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COMPARATIVE EVALUATION OF CLINICAL ANXIOLYTIC EFFICACY OF *SITADI AGADA* AND IMIPRAMINE (TCAS) IN THE MANAGEMENT OF GENERALIZED ANXIETY DISORDERS (GAD)- A REVERSE PHARMACOLOGY APPROACH

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Abstract:

Anxiety a psychosomatic disorder represents mental sickness, and the affliction they cause can keep yourself away from your normal life. Anxiety disorders affect 16.6% of population worldwide and according to W.H.O. In India generalized anxiety disorder is 8.5% which is very high. Today allopathic medicine like Benzodiazepines,Tricyclic Antidepressant (TCAs) and Selective Serotonin Re-uptake Inhibitors (SSRIs) are commonly used for treatment of anxiety disorders.

There are no exact terms for Generalized Anxiety Disorders (GAD) in the classics of Ayurveda. Several scholars have used terms such as *Chittodvega* or *udvega*, *Vishaad*, *Attatvabhinivesh*, *AnavasthitaChita*, etc., to explain GAD.In ayurvedic classics, *udvega* or *chittoodvega* is symptom in *manasroga*, which is developed due to vitiation of *raja* and *tama* along with *vata* and *pitta*. It may be mentioned as *chitta* (Mind) + *udvega* (anxiety) i.e. anxious state of mind.

The treatment of psychosomatic diseases in Ayurveda is Medhya, & Rasayan drugs, whichnot only involves enhancement of *Dhee, Dhrithi, Smriti*but also produce Neuro-Nutritive effect by enhancing cerebral metabolism thereby useful in managing the mental dysfunction and suppressing the symptoms.Various researches show formulation having Medhya and Rasayan properties are effective in GAD. Some traditional healers or *vruddhavaidya* quotes that *SitadiAgada* is useful in generalized anxiety disorders (GAD).*Sitadi Agada*is a Madhur, sheet, Medhya & rasayan ayurvedic formulation which has drugs or contents

viz.*Sharkara* (Rock Candy\sugar candy), *Vaigandhiko* (Sulphur), *Draksha*(*Vitis vinifera* L.) *Payasya* (Asparagus recemosusWilld*), Madhuka* (Glycyrrhiza glabra L.) and Honey.

The proposed work will be conducted in the light of reverse pharmacology approach; step one is identification of the remedy (Ayurvedic Literature), step two is dose escalation studies; to find out most efficacious and safe dose of Sitadi Agada. And finally step three is to conduct a randomized clinical trial of *Sitadi Agada* compared with standard first line drug Imipramine (TCAs).

If the trial drug is proven as a better anxiolytic drug, it can be prescribed as a main drug in anxiety management or along with other drugs to reduce fear related anxiety.

Keywords: Reverse Pharmacology Approach, Generalized Anxiety Disorders, Udvega, Sitadi Agada, Imipramine.

INTRODUCTION:

Anxiety is an emotional state characterized by inner turmoil, confusion, and nervous behavior such as restlessness, somatic complaints, and excessive worry.[1] It is associated with various psychiatric disorders including panic disorder, phobias, depression, generalized anxiety disorder (GAD), obsessive–compulsive disorder, and post-traumatic stress disorder.[2] Persistent anxiety significantly disrupts normal life and may lead to serious health consequences. Globally, anxiety disorders affect about 16.6% of the population, while in India the prevalence of GAD is approximately 8.5%, indicating a substantial public health burden.[3]

Conventional allopathic treatments for anxiety include benzodiazepines, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs).[4] Although effective, these drugs are associated with adverse effects such as sedation, cognitive impairment, and dependence, particularly with long-term use. In contrast, Ayurvedic anxiolytic therapies—especially Rasayana and Medhya drugs—aim to enhance intellect (Dhi), retention (Dhriti), and memory (Smriti), while exerting neuro-nutrient effects that support cerebral metabolism and mental balance.[5]

Sitadi Agada is a classical herbo-mineral Ayurvedic formulation traditionally used in Shankavisha (pseudo-poisoning), a condition arising from fear-induced illusion of snake bite. Classical texts describe Shankavisha as resulting from udvega (anxiety), producing symptoms such as agitation, fainting, vomiting, and mental confusion, which closely resemble those of anxiety disorders. [6] On the basis of etiological factors, symptom similarity, and psychological mechanisms, Shankavisha can be correlated with generalized anxiety disorder.[7,2]

