RESEARCH PAPER

Vacha (Acorus Calamus): A Promising Medicinal Plant For The Management Of Neurodegenerative Disorders – A Review

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Abstract

Introduction: Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and dementia are characterized by progressive neuronal loss, oxidative stress, neuroinflammation, mitochondrial dysfunction, and abnormal protein aggregation. Current therapies are mainly symptomatic and do not effectively halt disease progression. *Acorus calamus* L. (Vacha), a medicinal plant widely used in Ayurveda as a *Medhya Rasayana*, has gained attention for its potential neuroprotective effects.

Methods: This review compiled and analyzed available ethnopharmacological, phytochemical, and pharmacological evidence on *Acorus calamus*, with emphasis on its traditional uses, major bioactive constituents, mechanisms of neuroprotection, therapeutic relevance in neurodegenerative disorders, and safety concerns. Literature cited in the review focused mainly on preclinical and experimental studies involving plant extracts and active compounds such as α-asarone and β-asarone.

Results: The rhizome of *Acorus calamus* contains several biologically active compounds, including α-asarone, β-asarone, eugenol, calarene, flavonoids, and phenylpropanoids. These constituents exhibit antioxidant, anti-inflammatory, anti-apoptotic, and cholinergic modulatory effects. Experimental studies indicate that *Acorus calamus* reduces oxidative stress, suppresses microglial activation and inflammatory cytokines, inhibits neuronal apoptosis, improves cholinergic neurotransmission, and enhances learning and memory. Preclinical evidence suggests beneficial effects in Alzheimer's disease, Parkinson's disease, ischemic brain injury, and cognitive dysfunction models.

Conclusion: *Acorus calamus* demonstrates promising multifunctional neuroprotective potential and may serve as a valuable therapeutic candidate for neurodegenerative disorders. However, toxicity concerns, particularly related to β-asarone, and the absence of robust human clinical trials limit its immediate clinical application. Further standardized studies are needed to confirm its efficacy and safety in humans.

Keywords: Acorus calamus, Alzheimer's disease, Neurodegeneration, Neuroprotection, Phytochemicals

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1. Introduction

Neurodegenerative disorders represent a major global health challenge and are characterized by the progressive loss of neuronal structure and function in the central nervous system. Among the most prevalent neurodegenerative diseases are Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and various forms of dementia. These conditions share several common pathological features, including oxidative stress, mitochondrial dysfunction, neuroinflammation, abnormal protein aggregation, and progressive neuronal death **(Sharma et al., 2020; Lim et al., 2024)**. The increasing prevalence of these disorders, particularly among the aging population, has created an urgent need for effective therapeutic strategies that can slow or halt disease progression.

Alzheimer's disease is the most common form of dementia and is primarily characterized by progressive cognitive decline, memory impairment, and behavioral disturbances. Pathologically, AD is associated with the accumulation of extracellular amyloid-β plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. These pathological changes disrupt synaptic communication and lead to widespread neuronal degeneration, particularly in the hippocampus and cerebral cortex **(Balakrishnan et al., 2022; DeTure & Dickson, 2019)**. Similarly, Parkinson's disease is a chronic neurodegenerative disorder marked by the degeneration of dopaminergic neurons in the substantia nigra pars compacta. The loss of dopamine-producing neurons results in classical motor symptoms such as tremors, rigidity,

bradykinesia, and postural instability. In addition to motor dysfunction, PD is also associated with cognitive impairment and neuropsychiatric symptoms **(Poewe et al., 2017)**.

Despite considerable advances in understanding the molecular mechanisms underlying these diseases, current pharmacological treatments remain largely symptomatic. For example, acetylcholinesterase inhibitors such as donepezil and rivastigmine are commonly used to manage cognitive symptoms in Alzheimer's disease, while levodopa and dopamine agonists are employed to alleviate motor symptoms in Parkinson's disease. However, these drugs do not prevent neuronal degeneration or significantly alter disease progression. Moreover, long-term use of these medications may result in adverse effects and reduced therapeutic efficacy over time **(Zhao et al., 2023; Cummings et al., 2019)**. Consequently, there is growing interest in identifying alternative therapeutic approaches that can target multiple pathological mechanisms simultaneously.

In recent years, medicinal plants and natural products have attracted significant attention as potential therapeutic agents for neurodegenerative disorders. Plant-derived compounds often possess diverse pharmacological properties and may act on multiple molecular targets, making them promising candidates for the management of complex diseases such as neurodegeneration. Traditional medicinal systems, including Ayurveda, Traditional Chinese Medicine, and other ethnomedicinal practices, have long utilized herbal remedies to treat neurological conditions. These traditional remedies are increasingly being investigated using modern pharmacological and biochemical techniques to validate their therapeutic potential **(Bai et al., 2022; Ara et al., 2022)**.

One such medicinal plant of considerable interest is *Acorus calamus* Linn., commonly known as Vacha or sweet flag. *Acorus calamus* is a perennial semi-aquatic herb belonging to the family Acoraceae and has been widely used in traditional Ayurvedic medicine for centuries. In Ayurveda, Vacha is categorized as a "Medhya Rasayana," a class of herbs known to enhance cognitive function, memory, and mental clarity. Traditionally, the rhizome of *Acorus calamus* has been used to treat various neurological and psychiatric conditions, including epilepsy, speech disorders, insomnia, anxiety, and memory loss **(Sharma et al., 2020; Zhao et al., 2023)**.

The pharmacological properties of *Acorus calamus* are largely attributed to its rich phytochemical composition. The rhizomes contain several bioactive compounds, including α-asarone, β-asarone, eugenol, calarene, and various flavonoids and phenylpropanoids. Among these compounds, α-asarone and β-asarone are considered the primary active constituents responsible for many of the plant's neuroprotective effects **(Balakrishnan et al., 2022)**.

