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A COMPREHENSIVE REVIEW ON NEUROPHARMACOLOGICAL POTENTIAL OF *ACORUS CALAMUS* LINN.

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Abstract

Acorus calamus Linn is a species of perennial, semiaquatic, aromatic herb with creeping rhizomes, it belongs to the family Acoraceae. In Ayurveda *Acorus calamus* Linn. is also known as VACHA and publically known as Bacha or sweet flag. It is a highly valued herb as it acts as a rejuvenator for brain and nervous system. It is a main medhya drug, which has the property of improving the memory power and intellect. *Acorus calamus* Linn. (AC) has been used as traditional Indian and Chinese prescriptions for its beneficial effects on cognitive and memory enhancement, anti-aging and anticholinergic activity. Scientific studies reported AC and its active constituents α and β-asarone possessed to have antidepressant, anticonvulsant, anti-inflammatory, analgesic, antipyretic, antispasmodic, cytoprotective, immunomodulatory, antidiarrheal, antimicrobial, anthelmintic, insecticidal, and hypolipidemic effects. This review presents a pragmatic description that deals with chemical constituents and neuropharmacological properties of *Acorus calamus* Linn. for easy and better understanding of the outstanding medicinal potential of this very special plant.

Key words : Neuropharmacology; Anti-depressant; Anti-convulsant; Nervous system; Traditional medicine.

Introduction

Acorus calamus Linn. (Family:Acoraceae) is an important herb in the Ayurvedic medicine, also known as Vacha or Sweet flag. This is a species of perennial, semiaquatic, aromatic herb with creeping rhizomes. (Yende *et al.,*2008). The plant is wildly distributed subtropical regions of Asia, North America, and Europe. (Pattanaik *et al.,*2013). *A.calamus* Linn. (AC) has been used as traditional Indian and Chinese prescriptions for its beneficial effects on cognitive and memory enhancement, anti-aging and anticholinergic activity. Research studies revealed that *Acorus calamus* and its constituents, particularly α- and β-asarone, possess a wide range of pharmacological activities such as anticonvulsant, acetylcholinesterase inhibitory, sedative, CNS depressant, memory enhancing, behaviour modifying, anti-inflammatory, antioxidant, antispasmodic, hypolipidemic, immuno- suppressive, cytoprotective, antidiarrheal, anthelmintic, antimicrobial, and insecticidal etc. (Mukherjee *et al.,*2008). Present review is trying to discuss and summarise the neuropharmacological potential of *Acorus calamus* Linn.

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Taxonomy

Kingdom: Plantae

Division: Magnoliophyta

Class: Liliopsida

Order: Acorales

Family: Acoraceae

Genus: *Acorus*

Species: *Calamus*

Phytochemical constituents of *Acorus calamus* Linn.

The major chemical constituents of *Acorus calamus* are volatile oil. The volatile oil contains mainly two active substances such as α-asarone and β-asarone. The other components of volatile oil, identified by GC/MS studies were acorenone, iso-acorone, dehydroxyisocalamendiol and (Z)-sesquilavandulol. Other phytoconstituents of

A.calamus include a sesquiterpenoidacofuran, coumarine and saponin. Apart from these content plant also containmethyleugenol, calamenol, asamyl alcohol, acorine, acoretine, acoradin, α- pinene, lucenin, asaronaldehyde, calamenone,shyobunone, starch and tannine. (Yende *et al.,*2008; Pattanaik *et al.,*2013).

Neuro pharmacological effects of *Acorus calamus* Linn.

1. Sedative/Calming and hypothermic Effects of *Acorus calamus* Linn

Various research studies pointed out the sedative and calming effects of *Acorus calamus*. Asarone is one of the active component present in the volatile oil of *Acorus calamus,* Dandiya PC & Menon MK (1964) studied the actions of asarone on behavior, stress, and hyperpyrexia, the results showed that Asarone even in law doses, reduced the spontaneous motor activity of rats and caused reduction in anxiety without disturbing the perception of trained rats. In monkeys it produced a long lasting calming effect, which was produced more quickly than with reserpine. Asarone produced hypothermia in mice, it counteracted LSD-25-induced hyperpyrexia even at a lower dose. In rats subjected to acute cold stress, asarone prevented the depletion of adrenal ascorbic acid showing thereby that it is an agent specific in counteracting stress. (Dandiya *et al.,*1964).