Sitadi Agada contains Sharkara[8], Sulphur,[9] Vitis vinifera,[10] Asparagus racemosus,[11] and Glycyrrhiza glabra,[12] and honey[13]— ingredients shown experimentally to possess anxiolytic properties. The present study adopts a Reverse Pharmacology approach,[14] beginning with classical evidence and clinical experience, followed by dose-optimization and a randomized clinical trial. The study aims to evaluate the efficacy, safety, and optimal dose of Sitadi Agada in GAD patients and to compare its effects with the standard drug Imipramine using the Hamilton Anxiety Rating Scale (HARS).

RESEARCH QUESTION:

R.Q. 1: (Phase-1) What is the most efficacious and safe dose of *Sitadi Agada* with management of generalized anxiety disorder (GAD)?

R.Q. 2: (Phase-2) Whether *Sitadi Agada* is more efficacious as compare to imipramine in the management of generalized anxiety disorder?

HYPOTHESIS

Alternative Hypothesis:

Sitadi Agada is more efficacious as compare to Imipramine (TCAs) in the management of generalized anxiety disorder?

Null Hypothesis:

There is no difference in the efficacy of Sitadi Agada versus Imipramine (TCAs) in the management of generalized anxiety disorder?

RESEARCH GAP ANALYSIS:

Chakrapani in *Vishachikitsaadhyaya* mentioned that, *Shankavisha* is produced because of *udvega* of *visha*.[15] *Udvega* means anxiety; *chittodvega* means anxious status of mind. There are no exact terms for generalized anxiety disorders (GAD) in the classics of Ayurveda. Several scholars have used terms such as *Chittodvega* or *udvega*, *Vishaad*, *Attatvabhinivesh*, *AnavasthitaChita*, etc., to explain GAD.[16]

Some traditional healers or *vrudha vaidya* quotes *Sitadi Agada* will be useful in generalized anxiety disorders (GAD).[17] Various researches show *medhya, rasayana* properties of different formulations which are efficacious in GAD.[18-23]

Sitadi Agada contains six ingredients. *Draksha* (*Vitis vinifera* Linn) is *madhura, sheeta, vrushya* and has anxiolytic effect with 4ml/kg and 8ml/kg once daily dose up to 60 days on experimental study.[10] *Shatavari* (*Asparagus recemosus* Willd) is *madhura, sheeta, rasayana* and has anxiolytic effect with 50, 100, and 200mg/kg two times daily dose up to 7 days on experimental study out of them doses minimum effective dose 100mg/kg.[11] *Madhuka* (*Glycyrrhiza glabra* Linn) is *madhura, sheeta, medhya rasayana* and has anxiolytic effect by varied dose 10 to 300mg/kg on experimental study.[12] *Gandhaka* (sulfur) is *maharasayan,* and has anxiolytic effect with 1.68 or 5.6mg/kg dose up to 7 days on experimental study.[9] *Sita* (Rock candy/Sugar candy) is *madhura, sheeta, rasayana and* has anxiolytic effect.[8] *Madhu* (honey) is *ushna, yogavahi* and has anxiolytic properties.[13] All the six ingredients in *Sitadi Agada* show anxiolytic activity individually with different dose and duration. The efficacy is observed in animal, but there is no any previous clinical study. There is no any research study like pharmaceutical or physicochemical analysis, animal or clinical study on *Sitadi Agada*.

None of the earlier studies have incorporated quality control parameters or dosage modifications to make Sitadi Agada easier to administer and more acceptable to patients in a fixed-dose form such as Vati (tablet). Therefore, sufficient scientific evidence is required to establish the efficacy of a modified dosage form of Sitadi Agada in patients with generalized anxiety disorder (GAD) using a reverse pharmacological approach. If its anxiolytic efficacy is proven, Sitadi Agada may also be utilized in other disease conditions associated with anxiety. Currently available anti-anxiety medications are associated with significant systemic adverse

effects and a high risk of drug dependence, posing serious safety concerns. Imipramine, a tricyclic antidepressant, is considered effective with fewer side effects than benzodiazepines and is used as the standard comparator in this study. If Sitadi Agada demonstrates efficacy equal to or superior to Imipramine, it could expand safer therapeutic options, justifying this clinical evaluation of its efficacy and safety in GAD using the Hamilton Anxiety Rating Scale (HARS).

