MINI- REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Pharmacological Properties and Therapeutic Potential of α-Asarone: A Comprehensive Review

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Abstract

This review examines the pharmacological properties and therapeutic possibilities of α-asarone, a phenylpropene compound derived from *Acorus calamus Linn.* (sweet flag), a plant widely utilized in traditional medicine. α-Asarone, represented by the chemical formula $C_{12}H_{16}O_3$, demonstrates a wide range of pharmacological effects, such as neuroprotection, hepatoprotection, nephroprotection, analgesia, antidepressant, anticancer, antimicrobial, anticholinesterase, antidiabetic, anti-inflammatory, antioxidant, and immunomodulatory activities. The main cause of these effects is mainly due to the antioxidant characteristics of α-asarone and its capacity to regulate several metabolic pathways. α-asarone has exhibited notable neuroprotective benefits through the reduction of oxidative stress and inhibition of N-methyl-D-aspartate (NMDA) receptor activity. Additionally, it has demonstrated hepatoprotective and nephroprotective capabilities, effectively mitigating acetaminophen-induced damage. Furthermore, α-asarone shows promise in the therapy of cancer by controlling the growth and death of cells. Furthermore, its ability to reduce inflammation, fight against microorganisms, and regulate blood sugar levels emphasizes its wide range of therapeutic benefits. The results indicate that α-asarone, obtained from *Acorus calamus*, shows great potential as a natural remedy for several human conditions.

Keywords: α-Asarone; *Acorus calamus;* anticancer; antimicrobial; antioxidant; traditional medicine.

1. Background

Various herbs, spices, and medicinal plants produce phenylpropenes through the shikimate pathway, such as α-asarone. Phenylpropenes are present in plants such as basil, estragon, fennel, nutmeg, and calamus. The concentration of phenylpropenes is influenced by various factors such as plant type, climate, and regional conditions. *Acorus calamus Linn.*, also referred to as sweet flag or sweet cane (Family: Araceae), has been extensively employed in traditional Indian and Chinese medicine for centuries owing to its favorable effects on cognitive function and lifespan. Three active compounds, namely α-asarone, β-asarone, and γ-asarone, have been extracted from the volatile oil of *Acorus calamus L* **(Uebel et al., 2021)**.

Antioxidants can hinder the oxidation process by interacting with free radicals and chelating free catalytic metals, thereby scavenging oxygen. The antioxidant properties of plants may be associated with safeguarding against oxidative stress in various human ailments, such as cancer, atherosclerosis, Alzheimer's disease, and the aging process **(Khanal et al., 2020)**.

2. The chemical form and characteristics of α-asarone

The chemical formula for α-asarone is $C_{12}H_{16}O_3$. When α-asarone is separated, it forms a white crystalline solid with a melting point of 62°C. The rhizome of Acorus, which can be extracted or dried using alcohol, is utilized as a flavoring agent in bitter alcoholic beverages and herbal infusions. Furthermore, preparations of the bark of the Mexican tree *Guatteria gaumeri Greenman* ("Yumel"), which belongs to the Annonaceae family, contain the active ingredient α-asarone **(Chellian and Pandy, 2018)**.

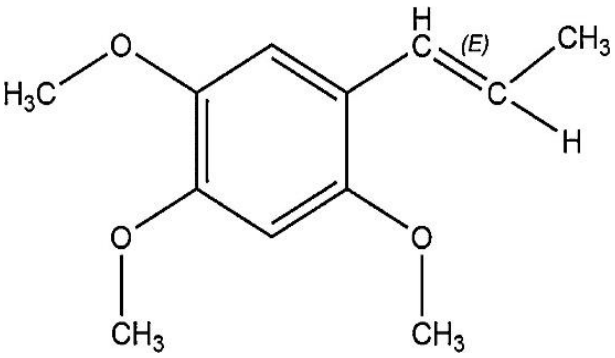

Figure 1. Chemical structure of α-asarone (1, 2, 4-trimethoxy-5-[(E)-prop-1-enyl] benzene) **(Chellian and Pandy, 2018)**.

3. Pharmacological characteristics of extracts containing asarone

Previous studies have investigated the pharmacological importance of propenylic asarones and extracts that contain asarone, such as essential oils. Asarone isomers or dosed forms of *Acorus calamus* (*A. calamus*) extracts have been proposed to exhibit a variety of properties, such as antidepressant, antihyperlipidemic, antiinflammatory, anticonvulsive, mucoid, insecticidal, antioxidant, anxiolytic, neuroprotective, and radioprotective effects. The aforementioned effects have been found in laboratory settings (in vitro) and/or in living organisms (*in vivo*) **(Khan et al., 2017)**.