In another study conducted by Qiu G *et al.* (2016) on Fmr 1 knockout (KO) mice showed that the Alpha-asarone improves locomotor hyperactivity and striatal cholinergic function. One of the characteristic clinical symptom found in several neurological and psychiatric disorders, including Fragile X syndrome (FXS) is hyperactivity. In this study the researchers used fragile X mental retardation gene (Fmr1) knockout (KO) mouse which exhibits robust locomotor hyperactivity as the animal model of FXS. Striatal samples from Fmr1 KO mice showed decreased m1 muscarinic acetylcholine receptor (m1 mAChR) expression, increased AChE activity, and reduced ACh levels. Treatment with α-asarone, major bioactive compound isolated from *Acorus calamus*, improved and Ach levels and m1 mAChR expression, and attenuated the increased AChE activity in the striatum of Fmr1 KO mice might contribute to the beneficial effects of alleviation of locomotor hyperactivity in Fmr1 KO mice. (Qiu G *et al.,* 2016).

Experimental studies conducted by V Pandy*et al* (2009) evaluated the CNS depression or analeptic activity of acute oral administration of methanol and acetone leaves extract of *Acorus calamus* in mice. The results provided the evidences that *Acorus calamus* may contain psychoactive substances that are depressant in nature. The extract produced alteration in general behavioral pattern, increase in the immobility time in behavior despair swim test, significant reduction of spontaneous motor activity, potentiation of the diazepam-induced sleeping time without inducing disturbances in motor co-ordination. (Pandy *et al.,* 2009). Research studies conducted by GM Panchal *et al* (1989) (Panchal GM *et al.,* 1989) and P Zanoli*et al* (1998) (Zanoli *et al.,*1998) also showed the sedative and hypothermic effects of *Acorus calamus* and its active constituent β-asarone.

Menon MK & Dandiya PC (1967) conducted different studies to find out the mechanism of the tranquillizing action of asarone from *Acorus calamus* Linn. Their study results concluded that sedative effect of asarone may reliant on the ergotropic division of the hypothalamus depression. (Menon *et al.,*1967). D Bhattacharyya 1 *et al.,* (2011) conducted a clinical study on the management of generalized anxiety disorder (GAD) with *Acorus calamus*. Programmed clinical study was performed in the Out-Patient Clinics of the State Ayurvedic Medical College & Hospital, Govt. of West Bengal, Kolkata. 33 GAD identified subjects were participated in the study. The subjects were given 500mg plant extract encapsulated capsule orally in dose of one capsule, twice daily after meal. Subjects were screened thoroughly by Hamilton's Brief Psychiatric Rating Scale (BPRS) and rigorous clinical investigations. The observations demonstrated that, *Acorus calamus* can significantly reduce anxiety related disorders also consider ablyreduce stress phenomenon and its correlated depression. Plant extract also improved the willingness to adjustment in the subjects. (Bhattacharyya *et al.,*2011).

2. Acetylcholinesterase-inhibitory and memory-enhancing effects

In Ayurvedic medicine *Acorus calamus* has been used to treat memory loss. (Kirtikar *et al.,*1954; Mukherjee *et al.,*2006). In vitro Acetylcholinesterase inhibitory activity of *Acorus calamus* and its active constituent asarone was reported by Pulok Kumar Mukherjee *et al.,* (2007) (Mukherjee *et al.,* 2007) and Pandy Vijayapandi *et al* (2013) (Vijayapandia *et al.,*2013). Cognitive and memory enhancement activity of *Acorus calamus* were studies and reported by various researchers. Yutao GENG *et al.,* (2010) studied about cognitive improvement effect of β-asarone against beta-amyloid hippocampus injection in rats. Study results showed that β-asarone ameliorated the impairment of spatial memory which was evaluated by Morris water maze analysis, the mechanism for this effect was suggested by attenuating neuronal apoptos is in rats

induced by Aβ. The attenuation is associated with up regulation of Bcl-w, Bcl-2, inhibition of JNK activation, and inhibition of caspase-3 activation, finally the researchers concluded that β-asarone can be a potential drug for the Alzheimer's disease (AD) to suppress both AD-related dysfunction of the memory system and neuronal cell apoptosis. (Geng *et al.,*2010).

S. Reddy *et al.,* (2015) studied about the neuromodulatory effects of *Acorus calamus* rhizome extract (AC) on restraint stress male rats. Adult *Wistar* male rats were subjected to restrained stress for 21 days (6hr/day) and the animals were concurrently administered AC for 21 days orally. The elevated plus maze and Hebb-Williams maze used as standard behavioural models for testing memory. After the treatment regimen homogenate of rat brain used for various biochemical estimation. The study results showed the preventive action of AC rhizome powder on stress induced cognitive dysfunctions and modulatory effect on antioxidants and Na^+-K^+-ATPase activity. (Reddy *et al.,*2015). In another study protective effects of hydro alcoholic root extract of *Acorus calamus* in preventing memory loss, anxiety, and oxidative Stress on Lipopolysaccharide-induced neuroinflammation in rats were evaluated by E Esfandiar *et al.,* (2018), the study results revealed that different fractions of *Acorus calamus* are dose-dependently effective in preventing stress development and memory impairment through controlling oxidative stress and neuro inflammation. Passive avoidance test and elevated plus maze test were used to analyse behaviour changes, and various anti-oxidant parameters were evaluated in brain tissue homogenates. (Esfandiari *et al.,*2018).

