MINI REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Therapeutic Effects of Asarone Species in Alleviating Oxidative Stress and Regulating Cell Death Pathways for Managing Diseases

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Abstract

Asarone, a phytochemical compound prevalent in various plant species such as Acorus and Guatteria gaumeri Greenman, has emerged as a subject of extensive scientific investigation. Its two primary isomeric forms, alpha and beta asarone, have been the focus of numerous studies due to their diverse pharmacological activities. These activities encompass a wide range of therapeutic potentials, including antidepressant, anxiolytic, anti-Alzheimer's, anti-Parkinson's, antiepileptic, anticancer, antihyperlipidemic, antithrombotic, anticholestatic, and radioprotective effects. The mechanisms underlying these pharmacological actions involve the modulation of various molecular targets within the central nervous system, cardiovascular system, and other physiological pathways. While the pharmacological properties of asarone compounds offer considerable therapeutic promise, it is essential to consider their potential adverse effects. Toxicological studies have revealed concerns regarding the mutagenic, genotoxic, and teratogenic properties of both alpha and beta asarone. These findings underscore the importance of cautious evaluation and monitoring when considering the therapeutic application of these compounds. In summary, this comprehensive review provides valuable insights of pharmacological profiles of alpha and beta asarone. By elucidating their mechanisms of action, metabolic pathways, and potential risks, this body of knowledge serves as a foundation for further research aimed at harnessing the therapeutic benefits of asarone compounds while mitigating their associated risks.

Keywords: Asarone species, Pharmacological activities, Oxidative stress, Autophagy.

1. Introduction

Asarone is naturally found in plants such as Acorus calamus Linné, Guatteria gaumeri Greenman, and Aniba hostmanniana Nees. These compounds, categorized as phenylpropenes or alkenylbenzenes, are secondary metabolites of these plants. Chemically, they are divided into two main groups:

the propenyl trans- and cis-isomers known as α-asarone and β-asarone, and the allylic γ-asarone (Uebel, Hermes et al. 2021). Our study has recognized alpha and beta asarone exhibit multiple pharmacological properties including antioxidant, anti-inflammatory, antiapoptotic, anticancer, and neuroprotective effects holding promise for the management of Alzheimer's disease (AD), Parkinson's disease (PD), thrombosis, hyperlipidemia, cholestasis, and additional neurological conditions (Balakrishnan, Cho et al. 2022). The emerging evidence in disease management by influencing oxidative stress and apoptotic-autophagic pathways (Sies and Jones 2020). Oxidative stress arises when there is an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and the effectiveness of antioxidant defense systems. This imbalance has been associated with the onset and progression of various neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), and contributes to the damage linked with other neurological conditions such as ischemic stroke and schizophrenia (Murray, Rogers et al. 2021). Asarone species have been shown to possess potent antioxidant properties, scavenging ROS, enhancing antioxidant enzyme activities, and modulating redox signaling pathways (Jayaprakasam, Seeram et al. 2003, Hosein Farzaei, Bahramsoltani et al. 2016). Furthermore, accumulating evidence suggests that asarone compounds exert regulatory effects on apoptotic and autophagic processes, which are critical cellular mechanisms involved in maintaining tissue homeostasis and responding to stressors (DAVE 2014, Chellian and Pandy 2018). Despite the promising therapeutic potential of asarone species, there remain challenges and controversies surrounding their use, including issues related to bioavailability, metabolism, and potential toxicity (An, Li et al. 2014). Hence, acquiring a comprehensive comprehension of the pharmacological effects and mechanisms of action of asarone species becomes imperative to optimize their therapeutic advantages while mitigating associated risks. This review aims to delve into the therapeutic implications of asarone species in disease management with a specific focus on their capacity to alleviate oxidative stress and modulate apoptotic-autophagic pathways. Our objective is to offer insights into the potential therapeutic applications of asarone compounds as innovative agents across various diseases by amalgamating evidence from both preclinical and clinical studies. Furthermore, we will address existing challenges and future directions in this realm, underscoring the necessity for continued research to fully exploit the therapeutic potential of asarone species.