3.1. Neuroprotection impact of α-Asarone

α-Asarone exhibits neuroprotective effects via suppressing excessive nitric oxide generation in brain tissue and by inhibiting the function of N-methyl-D-aspartate (NMDA) receptors. Administering a 50% ethanolic extract of the rhizome at a dosage of 25mg/kg to rats for a duration of 10 days resulted in a reduction of acrylamide-induced neurotoxicity. This was observed through a decrease in limb paralysis and a restoration of dopamine receptor content and glutathione levels **(Chellian and Pandy, 2018)**.

The herb's neuroprotective properties are attributed to the modulation of its antioxidant activity. Rats administered a rhizome extract for a period of five days before and three days after an experimental operation exhibited indications of brain preservation. The behavioral rating score showed improvement 72 hours after the occlusion. The administration of acrylamide in rats resulted in hind limb paralysis, which was subsequently alleviated by the application of the extract, leading to a decrease in the occurrence of paralysis. The neuroprotective effects of the essential oil derived from *Acorus gramineus*, a plant characterized by subterranean stems and roots, were seen in a culture of cortical neurons. These effects were achieved by the inhibition of NMDA receptor activation. The presence of asarone, the main constituent of the essential oil, was found to inhibit NMDA- or glutamate-induced excitotoxicity **(Saroya and Singh, 2018)**.

A separate study investigated the potential of α-asarone to relieve chronic sciatica. Following the onset of chronic neuralgia, the pain was shown to be alleviated by the discovery of α-asarone. In addition, the levels of serum Interleukin-1 (IL)-10 were increased by α-asarone, while the levels of Tumor Necrosis Factor-alpha (TNF-α), and lipopolysaccharide (LPS) were lowered. Exposure to α-asarone resulted in decreased levels of IL-1 and TNF-α mRNA in dorsal root ganglion neurons. The administration of α-asarone resulted in enhanced nerve regeneration by reducing the number of inflammatory cells and promoting the proliferation of Schwann cells along the sciatic nerve. The evidence indicates that α-asarone is efficacious in the treatment of chronic sciatica due to its ability to diminish inflammatory factors,