3. Anticonvulsant activity

Acorus oil investigated for its antiepilepticactivity, it was given as saline suspension 1 h prior to production of convulsions in adult albino mice. It successfully prevented seizures in maximal electroshock seizures test. (Khare *et al.,*1982). In a study using electroconvulsions, α-asaroneincreased the percentage mortality of animals treated with chlorpromazine but not of those treated with reserpine. (Dandiya *et al.,*1962; Dandiya *et al.,*1963). The aqueous and alcohol extracts of *Acorus calamus* were found to reduce the severity of maximum electric shock–induced seizure in rats. β-Asarone caused generalized convulsion and potentiated metrazol seizures in rats, while α-asarone showed a tendency to protect against metrazol convulsions and modified electroshocks. (Sharma *et al.,*1961). Further, the ethanolic extracts of *Acorus calamus* significantly increased the pentylenetetrazole-induced seizure latency. (Martis *et al.,*1991). The essential oil from *Acorus calamus* showed the protective effect against electroshock seizures in rats. (Madan *et al.,*1960).

4. Antidepressant Effects

AK Tripathi& RH Singh reported the anti-depressant effects of ethanolic root extracts of *Acorus calamus* by evaluating the activity on rat model of open field test and high plus maze. (Tripathi *et al.,*2010). Antidepressant-like effects of *Acorus calamus* was also reported by Baokar (2011) in forced swimming and tail suspension test in mice. (Pawar *et al.,*2011). Chellian *et al.,* (2016), evaluated anti-depressant effects of α-asarone on mouse model tail suspension test, their study results showed the biphasic effects of α-Asarone on immobility in the tail suspension test. Acute treatment with α-asarone produced antidepressant like effect at relatively lower doses (15 and 20 mg/kg, i.p). and depressive-like activity at relatively higher doses (50 and 100 mg/kg, i.p.). (Chellian *et al.,*2016).

5. Antioxidant, Anti-inflammatory and Neuroprotective effects of *Acorus calamus* L.

Several studies reported the in vitro antioxidant potential of various extracts of *Acorus calamus*. (Acuña *et al.,*2002; Govindarajan *et al.,*2003). Manikandan*et al* (2005) evaluated in vivo antioxidant potential of ethanolic extracts of rhizomes of *Acorus calamus* (Manikandan *et al.,*2005) α-asarone (Manikandan *et al.,*2005) by producing excess amount of free radicals and oxidative stress in various parts of rat brain. Exposure to continuous loud noise (30 days: 100 dBA/4h/d) induced noise stress changes in the rat brain which was measured by determining the activity of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and the levels of reduced glutathione (GSH), vitamin C, vitamin E, protein thiols and lipid peroxidation (LPO) in discrete regions of the rat brain like cerebral cortex, cerebellum, pons-medulla, midbrain, hippocampus and hypothalamus. The study results showed that *Acorus calamus* and α-asarone effectively prevented the noise stress-induced changes in the rat brain. This anti-stressor effect might be due to an increase in brain antioxidative capacity which in turn could be achieved by protection of decreasing GSH, vitamins C, and E levels and restoring free radical scavenger's enzymatic activity.

Esfandiar *et al.,* (2018) reported the effects of hydroalcoholic root extract of *Acorus calamus* in preventing memory loss, anxiety, and oxidative stress on neuroinflammation induced rats. Intraperitonial injection of lipopolysaccharide (LPS) was used to induce neuroinflammation in rats. Various behavioral tests, including passive avoidance and elevated plus-maze

(EPM) tests were conducted to evaluate the memory power and anxiety levels of the rats. Levels of various oxidative stress markers were determined in hippocampus tissue homogenates of rats. Study results showed that oral administration of *A. calamus* prevented the rats from memory deficits and stress through controlling oxidative stress and inflammation processes. (Esfandiari *et al.,*2018).