AIM AND OBJECTIVES

Aim:

Comparative Assessment of anxiolytic efficacy of Sitadi Agada and Imipramine (TCAs) in the management of generalized anxiety disorders.

Objectives:

i. To prepare *Sitadi Agada* and study of physicochemical parameters of *Sitadi Agada.*

ii. To study the efficacy of *Sitadi Agada* and Imipramine (TCAs) in the management of generalized anxiety disorders patient.

iii. To compare the efficacy of *Sitadi Agada* and Imipramine (TCAs) in the management of generalized anxiety disorders patient.

iv. To study the adverse effect of *Sitadi Agada* if any.

MATERIAL AND METHODS:

Present work will be conducted with following details;

Stages of study:

The study will be carried out in the following steps:

a. Identification & Authentication of Drugs

b. Preparation of *Sitadi Agada*

c. Analytical Study of *Sitadi Agada*

d. Pilot Clinical Study to identify the best dose of *Sitadi Agada* in patients of GAD.

e. Randomized comparative open labeled Clinical Trial (RCT) to assess the efficacy of *Sitadi Agada* in patients of Generalized Anxiety Disorders (GAD)

Pharmaceutical Study:

Collection, Identification and Authentification of Drug:

The genuine and authenticated raw materials of the test formulation will be purchase from GMP certified pharmacy. The drugs will be authenticated from FRLHT, Bangalore or a Centre recognized by DMIMS (DU).

Table No:1 Preparation of *Sitadi Agada:*

Sr. No.	Name of Drug (IUPAC)	Scientific / Latin name	Quantity required
1	*Sita*	Rock Candy derived from Saccharum officinarum	2 kg
2	*Vaigandhico*	Sulphur	2 kg
3	*Draksha*	Vitis vinifera Linn	2 kg
4	*Payasya*	Asparagus recemosus Willd	2 kg
5	*Madhuka*	Glycyrrhiza glabra Linn	2 kg
6	*Madhu (*as Anupan)	Honey	2 kg

Sitadi Agada preparation *: Shodhana* of *Vaigandhiko* (Sulphur) will be done as per standard established methods of *Shodhana Sanskara* in Ayurveda. Powder of all (four) the raw drugs & Draksha overnight soaked will be prepared and taken in equal quantity. They will be mixed properly to form a homogenous mixture and tablet will be prepared.

Analytical study of *Sitadi Agada:-*

Physicochemical study will be conducted in Analytical Laboratory, M.G.A.C.H. & R. C. Salod (H), Wardha.

CLINICAL STUDY

STUDY DESIGN: Randomized Interventional comparative open label study by reverse pharmacology Approach.

SELECTION OF PATIENT:

Screening:

A) Patient fulfilling the (DSM – IV) & who score at least 14 on the Hamilton Anxiety Rating Scale (HARS – A) at baseline visit.

PARTICIPANT'S INCLUSION CRITERIA:

a) Patient willing to sign the consent forms.

b) Patients of either sex with age between 18 to 60 years.

c) Patient fulfilling the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM – IV).

e) Patient who score at least 14 on the Hamilton Anxiety Rating Scale (HARS– A) at baseline visit.

PARTICIPANT'S EXCLUSION CRITERIA:

a) Anxiety due to direct physiological effect of a substance (e.g. alcohol etc) or a general medical condition (e.g. Hyperthyroidism).

b) Occurrence of anxiety exclusively during mood disorder, a psychotic disorder or a pervasive development disorder.

c) Patients having history of chronic diseases like Diabetes Mellitus, Ischemic Disease, Dyslipidemia, Hypertension, Malignancies, Chronic Renal Failure, Any Endochrinological disorders etc. will be excluded.

d) Patients who have completed participation in any other clinical trial during the past six months.

e) Pregnant or lactating women.

f) Any other condition which the investigator thinks may jeopardize the study.

g) Patients receiving Anxiolytic Drugs will be excluded.

