ABSTRACT

INTRODUCTION:
In view of the increasing incidence of anxiety day by day, that causes clinically significant distress or impairment in important areas of functioning of life routine; and no satisfactory and safe solution available in the conventional medicine, the present study was planned in search of any natural drug which could be proved as safer and effective anti-anxiety agent. In literature survey it was observed that the Chandana (*Santalum album, Linn.*) is one of such drug that is used in Indian tradition for the peace of mind.

SELECTION OF THE TOPIC:

Why Chandana?
History reveals that Chandana is used for its soothing effects on the mind, since a long time in Ayurveda. The Sandalwood paste application on the forehead, between the eyebrows, is a common Indian tradition practiced by the religious persons for achieving the peace of mind. Interestingly, Ayurveda says there is a central node of nerves on the forehead (*sthapani marma*), and the application of cooling Sandalwood at this spot serves to tranquilize the individual.

Why Generalized Anxiety Disorder (G.A.D.)?
The generalized anxiety disorder (GAD) is the commonest type among the nine types of anxiety. Its prevalence is increasing globally, day by day. Among all anxiety states, the lifetime prevalence of G.A.D. has been estimated as 5%; and according to another study the one year prevalence of G.A.D. has been reported as 3.8%. It causes clinically significant distress or impairment in social, occupational and other important areas of functioning, and the sufferer becomes like a handicapped person and can not perform his work and duties properly, that affects the whole set-up of the family. Therefore this problem was selected for the present study.
Why Chandana in Generalized Anxiety Disorder (G.A.D.)?

There are many references in classical Ayurvedic literature, Unani medicine, and modern Aromatherapy regarding usefulness of Chandana in anxiety, nervous tension, stress and associated problems. Some previous pharmacological studies reveal effects of Chandana on the autonomic nervous system, but there is no satisfactory clinical study available to show the effect of essential oil of Chandana on any type of anxiety. Therefore, Chandana was selected for the present study to evaluate its effects on the G.A.D.

AIMS:

To clinically evaluate the effects of Chandana (Sandalwood) oil used as aroma inhalation in Generalized Anxiety Disorder (G.A.D.) in the human individuals.

OBJECTS:

To evaluate whether the Aromatherapy could prove, as an effective route of administration for the treatment of G.A.D. with the Chandana oil.

PLAN OF WORK:
The study was done in the following way:
Review of the literature – Drug standardization – Clinical Trial

1. Review of the literature

A comprehensive review of the literature on Chandana was done from Vedic era till date; from the Ayurveda, Unani medicine and modern aromatherapy. A thorough survey was undertaken regarding the experimental or clinical research studies already done on Chandana.

A. Review of Chandana:
Ayurveda

There are many references in classical Ayurvedic literature, regarding its actions like - improves brain functions and intelligence (medhya, smrutivardhaka, buddhivardhaka), aromatic (surabhi), calms down mental...
irritability (santāpa-ṣantipradam), soothing for manas (saumanasyajanana), protective action on seat of manas (hrudya), suppresses the vitiated pitta and vāta (pittashāmaka, vataroganashak) etc.

**Unani Medicine:**

In Unani medicine, the Sandal Safaid (white Sandalwood) is described as soothing / sedating (musakkin), cooling (mubarrid), exhilarant or pleasure promoting (mufrarreh), useful in headache (sūdā) and palpitation (khafqān).

**Modern Aromatherapy**

The actions of Sandalwood described in modern aromatherapy, are - calming, relaxing, soothing, anti-stress, exhilarant, euphoric, anti-depressant, sensual stimulant, cooling, sedative, improves concentration, build-up self esteem and confidence etc. It is useful in insomnia, nervous tension and stress.

**Pharmacological studies:**

We did not find any satisfactory scientific study done by the earlier research workers on its anti-anxiety effect of Sandalwood through aromatherapy. Only some clinical studies were done regarding effect on Sandalwood oil on the autonomic nervous system (Block, 2003; Heuberger, 2006).

Only one pilot study we found related to the evaluation of the aromatherapy massage with Sandalwood oil in reducing levels of anxiety in palliative care. Due to limited data, the results were not substantial enough to generate coherent statistics; but assumption was made that Sandalwood oil could be effective in reducing anxiety (Kyle, 2006).

It is clear that the Sandalwood oil is active pharmacologically through inhalation also. As in a previous study, santalols and related compounds have been identified in the blood of mice that inhaled sandalwood fumes under experimental conditions, indicating that systemic absorption of these compounds can occur (Jirovetz et al., 1992). A study reveals presence of olfactory receptor neurons those were specifically stimulated by sandalwood compounds (Okugava, et al., 1995).
B. Review of Generalized Anxiety Disorder (G.A.D.):
A thorough review of the G.A.D. from modern literature and Ayurvedic concept of Chittodvega from classical literature of Ayurveda was done.