Protective effect of *Acorus calamus* against acrylamide induced neurotoxicity in rats was reported by PK Shukla *et al.,* (2002). Exposure of acrylamide (ACR) in animals produced hind limb paralysis (in 58%) and reduced behavioural parameters, like distance travelled, ambulatory time, stereotypic time and basal stereotypic movements compared with the normal control group. Exposed rats also showed reduced glutathione (GSH) content and glutathione-S-transferase (GST) activity in the corpus striatum and an increase in striatal dopamine receptors. Treatment with hydroalcoholic extract of the rhizomes of *Acorus calamus* lowered the incidence of paralysis (18%) also increased the GSH content and GST activity in the corpus striatum of rats. Rats treated with *Acorus calamus*also showed a partial recovery in other behavioural parameters. (Shukla *et al.,*2002).

Muthuraman *et al.,* (2010) evaluated the therapeutic potential of hydroalcoholic extracts of *Acorus calamus* (AC) in tibial and sural nerve transection (TST)-induced neuropathic pain in rats. The hot plate, paw heat allodynia, acetone drop, and pinprick tests were performed to assess the degree of heat hyperalgesia. The oxidative stress degree was evaluated by determining the tissue superoxide anion and total calcium levels. Tissue myeloperoxidase activity was measured as a specific marker of inflammation, Study results reported that TST in rats significantly induced mechanical hyperalgesia, thermal hyperalgesia and allodynia also increased the levels of superoxide anion, total calcium, and myeloperoxidase (MPO) activity. Oral administration of AC attenuated TST-induced behavioural and biochemical changes. Researchers pointing out this ameliorative potential of AC in TST-induced painful neuropathy is attributed to its various actions comprising anti-inflammatory, antioxidant, and neuroprotective actions. (Muthuraman *et al.,* (2010). In another study PK Shukla *et al.,* (2006) reported the neuroprotective potential of ethanol: water (1:1) extract of rhizomes of *Acorus calamus* against middle cerebral artery occlusion (MCAO)-induced ischaemia in rats. In this study antioxidant potential of *Acorus calamus* was analysed by evaluating various oxidative stress parameters in rat brain tissues, the study concluded by reporting potent antioxidant and neuroprotective effects of *Acorus calamus.* (Shukla *et al.,*2006). Several other studies also reported the antioxidant, anti-inflammatory and neuroprotective effects of different extracts of *Acorus calamus*, such as Muthuraman A *et al.,* (2011) reported the protective effect of *Acorus calamus L.* in rat model of vincristine induced painful neuropathy. (Muthuraman *et al.,*2011). Muthuraman A *et al.,* (2012) reported the neuroprotective effect of saponin rich extract of *Acorus calamus* L. in rat model of chronic constriction injury (CCI) of sciatic nerve-induced neuropathic pain. (Muthuraman *et al.,*2012).

6. Neuromodulatory Effects of *Acorus calamus* Linn.

Many researchers reported the in vitro and in vivo Acetylcholinesterase inhibitory effects of different extracts of *Acorus calamus*. (Qiu G *et al.,*2016; Mukherjee *et al.,*2007; Vijayapandia *et al.,*2013). Vengadesh Prabu K *et al.,* (2009) reported the neuromodulatory effect of *Acrouscalamus* leaves extract on dopaminergic system in mice. They have used methanol (ACME) and acetone (ACAE) extract of *Acorus calamus* leaves to investigate the effect against APM induced stereotypy and haloperidol (HP) induced catalepsy. Dopamine present in the region of nucleus accumbens is responsible for locomotor activity, stereotypy behaviour is mediated by striatal dopaminergic neuron. (Sanberg *et al.,*1988). Haloperidol produces its catalepsy effects through striatal dopaminergic system so that HP induced catalepsy in rodents became a simple and reliable test for investigation that involves nigrostriatal dopaminergic function especially involving D2 receptor. (Pires *et al.,*1996; Jaskiw *et al.,*2004). Study results showed that ACME (20, 50 mg/kg bwp.o) significantly reversed stereotypy induced by APM, when administered 6 h prior to APM and it was also found that ACME (50 mg/kg bwp.o.) and ACAE (20, 50 mg/kg bwp.o.) administration significantly potentiated the haloperidol induced catalepsy in mice. Finally, the reserchers concluded that *Acorus calamus* leaves extracts exerts neuromodulatory effects on nigro-striatal dopaminergic system. (Vengadesh Prabu *et al.,*2009).

PC Dandiya & MK Menon (1963) studied the effects of α and β-asarone (active principles of *Acorus calamus* oil) on 5-hydroxytryptamine content of rat brain. The study results showed that neither α nor β-asarone increase the concentration of 5-hydroxytryptamine. Also these compounds failed to produce an additional decrease in the 5-hydroxytryptamine content of the animal brains treated with reserpine. With all these study results researchers concluded that the neuromodulatory effects of these principles is unrelated to 5-hydroxytryptamine

Table 1: Summary of Major Neuro- pharmacological activities reported on *Acorus calamus* L.

