A clinical study on the management of generalized anxiety disorder with *Centella asiatica*

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ABSTRACT

Centella asiatica is reputed for its beneficial effects in various neurological disorders. The present investigation was undertaken to evaluate the role of 70% hydro-ethanolic extract of *Centella asiatica* (CA) on generalized anxiety disorder (GAD) in man. Hamilton's Brief Psychiatric Rating Scale (BPRS) was used to screen the subjects. Thirty-three participants (18 male and 15 female; average age 33 yrs) were medicated with the CA in a fixed dose regime (500 mg/capsule, twice daily, after meal). They were thoroughly investigated using standard questionnaires based on psychological rating scale at baseline (day 0), mid-term (day 30) and final (day 60). The scale also includes a number of direct queries about current levels of experienced stress. The observations revealed that, CA not only significantly ($p<0.01$) attenuated anxiety related disorders but it also significantly ($p<0.01$) reduced stress phenomenon and its correlated depression. CA further significantly ($p<0.01$) improved the willingness for adjustment and cognition. Results indicated that *Centella asiatica* may be useful in the treatment of GAD and may be used as a promising anxiolytic agent in near future.

Keywords: Anxiety, stress, depression, *Centella asiatica*, adjustment, attention.

INTRODUCTION

The facets of stress are essentially limitless; however, broad categories include physical exertion, emotional upset, persistent psychological pressure, existential crisis and residual effects of emotional trauma. It has consistently been shown that individuals experiencing stress have impaired physical and mental functioning and needed more use of healthcare services.[1] 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.[2] The current therapies for dealing with 'stress' are extensive but perhaps not ideally targeted in most of the cases. Pharmacological approaches are principally focused on the treatment of depression and the manifestations of both acute and chronic anxiety disorders.[3] A potentially beneficial use of herbal medicine involves the use of herbs as adaptogens in order to prevent stress-induced morbidity.[4] Ayurveda, Indian system of traditional medicine has described CNS-activity under *rasayana* categories. *Sushruta*-described *rasayana,* deals with the drugs and the methods to maintain youth, to increase longevity, intellectual capacity and to maintain a disease-free life.[5] A number of medicinal plants from Ayurveda have been shown to have such activity; *Centella asiatica* (CA), is one of them.[6] *C. asiatica* (Family: *Apiaceae*) is also known as *Gotu kola*, Indian Pennywort, *Jal Brahmi* and *Mandookaparni.* It is a small herbaceous plant found throughout India, Asia, and the Middle East. CA has been referred into the French pharmacopoeia in 1884, in the ancient Chinese Shennong Herbal 2,000 years ago and in Indian Ayurvedic medicine 3,000 years ago.[7-8] In ancient *Ayurvedic* texts, *Charaka* has categorized it as *medha* (intellect promoting) or nervine tonic.[9] Many ethnomedicinal and ethnobotanical uses have been ascribed to the whole plant. Moreover, pharmacological studies have revealed that CA and its constituents, mainly asiaticoside[10] and ursolic acid[11] have wide range of pharmacological activities such as wound healing properties,[12] memory enhancer,[13] sedative action,[14] anxiolytic action[15] and antioxidant properties.[16] Other studies revealed that CA has the ability to repair damaged neurons,[17] stimulate the neuronal dendritic growth in neurodegeneration[18] and against age related oxidative damage[16]. Relatively little clinical research has been conducted on the use of CA for stress. In this study, we aimed to investigate the therapeutic role of CA in mental disorders, especially in generalized anxiety disorders (GAD).

MATERIALS AND METHODS

The freshly crude plant CA identified by Botanical Survey of India, Kolkata was preserved in the

Table-1: The distribution of participants for trial

	Centella asiatica
Total Subjects (N)	33
Male	18
Female	15
Religion	
Hindu	26
Muslim	07
Average age	33
18-35 years	23
36-60 years	10
> 60 years	0
Occupation	
Service holder	10
House maker	08
Business	03
Student	11
Others	01

departmental herbarium (voucher No. Ph/DB/CA/104). The aerial parts of CA was washed, dried and made into fine powder. This powder was soaked in 70% ethanol for 24 hrs at room temperature and then filtered under vacuum. This process of extraction was further repeated for three times. The combined alcoholic extract of the plant was concentrated under reduced pressure in a rotary evaporator (extractive value 10-12%w/w). The concentrated material was then lyophilized and the ultimate product was filled in gelatin capsules (500 mg equivalent weight).[19] The product was tested for quality control using HPTLC[11] and demonstrated consistent concentration (ursolic acid 1.5-1.8%) of the plant extract.

Programmed clinical trial was done in the Out-Patient Clinics of Institute of Post Graduate Ayurvedic Education & Research and J. B. Roy State Ayurvedic Medical College & Hospital, Kolkata. Only subjective questionnaires were used to measure the overall changes in quality of life. The trial was conducted in accordance with good clinical practice guidelines and conforming to the declaration of Helsinki, following approval by the Institutional Ethical Committee. Participants of both sexes, of age group 18-60 years, suffering from GAD, diagnosed during initial observation of the participant took part in this study. General examination of the participants was done and Brief Psychiatric Rating Scale (BPRS)[20] was used to assess the mental status. Participants having hepatic and/or renal disease, severe depression, organic lesion, uncontrolled diabetes, pregnancy/ lactation were not included in the study.