2. Drug Standardization:
The test drug i.e. Sandalwood essential oil, was procured from the genuine source, through the scientists of Fragrance & Flavour Development Centre (FFDC), Kannauj, U.P., India.
Standardization of the essential oil of Chandana was made to ensure its identity, purity and quality. The authentication of the oil was done through the Holistic Health Care & Research Organization, Pune, India with arrangements of Gas Chromatography made by the Aromatics International Inc. U.S.A.

3. Clinical Trial:
Clinical trial was carried out to clinically evaluate the effects of Sandalwood oil, through aroma inhalation, in the patients of G.A.D.

Trial Design:
Controlled, randomized, single-blind, prospective, parallel designed, clinical trial was conducted, as per G.C.P. guidelines.

Sample Size:
The clinical trial was conducted on 100 completed patients.

Ethical clearance:
- Written permission of the Institutional Ethics Committee (IEC) of Tilak Ayurved Mahavidyalaya, Pune was taken prior to the initiation of the clinical trial.
- Written permission was obtained from the Principal and Superintendent of Tilak Ayurved Mahavidyalaya, Pune to carry out clinical trials at the Seth Tarachand Ramnath Charitable Ayurvedic Hospital, Pune.
• The Informed Consent Form was provided to each individual prior to the initiation of the clinical trial, and every individual was included in the study only after getting his consent and acceptance for taking the treatment regimen.

Criteria of Selection (Baseline Screening):

In the initial (baseline) phase of the clinical trial, the patients were diagnosed through the DSM-IV-TR diagnostic criteria. The essential feature of the G.A.D., according to DSM-IV, is persistent anxiety lasting at least 6 months. Its symptoms fall within two categories: 1) apprehensive expectation and worry and 2) physical symptoms those include muscle tension, restlessness, difficulty in concentrating, insomnia, irritability, and fatigue.

Further diagnosis and assessment was done through the Hamilton Rating Scale for Anxiety (HAM-A) that has 14 major components (categories) viz. anxious mood, tension, fears, insomnia, difficulty in concentration, depressed mood, somatic muscular and sensory symptoms; cardiovascular, respiratory, gastrointestinal, genitor-urinary, autonomic and other behavioural symptoms etc. These categories include many sub-parameters (symptoms) to determine their severity.

Inclusion Criteria:

1. Patients of same socio-economic status, irrespective of sex and religion. The majority of patients enrolled were from the middle class group.
2. Patients either male or female, between the age group of 25 to 40 years. This age group was included to prevent the inclusion of patients suffering from chronic ailments that occur after the age of 40 years.
4. Patients suffering from mild to moderate G.A.D.
Exclusion Criteria:

1. Patients having other types of anxiety disorders i.e. anxiety disorder due to general medical condition, panic disorder with or without agoraphobia, social phobia, specific phobias, separation anxiety disorder, obsessive-compulsive disorder (OCD), substance-induced anxiety disorder, post-traumatic stress disorder (PTSD) and acute stress disorder.

2. Patients having secondary G.A.D. due to neurological disorders, systemic conditions, endocrine disturbances, inflammatory disorders, deficiency states and miscellaneous conditions.

3. Patients suffering from severe G.A.D.

4. Patients having tuberculosis, bronchial asthma, atrophic rhinitis, allergic rhinitis, diabetes, hypertension, renal disorders, cardiac disorders and other psychiatric problems and life threatening diseases.

5. Patients not willingly accepting the treatment.

Grouping:

Total 110 individuals were recruited for the study. But the final inferences were made from the records of 100 completed patients. They were divided by random sampling, according to lottery method, into following groups, comprising of 50 individuals in each group.

**Test Group:** Sandalwood oil + Placebo (starch) capsules

**Control Group:** Placebo (starch) capsules

The placebo was given in both the groups to nullify the bias of the effect of counseling during the treatment phase.

Dosage and Route of administration:

- Two drops (0.1 ml.) Sandalwood oil with one ml. of distilled water, through nebulizer for 5 minutes, twice a day.
- Placebo (starch) capsule of 500 mg. orally, B.D.
Time of Administration:

Sandalwood oil by inhalation and starch capsules orally, after breakfast (9 A.M.) and evening (5 P.M.) that is considered as pitta vitiated period.

Duration of administration of the drugs:

Total duration of study was two months. However, the follow-up was done for a period of another one month (at every 15 days) to assess the relapse cases.