Oxidative stress plays a central role in the pathogenesis of neurodegenerative diseases. Excessive production of reactive oxygen species (ROS) can damage cellular components such as lipids, proteins, and DNA, ultimately leading to neuronal death. Studies have demonstrated that extracts of *Acorus calamus* exhibit strong antioxidant activity by scavenging free radicals and enhancing the activity of endogenous antioxidant enzymes such as superoxide dismutase and catalase **(Bai et al., 2022)**.

Another important mechanism underlying neurodegeneration is chronic neuroinflammation. Activated microglial cells release pro-inflammatory cytokines and mediators that contribute to neuronal injury. Compounds isolated from *Acorus calamus*, particularly α-asarone and β-asarone, have been shown to inhibit inflammatory signaling pathways and suppress the production of pro-inflammatory cytokines **(Jiang et al., 2012)**.

In addition to its antioxidant and anti-inflammatory properties, *Acorus calamus* also exhibits significant effects on neurotransmitter systems. Studies have shown that extracts of the plant can modulate cholinergic and monoaminergic neurotransmission, which are crucial for cognitive function and motor control **(Kim et al., 2022)**.

Experimental studies using animal and cellular models have provided further evidence supporting the neuroprotective potential of *Acorus calamus*. For instance, β-asarone has been shown to reduce β-amyloid toxicity in Alzheimer's disease models by inhibiting amyloid aggregation and protecting neuronal cells from apoptosis **(Jiang et al., 2012)**.

Furthermore, behavioral studies in experimental animals have indicated that treatment with *Acorus calamus* extracts can improve learning and memory performance **(Sharma et al., 2020)**.

Overall, the available evidence suggests that *Acorus calamus* possesses significant neuroprotective potential and may serve as a multifunctional therapeutic agent for the management of neurodegenerative disorders.

2. Botanical Description and Traditional Uses

Acorus calamus L., commonly known as sweet flag or Vacha, is a perennial semi-aquatic medicinal plant belonging to the family **Acoraceae**. The plant has been widely recognized for its medicinal value in various traditional medical systems, particularly **Ayurveda, Traditional Chinese Medicine, and several indigenous healing traditions across Asia and Europe**. It naturally grows in marshy environments such as riverbanks, wetlands, and shallow water bodies, where the soil remains moist and rich in organic matter. The plant is widely distributed throughout **Asia, Europe, and North America**, although it is believed that its origin lies primarily in the **Indian subcontinent and parts of Southeast Asia** (Zhao et al., 2023; Sharma et al., 2020). Due to its significant medicinal properties and adaptability to different environmental conditions, *Acorus calamus* has been cultivated and naturalized in many regions around the world (Balakrishnan et al., 2022).

Acorus calamus L., commonly known as sweet flag or Vacha, is a perennial semi-aquatic medicinal plant belonging to the family **Acoraceae**. The plant has been widely recognized for its medicinal value in various traditional medical systems, particularly Ayurveda, Traditional Chinese Medicine, and several indigenous healing traditions across Asia and Europe. It naturally grows in marshy environments such as riverbanks, wetlands, and shallow water bodies, where the soil remains moist and rich in organic matter. The plant is widely distributed throughout **Asia, Europe, and North America**, although it is believed that its origin lies primarily in the Indian subcontinent and parts of Southeast Asia (Zhao et al., 2023). Due to its significant medicinal properties and adaptability to different environmental conditions, *Acorus calamus* has been cultivated and naturalized in many regions around the world.

Botanical Characteristics

Acorus calamus is a **perennial, aromatic, herbaceous plant** characterized by a creeping rhizome and sword-shaped leaves. The rhizome, which is the most pharmacologically important part of the plant, is thick, branched, and aromatic with a characteristic spicy fragrance. The rhizomes grow horizontally beneath the soil surface and produce numerous fibrous roots that help anchor the plant in wet soil conditions. The rhizome is typically light brown externally and white internally, and it contains several bioactive compounds responsible for the plant's therapeutic effects (Sharma et al., 2020).

The plant produces **long, erect, and sword-shaped leaves** that can grow up to 1–1.5 meters in height. These leaves are bright green, narrow, and possess a distinctive midrib. They are arranged in two rows and arise directly from the rhizome. When crushed, the leaves emit a pleasant aromatic odor due to the presence of volatile oils.

The inflorescence of *Acorus calamus* consists of a cylindrical **spadix**, which is densely covered with small yellowish-green flowers. Unlike many flowering plants, the spadix is not surrounded by a prominent spathe, which is a distinguishing feature of the genus *Acorus*. The flowers are small and bisexual, containing both male and female reproductive structures. Although flowering occurs in many regions, seed production is relatively rare in some cultivated varieties, and the plant often propagates vegetatively through rhizome division (Bai et al., 2022).

From a taxonomic perspective, the classification of *Acorus calamus* is as follows:

Taxonomy

Kingdom:	Plantae
Division:	Magnoliophyta
Class:	Liliopsida
Order:	Acorales
Family:	Acoraceae
Genus:	*Acorus*
Species: *Acorus calamus*	

The genus *Acorus* includes several species, but *Acorus calamus* is the most widely studied and utilized for medicinal purposes. Different cytotypes of *Acorus calamus* exist, including diploid, triploid, and tetraploid varieties, which may vary in their chemical composition, particularly in the content of β-asarone, a major bioactive compound found in the rhizome (Balakrishnan et al., 2022).