METHODOLOGY:

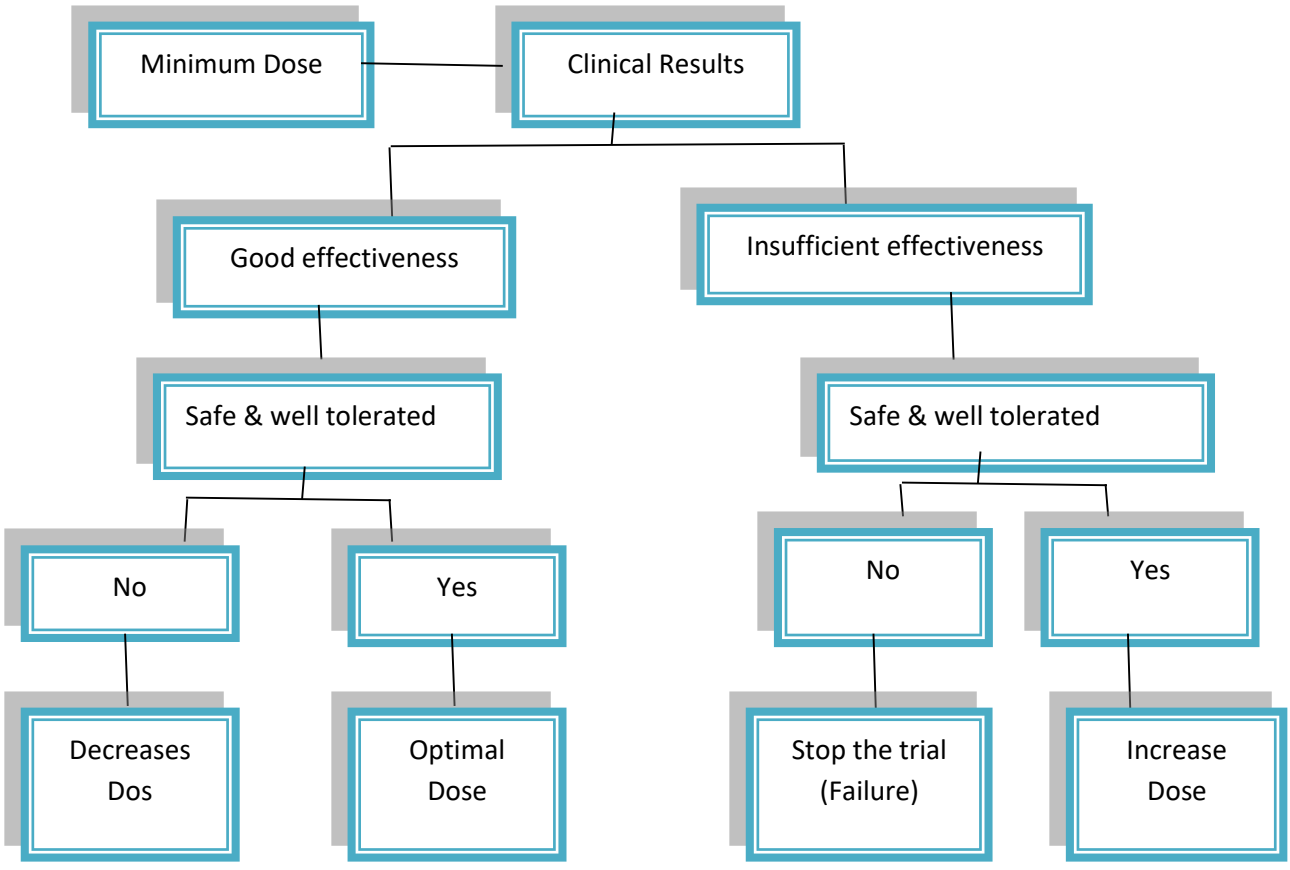
IEC Approval received with reference number MGACHRC/IEC/JULY-2021/259 Dated 10 July 2021.

The proposed work is based on the principles of Reverse Pharmacology consisting of different steps as described in literature review. The initial stage of selection of herbal remedy has already been described under Literary Review. Further stages involve administration of drug to human participants for fixation of dose and randomized clinical trials. The methodology for these stages is described under this section.

Stage 2- Dose- escalating clinical trial (Reverse Pharmacology)

This stage aims to determine the most effective dose of Sitadi Agada with minimal side effects. A pilot study will be conducted on three groups of 10 GAD patients each, receiving Sitadi Agada Vati at doses of 250 mg, 500 mg, and 1 g respectively, administered twice daily after meals with honey as the vehicle. The pilot study will be carried out for duration of 30 days following the same methodology as the randomized controlled trial. Based on the outcomes, the most effective and safest dose will be selected for the main study.

