27] C. Zaza and N. Baine, "Cancer pain and psychosocial factors: a critical review of the literature," *Journal of Pain and Symptom Management*, vol. 24, no. 5, pp. 526–542, 2002.

[28] T. P. Haines, P. Sinnamon, N. G. Wetzig et al., "Multimodal exercise improves quality of life of women being treated for breast cancer, but at what cost? Randomized trial with economic evaluation," *Breast Cancer Research and Treatment*, vol. 124, no. 1, pp. 163–175, 2010.