Common Names and Cultural Significance

Due to its extensive geographical distribution and long history of traditional use, *Acorus calamus* is known by various common names in different cultures and languages. In Ayurveda, it is commonly referred to as **"Vacha,"** a Sanskrit term that means "speech," reflecting its traditional use in improving speech and cognitive functions. In English, the plant is widely known as **"sweet flag"** due to its aromatic rhizome and grass-like leaves. In Nepal and certain Himalayan regions, it is called **"Bojho."** Other common names include **calamus root**, **sweet root**, and **muskrat root** (Zhao et al., 2023).

The plant holds cultural and medicinal significance in many traditional societies. In some cultures, it has been

used not only as a medicinal herb but also as a flavoring agent, insect repellent, and ritualistic plant. Historically, the rhizome has been chewed to relieve digestive problems, improve voice clarity, and enhance mental alertness.

Traditional Medicinal Uses

In Ayurvedic medicine, *Acorus calamus* occupies an important place among herbs used to support brain health and cognitive function. It is classified as a **"Medhya Rasayana,"** which refers to a group of rejuvenating herbs believed to enhance memory, intellect, concentration, and overall mental performance. Medhya Rasayana herbs are traditionally prescribed to improve learning ability, strengthen the nervous system, and delay cognitive decline associated with aging (Sharma et al., 2020).

The rhizome of *Acorus calamus* has been used in Ayurvedic formulations for centuries to treat a variety of neurological and psychological conditions. One of its most well-known traditional uses is **memory enhancement**. The herb is believed to stimulate brain function and improve cognitive abilities, making it particularly useful for individuals experiencing memory loss, poor concentration, or mental fatigue.

Another traditional application of Vacha is in the treatment of **epilepsy and convulsive disorders**. Ayurvedic practitioners have historically used preparations containing *Acorus calamus* to reduce seizure frequency and calm the nervous system. The plant's neuroprotective and anticonvulsant properties are believed to contribute to its therapeutic effectiveness in such conditions.

The herb has also been widely used for the management of **speech disorders**, especially in children. In traditional Ayurvedic practice, powdered rhizome is sometimes administered with honey to improve speech clarity and articulation. This practice reflects the traditional belief that Vacha stimulates the nervous system and enhances communication abilities.

In addition to neurological disorders, *Acorus calamus* has been used to manage **anxiety, depression, and other mental health conditions**. Traditional healers often prescribe the herb as a nerve tonic to calm the mind, reduce stress, and improve emotional balance. Its calming effects on the central nervous system make it a valuable remedy for individuals experiencing psychological distress or nervous exhaustion (Bai et al., 2022).

Another important traditional use of Vacha is in the treatment of **insomnia and sleep disturbances**. Due to its mild sedative and anxiolytic properties, the plant has been used to promote restful sleep and alleviate sleep disorders associated with anxiety and mental overactivity. Traditional formulations containing *Acorus calamus* are often recommended for individuals who suffer from chronic insomnia or irregular sleep patterns.

Furthermore, the herb has been traditionally used to manage **cognitive decline associated with aging**, including memory impairment and dementia-like symptoms. In Ayurvedic practice, Vacha is believed to rejuvenate the nervous system and maintain mental clarity in older adults. These traditional uses have attracted the attention of modern researchers investigating the potential role of *Acorus calamus* in neurodegenerative diseases such as Alzheimer's and Parkinson's disease (Balakrishnan et al., 2022).

Ethnopharmacological Significance

Ethnopharmacological studies have documented the widespread use of *Acorus calamus* across different cultures for neurological and cognitive disorders. The rhizome is often described as a **brain tonic and nerve stimulant**, supporting its traditional reputation as a herb that enhances mental performance and neurological health. Modern pharmacological research has increasingly validated many of these traditional claims by demonstrating the plant's antioxidant, anti-inflammatory, and neuroprotective properties.

Several experimental studies have shown that extracts of *Acorus calamus* can improve learning and memory in animal models, protect neurons from oxidative damage, and modulate neurotransmitter systems involved in cognitive processes. These findings support the ethnopharmacological evidence that the plant may possess significant therapeutic potential in the management of neurodegenerative disorders and cognitive dysfunction (Zhao et al., 2023).

Overall, the botanical characteristics and traditional medicinal uses of *Acorus calamus* highlight its importance as a valuable medicinal plant with a long history of use in neurological and cognitive health. The integration of traditional knowledge with modern scientific research continues to provide insights into the potential therapeutic applications of this plant, particularly in the context of neurodegenerative diseases.

3. Phytochemical Composition

The therapeutic potential of *Acorus calamus* L. is largely attributed to its diverse **phytochemical composition**, particularly the bioactive compounds present in its rhizome. The rhizome contains a variety of **volatile oils, phenylpropanoids, flavonoids,**

terpenoids, alkaloids, tannins, and other secondary metabolites that contribute to the plant's pharmacological activities. Among these constituents, the volatile oil fraction is considered the most important, as it contains several neuroactive compounds responsible for the plant's antioxidant, anti-inflammatory, and neuroprotective effects (Balakrishnan et al., 2022). The concentration and composition of these phytochemicals may vary depending on factors such as plant species, geographical location, cultivation conditions, and cytotype (diploid, triploid, or tetraploid varieties).

Volatile Oils and Major Active Constituents

The rhizome of *Acorus calamus* contains approximately **1.5–3.5% essential oil**, which is rich in aromatic compounds that contribute to both the medicinal and aromatic properties of the plant. The major constituents of this essential oil include **α-asarone, β-asarone, eugenol, calarene, and other phenylpropanoid derivatives** (Zhao et al., 2023). These compounds are responsible for the plant's characteristic fragrance and are widely studied for their pharmacological activities, particularly in neurological disorders.

