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Central Nervous System (CNS) Activity of *Argyreia speciosa* and *Acorus calamus*: A Review.

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Review Article

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ABSTRACT

Acorus calamus and *Argyreia speciosa* are useful medicinal plants which gave the varied effects on CNS. These plants have been tested in various animal models for testing their activity in the CNS disorders. There is always a need to clearly define the nature of CNS activity of new chemical entity (NCEs) or medicinal plants. This classification is important to categorized the CNS effects into: beneficial and adverse effects. Various animal models are enlisted using which the CNS effects of the *Acorus calamus* and *Argyreia speciosa* could be tested other than which is generally used in the review literature. An attempt have been made in this review to clearly classify the pre-clinical CNS effect of *Acorus calamus* and *Argyreia speciosa* using WHO classification (1967) of CNS active drugs. It is observed that there is lacuna in studies for clinical, toxicological and safety pharmacological evaluation of *Acorus calamus* and *Argyreia speciosa.* In the review literature there only few report of clinical studies of *Acorus calamus* whereas there is no such report of *Argyreia speciosa.* It is suggested that there should be conduct of clinical studies/trials to open the gate of use of these potential plants in the various humans CNS disorders. As little is known regarding adverse effects of *Acorus calamus* and *Argyreia speciosa* and their frequencies, the chronic exposure of these herbals may cause health risks. Hence, safety pharmacological core battery test shall be performed on *Acorus calamus* and *Argyreia speciosa* to establish them as efficacious and safe alternative for the CNS disorder. Moreover, the use of herbal medicines, as health promoting agents, in developed countries has also increased and this trend is continuing. Healthcare professionals need to be aware of the pharmacology of these herbal medicines in order to provide well informed advice to patients.

INTRODUCTION

The human nervous system is an extremely complex structure, having more than 12 billion nerve cells or neurons. Together with the endocrine system, it coordinates and regulates the functioning of all body organs. Transmission of information in the endocrine system is by circulating hormones, and this provides for a slowly developing but long-lasting control, i.e. it functions as a slow communication system. In contrast the nervous can evoke rapid changes in body function as transmission of information is through electrical conduction of impulses along nerve fibres, and chemical transmission of impulses by neurotransmitters between nerve fibres, resulting in a moment-moment control i.e., it functions as a rapid communication system [1].

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Central nervous system (CNS) is vital organ system. Hence, the drugs acting on the CNS are very important by both perspective i.e. their effects and adverse effects. Drugs acting in the central nervous system (CNS) were among the first to be discovered by primitive humans and are still the most widely used group of pharmacologic agents. In addition to their use in therapy, many drugs acting on the CNS are used without prescription to increase one's sense of well-being. The mechanisms by which various drugs act in the CNS have not always been clearly understood. Since the causes of many of the conditions for which these drugs are used (schizophrenia, anxiety, etc) are themselves poorly understood [2].

Drugs acting in the central nervous system (CNS) were among the first to be discovered by primitive human and are still the most widely used group of pharmacological agents. From the vast array of materia medica of the indigenous system, many plants have been reported to have activity against CNS disorders and act as very useful remedies for the alleviation of human suffering [3].

Increasing number of patients express a preference for the use of remedies they perceive to be natural and Physicians recommend herbal remedies in the selected cases. It is becoming increasingly important for physician to be familiar with the herbal remedies commonly used in the patient problems they serve. Since the mental illness are diverse and individual patients are biochemically unique, a larger number of drugs will increase the likelihood of finding a beneficial medication, Hence in future times psychiatric patients will probably have medications with improved effectiveness and with less side effects. Although evidence of the efficacy of the herbal preparation in treating psychiatric conditions is growing translating the results of efficacy studies into effective treatment for patients is hampered by the chemical complexity of the products. There is lack of standardization of commonly available preparation and the paucity of well-controlled studies. This reveals that number of herbal drugs are available for the treatment of various mental disorders but there is a need to explore efficacy of many of them [4].

Acorus calamus (sweet flag) is a tall perennial wetland monocot plant from the *Acoraceae* family. The scented leaves and rhizomes of sweet flag have been traditionally used as a medicine and the dried and powdered rhizome has a spicy flavor and is used as a substitute for ginger, cinnamon and nutmeg for its odor. *A. calamus* is probably indigenous to India and now found across Europe, Southern Russia, Northern Asia Minor, China, Japan, Burma, Sri Lanka, and Northern USA [5].

