

Original Article

Adaptogenic Potential of a Polyherbal Natural Health Product: Report on a Longitudinal Clinical Trial

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Stress is a risk factor for a number of diseases and is an important predictor of health in general. Herbal medicines have been used as adaptogens to regulate and improve the stress response and there is evidence to support the use of herbal medicines for this purpose. We conducted an open-label longitudinal study on the natural health product, OCTA®, a compound mixture of eight herbs, to determine its effects on perceptions of stress. Eighteen participants were enrolled in the study and were followed over a period of 3 months. Primary endpoints included scores from four validated questionnaires (SF-36v2, PSS, STAI and BDI-II), serum DHEA, ALT, AST and creatinine all measured at 12 weeks. Seventeen patients completed the study. Except for the physical summary score of the SF36 questionnaire, all the subjective scores indicated a highly significant ($P < 0.0001$) improvement in the participants' ability to cope with stress. No adverse effects were reported and there was no evidence of damage to the liver or kidney based on serum markers. Initial evidence for this polyherbal compound supports its potential as an effective 'adaptogenic' aid in dealing with stress. Further research using a randomized controlled design is necessary to confirm the findings from this pilot study.

Keywords: adaptogen – CAM – clinical trial – complementary and alternative medicine – herbal medicine – stress

Introduction

Stress is an extremely broad term that serves to define a wide variety of phenomena that humans are exposed to throughout their lives. The facets of stress are essentially limitless; however, broad categories include physical exertion, emotional upset, persistent psychological pressure, existential crisis and the residual effects of emotional trauma. The 1993 World Labour Report by the UN's International Labour Organization claimed that stress had become one of the most serious health issues of the 20th century (1). Stress and its resultant comorbidity are responsible for a large proportion of disability worldwide. It has consistently been shown that individuals experiencing stress have impaired physical and mental functioning; more workdays lost, impairment at work and increased use of healthcare services. The disability caused

by stress is just as great as the disability caused by workplace accidents or other common medical conditions such as hypertension, diabetes and arthritis (2). The World Health Organization (WHO) Global Burden of Disease Survey estimates that mental disease, including stress-related disorders, will be the second leading cause of disability by the year 2020 (3).

Since the characterization of the generalized adaptation syndrome (GAS) by Hans Selye, the issue of stress has come to be viewed as a risk factor in both the etiology and progression of a wide variety of diseases. Chronic and post-traumatic stress has been implicated in cardiovascular disease (4–6), gastrointestinal ulceration (7), inflammatory bowel disease (7), depression (8,9), anxiety (9), fibromyalgia (10), autoimmune disease (11) and schizophrenia (12). In addition, chronic stress clearly demonstrates the ability to negatively impact immune system function and can predispose a person toward infection (13–15). Evidence also demonstrates that stress very early in life, i.e. within the first few years of childhood, may be an etiological agent for the development of type 1 diabetes (16) and also potentially in the development and severity of asthma (17).

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Normally the stress response is activated on an acute basis and the body is able to return to normal parasympathetic homeostasis. Stress becomes pathologic, however, when it is chronic or when the body acquires an inherent tendency towards activation of the sympathetic nervous system (15,18). Current therapies for dealing with 'stress' are extensive but perhaps not ideally targeted in most cases. Pharmacological approaches are principally focused on the treatment of depression and the manifestations of both acute and chronic anxiety disorders (19).

A potentially beneficial use of herbal medicine involves the use of herbs as 'adaptogens' in order to prevent stress-induced morbidity. From an herbalist's perspective, the therapeutic intent of an adaptogen is to promote an optimal physiological response to both internal and external stresses. Essentially the adaptogen supports the body's ability to 'adapt' ideally to its environment. These herbs are believed to have a bimodal function of action either by providing a stimulant effect or a sedative effect depending on the needs of the individual in a particular situation. Common examples of adaptogens include Asian ginseng (*L. Panax ginseng*), Siberian ginseng (*Eleutherococcus senticosus*), Ashwagandha root (*Withania somnifera*) and rhodiola (*L. Rhodiola rosea*) (20). Herbs are not the only potential adaptogens as other agents like vitamins and even amino acids have also exhibited this kind of activity (21).

In the 1950s, Russian scientists set out specific criteria that an herb had to incorporate in order to be considered an adaptogen. The criteria were that the herb must (i) only cause minimal disorders in physiological function; (ii) must increase resistance to external and internal stresses through a wide range of physical, chemical, and biochemical factors; and (iii) must have a normalizing effect, improving all types of conditions while aggravating none (22,23). Specific examples of how adaptogens have been taken to improve health include their usage to: reduce fatigue, regain or improve athletic performance, regain or improve mental acuity, increase appetite, relieve insomnia, improve mood and increase resistance against infection (15,23,24). For an intriguing discussion on how adaptogens may impact health, the reader is referred to a series of articles published by Olalde Rangel *et al.* in 2005 (25–28).

