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RESEARCH ARTICLE

A MULTI-CENTRIC, DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIAL TO ASSESS SAFETY AND EFFICACY OF A PROPRIETARY AYURVEDIC MEDICINE, TAB. PRASHAM IN THE MANAGEMENT OF ANXIETY DISORDERS AS AN ADD-ON TREATMENT TO THE STANDARD OF CARE

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Abstract

A randomized, double-blind, placebo-controlled interventional clinical study was conducted for 71 eligible patients of age >18 years, having anxiety disorder. At the end of the study, when the blind was broken, it was revealed that 36 patients had received the IP and 35 had received placebo. Tab. Prasham was found to be effective in reducing the anxiety when given as an add-on to the standard of care. P value was statistically significant in reducing HAM-A score at day 15 and at day 60. The proprietary Ayurvedic medicine is safe to consume. Tab. Prasham was found to be useful in increasing duration and quality of sleep.

Introduction: -

Anxiety disorders form the most common group of mental disorders and generally start before or in early adulthood. Core features include excessive fear and anxiety or avoidance of perceived threats that are persistent and impairing. Anxiety disorders are characterised by impairment of neural pathway of brain.[1,2] Excessive stress is associated with increased risk of cardiovascular diseases, gastrointestinal issues, and mental health disorders, including anxiety and depression.[3,4] Stress leads to disturbances in sleep patterns, such as insomnia.[5]

Insomnia can be short term or may persist over a longer period, leading to symptoms like low energy, daytime fatigue, irritability, and mood disorders.[6] The primary line of treatment is tranquilizers and antidepressants, which may have undesired effects such as nausea, weight gain, and drowsiness.[7] This has prompted the exploration of alternative therapies, including herbal formulations, for safer and effective management of these conditions.[8]

Ayurveda, the traditional system of medicine, offers a holistic approach for managing stress and insomnia. Tab. Prasham, an Ayurvedic formulation, is composed of potent herbs such as Vacha (Acorus calamus), Pippalimool (Piper longum), Sarpagandha (Rauvolfia serpentina), Khurasaniowa (Hyoscyamus niger), Tagar

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(Valerianawallichii), and Brahmi (Bacopa monnieri), which have documented anxiolytic, sedative, and adaptogenic properties.[9,10] These herbs work synergistically to alleviate anxiety and promote better sleep.
The current study is aimed to evaluate the efficacy and safety of Tab. Prasham as an add-on therapy to the Standard of Care in managing anxiety and insomnia through a randomized, double-blind, placebo-controlled trial. The assessment of the treatment was carried out using validated scales like the Hamilton Anxiety Rating Scale (HAM-A) which is commonly used in clinical trials.[11,12]

Primary Objective was to assess improvement in the Hamilton Anxiety Rating Scale in Anxiety Disorders and Secondary Objectives included assessment an improvement in sleep through a questionnaire, and assessments of incidences of adverse events and treatment emergent adverse events during the treatment period.

Methods: -

Study Design

The present trial was conducted by adopting the Guidelines of the International Conference on Harmonization (ICH) for Good Clinical Practice in compliance with the Declaration of Helsinki. Prior to initiating the study. The protocol was reviewed and approved by the Institutional Ethics Committee of Dr D. Y. Patil Medical College, Hospital & Research Centre (DYPCARC/IEC/3622/2022 dated 25/10/2022), Pimpri, Pune India. The study protocol was registered (CTRI number: CTRI/2023/01/049009) on 13/01/2023 at the Central Trial Registry of India. The study was carried out jointly by the clinician from allopathic and Ayurvedic medicines during January 2023– May 2024.

This was an interventional, prospective, randomized, double-blind, placebo-controlled, multi-centric study evaluating the efficacy and safety of Tab. Prasham. Written informed consent was obtained from all the subjects before enrolment in the study. This was a double-blind trial and neither the patients nor the investigators were aware if the container had Tab. Prasham or Placebo in it. 71 patients were enrolled in the trial.
Sleep was assessed by a questionnaire for assessing quality and duration of sleep. The questionnaires designed to capture sleep onset time, number of night awakenings, WASO, qualitative assessment, total duration of sleep in 24 hours

Investigational Drug Tab Prasham

Investigational drug Tab Prasham was supplied by M/s Ayurveda Rasashala, Pune. Tablet Prasham contained a blend of Ayurvedic herbs, known for their anxiolytic and sedative properties, which are relevant to the management of **anxiety and insomnia:**