Argyreia speciosa (convolvulaceae) commonly known as 'Elephant creeper' is a woody climber distributed throughout the India up to an altitude of 300 meters2. It has been used as 'Rasayan' drug in the ayurvedic system of medicine to cure diseases of nervous system. The roots of this plant have been regarded as tonic, aphrodisiac, bitter and used in rheumatism, gonorrhea, chronic ulcer and diseases of nervous system [6].

Animal Models for Evaluation of CNS Activity

Animal's models plays vital role in drug discovery and development. Here are some of the methods which could be used routinely for screening of drugs for CNS activities (Table No.1) in addition to test presented in table nos. 3 & 4.

Table No.1: Pre-clinical Test used for Screening of CNS activity of drug [7, 8]

Sr. No.	Name of the Test	Parameters Evaluated	Application
1.	Observational assessment	Effects on CNS, Effects after manipulations, Effects on reflexes, Effects on autonomic nervous system	It allows to identify and differentiate the profile pattern of various classes of pharmacological agents. Furthermore, observational assessment allows into the safety and potential toxicity profile of a new drug.
2.	Effects on motility	Locomotion, rearing, sniffing, grooming, eating and drinking.	sedative or stimulatory activity

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Table No.1: Pre-clinical Test used for Screening of CNS activity of drug Cont...[7, 8]

Sr. No.	Name of the Test	Parameters Evaluated	Application
3.	Hole-board test	The number of counts for nose-poking of treated animals	curiosity or exploration
4.	Combined open field test	Counts for motility (interruption of photo cell beams inside the cage) and for curiosity (interruption of photo cell beams outside the cage due to nose-poking)	The simultaneous determination of locomotion and curiosity
5.		Tests for muscle coordination	
5.1	Inclined plane	The peak time is determined as the time at which a compound produces the maximum performance deficit.	for differentiating neuroleptics from other centrally active drugs, skeletal muscle relaxation.
5.2	Chimney test	The *ED*50 (with 95% confidence limits), the dose for which 50% of the animals fail to climb backwards out of the tube within 30 s,	test for tranquilizing and muscle relaxant activity.
5.3	Grip strength	The percentage of animals loosing the catching reflex is calculated.	To assess muscular strength or neuromuscular function in rodents which can be influenced not only by sedative drugs and muscle relaxant compounds but also by toxic agents.
5.4	Rotarod method	Percent animals falling from the rotarod within the test period is calculated for every drug concentration tested.	The test is used to evaluate the activity of drugs interfering with motor coordination
6.	marble-burying tests	Animals were individually placed in the cage for 10 min. They will be removed and the burying response quantified by counting the number of marbles that were more than two thirds covered with sawdust. A diminution of the burying response reveals a positive anxiolytic-like effect	To test anxiolytic activity

Preclinical CNS Activities of *Argyreia speciosa* and *Acorus calamus*

Psychotropic drugs are defined as those that affect mood and behaviour. Because these indices of brain function are difficult to define and measure, there is no consistent basis for classifying psychotropic drugs. However, grumbling about terminology is fruitless. The following classification is based on that suggested in 1967 by the World Health Organization (WHO). Although flawed, using this classification system an attempt has been made to classify the pharmacological action of *Acorus calamus* and *Argyreia speciosa* on CNS in the table no. 3 and 4 respectively [9].

Table No.2: Classification of Drugs acting on CNS (WHO, 1967)

- Anaesthetic agents
  Definition: drugs used to produce surgical anaesthesia.
  Examples: **halothane , propofol**
- Anxiolytics and sedatives
  Synonyms: hypnotics, sedatives, minor tranquillisers
  Definition: drugs that cause sleep and reduce anxiety
  Examples: **barbiturates, benzodiazepines**.
- Antipsychotic drugs
  Synonyms: neuroleptic drugs, antischizophrenic drugs, major tranquillisers
  Definition: drugs that are effective in relieving the symptoms of schizophrenic illness
  Examples: **clozapine , chlorpromazine, haloperidol**
- Antidepressant drugs
  Synonym: thymoleptics
  Definition: drugs that alleviate the symptoms of depressive illness
  Examples: monoamine oxidase inhibitors and tricyclic antidepressants
- Analgesic drugs
  Definition: drugs used clinically for controlling pain
  Examples: **opiates, carbamazepine**