2. Chemical composition and sources of asarone species

The plant Acorus calamus Linn (Acoraceae), commonly referred to "sweet flag," has been extensively utilized in traditional Indian and Chinese medicine, either independently or in conjunction with other botanicals (Rajput, Tonge et al. 2014). Similarly, Acorus tatarinowii Schott (Acoraceae) and Acorus gramineus Solander (Acoraceae) are esteemed native Chinese medicinal plants, recognized in the Chinese Pharmacopoeia (Huang, Li et al. 2013, Wang, Levinson et al. 2014). The rhizomes of these plants contain bioactive compounds, predominantly alpha (α)- and beta (β)-asarone, albeit in varying concentrations depending on the Acorus species and its geographical origin (Liao, Huang et al. 1998, Hanson, Gayton-Ely et al. 2005).

3. Pharmacological activities of asarone species

3.1. Activity on central nervous system disorders

Asarone species, comprising alpha-asarone and beta-asarone, have attracted attention in pharmacological research for their neuroprotective effect on central nervous system (CNS) diseases (Balakrishnan, Cho et al. 2022). Alzheimer's disease, Parkinson's disease, epilepsy, and anxiety disorders are among the conditions targeted by these compounds due to their diverse pharmacological properties (Reddy, Rao et al. 2015) . The neuroprotective effects of alpha and beta asarone involve multiple mechanisms, including antioxidant, anti-apoptotic, and anti-neuroinflammatory actions, along with the modulation of various cellular and molecular targets. These combined actions may ultimately lead to the ability of alpha and beta asarone to reduce the severity of neurological disorders (Chellian, Pandy et al. 2017, Lee, Ahn et al. 2018). (Figure1)

3.2. Effect on hyperlipidemia

chemical analysis of ethanolic extracts of guatteria gaumeri has the presence of asarone, a compound with reputed hypocholesterolemic properties

(Sharma, Rami et al. 2020). Asarone may modulate the activity of enzymes involved in lipid metabolism, such as lipoprotein lipase (LPL), which plays a key role in the hydrolysis of triglycerides (Maurya R 2013). Moreover, it may influence hypocholesterolemic effect through an increased bile acid synthesis for elimination of body cholesterol (Sharma, Rami et al. 2020). However, further researches are required to clarify the mechanism of this effect.

3.3. Actions on cholestasis

Asarone has been shown to possess anti-inflammatory properties, which may help reduce inflammation and damage to the liver caused by cholestasis. It could potentially alleviate some of the symptoms and complications associated with cholestasis by attenuating inflammation (Reddy, Gayathri et al. 2015). Also, asarone may influence the metabolism and excretion of bile acids, which are crucial components of bile and play a central role in cholestasis. Asarone could potentially affect bile flow and alleviate cholestatic symptoms by modulating bile acid synthesis, transport, or excretion (Wei, Chen et al. 2013). Furthermore, asarone has been reported to exert hepatoprotective effects in various experimental models of liver injury. These effects may involve the preservation of liver function and integrity, which could be beneficial in the context of cholestasis-induced liver damage (Kulkarni SK 2008).