Table1:-Tab. Prasham contents

Constituent	Botanical Name	Qty (mg)
Vacha	*Acorus calamus*	18.93
Pippalimool	*Piper longum*	18.93
Sarpagandha	*Rauvolfia serpentina*	37.87
Khurasaniowa	*Hyoscyamus niger*	18.93
Tagar	*Valerianawallichii*	37.87
Brahmi	*Bacopa monnieri*	75.75

Placebo tablets:

The placebo tablets were prepared using microcrystalline cellulose, similar in appearance to the Prasham tablets.

Sample size and patient recruitment

Sample size was calculated by a biostatistician.

Randomization and concealment:

The OPD patients were screened for the study. The weight, look and feel of the containers was kept same for Prasham and Placebo by the manufacturing company; and hence it was not possible to know what is what from the outside. Alphanumeric code was printed on each container and there were four containers for each code (either having tab. Prasham in it or Placebo At baseline, when the container was dispensed, the unique alphanumeric code was noted in the corresponding Case Record Form(CRF). The same coded container was given during consecutive follow-up visits for that patient. This way, each patient kept on receiving either Prasham or Placebo during the entire

study period of 60 days. Neither the patient receiving the containers nor the PI / CRC was aware of the content of the container. Only after the study was over, and the data-sheet freezed and locked, the blind was broken to know the two complete sets of patients: those who received tab. Prasham and those who received Placebo.

The Inclusion criteria were, age >18 and < 70 years at the time of signing ICF, patients fulfilling the diagnostic criteria for any of the anxiety disorders as per DSM 5, voluntarily participation in the clinical trial and agreeing to follow study procedures and not participating in any other interventional drug clinical studies before completion of the present study. The exclusion criteria were: Inability to intake or tolerate oral medications; Known pregnant or lactating women; Patients with current or has a history of substance use disorder; Patients having severe renal and hepatic impairment; Patients who displayed marked suicidal intent or known suicidal tendencies; Where, in the opinion of the investigator, participation in this study will not be in the best interest of the subject, or any other circumstances that prevent the subject from participating in the study safely; Known allergies to components of the Investigational Product(IP).

Intervention
The IP was in addition to the anxiolytics prescribed as a SoC. Patients either received Tab. Prasham or Tab. Placebo as an add-on regimen.

Outcomes
Primary outcome of reduction in anxiety levels was assessed using the Hamilton Anxiety Scale (HAM-A), from baseline to the end of the study period (60 days). The change in anxiety levels was compared within the group (before-after) and between the groups receiving the Tab. Prasham and the Placebo group. The SoC was given to all the patients. Sleep was assessed by a questionnaire for assessing quality and duration of sleep. The questionnaires included questions to capture sleep onset time, number of night awakenings, WASO, qualitative assessment, total duration of sleep in 24 hours.

Statistical analysis
The analysis was performed using Microsoft-Excel and SPSS version-21 (IBM, Statistics software). Mann-Whitney test was used for group comparison and Wilcoxon Signed Rank test was applied for **within** the group analysis.

Results:-

First patient was enrolled on 16th June 2023 and last patient was enrolled on 22nd May 2024.
All the patients were followed up for 60 days with an interim follow-up at every 15 days. (Chart 1 below)
Average age of all the patients in the current study was 38.9 (+12.15) years. Average age of patients in both the groups was close to 39 years. (Chart 2 below)
There were slightly more males (37) than females (34) in the study. (chart3 below)

Table 2 below illustrates demographics and HAM-A scores, anxiety on various days, statistical tests applied and corresponding Probabilityvalues where applicable.

Table 2:- Demographics and HAM-A stats for Controls and Cases.