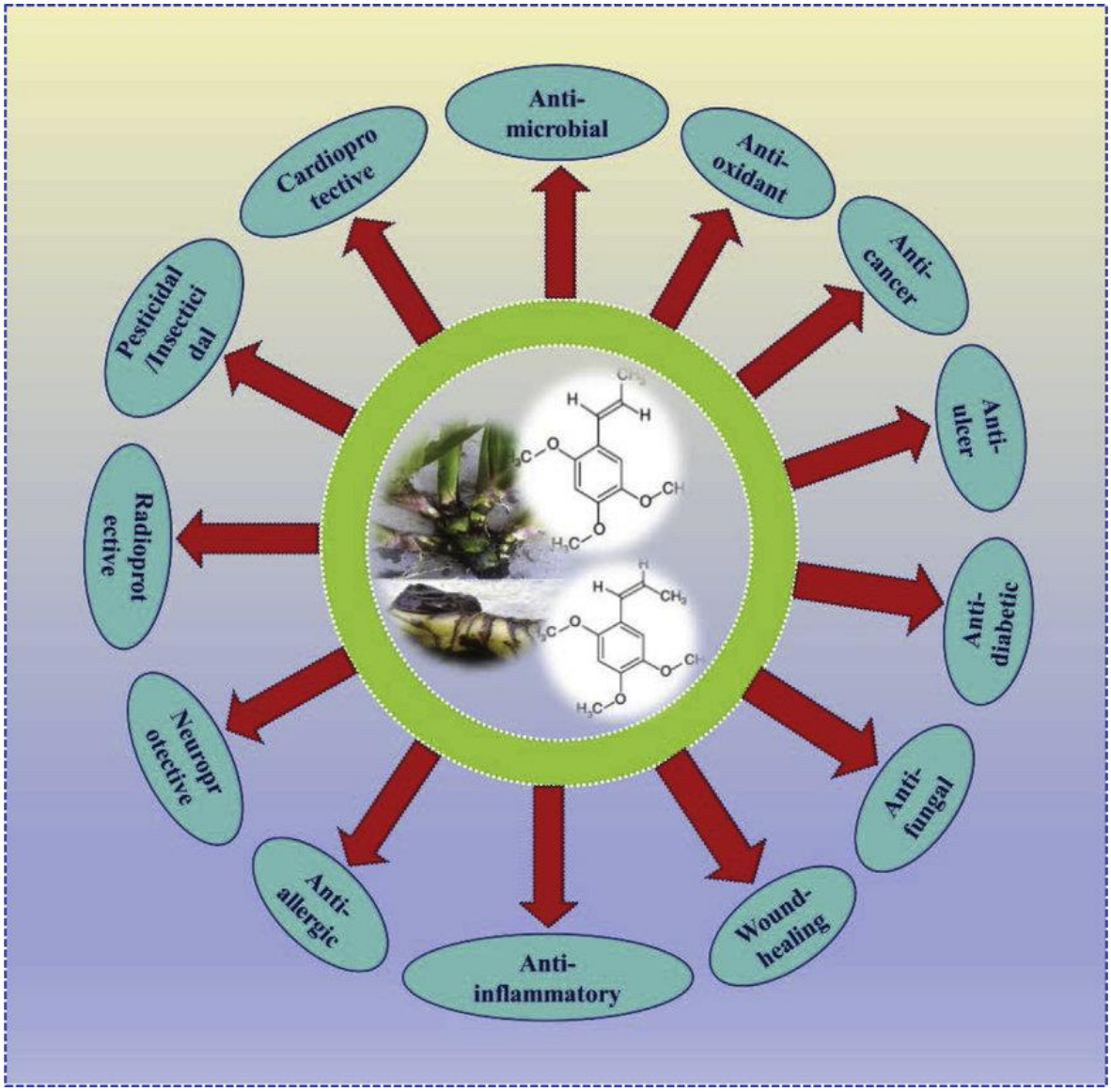

Figure 2. Schematic representation of the pharmacological activity of *A. calamus* and/or its bioactive phytochemicals α- and β-asarone **(Das et al., 2019).**

inhibit peripheral sensitization, and facilitate the regeneration of damaged nerves **(Zhang et al., 2022)**.

3.2. Hepatoprotective and nephroprotective impacts of α-Asarone

The presence of asarone-containing extract leads to a decrease in the severity of acetaminophen poisoning, while simultaneously increasing the levels of superoxide dismutase, glutathione peroxidase, and catalase in the kidneys. **Nasir (2021)** demonstrated that it effectively inhibits kidney damage and necrotic tissue caused by acetaminophen in rats.

3.3. Analgesia and Antidepressant impacts of α-Asarone

The alcoholic extract of the rhizome, when given at a dose of 250mg/kg or 500 mg/kg, significantly reduces the acetic acid-induced writhing response by 15.16% and 54.51% respectively. The administration of rhizome extract orally, at a dosage of 100-200 mg/kg, over a period of 14 days, along with vincristine, leads to a considerable reduction in neuropathic pain. This reduction is measured by Von Frey hair tests and the sciatic functional index. This impact is comparable to the effectiveness of pregabalin at a dosage of 10 mg/kg **(Khan and Islam, 2012)**. Both a tibial and sural

nerve transection model of neuropathic pain, as well as a chronic constriction damage model of sciatic pain, have shown efficacy with the same dosage of this extract **(Forouzanfar and Hosseinzadeh, 2018)**. The rats were given a methanolic extract of *Acorus calamus* at a dosage of 50-100 mg/kg for seven consecutive days. This resulted in an anti-depressant effect that increased with the dose. The study demonstrated that this effect was as powerful to the administration of 5 mg/kg of imipramine **(Chellian et al., 2018)**.

3.4. Anticancer effects impact of α-Asarone

Signal transduction pathways exert control over cell behavior by regulating processes such as cell proliferation and cell cycle arrest, activating apoptosis, and suppressing angiogenesis. The addition of lectins isolated from calamus rhizomes to culture conditions resulted in the suppression of cell proliferation. The ethanol extract of Calamus rhizome had inhibitory effects on the proliferation of many human and murine cell lines, indicating that its antiproliferative properties are not specific to any one kind of cell. The putative areas of action for A. calamus and/or its bioactive phytochemicals asarone are cellular senescence and autophagy. By activating lamin B1, it inhibits the development of cancer and enhances cellular senescence. Elevated levels of lamin B1 enhance the synthesis of tumor protein 53 (p53). Conversely, the activation of p53 inhibits B-cell lymphoma-2 (Bcl-2), leading to the initiation of apoptosis. Autophagy is further enhanced by increasing the expression of autophagy-related proteins (LC3-B/A) and reducing the levels of Bcl-2 **(Das et al., 2019)**.

A further investigation on human colon cancer cells revealed the presence of anti-cancer characteristics linked to the enhancement of caspase activity through the activation of the mitochondrial pathway. **Zou et al. (2012)** discovered that asarone decreased cell viability and triggered apoptosis in human LoVo colon cancer cells in a dose- and time-dependent manner, using a fluorescein isothiocyanate/propidium iodide assay conducted by flow cytometry.

Further investigation revealed that asarone effectively targets cellular senescence by suppressing the function of the lamin protein, therefore enhancing cell viability. Over time and at increasing doses, the viability of the human colorectal cell lines HT29 and SW480 was considerably reduced by treatment with asarone. According to the scientists, asarone protects colorectal cancer by activating the lamin B1 gene, which in turn triggers cellular senescence. As a result, p53 was increased **(Liu et al., 2013)**.