Relatively little clinical research has been conducted on the use of herbal adaptogens for stress, and still less on combinations of herbal medications. In this paper, we report on the results of an open-label uncontrolled longitudinal trial on the use of a proprietary herbal compound mixture, OCTA©, on subjective parameters of stress as well as objective measures.

Methods

Design and Participants

We conducted an open-label and uncontrolled clinical trial to evaluate the impact of OCTA© on known parameters of stress. We enrolled 18 participants between the ages of 21 and 58 years old (mean 39.5 years) with a relatively even sex

distribution (8 males and 10 females). Self-reported stress levels at enrollment were initially evaluated using the Perceived Stress Level test. For inclusion, participants had to have experienced one or more illnesses potentially related to stress including anxiety, arthritis, chronic pain, depression, diabetes, eczema, headaches, heart attacks, heart disease, impotence, decreased libido, high blood pressure or peptic ulceration. Participants were excluded from enrollment if they were under 18 years old, were pregnant, planning to become pregnant or were taking any of the following medications: glucocorticoids, androgens, birth control pills, anti-seizure drugs, diuretics, barbiturates, sedatives or anxiolytics.

Participants were recruited through newspaper and radio advertisements run for a period of 2 weeks. The message conveyed was that we were looking for individuals adversely affected by stress. As compensation for their involvement, participants were offered a \$50 gift certificate and a free nutritional consultation at the completion of the study. Participants were not required to be actively seeking treatment. Interested participants contacted the study coordinator (R.S.) and attended an information session that detailed the protocol. The timing, severity and history of the participants' complaints were not assessed. Only subjective questionnaires were used to measure changes in outcome but not with respect to the particular complaint or chief concern of the participants but rather to measure overall changes in quality of life.

We conducted a physical examination to rule out underlying pathology. Participants were advised to exclude any supplements designed to mitigate the effects of stress including any natural health products that weren't taken for general health. The only supplements consumed by any of the participants included multivitamins, flax oil and vitamin C. The participants were advised to continue their lifestyle, maintain their normal diet and vitamin consumption and change nothing except for the addition of the OCTA©. Participants were followed over a 3 month period and asked to come in for assessment at predefined time points including at baseline, 2 weeks, 4 weeks, 8 weeks, and 12 weeks. At each time point, the participants were administered self-reported standardized questionnaires, had their blood pressure monitored and had blood samples taken for specific laboratory tests. To be enrolled, participants had to sign an informed consent form and be assessed by a physician. Participants were permitted to ask questions at any time during the study.

Intervention

Participants were provided with the proprietary herbal compound OCTA©, an aqueous-based liquid herbal preparation consisting of eight herbs as follows: *W. somnifera*, *Lagerstroemia speciosa*, *Bacopa monniera*, *Zizyphus jujuba*, *Morinda citrifolia*, *Punica granatum*, *Shisandrae chinensis* and *Lycium barbarum* (listed in descending order according to respective concentrations). Participants were instructed to consume two tablespoons (30 ml) of the herbal compound per day each morning for a total period of 3 months.

The product has been through quality control testing and has demonstrated consistent concentrations of the herbal extracts. The two main ingredients are derived from standardized extracts (*W. somnifera*: 2.5% with anolides; and *L. speciosa*: 1% corosolic acid). OCTA© has been under review by Health Canada's Natural Health Products Directorate (NHPD) since 2004 but due to a backlog of requests has yet to be processed. The manufacturer adheres to GMP standards and is certified by Australia's Therapeutics Goods Administration (TGA), the Department of Health of the State of New Jersey, and has received an 'A' rating from the National Nutritional Foods Association (NNFA).

Outcome Measures

Study endpoints assessed and analyzed for each of the participants consisted of both objective and subjective measures. Aside from serum dehydroepiandrosterone (DHEA), the objective measures were not primary outcomes but were included in order to assess for patient safety and the potential for liver or kidney toxicity. Secondary objective measures included blood pressure, cholesterol levels, aspartate transaminase (AST), alanine transaminase (ALT) and urinary creatinine. Primary outcome measures consisted of subjective scores from four self-reported questionnaires including the perceived stress scale, the state/trait anxiety scale, the beck depression index and the SF36 Health Survey (Version 2) questionnaire. These questionnaires, described briefly below, were chosen because they have been validated and are widely accepted amongst healthcare professionals.