Sl.No	Plant part used for the study	Active constituent/ Extract type	Reported Effects	References
1	Volatile oil from Rhizome	Asarone	Sedative and calming effects	Dandiya *et al.*,1964
2	Volatile oil from Rhizome	Alpha - asarone	Improvement of locomotor hyperactivity and striatal cholinergic function on Fmr1 knockout (KO) mice	Qiu G *et al.,* 2016
3	Leaves	Methanol and acetone extracts	Reported the CNS depression or analeptic activity of the extract on mice	Pandy *et al.,* 2009
4	Volatile oil from Rhizome	Alpha and Beta - asarone	In vitro Acetylcholinesterase inhibitory activity	Mukherjee *et al.,*2007 and Vijayapandia *et al.,* 2013
5	Volatile oil from Rhizome	Beta - asarone	Cognitive improvement effect of β-asarone against beta-amyloid hippocampus injection in rats	Geng *et al.,* 2010
6	Rhizome	Rhizome powder	Reported the preventive action of rhizome powder on stress induced cognitive dysfunctions and modulatory effect on antioxidants and Na^+-K^+-ATPase activity on *wistar* rats	Reddy *et al.,* 2015
7	Root	Hydro-alcoholic extract	The preventive effects on memory loss, anxiety, and oxidative Stress against Lipopolysaccharide -induced neuro-inflammation in rats	Esfandiari *et al.,* 2018
8	Acorus oil	Alpha and Beta Asarone	Anticonvulsant effects	Khare *et al.,* 1982 and Sharma *et al.,* 1961
9	Root	Ethanolicextract	Antidepressant effects	Tripathi *et al.,* 2010
10	Rhizome oil	Alpha asarone	Antidepressant effects	Chellian *et al.,* 2016
11	Rhizome	Ethanolic extract	*In vivo* antioxidant potential	Manikandan *et al.,* 2005
12	Rhizome	Hydro-alcoholic extract	Reported the protective effect against acrylamide induced neurotoxicity in rats.	Shukla *et al.,* 2002
13	Rhizome	Ethanol:water extract (1:1)	Reported the neuroprotective potential against middle cerebral artery occlusion (MCAO)-induced ischaemia in rats.	Shukla *et al.,* 2006
14	Leaves	Methanol and acetone extract	Reported the neuromodulatory effect of theextract on dopaminergic system in mice	VengadeshPrabu *et al.,* 2009

concentration. (Dandiya *et al.,*1963).

R. Chellian *et al.,* (2016) studied about the biphasic effects of α-Asarone on immobility in the tail suspension test (TST). The study results reported that acute treatment of α-asarone exhibited a biphasic effect on the TST immobility time. It showed an antidepressant-like activity at lower doses and depressive- like effect at higher doses. Additionally, to find out the possible mechanism(s) involved in the antidepressant-like effect of α-asarone researchers studied about the interaction of α-asarone with noradrenergic and serotonergic neuromodulators in the TST. Pretreatment of mice with noradrenergic neuromodulators such as AMPT (a catecholamine synthesis inhibitor) at a dose 100 mg/kg via intra peritoneal (i.p) route, yohimbine (an α2-adrenoceptor antagonist) at a dose of 1 mg/kg, i.p, prazosin (an α1-adrenoceptor antagonist) at a dose of 1 mg/kg, i.p. Involvement of serotonergic neuromodulation of α-asarone was

evaluated by administering a serotonin synthesis inhibitor such as PCPA (100 mg/kg, i.p., once daily for four consecutive days) and a selective 5-HT1A receptor antagonist WAY100635 (0.1 mg/kg via subcutaneous route) signiffcantly reversed the anti-immobility effect of α-asarone (20 mg/kg, i.p.). With the help of all these study evidences researchers summarised that the antidepressant-like effect of α-asarone could be mediated through both noradrenergic (α1 and α2 adrenoceptors) and serotonergic (particularly, 5-HT1A receptors) systems. (Chellian *et al.,*2016).

Furthermore, research works have to be done to identify and prove the molecular mechanisms involved in the neuropharmacological potential of *Acorus calamus* Linn.

Conclusion

The paper reviewed *Acorus calamus* Linn. as promising medicinal plant with wide range of neuro pharmacological activities (summarised in Table1) which could be utilized in several medical applications especially for the treatment of various neurodegenerative disorders because of its effectiveness and safety.

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Conflict of interest

The authors declare no conflict of interest.

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