S. No.	Variable		Control	Case	% or p-value
1	Age in years (Median)		38	37.5	
2	Gender	Male	18	19	52%
		Female	17	17	48%
3	Average BMI		24.8	26	
4	HAM Score	Baseline HAM Score	18.5	9.5	
		HAM Score Day 15	15.7	10.9	
		HAM Score Day 30	13	9.6	
		HAM Score Day 45	10.1	7	
		HAM Score Day 60	8.3	5.1	
5	Anxiety	No Anxiety at baseline	0	0	
		Mild Anxiety at baseline	19	17	

		Mild to Moderate	9	11	
		Moderate to Severe at baseline	5	5	
		Severe Anxiety at baseline	2	3	
		No Anxiety at 15th day	0	0	
		Mild Anxiety at 15th day	18	28	
		Mild to Moderate	12	4	
		Moderate to Severe at 15th day	4	1	
		Severe Anxiety at 15th day	0	0	
6	Mann–Whitney U test baseline between the groups		35 (n)	36 (n)	0.73
7	Mann–Whitney U test Day 15 between the groups		34 (n)	33 (n)	0.04
8	Mann–Whitney U test Day 60 between the groups		34 (n)	34 (n)	0.02

Average BMI (basal Metabolic Index) was 25.3 (+ 4.47) kg/m^2, with lowest at 16.4 kg/m^2 to and highest being 38.6 kg/m^2. With the sample size of current study, it is difficult to study such association or cause-effect relationship. There was a range of uneducated, graduates, post graduates, engineers, nursing staff and medical students in the 71 patients enrolled.

The distribution in the field of employment ranged from homemakers, farmers, clerks, businessmen to students. 26 patients of 71 (36.6%) reported consumption of tobacco in form of chewing or smoking; 14 out of 71 (19.7%) reported of regular alcohol consumption. Like the other factors discussed earlier, anxiety contributes to smoking and once there in addiction to nicotine and people experience acute withdrawal, the symptoms very much mimic anxiety. 17 patients were hypertensive and on medication and 4 were diabetic on OHA, 2 women were with hypothyroidism. 7 patients were habitually consuming tobacco by chewing or smoking; and 9 reported social drinking with moderate quantity.

The distribution of these conditions was similar in both the groups.

Safety Evaluation

There was no single patient to report any adverse event during the 60-day period, apart from sporadic cases of fever due to infection. Also, there was no clinical sign in any of the patients during follow-up that suggests adverse event or reaction. The Investigational Product is marketed since last more than thirty years and safety is very-well established by its use by thousands of practitioners across the country and outside. Hence there was no separate biomarker considered for evaluation of safety in the study.

Chart 1:- Flow-chart depicting journey of patients from screening to last follow-up.