Participants were formally informed about the study and those who gave written informed consent were enrolled. The encapsulation contained 500 mg of the plant extract (CA) and was administered orally in dose of one capsule, twice daily after meal. The dose remained constant throughout the study. Any concomitant illness and medication during study period were recorded. No anxiolytic medication including b-blockers anti-depressants, etc. was permitted throughout the study. The participants were followed-up at day 30 and finally at day 60 from the starting of medication. Study endpoints assessed and analyzed for each of the participants consisted of subjective scores from five self reported questionnaires including stress scale, anxiety scale, depression scale, adjustment scale and attention scale.[20-22] The questionnaires chosen, were valid and widely accepted amongst healthcare professionals.[23-24] The scales also include a number of direct queries about current levels of experienced stress. The statistical analysis of the data was performed according to by *Chi-square test* and percentile change compared to baseline results.[25]

RESULTS

In this clinical trial, we enrolled 35 participants (age 18-35 years) for 60 days, but 33 participants completed the trial. The demographic distribution of participants was tabulated in Table-1. None of them reported self-perceived adverse events. Majority of them were either students or service holders.

The results indicate that CA ingestion (500 mg capsule, twice daily for 60 days) significantly attenuated stress-anxiety-depression related disorders (Table-2). The baseline score of anxiety index was declined to 13.1% in 30 days and 26.0% in 60 days after the treatment of CA (Table-2). An improvement (12.5%) in self-perceived stress within 30 days and 23.2% within 60 days were noted.

Depression index also reduced from 10.2% (30 days) to 21.8% (60 days) in case of CA trial (Table-2). After treatment, adjustment score finally improved by 35.2% and attention level improved by 27.8%. Each of these results was statistically significant with *P-values* all <0.01 (Table-2).

DISCUSSION

The lifetime prevalence of generalized anxiety disorders (GAD) is quite high (approximately 5% of the general population).[2] It generally first appears during adolescence, although many affected individuals refer that they have always suffered from this condition.[26] Stressful life events seem to play some role in its onset and its frequency is twice as high amongst women as

Table-2: Role of CA (500mg equivalent capsule, twice daily, p.o.) on Stress, Anxiety and Depression in human subject

	Psychological Score (mean ± SEM)						
	Baseline (Day 0)	**Visit I (Day 30)**	**% Change**	**p-value**	**Visit II** (Day 60)	**% Change**	**p-value**
Stress	95.93±1.28	83.87±1.38	-12.5	0.01	73.63±1.29	-23.2	0.01
Anxiety	68.24±1.55	59.27±1.45	-13.1	0.01	50.48±1.13	-26.0	0.01
Depression	56.90±1.22	51.06±1.07	-10.2	0.01	44.48±0.98	-21.8	0.01
Adjustment	29.25±5.98	47.16±4.62	-20.1	0.01	53.06±6.07	-35.2	0.01
Attention	2.98±0.71	3.38±0.96	-13.4	0.01	3.81±0.28	-27.8	0.01

N=33; Results were Mean±SEM; The results were statistically compared to baseline using Chi-square test

found in men.[2] It also presents a high degree of co-morbidity with other anxiety disorders or mood disorders.[27] The failure of successful adaptation during stressful situations resulted in stress-related illness that result from, or are associated with, dysregulation of the stress response.[1] A group of plant-based drugs, the adaptogens, appears to induce a state of nonspecific resistance, enabling the organism to counteract and adapt to various stressors that can adversely affect the physiological system. It has been documented that several plants have adaptogenic activity.[4] Indian ancient medicinal system, *Ayurveda* documented many such plants, including CA which is categorized as *rasayana*.[9,28] The properties ascribed to *rasayanas* in Ayurveda are remarkably similar to those of adaptogens.[4,28] Adaptogens are believed to have bimodal function of action either by providing a stimulant effect or sedative effect depending on the needs of the individual in a particular situation.[29]

To the best of our knowledge, this is the first attempt to assess CA alone 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. To establish significance we used cut-offs (Pd"0.01) far beyond the standard significance threshold (Pd"0.05). The participants were selected on the basis of seven point scoring system of modified Hamilton's Brief Psychiatric Rating Scale. The BPRS is one of the most frequently used instruments for evaluating psychopathology in patients with GAD.[30]

The overall clinical features were improved after the treatment of CA extract. The treatment also helped in mental overwork in daily life. Prolonged treatment of CA extract showed to inhibit stress in volunteers, without any side effects like vertigo, nausea, and dizziness or mental weakness. Symptoms of anxiety commonly associated with panic disorder, agoraphobia, obsessive-compulsive disorder, eating disorder and many personalities disorders.[28] In the present clinical trial 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.

Continuous generalized stress is known to induce melancholic depression. It has been suggested that the symptoms of endogenous depression represent tolerance of the mesocortical system to chronic activation of the stress system.[31] Physical changes also occur particularly in severe or melancholic depression with insomnia or hypersomnia, anorexia and weight loss (or sometime over eating), decreased energy and libido, and disruption of the normal circadian rhythms of activity, body temperature, and many endocrine functions.[32-33]

The present clinical trial revealed that, administration of *C. asiatica* regularly for two months reduced stress, attenuated anxiety, negated depression and enhanced adjustment and attention in patients without any side effects like vertigo, nausea, and dizziness or mental weakness. The treatment also helped in mental overwork in daily life. These observations clearly indicated that CA has potential action in the regulation of hypothalamo-pituitary-adrenocortical axis (HPA axis) especially, during stress related disorders. It appears that *C. asiatica* may be a safer alternative to Benzodiazepines for the therapy of stress related clinical disorders.

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