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- Psychomotor stimulants
  Synonym: psychostimulants
  Definition: drugs that cause wakefulness and euphoria
  Examples: **amphetamine, cocaine** and **caffeine**
- Psychotomimetic drugs
  Synonyms: hallucinogens, psychodysleptics
  Definition: drugs that cause disturbance of perception (particularly visual hallucinations) and of behaviour in ways that cannot be simply characterised as sedative or stimulant effects
  Examples: **lysergic acid diethylamide** (LSD), **mescaline** and **phencyclidine**
- Cognition enhancers: perhaps this is more of a wishful than a real category
  Synonyms: nootropic drugs
  Definition: drugs that improve memory and cognitive performance
  Examples: **tacrine, donepezil, piracetam**

Table No. 3: CNS Activity of *Acorus Calamus* (AC)

Sr. No.	Plant Part	Solvents	Activity	Model Used	Results	Researcher
			Analgesic Activity			
1.	Roots	Methanol	Analgesic	Acetic acid induced writhing in Rat	Showed Analgesic Activity	Jayaraman et. al [10]
			Analgesic	Rat caudal immersion	Showed Analgesic Activity	
			Anxiolytics and sedatives Activity			
2.	Leaves	Methanol	CNS depressant activity	Diazepam Induced Sleeping Time Mice	Showed CNS Depressant Activity	Pandy et.al [11]
				Spontaneous Locomotor Activity in Mice	Showed CNS Depressant Activity	
			Antidepressant Activity			
3.	Leaves	Methanol	Antidepressant	Behvioral Despair Swim Test in Mice	Showed CNS Anti-depressant Activity	Pandy et.al [11]
			Antipsychotic Activity			
4.	Leaves	Methanol	Antipsychotic	Apomorphine Induced Stereotypy Mice	Showed Antipsychotic Activity	Vengadesh et.al [12]
				Haloperidol Induced Catalepsy Mice	Potentiated Haloperidol Induced Catalepsy	
		Acetone	Antipsychotic	Apomorphine Induced Stereotypy Mice	Not Shown Antipsychotic Activity	
				Haloperidol Induced Catalepsy Mice	Potentiated Haloperidol Induced Catalepsy	

Table No. 3: CNS Activity of *Acorus Calamus* (AC) Cont....

Sr. No.	Plant Part	Solvents	Activity	Model Used	Results	Researcher
			Miscellaneous Activity			
5.	Roots	Methanol	Anticonvulsant	PTZ-induced seizures	Showed Anticonvulsant Activity	Jayaraman et. al [10]
6.	Leaves	Methanol	Motor In-cordination	Rotarod Test in Mice	Not showed motor incordination	Pandy et.al [11]

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Table No. 4: CNS Activity of Argyreia Speciosa (AS)

Sr. No.	Plant Part	Solvents	Activity	Model Used	Results	Researcher
			Anxiolytics and sedatives Activity			
1.	Root	N-Hexane, Chloroform, Ethylactate	CNS Depressant/Stimulation	Spontaneous locomotor activity (SMA) in Mice using Actophotometer	Showed CNS Depressant Activity1	Galani et. al [13]
			Pentobarbitone sleeping time (PST)	Pentobarbitone sleeping time in Mice	Potentiation of PST i.e. CNS Depressant	
2.	Root	Hydroalcoholic	CNS Depressant/Stimulation	Spontaneous Locomotor Activity (SMA)	Showed No CNS depressant or Stimulation Activity	Vyawh-are et. al [14]
		Hydroalcoholic	Anxiolytic activity	Elevated Plus maze in Mice	Lack of anxiolytic activity	
		Hydroalcoholic	Anxiolytic activity	Double unit mirror chamber	Not showed anxiolytic activity	

Table No. 4: CNS Activity of Argyreia Speciosa (AS) Cont.....

Sr. No.	Plant Part	Solvents	Activity	Model Used	Results	Researcher
3.	Root	Hydroalcoholic	Central Nervous System Depressant/Stimulant	Spontaneous Motor Activity in Mice	Showed CNS Depressant Activity	Galani et.al [15]
		Hydroalcoholic	Sedative Activity	Pentobarbitone Induced Hypnosis	Showed Sedative and/or Hypnotic Activity	
		Hydroalcoholic	Exploratory Activity	Head Dip Test in Mice	Showed CNS Depressant Activity	
		Hydroalcoholic	Exploratory Activity	Evasion Test in Mice	Showed CNS Depressant Activity	
		Hydroalcoholic	Hyperthermia/Hyperthermia	Rectal Temperature in Mice	Showed Hypothermia and Indicate CNS Depressant Activity	
			Antidepressant Activity			
4	Root	Hydroalcoholic	Anti-stress Activity	Swimming Endurance Test in Mice	Showed Anti-stress Activity	Patel et.al [16]
				Anoxic Tolerance Test Mice	Showed Anti-stress Activity	
				Cold Restrained Test in Rat	Showed Anti-stress Activity	
			Antipsychotic Activity			
5.	Root	Hydroalcoholic	Antidopaminergic	Haloperidol induced catalepsy in Mice	Anti-dopaminergic activity	Vyawhare et. al [14]
6.	Root	Hydroalcoholic	Neuroleptic Activity	Catalepsy in Rat	Potentiated Catalepsy thus, indicated Neuroleptic Activity	Galani et.al [15]
				Apomorphine Induced Stereotypy	Reverse Apomorphine Induced Stereo indicated Neuroleptic Activity	