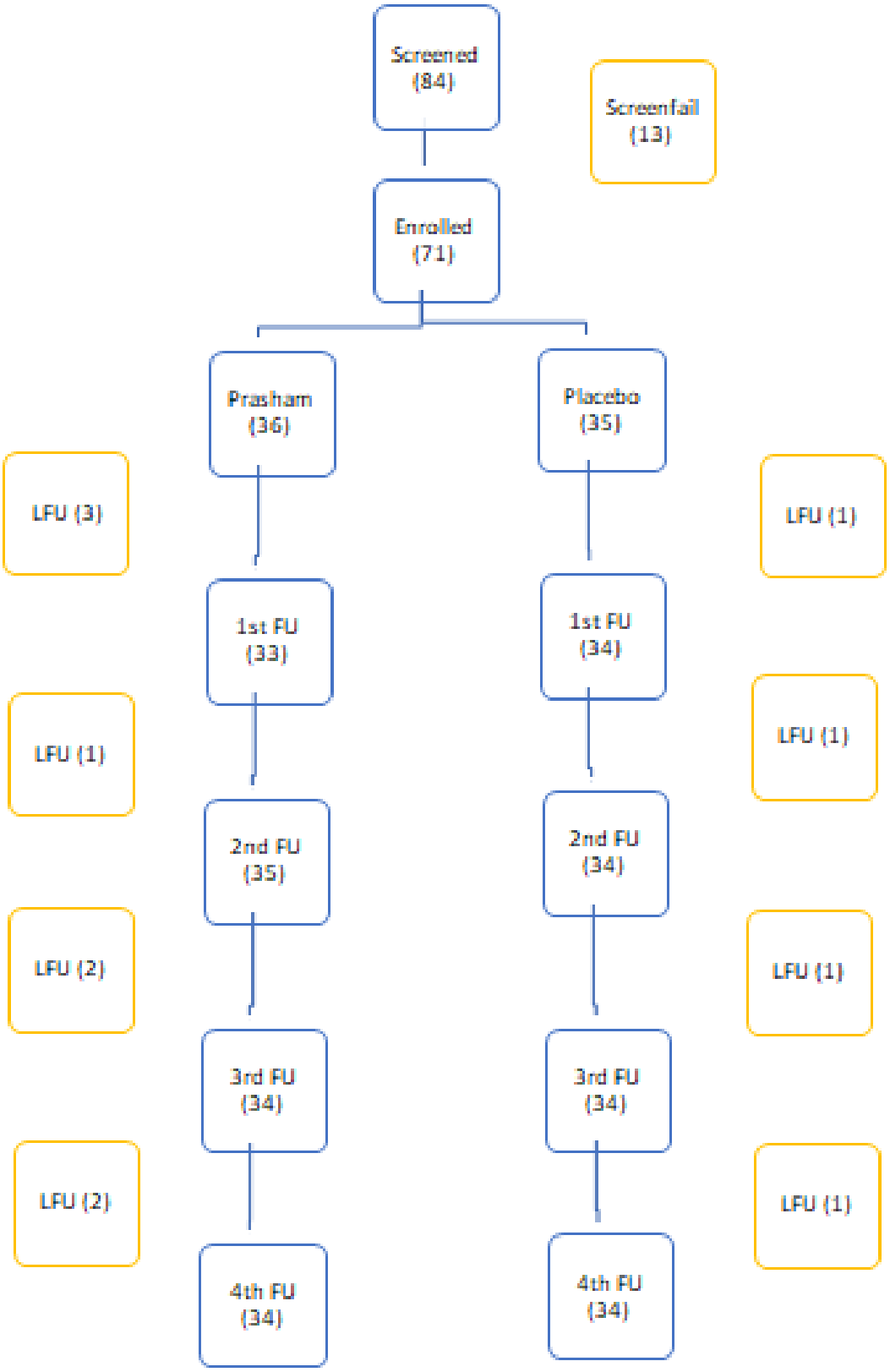


Chart 2:- Age-wise comparative distribution in Cases (Prasham) and Controls (Placebo) groups.

