Initial exploratory observational pharmacology of *Valeriana wallichii* on stress management : A clinical report

Dipankar Bhattacharyya,[1] Utpalendu Jana,[2] Pratip Kumar Debnath[2] and Tapas Kumar Sur[1]

[1]Department of Pharmacology, Institute of Post Graduate Medical Education and Research, Kolkata, India
[2]JB Roy State Ayurvedic Medical College and Hospital, Kolkata, India

Corresponding author: Dr. Dipankar Bhattacharyya, Professor and Head Department of Pharmacology, Institute of Post Graduate Medical Education and Research,
244B, Acharya J.C. Bose Road, Kolkata 700020, India, e-mail : surtapas@rediffmail.com

ABSTRACT

Valeriana wallichii, an Indian medicinal plant, has been on trial for its role in stress disorders in hospital based clinical set-up. Hamilton's Brief Psychiatric Rating Scale (BPRS) was used and thorough clinical investigations were carried out to screen the subjects. Thirty-three subjects (20 male and 13 female; average age 34.2 years) were medicated with the plant extract in a fixed dose regime (500 mg/capsule, twice daily, p.o. after meal). They were thoroughly investigated clinically and using standard questionnaires based on different psychological rating scale at baseline (day 0), mid-term (day 30) and final (day 60). The observations exhibited that, *V. wallichii* not only significantly ($p<0.001$) attenuated stress and anxiety, but also significantly ($p<0.001$) improved depression and also enhanced the willingness to adjustment. Nevertheless it did not alter memory, concentration or attention of the volunteers. The results suggest that *V. wallichii* may be useful in the treatment of stress related disorders in human and may be a promising anti-stress agent in near future.

Keywords: Anxiety, stress, depression, adjustment, memory, v*aleriana wallichii.*

INTRODUCTION

Anxiety or stress is a cardinal symptom of many psychiatric disorders and an almost inevitable component of many medicinal and surgical conditions. Symptoms of anxiety commonly associated with dysthymic disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, eating disorder and many personalities disorders, while, with lifetime morbid risk of over 10.0% in the general population, major depression is one of the most common mental illnesses.[1,2] Throughout human history there have been searches for antidotes for the symptoms of anxiety and stress. In the late 1950s, the benzodiazepines were discovered, and have been widely used. Since the development of the first benzodiazepine, more than 2,000 related compounds have been synthesized, but few of them have been found to be clinically useful.[3] This provides impetus in the search for newer and more effective anti-stress drugs. Natural products have played a significant role in the management of neuropsychiatric disorders.

Ayurveda, Indian system of traditional medicine has described CNS-activity under different categories. A number of medicinal plants from India have been shown to have activity by the traditional methods of psychopharmacology, *Valeriana wallichii* is one of them.[4] Indian medicinal plant, *V. wallichii* (VW), a natural source of the sedative and tranquilizing *valepotriates,* is well documented.[5] *Valepotriates* are responsible for the sedative action of the plant.[6] Different *in vitro* cultures of *valerianacieae* were analyzed for *valepotriate* content. Using TLC and HPLC, twelve *valepotriates has* been isolated and identified by Proton Mass Resonance (PMR), Citron Mass Resonance (CMR) and Mass Resonance (MS). The rhizomes contained significantly higher levels of *valepotriates* than the roots.[7-10] *Valeriana* belongs to the principal remedies in insomnia especially due to nervous exhaustion and mental overwork.[11,12] Although the plant has been in traditional use for thousands of years in India, but till date there is no evidence-based clinical report. In this context, we aimed to investigate the Indian medicinal plant, *V. wallichii* for its role in mental disorders specially stress related disorders in human.

MATERIALS AND METHODS

The rhizomes of the *V. wallichii* were collected and identified from the Botanical Survey of India, West Bengal. Then they were washed, dried and made into fine powder. This powder was soaked in 70.0% ethanol. After 24 h at room temperature, the materials were 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. The concentrated material was then lyophilized and the ultimate product was filled in gelatin capsules.[13]

The programmed clinical trail was done in the Out-Patient Clinics of the J. B. Roy State Ayurvedic Medical College and Hospital, Kolkata, India from the year 2001-2004. The trial was conducted in accordance with good clinical practice guidelines and conforming to the declaration of Helsinki, following approval by the Institutional Ethics Committee.

Patients of both sexes, of age group 18-60 years, suffering from *Anxiety-Stress-Disorder*, diagnosed during initial observation underwent detailed general health check up and their anxiety index was measured by using the Brief Psychiatric Rating Scale (BPRS).[14,15] The exclusion criteria of this study were : (i) hepatic and/or renal disease, (ii) severe depression, (iii) organic lesion, (iv) uncontrolled diabetic patient.