3.5. Microbial inhibitory properties of α-Asarone

When tested in a laboratory setting, the rhizome showed areas where the growth of methicillin-resistant Staphylococcus aureus (MRSA) and some types of gram-negative bacteria that produce β-lactamase, such as *Escherichia coli*, *Shigella dysenteriae*, and *S. sonnei*, was inhibited. The rhizome contains flavonoids and phenolic chemicals that have been found to possess antimicrobial properties **(Pawar et al., 2020)**.

Furthermore, it has been found that material derived from the rhizome of *A. gramineus* possesses antifungal capabilities, in addition to its ability to cause diseases in people. The compounds asaronaldehyde and α-asarone, found in rhizome material, have fungicidal effects and can efficiently eliminate several diseases such as *Botrytis cineria*, *Erysiphe graminis*, *Phytophthora infestans*, *Puccinia recondita*, *Pyricularia grisea*, and *Rhizoctonia solani* **(Bayyinatul et al., 2017)**.

3.6. Anticholinesterase effects of α-Asarone

The methanolic root extracts experiments shown that calamus essential oil effectively suppresses acetylcholinesterase activity in a controlled laboratory setting. The water and dichloromethylene fractions of a rhizome were both able to inhibit acetylcholinesterase, as demonstrated by their measurable IC50 values **(Mathew and Subramanian, 2014)**.

3.7. Anti-diabetic effects of α-Asarone

A. calamus activates Wnt signaling, which in turn increases the gene expression of pc3. This leads to an increased production of glucagon-like peptide 1, which can lower blood glucose levels either directly or indirectly. This might result in incretin actions, specifically insulinotropic and islet protection **(Khwairakpam et al., 2018)**. Another study proposed that the methanol extract of A. calamus may have potential use in the treatment and control of diabetes in both normal and

streptozotocin-induced diabetic mice. The phyto-treatment had a more pronounced antihyperglycemic effect compared to the gold standard medication glibenclamide (**Prisilla et al., 2012)**.

3.8. Anti-inflammatory effects of α-Asarone

Epidermal keratinocytes are the main cells responsible for the production of cytokines, such as IL-1, IL-3, IL-6, IL-8, and TNF. Under normal circumstances, cytokines are not actively released, but their production can be influenced by several stimuli, including other cytokines. The presence of microorganisms in the skin leads to the activation of inflammation and the mobilization of both innate and acquired immune responses. **Kim et al. (2009)** conducted experiments on keratinocytes using different inducing agents to evaluate the anti-inflammatory properties of *A. calamus*.

3.9. Antioxidant effects of α-Asarone

The rhizome extract is abundant in vitamin C and total polyphenolic compounds. Due to the presence of α-asarone, an active antioxidant compound, it has the capability to enhance the antioxidant capacity and function in the brain **(Rawat et al., 2016)**. According to histological research, rats that were administered a certain dose of i.p. α-asarone and then exposed to four hours of noise each day for 30 days showed typical characteristics in their cerebral cortical tissues. The cerebral cortex of rats exposed exclusively to this level of noise had fewer neurons and aberrant cortical layers. The combination of extract and acrylamide led to an increase in both glutathione content and glutathione-S-transferase activity in the striate body, as shown by **Esfandiari et al. (2018)**. However, when acrylamide was employed alone, both glutathione content and glutathione-S-transferase activity decreased.

3.10. Immunomodulatory effects of α-Asarone

The proliferation of human mononuclear cells, obtained from peripheral blood, was hindered by the alcoholic extract when cultured with either a mitogen (phytohemagglutinin) or an antigen (a pure protein derivative of tuberculin). The extract suppressed the production of IL-2 and TNF-α in human T lymphocytes, which are mononuclear cells derived from peripheral blood. Phytohemagglutinin was used to stimulate the production of IL-2, while LPS was used to stimulate the production of TNF-α. The application of a precise concentration of the extract inhibited the production of nitric oxide in a cell line of murine macrophages. However, it has been shown that lectins, which are present in another extract derived from rhizomes, have the ability to stimulate the growth of T cells **(Das et al., 2019)**.

4. Conclusion

α-Asarone, a compound derived from *Acorus calamus*, possesses a wide array of pharmacological properties. The therapeutic effects of this substance are mainly due to its capacity to regulate oxidative stress, block pro-inflammatory pathways, and control cellular mechanisms such as apoptosis and cell proliferation. The extensive pharmacological profile of α-asarone underscores its promise as a versatile therapeutic agent for the treatment of various human disorders. Continued research and clinical trials are necessary to gain a deeper understanding of how it works and to confirm its effectiveness and safety in human populations.

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