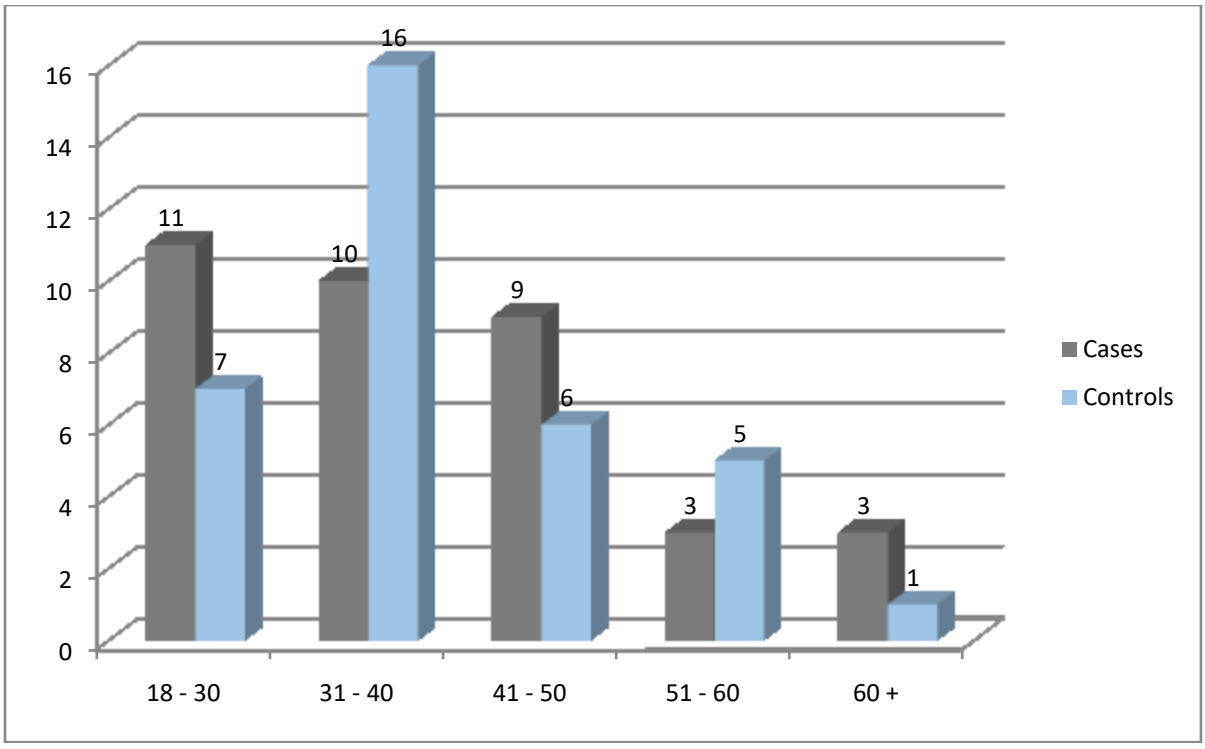
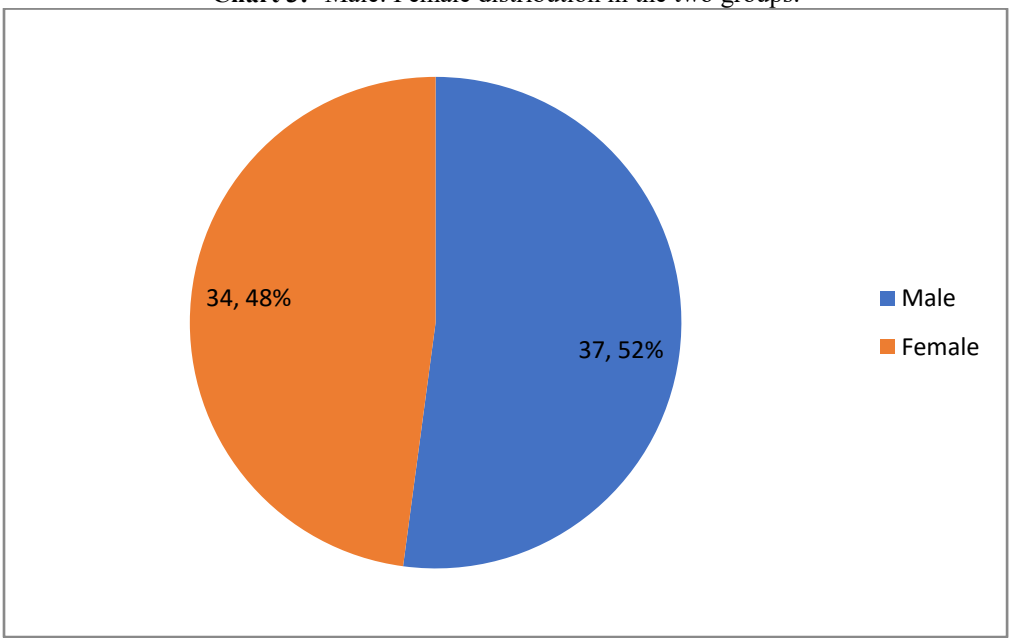