Among these compounds, **α-asarone and β-asarone** are the most extensively investigated due to their potent biological activities. Both compounds belong to the phenylpropanoid class and are considered key contributors to the neuroprotective effects of *Acorus calamus*. Research indicates that these compounds can modulate multiple biochemical pathways involved in neurodegeneration, including oxidative stress, neuroinflammation, apoptosis, and neurotransmitter regulation (Bai et al., 2022).

Major Phytochemicals and Their Pharmacological Activities

The primary phytochemical constituents of *Acorus calamus* rhizome and their associated pharmacological activities are summarized below.

Compound	Pharmacological Activity
α-Asarone	Neuroprotective, anti-inflammatory, anticonvulsant
β-Asarone	Anti-Alzheimer's, anti-Parkinson's, neuroprotective
Eugenol	Antioxidant, anti-inflammatory
Calarene	Anti-inflammatory
Flavonoids	Free radical scavenging, antioxidant
Phenylpropanoids	Neuroprotective, anti-apoptotic

These compounds act either individually or synergistically to produce the o verall therapeutic effects observed in *Acorus calamus* extracts.

α-Asarone

α-Asarone is one of the major bioactive constituents found in the essential oil of *Acorus calamus*. It is a phenylpropanoid compound known for its **neuroprotective, anti-inflammatory, anticonvulsant, and antioxidant properties**. Several experimental studies have demonstrated that α-asarone can modulate neurotransmitter levels in the brain and protect neurons from oxidative stress-induced damage (Balakrishnan et al., 2022).

One of the key mechanisms through which α-asarone exerts its neuroprotective effect is by **inhibiting neuroinflammation and regulating apoptotic signaling pathways**. It has been shown to suppress the activation of microglial cells, which are responsible for the release of pro-inflammatory cytokines during neurodegenerative processes. Additionally, α-asarone has been reported to reduce neuronal apoptosis by regulating proteins involved in cell survival pathways, thereby protecting neurons from degeneration.

Another important pharmacological property of α-asarone is its ability to enhance cognitive function. Experimental studies have shown that α-asarone improves learning and memory performance in animal models, suggesting potential therapeutic applications in neurodegenerative disorders such as Alzheimer's disease.

β-Asarone

Among all the compounds found in *Acorus calamus*, **β-asarone is considered the principal neuroactive compound**. This compound has attracted significant scientific interest due to its ability to cross the **blood–brain barrier (BBB)**, which allows it to exert direct pharmacological effects within the central nervous system. The ability of β-asarone to reach brain tissue enhances its potential as a therapeutic agent for neurological disorders (Balakrishnan et al., 2022).

β-Asarone has been extensively studied for its role in the treatment of **Alzheimer's disease and Parkinson's disease**. In Alzheimer's disease models, β-asarone has been shown to inhibit the formation and aggregation of **β-amyloid peptides**, which are responsible for the formation of amyloid plaques in the brain. These plaques are a hallmark pathological feature of Alzheimer's disease and contribute to neuronal damage and cognitive decline.

In addition to reducing amyloid toxicity, β-asarone also regulates **autophagy and apoptosis pathways**,

which play critical roles in neuronal survival. Studies suggest that β-asarone can protect neurons by promoting the removal of damaged proteins and organelles through autophagic mechanisms (Bai et al., 2022).

In Parkinson's disease models, β-asarone has demonstrated protective effects on **dopaminergic neurons** in the substantia nigra. The compound reduces oxidative stress, suppresses neuroinflammatory responses, and improves mitochondrial function, thereby helping to preserve neuronal integrity and motor function.

Eugenol

Eugenol is another important compound present in the rhizome of *Acorus calamus*. It is a well-known phenolic compound widely found in several medicinal plants, including clove and basil. Eugenol possesses strong **antioxidant and anti-inflammatory properties**, making it beneficial for the prevention of oxidative stress-related diseases.

The antioxidant activity of eugenol is primarily due to its ability to **neutralize reactive oxygen species (ROS)** and prevent lipid peroxidation in neuronal membranes. By reducing oxidative damage, eugenol contributes to the overall neuroprotective activity of *Acorus calamus* extracts (Zhao et al., 2023).

Calarene

Calarene is a sesquiterpene compound found in the essential oil of *Acorus calamus*. Although it is less extensively studied compared to α-asarone and β-asarone, calarene has been reported to exhibit **anti-inflammatory and antimicrobial properties**. These activities may indirectly contribute to neuroprotection by reducing inflammatory responses and maintaining cellular homeostasis.

Flavonoids and Phenylpropanoids

In addition to volatile oil components, *Acorus calamus* also contains various **flavonoids and phenylpropanoid compounds**. These compounds are well known for their potent antioxidant properties and play an important role in protecting cells from oxidative damage.

Flavonoids act as **free radical scavengers**, neutralizing reactive oxygen species and preventing oxidative stress-induced neuronal injury. They also enhance the activity of endogenous antioxidant enzymes such as superoxide dismutase and catalase, thereby strengthening the brain's natural defense mechanisms against oxidative damage (Sharma et al., 2020).

Phenylpropanoids, including asarones and related compounds, are involved in several biological activities such as **anti-inflammatory, anti-apoptotic, and neuroprotective effects**. These compounds interact with multiple signaling pathways in neuronal cells, helping to regulate cell survival, inflammation, and neurotransmitter balance.

Role of Phytochemicals in Neuroprotection

The neuroprotective properties of *Acorus calamus* are largely attributed to the combined action of its phytochemical constituents. These compounds target multiple molecular pathways involved in neurodegeneration, making the plant a promising candidate for the management of neurological disorders.