The SF36 Health Survey (SF-36v2) questionnaire is one of the most extensively used and validated quality of life measures. It is a self-administered, 36-item questionnaire that measures health-related quality of life in 8 domains that consist of both physical and mental-related issues. The physical and mental scores can be summarily added in order to obtain overall summaries of each of these two distinct areas. The reliability of the test is well documented with a Cronbach's alpha value greater than 0.85 (29).

The Perceived Stress Scale (PSS) is the most widely used psychological instrument for measuring the perception of stress. It is a self-reported, uni-dimensional instrument developed to measure a perceived stress in a person's life. It is a measure of the degree to which situations in one's life are appraised as stressful. The scale also includes a number of direct queries about current levels of experienced stress. Moreover, the questions are of a general nature and hence are relatively free of content specific to any subpopulation group.

The State-Trait Anxiety Inventory (STAI) was initially conceptualized as a research instrument for the study of anxiety in adults. It is a self-reported assessment device that includes separate measures of state and trait anxiety. According to the author of this tool, state anxiety reflects a 'transitory emotional state or condition of the human organism that is characterized by subjective, consciously perceived feelings of

tension and apprehension, and heightened autonomic nervous system activity'. State anxiety may fluctuate over time and can vary in intensity. In contrast, trait anxiety denotes 'relatively stable individual differences in anxiety proneness...' and refers to a general tendency to respond with anxiety to perceived threats in the environment (30).

The Beck Depression Inventory Second Edition (BDI-II) is a 21-item self-reporting instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV; 1994). This new revised edition replaces the BDI and the BDI-1A, and includes items intending to index symptoms of severe depression, which would require hospitalization. Items have been changed to indicate increases or decreases in sleep and appetite, items labeled body image, work difficulty, weight loss and somatic preoccupation were replaced with items labeled as agitation, concentration difficulty and loss of energy. Many statements were reworded resulting in a substantial revision of the original BDI and BDI-1A. When presented with the BDI-II, a patient is asked to consider each statement as it relates to the way they have felt for the past 2 weeks, to more accurately correspond to the DSM-IV criteria.

Statistical Analyses

Results were analyzed using one-way ANOVA. Scores for each test as well as the objective samples were independently assessed and only in the case of the SF-36v2 was the test divided into physical and psychological summary categories.

Results

We enrolled 18 participants for the 12 week period. Seventeen participants completed the trial. One participant withdrew due to scheduling conflicts. Table 1 displays the overall effects of OCTA© on primary subjective outcomes. Table 2 reports results from the SF-36v2 Quality of Life results in all eight domains. Table 3 displays selected objective outcome measures including serum DHEA levels, urinary creatinine and levels of the liver enzymes AST and ALT. No significant changes in blood pressure and cholesterol were observed in any of the participants (data not shown). None of the participants reported self-perceived adverse events, nor were any observed by the monitoring physician.

For our primary outcomes, we observed a 46% improvement in self-perceived stress. The state and trait anxiety scale reported overall changes from baseline of 40 and 26%, respectively. The Beck Depression Index improved by 67%. For the SF-36 questionnaire, the mental summary score improved by 72%. Each of these results was statistically significant with P -values all <0.0001 . The physical summary of the SF-36 demonstrated a modest improvement of 9%; however, this was not statistically significant ($P = 0.228$). ANOVA of serum DHEA demonstrated no change from baseline ($P = 0.98$).

Table 1. Subjective score summaries of the self-reported questionnaires

	Perceived stress scale	State anxiety scale	Trait anxiety scale	Beck depression scale	SF-36 physical summary	SF-36 mental summary
Initial	25.11	53.44	53.33	23.94	46.75	27.57
Week 2	20.29	44.65	50.18	16.65	50.29	34.25
Week 4	18.25	40.69	45.25	12.38	49.10	39.56
Week 8	15.88	35.94	42.82	10.35	51.84	41.78
Week 12	13.53	32.24	39.71	7.82	51.09	47.50
Change	11.58	21.21	13.63	16.12	4.35	19.92
% Change	46.12	39.68	25.55	67.33	9.30	72.25
F-value	10.95	10.67	7.09	9.33	1.44	11.51
P-value	<0.0001	<0.0001	<0.0001	<0.0001	0.23	<0.0001