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Table No. 4: CNS Activity of Argyreia Speciosa (AS) Cont.....

Sr. No.	Plant Part	Solvents	Activity	Model Used	Results	Researcher
			Cognition enhancers Activity			
7.	Root	Hydroalcoholic	Learning and Memory	Object Recognition Test in Mice	Showed Memory Improvement	Vyawhare et. al [14]
			Spatial Learning and Memory	Radial Arm maze Mice	Facilitation of spatial learning and memory.	Vyawhare et. al [17]
				Morris Water Maze Mice	Facilitation of spatial learning and memory.	
8.	Root	Aqueous	Nootropic	Elevated Plus Maze	Showed Nootropic Activity	Joshi et.al [18]
				Passive Shock Avoidance	Showed Nootropic Activity	
			Miscellaneous Activity			
9.	Root	Hydroalcoholic	Motor in-coordination	Rota Rod in Mice	Showed No motor in-coordination	Vyawhare et. al [14]
10.	Root	Hydroalcoholic	Effect on Motor Coordination	Rota Rod in Mice	Showed No Motor In-coordination	Galani et.al [15]
11.	Root	Hydroalcoholic	Anticonvulsant	PTZ-Induced Convulsion in Mice	Showed Anticonvulsant Action	Vyawhare et. al [19]
				Maximal Electroshock Induced Convulsions in Mice	Showed Anticonvulsant Action	

Table No. 4: CNS Activity of Argyreia Speciosa (AS) Cont.....

Sr. No.	Plant Part	Solvents	Activity	Model Used	Results	Researcher
			Miscellaneous Activity Cont....			
12.	Root	Hydroalcoholic	Anticonvulsant activity	PTZ and MES induced convulsion Mice	Modify the progress of convulsive episodes	Vyawhare et. al [14]
			Antisertonergic activity	5-HT induced head twitching in Mice	Showed reduction in central serotonergic transmission	
			Inhibition of noradrenergic transmission	Clonidine induced hyperthermia in Mice	Inhibition of noradrenergic transmission	
			Involvement of cholinergic transmission	Sodium nitrite induced respiratory arrest Mice	Devoid of chlolinergic transmission activity	

Clinical Studies of *Acorus calamus*

The clinical trial was carried on 40 healthy patients. The patients were divided into two groups randomly. The control and trial groups included 20 patients each of narrow age and weight distribution. The patients of group I (Control) were premedicated with Inj. Glycopyrrolate 0.2 mg IM and Tab. Phenergan 50 mg orally with one ounce of plain water. The patients of group II (Trial) were premedicated with Inj. Glycopyrrolate 0.2 mg I.M. and Vacha (Ghansatva) orally in recommended doses with one ounce of plain water 90 minutes prior to induction of anaesthesia. A standard anesthetic technique with pre oxygenation for 3 minutes & Nitrous oxide with Ether inhalation by spontaneous ventilation with Maggill's open circuit (Boyle's apparatus) was used. The following parameters were used to see the efficacy of the drug: Psychophysical effect before induction of anaesthesia, Cardio-respiratory and other

reflex response during the course of subsequent anaesthesia & Post operative sickness in immediate post operative period up to two hours. On the basis of observations, it was concluded that Vacha controls the raised body[20] temperature, produces good sedation and it may be helpful in the patients with pre-existing hyperthermia. It does not produce any C.V.S. & Respiratory depression

The present investigation was undertaken to evaluate the role of 70% hydro-ethanolic extract of *Vaca* or *Acorus calamus* (ACE) on generalized anxiety disorder (GAD) in human. Hamilton's Brief Psychiatric Rating Scale (BPRS) and thorough clinical investigations were used to screen the subjects. Thirty-three participants (20 male and 13 female; average age 36.2 yrs) were medicated with ACE 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 scale also includes a number of direct queries about current levels of experienced stress. Moreover, the questions are of a general nature and hence are relatively free of content specific to any subpopulation group. The observations exhibited that, ACE not only significantly ($p<0.001$) attenuated anxiety related disorders but it also significantly ($p<0.001$) reduced stress phenomenon and its correlated depression. ACE further significantly ($p<0.001$) improved the willingness to adjustment. Therefore, it may be concluded that *Vaca* may be useful in the treatment of GAD in human and may be a promising anxiolytic agent in near future [21].