The phytochemicals in *Acorus calamus* exert neuroprotective effects through several mechanisms, including:

• Reduction of oxidative stress by scavenging free radicals
• Inhibition of neuroinflammatory pathways
• Regulation of neurotransmitter systems such as acetylcholine and dopamine
• Prevention of neuronal apoptosis
• Modulation of mitochondrial function and cellular energy metabolism

By acting on these interconnected pathways, the bioactive compounds of *Acorus calamus* help maintain neuronal health and prevent progressive neuronal damage associated with neurodegenerative diseases.

4. Mechanisms of Neuroprotective Action

The neuroprotective effects of *Acorus calamus* are attributed to its ability to influence multiple molecular pathways involved in the pathogenesis of neurodegenerative diseases. Neurodegeneration is a complex process involving oxidative stress, neuroinflammation, mitochondrial dysfunction, apoptosis, and neurotransmitter imbalance. The bioactive compounds present in *Acorus calamus*, particularly **α-asarone and β-asarone**, interact with these pathways to protect neuronal cells and maintain brain function (Balakrishnan et al., 2022). Modern pharmacological studies have demonstrated that the plant exerts its neuroprotective actions through several mechanisms, including antioxidant activity, anti-inflammatory effects, inhibition of neuronal apoptosis, and modulation of cholinergic neurotransmission.

4.1 Antioxidant Activity

Oxidative stress plays a critical role in the development and progression of neurodegenerative disorders such as Alzheimer's disease, Parkinson's

disease, and Huntington's disease. It occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the capacity of the body's antioxidant defense systems to neutralize them. Excessive ROS can damage essential cellular components such as lipids, proteins, and DNA, ultimately leading to neuronal dysfunction and cell death (Sharma et al., 2020).

Neurons are particularly vulnerable to oxidative damage due to their high oxygen consumption, abundant lipid content, and relatively low antioxidant capacity. In neurodegenerative diseases, oxidative stress contributes to mitochondrial dysfunction, synaptic damage, and progressive neuronal loss.

Extracts of *Acorus calamus* have been reported to exhibit strong antioxidant activity, which helps protect neuronal cells from oxidative damage. One of the key mechanisms by which the plant exerts this effect is by **enhancing the activity of endogenous antioxidant enzymes**. Studies have shown that treatment with *Acorus calamus* extracts increases the levels of important antioxidant enzymes such as **superoxide dismutase (SOD)** and **catalase** in brain tissues.

Superoxide dismutase plays a vital role in converting superoxide radicals into hydrogen peroxide, which is then further detoxified by catalase into water and oxygen. By increasing the activity of these enzymes, *Acorus calamus* helps neutralize harmful reactive oxygen species and maintain cellular redox balance (Bai et al., 2022).

Another important antioxidant mechanism of *Acorus calamus* is its ability to **reduce lipid peroxidation**, a process in which free radicals attack the lipids present in neuronal membranes. Lipid peroxidation can compromise membrane integrity and disrupt neuronal signaling. Experimental studies have demonstrated that extracts of *Acorus calamus* significantly decrease malondialdehyde (MDA) levels, a commonly used marker of lipid peroxidation, thereby protecting neuronal membranes from oxidative damage.

The antioxidant activity of the plant is largely attributed to its phytochemical constituents, including **flavonoids, phenylpropanoids, and phenolic compounds**, which possess strong free radical scavenging properties. Through these mechanisms, *Acorus calamus* helps prevent oxidative stress–induced neuronal injury and contributes to the protection of brain cells.

4.2 Anti-Inflammatory Effects

Neuroinflammation is another major factor contributing to the pathogenesis of neurodegenerative diseases. In the central nervous system, inflammation is primarily mediated by **microglia**, the resident immune cells of the brain. When activated in response to injury or disease, microglial cells release a variety of pro-inflammatory mediators, including cytokines, chemokines, and reactive oxygen species. While acute inflammation may serve a protective role, chronic or excessive neuroinflammation can lead to neuronal damage and accelerate neurodegeneration (Zhao et al., 2023).

Studies have demonstrated that the bioactive constituents of *Acorus calamus*, particularly **α-asarone and β-asarone**, possess significant anti-inflammatory properties. These compounds exert their effects by modulating inflammatory signaling pathways within neuronal and glial cells.

One of the most important molecular targets affected by these compounds is the **nuclear factor kappa B (NF-κB) signaling pathway**. NF-κB is a key transcription factor that regulates the expression of genes involved in inflammation. Activation of NF-κB leads to the production of pro-inflammatory cytokines such as **tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6)**.

Research has shown that α-asarone and β-asarone can inhibit the activation of the NF-κB pathway, thereby reducing the expression of these pro-inflammatory cytokines (Balakrishnan et al., 2022). By suppressing inflammatory signaling, these compounds help limit neuronal damage associated with chronic inflammation.

Another important anti-inflammatory effect of *Acorus calamus* is its ability to **suppress microglial activation**. Activated microglia produce inflammatory mediators that can damage neurons and disrupt neural networks. Experimental studies have demonstrated that asarone compounds reduce microglial activation and decrease the production of inflammatory molecules, thereby protecting neurons from inflammation-induced injury.

Through the inhibition of inflammatory signaling pathways and reduction of microglial activation, *Acorus calamus* plays an important role in preventing neuroinflammation and maintaining neuronal health.

4.3 Anti-Apoptotic Mechanisms

Apoptosis, or programmed cell death, is a tightly regulated process that eliminates damaged or dysfunctional cells. However, excessive apoptosis in neuronal cells can contribute to the progression of neurodegenerative diseases. In conditions such as Alzheimer's disease and Parkinson's disease,

abnormal activation of apoptotic pathways leads to the gradual loss of neurons in critical regions of the brain (Bai et al., 2022).