Table 2. SF-36v2 Quality of life results: individual categories

	Physical function	Physical limitation	Body pain	General health	Vitality	Social function	Emotional limitation	Mental health
Initial	47.09	36.99	41.15	41.07	35.09	32.91	28.88	32.64
Week 2	48.86	43.02	46.33	44.94	43.64	38.88	34.16	37.75
Week 4	48.09	43.54	47.56	45.81	45.26	43.56	37.41	42.44
Week 8	51.59	45.90	50.11	49.23	47.50	44.34	40.79	45.37
Week 12	51.71	47.92	49.59	51.28	50.62	47.87	46.96	48.68
Change	4.61	10.93	8.44	10.21	15.53	14.95	18.08	16.04
% Change	9.80	29.56	20.50	24.86	44.25	45.44	62.58	49.14

Table 3. Objective measures including toxicity data

	Serum DHEA ($\mu\text{mol l}^{-1}$)	Aspartate transaminase (U l^{-1})	Alanine transaminase (U l^{-1})	Urinary creatinine ($\mu\text{mol l}^{-1}$)
Initial	4.12	21.50	20.50	11.84
Week 2	4.64	23.00	21.56	10.68
Week 4	4.20	22.44	20.79	11.46
Week 8	4.32	22.47	21.12	10.55
Week 12	4.65	21.88	20.24	11.27
Change	0.54	0.38	-0.26	-0.58
%	13.03	1.78	-1.29	-4.86
F-value	0.118	0.155	0.087	0.254
P-value	0.97	0.96	0.99	0.91

Discussion

The findings of this trial should be of interest to physicians and patients alike. We found an overall improvement in perceptions of stress and quality of life due to changes associated with stress as monitored by valid stress and quality of life markers.

Limitations

There are several limitations to consider in our trial. As this is a pilot trial, we did not use a randomized controlled

design, thus limiting the strength of inference. Additionally, we cannot determine the extent of any potential changes, benefit or harm, to internal organs apart from liver and renal function. It is also quite possible that even though acute adverse effects were not witnessed over the 3 month trial, a longer time period of consumption might lead to unforeseen side effects and possible organ toxicity.

Strengths

Several important strengths to this study deserve mention. Primarily, this trial is the first to assess this herbal combination on stress levels in a clinical setting. In addition, we used well-validated self-reporting tools and tested over an extended period of time. The participants were monitored for adverse effects and compliance through oral reporting and the use of a daily journal. Compliance as indicated by dosing times recorded in the journal was found to be excellent (>80%). To establish significance we used cut-offs ($P \leq 0.01$) far beyond the standard significance threshold ($P \leq 0.05$).

Complementary and alternative medicine (CAM) intervention research has often been based on a mind-body medicine approach with an emphasis on relaxation techniques like yoga, meditation and modified breathing techniques (31,32). Another approach in CAM which has not received as much attention is the use of ingested natural health products to provide a pharmacological action in order to provide an 'adaptogenic' or protective effect against stress. Our pilot

study addresses some of this knowledge gap by assessing the effects of a combined herbal compound, OCTA©, on parameters of stress and its effects on the mental state of the individual. If the results of our trial are to be trusted and assumed to not solely be due to placebo, then we can infer that this polyherbal compound does have a specific effect and could be an effective aid in controlling at least some of the negative psychological manifestations of stress.

Stress Physiology and Adaptogenic Effect

Exemplified in the relatively new field of psychoneuroimmunology, stress invariably leads to a systemic physiological response with implications for the maintenance of both health and predisposition towards disease (14,33). The physiology of stress has been well characterized with an emphasis on the hypothalamic–pituitary–adrenal axis. Briefly, we know that the immune system and the nervous system are in constant communication and are held in a subtle balance that can be distorted by the impact of stress. Three key players, the hypothalamus, pituitary gland and adrenal glands are considered principal effectors in transmitting and amplifying the stress signal (11). The hypothalamus releases corticotrophin-releasing hormone (CRH) that then stimulates the adjacent pituitary gland to secrete adrenocorticotropin hormone (ACTH). In turn, circulating ACTH stimulates the adrenal gland to secrete epinephrine, norepinephrine and ultimately cortisol into the bloodstream resulting in the classic symptoms of the fight or flight response (Fig. 1). It is important to note that many cytokines and inflammatory modulators feed into the stress signal at different physiological points and are also critical in their contribution to the overall picture.

With such a complex system involved in the body's realization of stress, it is plausible that a compound mixture of herbs could have a modulatory and adaptogenic effect on the body's overall response to stress. An analogous representation of the effects of an adaptogen is depicted in the change of a system's tendency towards balance as shown in Fig. 2. This is represented by a simple fulcrum and balance beam. When an adaptogen is added to the system, (i.e. stabilizing damping springs) additional force has to be applied to deviate the balance beam from the horizontal thereby making the system less likely to become perturbed to one side or the other. In this scenario, the adaptogen effectively counteracts the effective 'weight' that a stressor has on the system and thus makes it less likely to 'fall' into the sympathetic stressed state.