This study included 33 subjects. Regarding sex, 20 patients were male and 13 were female. While, 26 was religiously *Hindus* and 7 was *Muslims*. There were 21 patients (63.6%) who belonged to the age group of 18-35 years, 8 patients (24.2%) belonged to the age group of 36-50 years and only 1 patient was above 50 years. The average age of the subjects was 34.2 years. Regarding occupation there were service holders (12 patients), house wives (7 patients), businessmen (6 patients), students (5 patients) and others (3 patients) including unemployed, retired person etc.

Subjects were formally informed about the study and only those who gave written informed consent were enrolled. The encapsulation contained 500 mg of the plant extract and was administered orally in dose of one capsule twice daily after meal. Hence, each patient ingested two capsules per day. Any concomitant illness and medication during study period were recorded throughout the study. No other anxiolytic medication including β-blockers anti-depressants etc. were permitted throughout the study. The subjects were followed-up at day 30 and finally at day 60 from the starting of medication. They were thoroughly investigated clinically and their anxiety index was noted using questionnaires based on different psychological rating scales.[14,15] The data were analysed by using Student's paired t-test and percentile change compared to baseline results.[16]

RESULTS

The results indicated that *V. wallichii* ingestion significantly attenuated anxiety-stress-disorders (Table-1). The overall clinical features also improved after the treatment.

Before the test drug, *V. wallichii* therapy, the baseline score of anxiety index was 68.38±8.82, but it declined to 59.38±7.26 (-13.1%) after 30 days and 50.69±6.01 (-25.8%) after 60 days. Further, stress index at baseline was 98.48±8.23. *V. wallichii* treatment showed significant reduction to 83.47±9.84 (-15.2%, p<0.001) after 30 days and to 76.32±9.26 (-22.5%, p<0.001) on 60 days. On the other hand, depression index also reduced from 56.83±6.92 (at baseline) to 51.19±6.30 (30 days) and 44.97±5.74 (60 days), decline was 9.9% and 20.9% respectively. These results clearly indicated that the test drug, *V. wallichii* has significant anti-stress and anxiolytic properties. Furthermore, it significantly (p<0.001) improved the willingness of adjustment (20.2%) when it was compared with baseline score. But, the test drug did not alter memory, attention or concentration significantly in the selected subjects.

DISCUSSION

The human society has become complex and, in many ways, more demanding. However, our physiological responses designed to cope with the ever-increasing adverse situations have not evolved appreciably during the past thousand years. The failure of successful adaptation during stressful situations has resulted in stress-related illness that result from, or are associated with, dys-regulation of the stress response.[17] Various attempts have been made to counter the aversive effects of stress, ranging from meditation to anti-stress drugs, particularly the anxiolytic benzodiazepines (BDZ). However, these non pharmacological and pharmacological methods appear to have limited utility.[18] An answer to this perplexing problem of countering stress-induced perturbations of physiological homeostasis came from the plant kingdom. 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. The topic of adaptogens and their likely utility in stress medicine has been reviewed.[19] Several plants have been shown to have adaptogenic activity, the most prominent being *Panax ginseng.*[19,20]

Indian ancient medicinal system, *Ayurveda* documents several plants, including *V. wallichii*, which are, categorized as *rasayanas.*[6] The properties ascribed to rasayanas in *Ayurveda* are remarkably similar to those of adaptogens.[21] In this study, *V. wallichii* extract showed overall improvement in stress management. It reduced systolic blood pressure and promoted sleep in general. One of the active ingredient of the test plant is *valepotriates*. It has sedative action in human.[5,6] The treatment also helped in mental overwork in daily life. Prolonged treatment of *V. wallichii* extract showed to inhibit stress in human, without any side effects

like vertigo, nausea, and dizziness or mental weakness. In a separate study it was noted that *valerenic acid*, one of the active constituents of this plant, promoted sleep in healthy subjects.[22]

Further, the present results indicate that, *V. wallichii* has a good efficacy to negate anxiety related disorders in human subjects. Anxiety is a cardinal symptom of many psychiatric disorders and an almost inevitable component of many medicinal and surgical conditions. Symptoms of anxiety commonly associated with dysthymic disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, eating disorder and many personality disorders.[1-3]

Generalized stress, particularly if continued in nature, 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.[17] Physical changes also occur particularly in severe or melancholic depression: these include 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. Some of (10.0-15.0%) individuals with this disorder display suicidal behavior during their lifetime.[23] In that study, it was revealed that, depression index was also reduced after two-month continuous treatment with the test herb, *V. wallichii*. Furthermore, the plant also enhanced the willingness for adjustment in human, but has no role in the betterment of memory, concentration and attention.

The present clinical trial supports the contention that, two-month regular administration with *V. wallichii* reduced stress, attenuated anxiety, negated depression and enhanced adjustment but, could not alter memory, attention and concentration in human. This observations clearly indicate that *V. wallichii* has potential action in the regulation of hypothalamo-hypophyseal-adrenocortical axis (HHA axis) especially, during stress related disorders in human. It appears that *Valeriana wallichii* may be a safer alternative to benzodiazepines for the therapy of stress related clinical disorders.