Bioactive compounds present in *Acorus calamus* have been shown to regulate apoptotic pathways and prevent neuronal cell death. One of the key mechanisms involved is the modulation of **Bcl-2 family proteins**, which control mitochondrial-mediated apoptosis.

Studies have demonstrated that treatment with *Acorus calamus* extracts increases the expression of **Bcl-2**, an anti-apoptotic protein that promotes cell survival. At the same time, the plant compounds reduce the activity of **caspase-3**, a critical enzyme involved in the execution phase of apoptosis. By decreasing caspase-3 activation, *Acorus calamus* helps prevent the breakdown of cellular components and preserves neuronal integrity (Balakrishnan et al., 2022).

In addition, the plant's bioactive constituents help maintain **mitochondrial function**, which is essential for cellular energy production and survival. Mitochondrial dysfunction is a common feature of many neurodegenerative diseases and often triggers apoptotic signaling pathways. By stabilizing mitochondrial membranes and reducing oxidative stress, *Acorus calamus* helps prevent mitochondrial damage and subsequent neuronal apoptosis.

These anti-apoptotic effects contribute significantly to the neuroprotective properties of the plant and may help slow the progression of neurodegenerative diseases.

4.4 Cholinergic Modulation

The cholinergic system plays a crucial role in learning, memory, and cognitive function. In Alzheimer's disease, one of the hallmark pathological features is the **degeneration of cholinergic neurons** in the basal forebrain, leading to reduced levels of the neurotransmitter **acetylcholine (ACh)**. This deficiency in acetylcholine contributes to memory impairment and cognitive decline observed in Alzheimer's patients (Sharma et al., 2020).

Acorus calamus has been shown to exert beneficial effects on the cholinergic system through several mechanisms. One of the most important actions is the **inhibition of acetylcholinesterase (AChE)**, the enzyme responsible for breaking down acetylcholine in the synaptic cleft. By inhibiting AChE activity, *Acorus calamus* helps increase the availability of acetylcholine in the brain, thereby improving cholinergic neurotransmission.

Improved cholinergic signaling enhances communication between neurons and supports cognitive functions such as memory formation, attention, and learning. Several experimental studies using animal models have demonstrated that treatment with *Acorus calamus* extracts leads to **significant improvements in learning and memory performance**, particularly in tasks designed to evaluate spatial memory and cognitive abilities.

In addition to inhibiting acetylcholinesterase, the plant's bioactive compounds may also influence other neurotransmitter systems, including dopamine and serotonin pathways. This broader modulation of neurotransmitter activity further contributes to its potential therapeutic role in neurological disorders.

5. Role in Specific Neurodegenerative Disorders

Neurodegenerative disorders are characterized by progressive neuronal loss and impaired neural function, leading to cognitive decline, motor dysfunction, and behavioral abnormalities. The multifactorial nature of these diseases—including oxidative stress, mitochondrial dysfunction, neuroinflammation, and abnormal protein aggregation—makes them particularly challenging to treat using single-target pharmacological therapies. In this context, medicinal plants with **multi-target therapeutic properties** have attracted significant attention as potential alternatives or complementary treatments.

Acorus calamus has been extensively studied for its neuroprotective effects in various experimental models of neurodegenerative disorders. The plant's bioactive constituents, particularly **β-asarone and α-asarone**, have demonstrated significant protective effects against neuronal damage through antioxidant, anti-inflammatory, and anti-apoptotic mechanisms (Balakrishnan et al., 2022). These compounds have shown promising results in preclinical studies involving Alzheimer's disease, Parkinson's disease, and ischemic brain injury, suggesting that *Acorus calamus* may play an important role in preventing or slowing the progression of neurodegenerative disorders.

5.1 Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia and is characterized by progressive memory loss, cognitive impairment, and behavioral disturbances. Pathologically, the disease is associated with several key features, including **extracellular deposition of amyloid-β (Aβ) plaques**, **intracellular neurofibrillary tangles composed of**

hyperphosphorylated tau protein, **oxidative stress**, and **chronic neuroinflammation**. These pathological changes primarily affect brain regions involved in memory and cognition, such as the hippocampus and cerebral cortex (Sharma et al., 2020).

Accumulation of amyloid-β peptides is considered one of the central events in Alzheimer's disease pathology. These peptides aggregate to form insoluble plaques that disrupt neuronal communication and trigger inflammatory responses, ultimately leading to neuronal death. Several experimental studies have demonstrated that **β-asarone**, one of the major active components of *Acorus calamus*, can reduce the accumulation of amyloid-β peptides in the brain.

Research using animal models of Alzheimer's disease has shown that β-asarone can inhibit amyloid plaque formation by regulating pathways involved in amyloid precursor protein (APP) processing. By reducing amyloid deposition, the compound helps prevent neuronal toxicity and protects brain cells from degeneration (Balakrishnan et al., 2022).

In addition to reducing amyloid accumulation, β-asarone has also been reported to improve **memory and cognitive deficits** associated with Alzheimer's disease. Experimental studies in rodents have demonstrated that administration of *Acorus calamus* extracts or β-asarone significantly enhances learning and memory performance. These improvements are believed to be associated with increased cholinergic neurotransmission and reduced oxidative stress in the brain.

One of the commonly used behavioral tests to evaluate cognitive function in animal models is the **Morris water maze test**, which measures spatial learning and memory. In studies involving Alzheimer's disease models, animals treated with β-asarone showed improved performance in the Morris water maze, indicating enhanced memory retention and cognitive abilities (Bai et al., 2022).