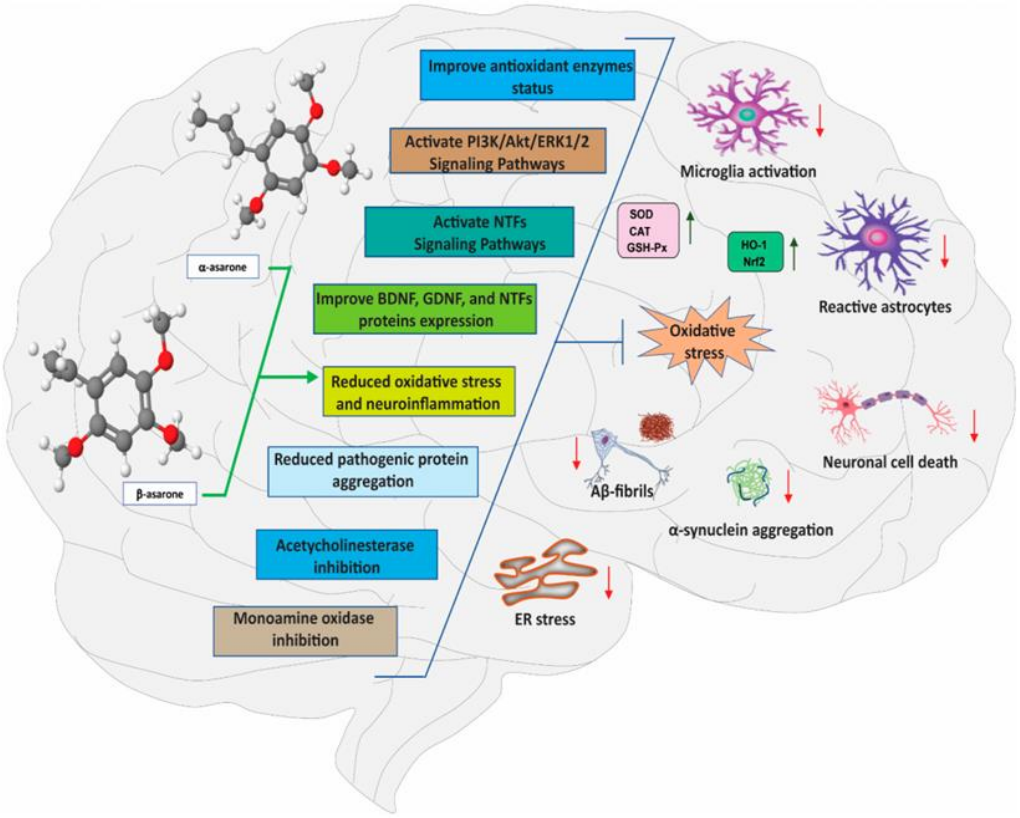

Figure 1: Molecular mechanism of neuroprotection by alpha and beta asarone (Balakrishnan, Cho et al. 2022)

The multi-target effects of α- and β-asarone in the brain include antioxidant: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-PX); mitochondrial protecting; endoplasmic reticulum (ER) regulating; anti-apoptotic; anti-aggregation; anti-inflammatory; and the regulation of various neuroprotective signaling pathways: heme oxygenase-1 (HO-1), nuclear factor erythroid 2-related factor 2 (Nrf2). Red down-arrow (↓) and green up-arrow (↑) signs indicate inhibition and activation by α- and β-asarone treatment, respectively. BDNF, brain-derived neurotrophic factor; ERK, extracellular signal-regulated kinase; GDNF, glial cell-derived neurotrophic factor; PI3K/Akt, phosphatidylinositol-3-kinase; NTFs, neurotrophic factors.