Efficacy of *Acorus calamus and Argyreia speciosa*

Herbal medicines have a long history of traditional use. However, from today's stand point, traditional claims need to be verified. A well-designed randomized controlled trial is essential to determine the efficacy and safety of herbal medicines. The use of standardized herbal extracts in clinical trials is important to obtain reproducible data on the efficacy and safety of herbal medicines. Standardization of herbal extracts has become a common practice in phytomedicines. It allows the establishment of reproducible pharmaceutical quality by comparing a product with established reference substances and by defining the specific quantity of one or several compounds. As the herbs are of natural origin, their chemical composition is affected by several factors (climate, growing conditions, time of harvesting, storage conditions and processing). Therefore, the use of standardized herbal extracts in preclinical and clinical research is helpful to develop evidence based traditional therapies. Although rigorous clinical investigations are lacking at present for many herbs used in CNS disorders, there is a vast literature on the *in vitro* and *in vivo* pharmacological effects of medicinal plants. These pre-clinical observations provide a rationale for *Acorus Calamus and Argyreia speciosa* [22].

Safety of *Argyreia speciosa* and *Acorus calamus*

The positive attitude towards herbal medicines is based on the indication that herbs have been used since ancient time and the belief that they have the advantage of being 'natural' rather than 'synthetic'. Traditional healing systems employed herbal medicines for the symptomatic management of diseases. However, these herbs are now being used extensively for health promotion and disease prevention not only in underdeveloped and developing nations, but also increasingly in developed nations. As little is known regarding adverse effects of herbal medicines and their frequencies, the chronic exposure of these herbal ingredients may pose health risks. In particular, when herbs are extracted and purified, their toxicity might be increased due to increased concentration of potential toxic compounds. Therefore, the common assumption that herbal medicines are by inference 'safe' may not be valid by today's health standards [22].

Acorus Calamus and Argyreia speciosa lack the following pharmacological data in humans:

- pharmacologically active chemical constituents and their metabolites
- mechanisms of action of active constituents/whole extract
- pharmacokinetics
- toxicology
- adverse effects and their frequencies
- drug–herb and food–herb interactions
- use in vulnerable individuals: children, elderly, individuals with renal or hepatic
- disease, gender effects, individuals with a different genetic profile
- contraindications

The purpose of the safety pharmacology core battery is to investigate the effects of the test substance on vital functions. In this regard, the cardiovascular, respiratory, and central nervous systems are usually considered the vital

organ systems that should be studied in the core battery In some instances, based on scientific rationale, the core battery should be supplemented or need not be implemented.

Effects of the test substance on the central nervous system should be assessed appropriately. Motor activity, behavioral changes, coordination, sensory /motor reflex responses and body temperature should be evaluated. For example, a functional observation battery (FOB) modified Irwin's or other appropriate test [23, 24].

CONCLUSION

Phytochemical and pharmacological (preclinical and clinical) studies are important for herbal medications. The *Acorus calamus* and *Argyreia speciosa* are majorly tested in animal's i.e. preclinical studies. The main focus of these studies has been determining the efficacy of herbal extracts to support their traditional claims. However, very few clinical studies have been conducted on *Acorus calamus and Argyreia speciosa*. Toxicological studies are important to provide in vivo data in a whole animal situation on the dose and adverse effects of these herbal extracts which may be relevant when tested in humans. Safety pharmacology S7A guidelines provide the basis for conducting the safety pharmacological screening of medications. Herbal medicines are an important part of the health care system in many developing countries. The use of herbal medicines, as health promoting agents, in developed countries has also increased and this trend is continuing. Healthcare professionals need to be aware of the pharmacology of these herbal medicines in order to provide well informed advice to patients. The critical question is: Does the remedy work for the patient's condition? Clinicians should not prescribe or recommend herbal remedies if that question cannot be answered with a firm Yes. Moreover, the active ingredients in herbal preparations can cause desirable as well as undesirable effects. *Acorus calamus and Argyreia speciosa* have the potential to treat CNS disorders. Additional studies on quality, efficacy and safety in animals and humans will be required to integrate them in mainstream medicine.

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