Another important neuroprotective effect of β-asarone is its ability to **protect hippocampal neurons**, which are particularly vulnerable in Alzheimer's disease. The compound has been shown to regulate apoptotic pathways, reduce oxidative stress, and promote neuronal survival in the hippocampus. By preserving the structural and functional integrity of hippocampal neurons, *Acorus calamus* may help maintain cognitive function and delay the progression of Alzheimer's disease.

Overall, the available evidence suggests that *Acorus calamus* and its bioactive constituents possess significant therapeutic potential in the management of Alzheimer's disease through multiple mechanisms, including inhibition of amyloid deposition, antioxidant activity, and improvement of cholinergic neurotransmission.

5.2 Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. It is primarily characterized by the progressive degeneration of **dopaminergic neurons in the substantia nigra pars compacta**, a region of the brain responsible for controlling movement. The loss of dopamine-producing neurons leads to the classical motor symptoms of Parkinson's disease, including **tremor, rigidity, bradykinesia, and postural instability** (Jiang et al., 2012).

In addition to motor symptoms, Parkinson's disease is also associated with non-motor symptoms such as cognitive impairment, depression, and sleep disturbances. The pathogenesis of PD involves several mechanisms, including oxidative stress, mitochondrial dysfunction, neuroinflammation, and abnormal protein aggregation, particularly the accumulation of **α-synuclein** in Lewy bodies.

Recent studies have shown that **β-asarone**, a major constituent of *Acorus calamus*, exhibits significant neuroprotective effects in experimental models of Parkinson's disease. One of the primary mechanisms of action involves the protection of **dopaminergic neurons** from oxidative damage and inflammatory injury.

Experimental research using toxin-induced models of Parkinson's disease has demonstrated that β-asarone can significantly reduce neuronal degeneration. For example, in **MPTP-induced Parkinson's disease models**, which mimic dopaminergic neuronal loss in humans, treatment with β-asarone resulted in improved neuronal survival and reduced oxidative damage in the substantia nigra (Jiang et al., 2012).

Another important effect of β-asarone is its ability to **reduce neuroinflammation**, which plays a crucial role in the progression of Parkinson's disease. By inhibiting inflammatory signaling pathways and suppressing microglial activation, the compound helps prevent further neuronal damage.

In addition to its neuroprotective properties, β-asarone has also been shown to **improve motor function** in Parkinsonian animal models. Behavioral studies have demonstrated that animals treated with β-asarone exhibit improved locomotor activity and reduced motor deficits compared with untreated controls.

These findings suggest that *Acorus calamus* may have significant therapeutic potential for the management of Parkinson's disease by protecting dopaminergic neurons and improving motor function.

5.3 Ischemic Brain Injury and Dementia

Ischemic brain injury, commonly associated with stroke, is another condition that can lead to neuronal damage and cognitive impairment. During cerebral ischemia, reduced blood supply to the brain results in oxygen and glucose deprivation, which triggers a cascade of pathological events including oxidative stress, inflammation, excitotoxicity, and apoptosis. These processes can lead to extensive neuronal death and long-term neurological deficits.

Several studies have suggested that *Acorus calamus* may provide protective effects against **ischemic brain injury** due to its antioxidant and anti-apoptotic properties. The bioactive compounds present in the plant, particularly asarones, have been shown to reduce oxidative stress and protect neuronal cells from ischemia-induced damage (Zhao et al., 2023).

One of the key mechanisms involved in this protective effect is the **reduction of oxidative stress**. During ischemic injury, excessive production of reactive oxygen species damages cellular components and disrupts neuronal function. The antioxidant compounds present in *Acorus calamus* help neutralize these free radicals and protect brain tissue from oxidative damage.

Another important protective mechanism involves the **regulation of apoptotic signaling pathways**. Studies have demonstrated that compounds from *Acorus calamus* can inhibit apoptosis by modulating the expression of pro- and anti-apoptotic proteins, thereby promoting neuronal survival.

Additionally, *Acorus calamus* has been reported to enhance **cerebral blood flow**, which may help improve oxygen and nutrient delivery to brain tissues during ischemic conditions. Improved blood circulation can support neuronal recovery and reduce the severity of ischemic injury.

These neuroprotective properties may also contribute to the prevention or management of **vascular dementia**, a condition resulting from reduced blood flow to the brain. By protecting neurons from ischemic damage and improving cerebral circulation, *Acorus calamus* may help preserve cognitive function and reduce the risk of dementia associated with cerebrovascular disorders.

6. Toxicity and Safety Considerations

Although *Acorus calamus* has demonstrated significant therapeutic potential for neurological and cognitive disorders, concerns regarding its **toxicity and safety profile** have been raised, particularly due to the presence of the bioactive compound **β-asarone**. While many experimental studies have highlighted the neuroprotective, antioxidant, and anti-inflammatory properties of *Acorus calamus*, the safety of long-term consumption and high-dose exposure remains a topic of scientific and regulatory scrutiny. Understanding the toxicological aspects of the plant is therefore essential before considering its clinical application in the management of neurodegenerative diseases.

β-Asarone and Toxicological Concerns

Among the phytochemicals present in *Acorus calamus*, **β-asarone** is considered the major active constituent responsible for many of the plant's pharmacological activities. However, this compound has also been associated with certain **toxicological effects**, particularly when consumed in high concentrations or over prolonged periods.

Several experimental studies have reported that excessive intake of β-asarone may produce **toxic effects on various organs**, including the liver. Hepatotoxicity is one of the primary safety concerns associated with high doses of β-asarone. In animal studies, prolonged exposure to high levels of β-asarone has been shown to cause alterations in liver enzymes and structural changes in hepatic tissues, indicating potential liver damage (Balakrishnan et al., 2022). These findings suggest that uncontrolled consumption of *Acorus calamus* extracts containing high concentrations of β-asarone could pose risks to liver health.