Drop-outs:

1. Patients following the treatment very irregularly
2. Patients absent in further follow-ups

Follow ups:

Follow ups were carried out on each fifteenth days for two months, and after the completion further at one month.

ASSESSMENT CRITERIA:

The assessments were made on each fifteen days, on the basis of the following parameters.

1. Case Report Form (CRF):

The patients were subjected to detailed clinical history and physical examination. The Daśavidha Parīkṣa was performed, in which the parameters observed were viz. Prakṛti, Vikṛti, Sāra, Saṃhanana, Pramāṇa, Satmya, Satva, Ahāra Śakti, Vyayama Śakti and Vaya.

2. Psychometric Analysis of G.A.D.:

The Hamilton Rating Scale for Anxiety (HAM-A) was used for the assessment of signs and symptoms of the G.A.D. The standardized Hindi version of HAM-A was used as a questionnaire to be given to the patients. The quantification / rating of the severity of signs and symptoms was done as - very severe (4), severe (3), moderate (2), mild (1) and none (0).
Criteria for assessing the anxiety was followed as - mild anxiety (minimum 18 up to 24); moderate anxiety (minimum 25 up to 29); and severe anxiety (minimum 30 and above).

**Statistical Analysis:**

The analysis of all the parameters was done statistically by the One-way Analysis of Variance (ANOVA) – Dunnett Multiple Comparisons Test using "Graph Pad InStat" of the Graph Pad Software Inc., San Diego, U.S.A.

**Adverse Drug Reactions (ADR):**

The ADR of the test drug on the patients taking treatment were checked if any! The individuals having mild reactions, like mucosal irritation, sneezing, rhinorrhea etc. were continued for the treatment.

**Criteria of Withdrawal:**

1. Patients having moderate to severe adverse effects of the Test Drug were planned to be withdrawn from the treatment, and they were further followed for some period to see either the negative effects were continued or not.

2. Patients unwilling to continue the treatment were discontinued and withdrawn from the study.

**OBSERVATIONS AND RESULTS OF CLINICAL STUDY:**

**Demographic Data:**

It was observed that among patients of GAD, 88% were male and 12% female; 64% were in 25-30 years age group, 36% were in 31-40 year age group. According to profession, 42% patients were students, 39% were in service and 19% were in business. According to marital status, 52% were single, 35% were married, 8% were separated, 5% were divorced. According to Prakruti Parikshan (investigation for constitution), 76% patients were of Vata-pitta prakruti, 16% of Pitta prakruti and 8% of Vata prakruti.

In Sara Parikshan it was observed that 10% patients were of Rasa Sara, 21% of Rakta Sara, 11% of Mamsa Sara, 10% of Meda Sara, 11% of Asthi Sara, 21% of Majja Sara, and 16% of Shukra Sara. According to
Samhanana Parikshan (investigation for the compactness of body - physique), 65% patients were possessing madhyama bala, while 35% were having alpa bala.

According to Satmaya Parikshan, 72% individuals liked madhura, amla, lavana, kashay and tikta rasa, 18% liked madhura, tikta and kashay rasa, while 10% liked madhura, amla and lavana rasa. In Sattva Parikshan, it was observed that 84% patients were of Rajasa prakruti (including 52% Asura Satwa, 11% Pishacha Satwa, 12% Shakuna Satwa and 9% Preta Satwa), while 16% of Tamasa prakruti (including 4% Pashava Satwa, 5% Matsya Satwa and 7% Vanaspatya Satwa).

In the Ahara shakti Parikshan, it was revealed that 68% were possessing madhyama abhyaharan shakti and 32% were having avara abhyaharan shakti. According to jaran shakti, 72% individuals were having mandagni and 28% were having vishamagni. The Vyayama shakti Parikshan, revealed that 81% patients were possessing madhyama bala, and 19% were having heen bala.

**Generalized Anxiety Disorder:**

The analysis of the results of the individual symptoms of Generalized Anxiety Disorder (G.A.D.) revealed that all were reduced very significantly (P<0.01) in the test group (treated with Sandalwood oil), as compared to the pre-treatment phase. While there was no significant change (P>0.05) seen in any symptoms in the control group. Overall severity of the G.A.D. also reflected the same pattern of very significant (P<0.01) reduction in the test group, as seen in its individual symptoms.

**DISCUSSION:**

Present study reveals that the patients included in the study, suffering from G.A.D., were from vata-pitta, vata and pitta prakruti. No patient was belonging to the kapha prakruti. It is proved from this study that the persons of vata and pitta prakruti are more prone to suffer from G.A.D.; and kapha persons being cool-minded have least tendency of the G.A.D.