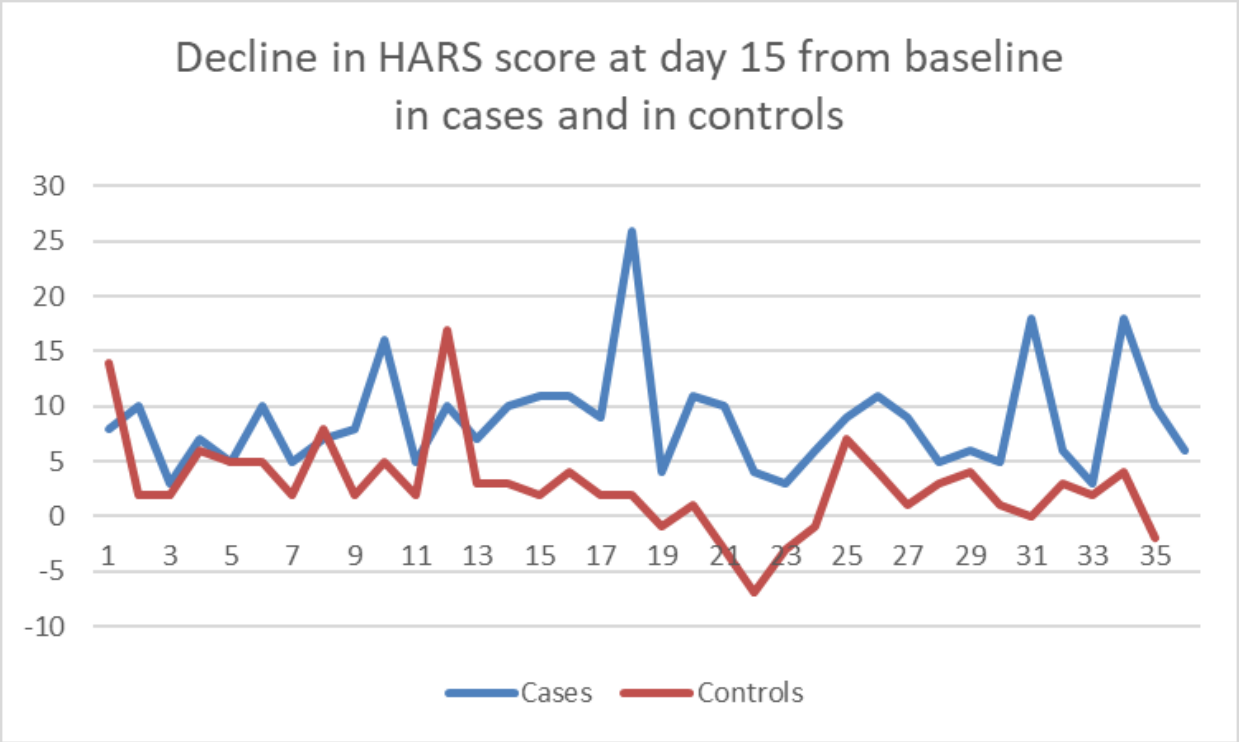
Chart 3:- Male: Female distribution in the two groups.



Hamilton Anxiety Scale (HAM-A) was assessed on baseline, day 15, day 30, day 45 and at the end of the study period (60 days). The scale has four different patient stages: 14-17 = Mild Anxiety,18-24 = Mild to Moderate,25-30 = Moderate to Severe,30+ = Severe.

Chart 4 below depicts the decline in HARS score in all the patients in both the groups at day 15. Patient no 22 in control group showed increase in the score, which is seen as a negative score in the graph.

Chart 4:- Decline in HARS Score at day 15 from baseline in cases and in controls.



Discussion: -

Anxiety is a feeling of fear, dread or uneasiness. Thoughts of future threat (verbal subjective), muscle tension (somato-visceral) and avoidance (overt motor).[13]

Ayurvedic approach in treating anxiety is holistic and often involves internal medication along with Sattvavajayachikitsa (Psychotherapy). McIntyre E have mentioned that 22% of adults with an anxiety disorder have tendency to use herbal medicine.[14]

The present study aimed to evaluate the efficacy and safety of the Tab. Prasham as an add-on therapy for participants suffering from anxiety disorder. Tab. Prasham is an approved proprietary Ayurvedic medicine being in the market since 2 decades. It was a double-blind trial. The investigators received the alphanumeric coded sealed containers with tablets inside it. The look and feel of the containers were similar in all the containers so that it was not possible for the investigators or for the patients to know if there were tablet Prasham inside or Placebo inside them.
The blind was broken at the end of the last follow-up of last enrolled patient's visit.

Statistically significant reductions in the mean scores of anxiety, assessed using the Hamilton Anxiety Scale (HAM-A), were observed from the baseline visit to all follow-up visits in the Tab. Prasham group. When comparing the two groups, a significantly greater reduction in anxiety was noted in the Tab. Prasham group compared to the placebo group at the end of 15 days and at day 60. Although numerically evident, the benefit of Prasham was not statistically significant for day 30 and day 45. (Chart 4)
Therefore, Tab. Prasham can be a good add-on to the contemporary standard of care in decreasing anxiety. Within first 15 days itself the patients are better off than those receiving only SoC (plus placebo).

There was improvement in sleep scores too in Prasham group; however, the change was not statistically significant.
The formulation of Tab. Prasham, which includes ingredients such as Vacha (Acorus calamus), Pippalimool (Piper longum), Sarpagandha (Rauvolfia serpentina), Khurasaniowa (Hyoscyamus niger), Tagar (Valerianawallichii), and Brahmi (Bacopa monnieri), is designed to address anxiety and insomnia through various mechanisms. Research

suggests that these herbal components possess anxiolytic properties, potentially influencing the gamma-aminobutyric acid (GABA) neurotransmission system to improve sleep quality and reduce anxiety levels.