Fig. 1 .Dose optimization of a drug through Reverse Pharmacology



Stage 3: Randomized Clinical Trial (Reverse pharmacology)

A randomized compared open label clinical trial with the best effective dose of *Sitadi Agada* shall be conducted in this stage. According to the CONSORT 2010 flow diagram, a total of 60 participants will be assessed for eligibility, of which eligible subjects will be randomized into Sitadi Agada (500mg bd with honey after meal) and Imipramine (with water hs) groups, followed up, and analyzed after accounting for exclusions, dropouts, and losses to follow-up.

METHODOLOGY FOR RCT:

ASSESSMENT CRITERIA:

Volunteers will be informed about the study protocol, and eligible participants will be randomly allocated to different treatment groups after obtaining written informed consent. Patients fulfilling DSM-IV diagnostic criteria and scoring at least 14 on the Hamilton Anxiety Rating Scale (HARS-A) at baseline will be included in the study. Following enrollment, participants will receive their respective interventions for a treatment period of 30 days, with medication dispensed every 15 days. Fortnightly in-person follow-ups will be conducted to ensure treatment compliance. At the end of the study period, participants will be reassessed using HARS-A, and those lost to follow-up will be excluded from the final analysis.

TYPE OF STUDY:

Randomized Interventional comparative open label study by reverse pharmacology Approach.

STUDY DURATION: 24 month

STUDY SITE:

- Department of RSBK, Analytical Laboratory, Mahatma Gandhi Ayurved College, Hospital and Research Institute, Salod (H) Wardha. Or a Centre recognized by DMIMS (DU).
- LRPAMCHPGI & RC Islampur.

STATISTICAL METHODS:

The data will be expressed as mean±standard error of mean. Data will be analyzed by using Wilcoxon sign rank test and Man Whitney U test or as per appropriate statistical formula.

DISCUSSION:

Anxiety is a normal emotional response to perceived danger; however, excessive or inappropriate anxiety may develop into a pathological disorder.[3-4] Anxiety disorders affect approximately 16.6% of the global population,[24] and in India the burden is particularly high, with nearly 19% of individuals experiencing anxiety disorders and an estimated 40 million adults affected. Generalized anxiety disorder (GAD) alone accounts for about 8.5% of the Indian population.[3,5,25] Stress plays a major role in precipitating anxiety,[3] and due to adverse effects and limited awareness of conventional treatments, many patients prefer alternative therapies.

GAD is a psychosomatic disorder with an incompletely understood pathophysiology, though altered serotonergic and noradrenergic activity is implicated. Consequently, SSRIs, SNRIs, and TCAs are commonly used, with antidepressants shown to be more effective than benzodiazepines in some cases.[26] In Ayurveda, anxiety-like conditions are described using terms such as Udvega or Chittodvega. Acharya Charaka described Sitadi Agada in the context of Shankavisha, a fear-induced condition characterized by anxiety-related manifestations.[27,28,29]

Ayurvedic management of psychosomatic disorders emphasizes Medhya and Rasayana drugs that enhance Dhee, Dhriti, and Smriti, while improving cerebral metabolism.[5] Sitadi Agada comprises Draksha (Vitis vinifera),[10] Shatavari (Asparagus racemosus), Madhuka (Glycyrrhiza glabra)[12], Gandhaka (sulphur),[9] Sita (rock sugar)[8], and Madhu (honey)[13], all of which possess anxiolytic, neuroprotective, and antioxidant properties. Traditional experience and emerging research suggest that Sitadi Agada, owing to its Madhura, Sheeta, Medhya, and Rasayana attributes, may be effective in alleviating generalized anxiety disorder.

OUTCOME:

Primary Outcome:

If there is enhancement in the Ayurvedic components of Psyche i.e. *Dhee, Dhriti, Smriti* by use of this study drug *Sitadi agada*, it will be very helpful in managing Generalized Anxiety Disorders (GAD).

Secondary Outcome:

In the selected clinical research works, if anxiolytic effect of the Sitadi Agada will be proved, it will establish anxiolytic effect of one of the AYUSH drug. It will be used as safe and without adverse effect drug in generalized anxiety disorders. It will be cost effective, easy available, easy administrable

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