ACKOWLEDGEMENTS

REFERENCES

1. Harrison's Internal Medicine. 14 th ed., Vol. II, London: Mc-Graw Hill; 1998.
2. Elliott GR, Eisdorfer C. Stress and Human Health. New York: Springer Publishing; 1982.
3. Feldman RS, Meyer JS, Quenzer LF. Principles of Neuropharmacology. Sunderland: Sinauer Associates Inc.; 1997.
4. Vaidya ADB. The status and scope of Indian medicinal plants acting on central nervous system. *Indian J Pharmacol* 1997; 29: 340-3.
5. Violon C, Van CN, Vereruysse A. *Valepotriate* content in different in vitro cultures of *Valerianaceae. Phar Weekbl Sci Ed* 1983; 5: 205-10.
6. Mishra LC. Scientific Basis for Ayurvedic Therapies. New York: CRC Press; 2004.
7. Konovalova OA, Ryalko KS. Quantitative determination of *valepotriates* in rhizomes and roots. *Khim Farm Zh Moscow* 1983; 17: 831-7.
8. Becker H, Chavadej S, Thies PW, Finner E. The structure of new valepotriates from tissue cultures of *Valeriana wallichii. Planta Med* 1984; 50: 245-53.
9. Mathur J, Ahuja PS, Mathur A, Shah NC. In vitro propagation of *Valeriana wallichii* DC. *Planta Med* 1988; 54: 82-6.
10. Mathur J. Plantlet regeneration from suspension cultures of *Valeriana wallichii*, DC. *Planta Med* 1992; 81: 111-8.
11. Nadkarni KM. Indian Meteria Medica. Mumbai : Bombay Popular Prakasan; 1976.
12. Kapoor LD. Handbook of Ayurvedic Medicinal Plants. Boca Raton: CRC Press Inc.; 1990.
13. Rammington's The Science of Practice of Pharmacy. (20th ed). London: Lippincott Willams and Wilkins; 2001.
14. Hamilton M: The assessment of anxiety state by rating. *Brit J Med Psychol* 1959; 32: 50-65.
15. Jacobson E. Modern treatment of tense patients. New York: Springfield; 1970.
16. Hicks CM. In: Research methods in clinical therapists. New York: Churchill-Livingstone; 1999.
17. Chrousos GP, Gold PW. The concept of stress and stress system disorders. *J Amer Med Assoc* 1992; 267: 1244-52.
18. Mason JW. A historical view of the stress field. *J hum Stress* 1975; 1: 6-14.
19. Wagner H, Norr H, Winterhoff H. Plant adaptogens. *Phytomed* 1994; 1: 63-78.
20. Sur TK, Bhattacharyya D. *Panax ginseng* on brain and hypothalamic 5-hydroxytrytamine during immobilization stress: and its modification by parachlorophenylalanine. *J Natural Remedies* 2003; 3: 90-4.
21. Sur TK, Pandit S, Mukherjee R *et al*. Effect of Sonachandi Chyawanprash and Chyawanprash Plus - two herbal formulations on immunomodulation. *Nepal Med Coll J* 2004; 6: 126-8.

22. Anderson GD, Elmer GW, Kantor ED, Templeton IE, Vitiello MV. Pharmacokinetics of valerenic acid after administration of valerian in healthy subjects. *Phytother Res* 2005; 19: 801-3.
23. Gold PW, Goodwin GP. Clinical and biochemical manifestations of depression: relationship to the neurobiology of stress. *New Engl J Med* 1988; 319: 348-53.

Table-1: Role of *Valeriana wallichii* (500mg/twice daily/p.o.) on psychological scoring during Stress Disorders in human

(N=33)	Psychological Score (mean $\pm$ SD)						
	Baseline **(Day 0)**	**4 week** **(Day 30)**	**% Change**	**p-value**	**8 week** **(Day 60)**	**%** **Change**	**p-value**
Stress	98.48 ± 8.23	83.47 ± 9.84	15.2	<0.001	76.32 ± 9.26	22.5	<0.001
Anxiety	68.38 ± 8.82	59.38 ± 7.26	13.1	<0.001	50.69 ± 6.01	25.8	<0.001
Depression	56.83 ± 6.92	51.19 ± 6.30	9.9	<0.01	44.97 ± 5.74	20.9	<0.001
Adjustment	47.0 ± 6.52	51.80 ± 6.14	10.2	<0.01	56.50 ± 4.28	20.2	<0.001
Memory	3.07 ± 1.32	3.50 ± 1.28	14	NS	3.54 ± 1.54	18.5	NS
Attention	2.53 ± 0.61	2.80 ± 0.72	10.7	NS	2.88 ± 0.95	17.9	NS
Concentration	2.50 ± 0.73	2.74 ± 0.69	9.6	NS	2.78 ± 0.82	15.2	NS

The results were compared to baseline using student's paired t-tests. NS= Not significant