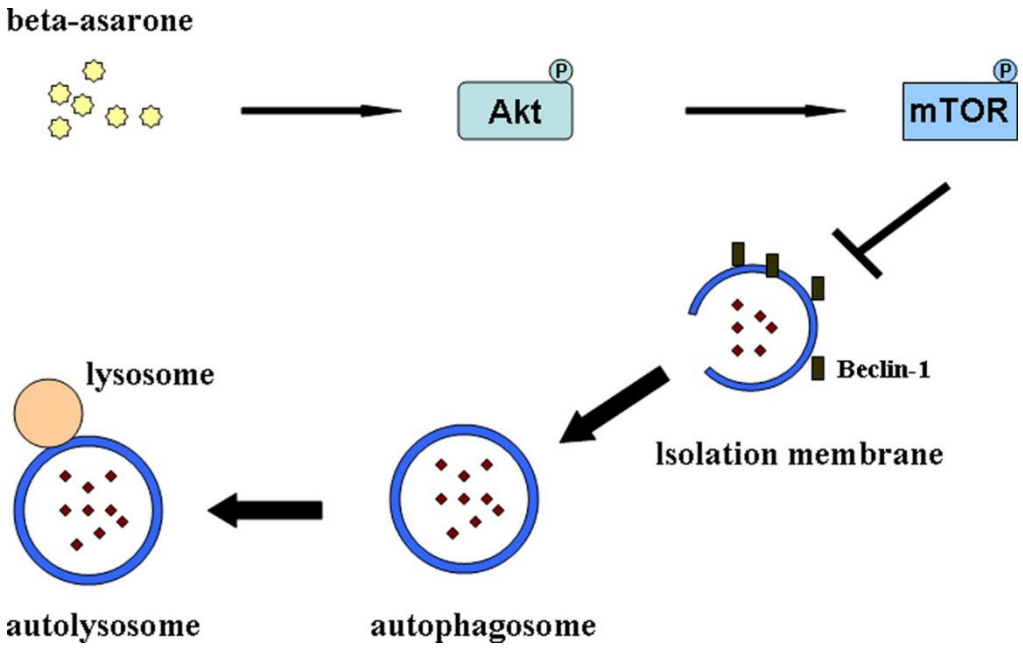

Figure 2: Schematic representation of β-asarone attenuates autophagy (Xue, Guo et al. 2014).
β-asarone attenuates autophagy via Akt-mTOR signaling pathway. β-asarone promotes Akt (Protein kinase B) phosphorylation, which in turn activates mTOR (Mammalian target of rapamycin). Further, this activation promotes mTOR phosphorylation, which serves to inhibit autophagy.

3.4. Effects on thrombosis

Asarone may exert antiplatelet effects by inhibiting platelet activation and aggregation, thereby reducing the risk of thrombus formation. This could be mediated through various mechanisms, such as inhibition of platelet adhesion molecules or interference with intracellular signaling pathways involved in platelet activation (Reddy, Gayathri et al. 2015). It also may possess anticoagulant properties by modulating the coagulation cascade and inhibiting clot formation. This could involve direct inhibition of coagulation factors or enhancement of endogenous anticoagulant pathways, such as activation of protein C or inhibition of thrombin generation (Wei, Chen et al. 2013). Moreover, asarone has been reported to exhibit vasodilatory effects, which could potentially influence blood flow dynamics and reduce the risk of thrombosis. Furthermore, asarone may improve blood flow and prevent stasis, a key contributor to thrombus formation, by promoting vasodilation (Kulkarni SK 2008).

4. Targeting oxidative stress

Asarone species, particularly alpha (α)-asarone and beta (β)-asarone, possess direct scavenging properties against ROS such as superoxide anion (O2•−), hydroxyl radical (•OH), and hydrogen peroxide (H2O2) (Rehman MU 2018). They have been shown to enhance the activity of endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Rehman MU 2018). Also, they may modulate redox signaling pathways involved in oxidative stress responses. This modulation can occur through various mechanisms, including regulation of transcription factors such as nuclear factor erythroid 2-related factor 2 (Nrf2) and activator protein 1 (AP-1) (Wei, Chen et al. 2013).

5. Modulating Apoptotic-Autophagic Pathways

The role of asarone species in regulating apoptotic and autophagic processes has been investigated extensively (Wei, Chen et al. 2013). Asarone

influences apoptotic and autophagic signaling pathways through various mechanisms (Liu Y 2013). These mechanisms include modulation of the PI3K/Akt/mTOR pathway (Figure 2), which plays a crucial role in regulating cell survival and apoptosis (Wei, Chen et al. 2013). Asarone also impacts Bcl-2 family proteins, which are key regulators of the mitochondrial apoptotic pathway (Liu Y 2013). Additionally, asarone influences MAPK signaling cascades, which are involved in the regulation of cell proliferation, differentiation, and apoptosis (Wei, Chen et al. 2013).

6. Conclusion

The therapeutic implications of asarone species, particularly alpha and beta asarone, in disease management are substantial. These compounds exhibit diverse pharmacological activities, ranging from neuroprotection and anti-inflammatory effects to lipid-lowering and anticoagulant properties. Asarone species offer promising therapeutic benefits across various diseases, by modulating oxidative stress and apoptotic-autophagic pathways. Continued investigation in this field is essential to unlock the full therapeutic benefits of asarone compounds and pave the way for the development of novel treatment strategies in disease management.

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