Another significant concern is the **carcinogenic potential** of β-asarone reported in some experimental animal studies. Research conducted on rodents has indicated that long-term exposure to high doses of β-asarone may increase the risk of tumor formation, particularly in the liver and other organs. These findings have raised safety concerns regarding the use of β-asarone-containing products in food and medicinal preparations (Zhao et al., 2023).

It is important to note, however, that most of the carcinogenic effects observed in these studies occurred at **extremely high doses** that exceed typical therapeutic levels used in traditional medicine. Nevertheless, these results have prompted regulatory agencies to carefully evaluate the safety of *Acorus calamus* and its derivatives.

Regulatory Restrictions

Due to concerns related to β-asarone toxicity, several regulatory authorities have imposed restrictions on the use of *Acorus calamus* in food and pharmaceutical products. The **United States Food and Drug Administration (FDA)** has classified β-asarone-containing calamus oil as unsafe for use as a food additive. Consequently, the use of *Acorus calamus* extracts containing significant amounts of β-asarone is restricted in food products within the United States.

Similarly, other regulatory bodies have implemented guidelines to limit the permissible levels of β-asarone in herbal preparations and dietary supplements. These regulations aim to ensure consumer safety while still allowing the potential therapeutic benefits of the plant to be explored in controlled settings.

Interestingly, different varieties of *Acorus calamus* contain varying amounts of β-asarone depending on their **cytotype**. For example, **diploid varieties** of the plant generally contain little or no β-asarone, whereas **triploid and tetraploid varieties** may contain higher concentrations of this compound. As a result, some researchers have suggested that diploid varieties could be safer alternatives for medicinal use (Sharma et al., 2020).

Dose-Dependent Safety

The toxicity of *Acorus calamus* appears to be **dose-dependent**, meaning that its safety profile may vary depending on the amount consumed. In traditional medicinal systems such as Ayurveda, the herb is typically administered in controlled doses and often in combination with other herbal ingredients. Such formulations may reduce the risk of adverse effects and enhance therapeutic efficacy.

Furthermore, modern pharmacological studies have indicated that **low to moderate doses of *Acorus calamus* extracts** generally exhibit beneficial effects without significant toxicity in experimental models. These findings suggest that careful dose regulation and standardized extraction methods may help minimize potential risks associated with the plant's use.

Nevertheless, the lack of comprehensive **human clinical trials** makes it difficult to establish definitive safety guidelines for long-term consumption. Therefore, caution should be exercised when using *Acorus calamus* preparations, particularly those with high β-asarone content.

Strategies for Improving Safety

Given the promising neuroprotective properties of *Acorus calamus*, researchers are exploring several strategies to improve its safety profile while preserving its therapeutic benefits. One important approach involves the development of **standardized herbal extracts**. Standardization ensures consistent concentrations of active compounds and allows better control over potentially harmful constituents such as β-asarone.

Another promising strategy is the development of **safer derivatives or analogs** of β-asarone. By modifying the chemical structure of the compound, scientists aim to retain its beneficial pharmacological effects while reducing its toxicity. Such derivatives could potentially serve as safer therapeutic agents for neurological disorders.

Advances in **pharmaceutical formulation technologies**, including nanoparticle-based delivery systems and targeted drug delivery, may also help improve the safety and efficacy of *Acorus calamus* compounds. These technologies can enhance the bioavailability of active compounds while reducing systemic toxicity.

8. Conclusion

Acorus calamus (Vacha) is a promising medicinal plant with significant potential in the management of neurodegenerative disorders. Its bioactive constituents, particularly α-asarone and β-asarone, exhibit multiple neuroprotective mechanisms including antioxidant, anti-inflammatory, anti-apoptotic, and cholinergic modulation.

Overall, the rhizome of *Acorus calamus* contains a complex mixture of bioactive phytochemicals that contribute to its diverse pharmacological activities. Among these compounds, **α-asarone and β-asarone play a central role in the plant's neuroprotective effects**, particularly in relation to Alzheimer's disease and Parkinson's disease. Other constituents such as eugenol, calarene, flavonoids, and phenylpropanoids further enhance the plant's therapeutic potential through antioxidant and anti-inflammatory mechanisms. The synergistic interaction of these compounds supports the traditional use of *Acorus calamus* as a medicinal herb for neurological disorders and highlights its potential as a source of novel therapeutic agents for neurodegenerative diseases.

The neuroprotective effects of *Acorus calamus* arise from its ability to target multiple pathological mechanisms involved in neurodegeneration. Through its antioxidant, anti-inflammatory, anti-apoptotic, and cholinergic modulatory activities, the plant helps protect neurons from damage and supports normal brain function. These multifaceted mechanisms highlight the potential of *Acorus calamus* as a

promising therapeutic candidate for the management of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

Overall, accumulating experimental evidence suggests that *Acorus calamus* possesses significant therapeutic potential in the management of various neurodegenerative disorders. Its bioactive compounds, particularly **β-asarone**, exert protective effects against neuronal damage through multiple mechanisms, including inhibition of amyloid deposition, protection of dopaminergic neurons, reduction of oxidative stress, and suppression of neuroinflammation. These multi-target actions make *Acorus calamus* a promising candidate for the development of novel treatments for Alzheimer's disease, Parkinson's disease, ischemic brain injury, and related cognitive disorders.

Preclinical studies demonstrate beneficial effects in **Alzheimer's disease, Parkinson's disease, and cognitive impairment models**. However, further clinical investigations are required to confirm its therapeutic efficacy and safety in humans.

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