XXV
As far as the sara is concerned, it was observed that the patients included in the study were belonging to all types of sara, i.e. rasa, rakta, mamsa, medha, asthi, majja and shukra. Therefore, no correlation was found regarding association of any type of Sara with the G.A.D.

It was also observed that in satwa parikshan, the patients were from either rājas or tāmasa type of psychological constitution. No person was belonging to the satwa type. It is known in Ayurveda, that rajas and tamas are both abnormal and so designated as doṣas (blemishes) of the manas (mind); and these mānasika prakṛtis are easily susceptible to mental disorders with trivial exciting causes (Srikantamurthy, 1996). According to Caraka – “mind is associated with rāja and tama; all defects are caused by ignorance (CS, Sa, 2/38). The satwa is said as devoid of defects due to having beneficial fraction of agitation and ignorance respectively (CS, Sa, 4/36).” So it becomes clear that the manas which becomes engrossed with rajas and tamas, loses its balanced working and gets disordered. That is why these two types of constitutions were found to possess G.A.D. in the present study.

The analysis of overall G.A.D. revealed that in control group, there were no significant (p>0.05) mean differences found at different stages of the treatment phase, as compared to the mean score of the pre-treatment phase. While in the test group, at each stage of the treatment phase, the mean differences (as reduction) in overall G.A.D. scores were found highly significant (p<0.01), as compared to the pre-treatment mean scores. Therefore it becomes clear that the test drug, Sandalwood essential oil suppressed the severity of the G.A.D. significantly.

When we analyzed the 14 individual groups of symptoms of the G.A.D., viz. anxious mood, tension, fears, insomnia, intellectual symptoms, depressed mood, somatic-muscular symptoms, somatic-sensory symptoms, CVS symptoms, respiratory symptoms, G.I.T. symptoms, genitor-urinary symptoms, autonomic symptoms, behaviour at interview ; the same pattern of responses in the control and test groups was found as in the analysis of the overall response of the G.A.D., and the severity of all symptoms was found suppressed by the test drug.
The present study is also revealing clear clinical evidences of actions and uses of Chandana described in Ayurvedic and Unani literature. Besides revealing very significant effect of the essential oil of Chandana on the overall Generalized Anxiety Disorder (G.A.D.), when we analyze individual parameters of the G.A.D. in the Hamilton scale, we find correlations in this study regarding very significant effects of the Sandalwood oil on some of the individual components of the generalized anxiety disorder.

This study is proving the actions of Sandalwood described in Ayurvedic and Unani literature as well as in modern aromatherapy. If we can say that the Sandalwood oil should be put forward for its clinical use at a wider level, through aromatherapy, in a larger population, to be used as a novel and safer therapeutic agent for Generalized Anxiety Disorder (G.A.D.) and related psychiatric disorders etc.

**Probable mode of action:**

So we can assume that, because of the actions of Chandana described in Ayurveda, Unani and Modern Aromatherapy earlier, it alleviates individual components of the G.A.D. \((\text{manakshobh, cittodvega or intesi, zahn})\).

Due to Tikta rasa and sheeta virya, the Candana acts as pittasa and has calming and soothing effect on agitated state of \((\text{saumanasyajanana})\). Because of laghu and ruksha guna it digests am\(\text{has raktarasaprasadana effect; and thereby, acts on hrudya (seat of m and control deranged functions of manas.}\)

**Scope and limitations:**

As we know that the inhalation is the safest mode of administration of drugs, and a drug like the essential oil of sandalwood used in the study, that is showing significant effect in the generalized anxiety disorder has a wider scope to be used in larger population as a safer remedy for anxiety. Further, there is a scope for future studies to be designed checking the efficacy of Sandalwood oil in other psychiatric disorders.
Limitation of the present study is that the effect of Sandalwood oil could be investigated on different neurotransmitters and biochemical parameters like epinephrine, norepinephrine, endorphins, acetylcholine, phenylethylamine, enkephalins, GABA, serotonin, melatonin, dopamine, corticotropin- releasing hormone, interleukin-1 (IL-1), corticotrophin-releasing factor mRNA and proenkephalin A mRNA etc. to elucidate a complete mechanism of its psychopharmacological activity.

CONCLUSION:

Highly significant results in the clinical study concluded that the inhalation of the essential oil of Chandana (Santalum album, Linn.) in a prescribed dose (0.1 ml. B.I.D.) is effective in alleviating the symptoms of Generalized Anxiety Disorder (G.A.D.) within two months, without showing any adverse effects.

In this study, Aromatherapy has been proved, as effective route of administration for the treatment of G.A.D. with the Chandana oil.