Vacha (Acoruscalamus) is a MedhyaRasayana (nootropic) and is frequently used to enhance intellect and mental clarity. It is also known for balancing the Kapha and Vata doshas. It might be enhancing GABA receptor activity, promoting relaxation and reducing anxiety. Research indicates that Acorus calamus can modulate neurotransmitter levels and exhibit neuroprotective effects, aiding in cognitive function and emotional stability.[15,16]Acorus calamus has been traditionally used to enhance memory and cognition. It has shown potential neuroprotective effects, especially relevant for neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Studies suggest that it can protect neurons from oxidative stress, thus supporting cognitive function.[17]
Pippalimool (Piperlongum) is known for its Deepana (digestive) and Pachana (metabolic) actions, widely used in digestive ailments and as a bio-enhancer in formulations.[18]It is described as beneficial for Kapha-Vata conditions and has rejuvenative effects. This herb has been shown to possess adaptogenic and anxiolytic effects. . Studies suggest that Piper longum enhances the efficacy of other herbal ingredients by improving bioavailability and absorption.[19]Piper longum has been studied for its role in regulating serotonin and dopamine systems, which can aid in managing mood disorders such as depression.[20] Additionally, its anticonvulsant activity helps in epilepsy management, offering stabilizing effects on neuronal excitability.[21]

Sarpagandha (Rauvolfiaserpentina) is known for its calming effects on the nervous system. As per Ayurvedic principles, it helps in harmonizing Rakta and Pitta dosha imbalances, particularly in hypertension. Sarpagandha contains reserpine, which is known for its antihypertensive and sedative properties. It works by depleting catecholamines (e.g., norepinephrine) in the central nervous system,thereby reducing anxiety levels. It also has been shown to influence GABAergic neurotransmission, promoting calmness. Given its antihypertensive properties, Sarpagandha also plays a role in preventing cognitive decline linked to chronic hypertension, enhancing mental clarity.[22,23]

KhurasaniOwa (Hyoscyamusniger), is an antispasmodic and sedative. It helps in pacifying Vata disorders. This herb exhibits anticholinergic properties, helping to alleviate anxiety and promote sleep by blocking the action of acetylcholine in the central nervous system. Its modulation of neurotransmitter activity provides protection against seizures and excitotoxicity. It has been shown to be effective in Parkinson's disease symptoms like tremors and rigidity.[24,25]

Tagar (Valerianawallichii) is used in Vata and Kapha imbalances, known for calming the mind and aiding in sleep-related disorders. Known for its sedative properties, Valeriana has been shown to increase GABA levels in the brain, promoting relaxation and improving sleep quality. It may also reduce the time taken to fall asleep and the frequency of night-time awakenings. [26,27]
Brahmi (Bacopamonnieri) is referred as a MedhyaRasayana, is known for enhancing memory, intellect, and cognitive function. It balances Kapha and Pitta doshas and is widely prescribed for mental and psychological wellness. This herb has been shown to modulate neurotransmitter systems, including GABA and serotonin. It hrlps in protecting against neurodegeneration and promoting overall mental well-being.[28] Studies show that Brahmi can improve attention and behaviour in children with Attention-Deficit Hyperactivity Disorder (ADHD), helping with cognitive performance and reducing hyperactivity.[29]

Overall activity of Tab. Prasham:
Mode of action of Tab. Prasham may be due to GABA either via direct receptor binding orionic channel or cell membrane modulation; GABA transaminase or glutamic acid decarboxylase inhibition; a range of monoaminergic effects; and potential cannabinoid receptor modulation.[30]

Strengths and Limitations
Although the study was an 'add-on' intervention, the double-blind design provided near-accurate estimate of the efficacy of Tab. Prasham in reducing anxiety. The 'placebo-effect' was nullified by the design. These were the strengths of the study.

Conclusion: -

Based on the double-blind trial conducted and statistical analysis it can be concluded that Tablet Prasham is effective in reducing the anxiety when given as an add-on to the standard of care. P value was statistically significant in reducing HAM-A score at day 15 and at day 60. The proprietary Ayurvedic medicine is safe to consume.

Tablet Prasham is also useful in increasing duration and quantity of sleep.

The overall results are encouraging in favour of the investigational product, Tab. Prasham.

Conflict of Interest

Nil.

Acknowledgements:-

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