Whether the potential adaptogenic effect of this compound occurs in the mental state and personal perception of stress, or through the provision of a more direct physico-chemical attenuating effect is not answerable by this study. An examination of the different changes in QOL measures, however, does have subtle implications. The fact that the score of mental components of the SF-36 showed dramatic improvements whereas the physical components score changed little implies that the effect may be more psychological than physical. In addition, a possible implication of a lack of

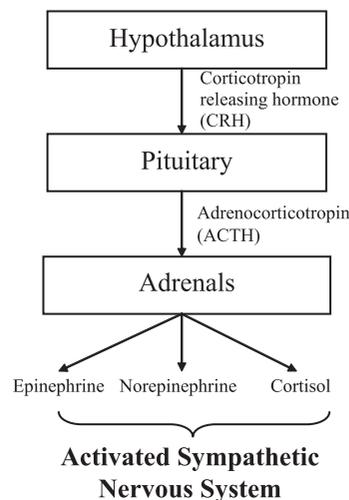


Figure 1. Principal endocrine axis of the sympathetic nervous system.

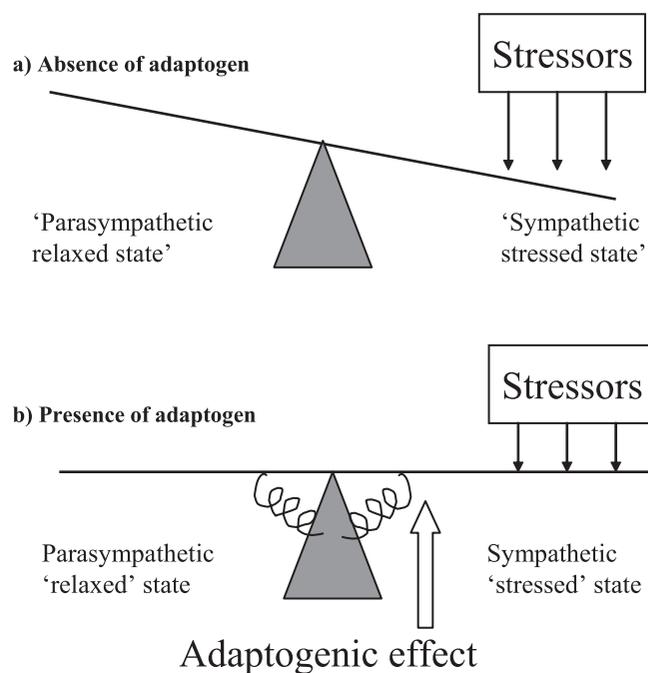


Figure 2. Counteractive adaptogenic effect against stress.

a change in physical symptoms from the SF-36 questionnaire is that placebo may not actually account for the lion's share of the changes in the psychological domain. If placebo was indeed the principle effector, then changes should have been noticeable in both the physical and psychological domains and not just in the latter. These implications are purely theoretical however and should be tested in more mechanistic-based research.

Further Research

As well as conducting a controlled trial to eliminate the placebo effect, it would be interesting to conduct research that

explores changes in important proinflammatory cytokines including IL-6, TNF and IL-1 as well as examining changes in lymphocyte and neutrophil counts. The use of antioxidants has been shown to reduce stress-induced lymphopenia (34) and it would be optimal to evaluate the impact of the herbs contained within OCTA© either individually or in combination on the immune system in further research.

Conclusion

The lack of adverse effects found in our study as well as an absence of changes in both liver and renal function tests tentatively supports the notion that this herbal mixture is non-toxic. Well-controlled and longer-term studies are needed, however, to establish the long-term effects of this mixture both with regards to efficacy and toxicity. In addition, the small number of participants in our pilot study does not preclude the possibility that serious side effects might occur. While inconclusive, the results from this study are encouraging. Albeit uncontrolled, the pilot study indicates that a polyherbal compound, OCTA©, provides a beneficial adaptogenic effect. The lack of overt and measurable toxicity in all participants is also encouraging and supports the need for more research to better evaluate this polyherbal compound.

Conflict of Interest

Dugald Seely has no conflict of interest to declare. Rana Singh was the clinician in charge of running the trial and was hired to do so by Destiny Health and Wellness the makers of the product OCTA©. Data analysis was conducted independently of the company sponsoring the trial. The sponsoring company, Destiny Health and Wellness, had no input in drafting the manuscript.

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