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Review article

Neuroprotective mechanisms of Asiatic acid

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ABSTRACT

Asiatic acid (AA) is the most crucial component of Asiaticoside in many edible and medicinal plants. It has diverse biological activities such as anti-inflammatory, antioxidant, anti-infective, and anti-tumor. Additionally, AA has been intensively studied in the last decades. It has shown great potential in the treatment of various neurological diseases such as spinal cord injury (SCI), cerebral ischemia, epilepsy, traumatic brain injury (TBI), neural tumors, Alzheimer's disease (AD), and Parkinson's disease (PD). Moreover, AA provides pertinent data for neuroprotective signaling pathways, and its substantial neuroprotective ability makes it a novel candidate for developing drugs that target the central nervous system.

1. Introduction

Asiatic acid (AA), the most crucial component of Asiaticoside, is a natural pentacyclic triterpenoid and the aglycone form of Asiaticoside. The chemical formula of AA is $C_{30}H_{48}O_5$, with a molecular weight of 488.70 kD. Its formation occurs under acidic conditions by hydrolysis of the sugar portion of the Asiaticoside structure. The molecular structure of AA is illustrated in Fig. 1 (PubChem database: https://pubchem.ncbi.nlm.nih.gov/compound/119034). Moreover, it has received significant attention because of its vast therapeutic potential and pharmacological properties against various diseases [1,2]. Many edible and medicinal plants contain large quantities of AA [3–6], including Asiaticoside, a significant source of this compound. The previous studies indicate that AA can serve as a crucial multi-target drug of natural origin with various clinical applications [7]. In addition, it has a wide range of biological activities, such as anti-inflammatory, antioxidant, anti-infective, and anti-tumor effects [8]. Intensive studies in the past decades have revealed that AA plays a crucial role in myocardial injury [9–11], hepatitis [12,13], osteoporosis [14,15], tumors [16–19], bacterial and fungal infection [20,21], skin diseases [22,23], wound healing [24], and diabetes [25,26]. Furthermore, it has great potential in treating various neurological diseases such as spinal cord injury (SCI), neural tumors, traumatic brain injury (TBI), epilepsy, cerebral ischemia, Alzheimer's disease (AD), and Parkinson's disease (PD). Previous studies have shown that AA has anti-inflammatory, anti-apoptotic, and antioxidant effects, which protect against neurotoxicity and neurodegeneration. For instance, AA inhibits neuronal mitochondrial apoptosis, reducing the level of pro-apoptotic Bax protein and increasing the concentration of anti-apoptotic Bcl-xL protein [8]. Therefore, the present study reviews the central neuroprotective effects of AA and its relevant mechanisms.

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2. Traumatic brain injury

Traumatic brain injury (TBI) is one of the leading causes of disability and death, especially in young adults [27]. Furthermore, oxidative stress performs an essential function in the onset and development of TBI. Plant compounds can improve neurological deficits, decrease neuronal apoptosis and brain edema, and counteract oxidative stress in TBI [8]. Han et al. [28] found that AA administration attenuated neurological deficits, reduced TBI-induced brain edema *in vivo*, and reduced neuronal apoptosis in a study of a TBI model in SD rats. In addition, AA was found to reverse the elevated levels of various compounds such as 8-hydroxy-2-deoxyguanosine (8-OHdG), malondialdehyde (MDA), and 4-hydroxy-2-nonenal (4-HNE), while elevating the levels of expression of HO-1 and Nrf2 in individuals suffering from TBI. Thus, the effect of AA is attributed to its capability to target the Nrf2/HO-1 pathway, which plays a key role in oxidative stress (Fig. 2). Gu et al. [29] assessed the protective effects of AA on craniocerebral injury in rats using the drop-weight method to create a closed craniocerebral injury model and the hydraulic-shock method to establish an open craniocerebral injury model. AA effectively reduced the water content of brain tissue in both craniocerebral injury animal models, thus improving the permeability of the damaged blood-brain barrier and protecting brain tissue. Furthermore, AA can effectively downregulate the expression of some inflammatory factors such as IL-1β, IL-6, and TNF-α in craniocerebral injury brain tissues, suggesting that AA can play a protective role against craniocerebral injury by inhibiting inflammation (Fig. 2).

Developing drugs that counteract oxidative stress and inhibit the inflammatory response may be a future direction for treating cranial brain injury. In this context, AA can be a potential candidate for TBI treatment.

3. Spinal cord injury

Spinal cord injury (SCI) can lead to neurodegeneration, accompanied by physiological, biochemical, and structural changes [30]. The combination of various factors such as immunoinflammatory responses, oxidative stress, ischemia, and excitotoxicity in locally injured tissues leads to apoptosis and necrosis of neurons and oligodendrocytes and the formation of cavities and glial scarring around the damaged areas of the spinal cord. In addition, the central nervous system has a slow and limited regenerative ability, which makes neural repair and functional recovery after SCI a long and troublesome process [31,32]. Oktay Gurcan et al. [33] conducted a study on the therapeutic effect of AA (75 mg/kg) on traumatic SCI in rats. They found an immediate reduction in the levels of pro-inflammatory cytokines such as TNF-α and IL1 and lipid peroxidation products such as MDA. Additionally, the recovery fraction of Tarlov function improved after AA treatment.

Moreover, AA can reduce many SCI-induced harmful reactions; for instance, a study by Wu et al. [34] regarding the effect of AA (30, 75 mg/kg) on SCI in rats revealed that it inhibited spinal cord peroxidase activity, decreased the levels of IL-1β, IL-18, and IL-6, TNF-α, reactive oxygen species (ROS), H_2O_2, and malondialdehyde, and increased glutathione production and the activity of superoxide dismutase. Moreover, AA therapy resulted in upregulated levels of Nrf2/HO-1 and downregulated the expression levels of NLRP3 inflammasome protein in the spinal cord tissue. Thus, AA plays its role in protecting against SCI by suppressing oxidative and inflammatory stress. The basic mechanism may involve HO-1 and Nrf2 activation and inhibition of NLRP3 and ROS inflammasome pathways (Fig. 2).

Currently, effective treatment options for SCI are lacking, but in recent years some herbal medicines have displayed protective

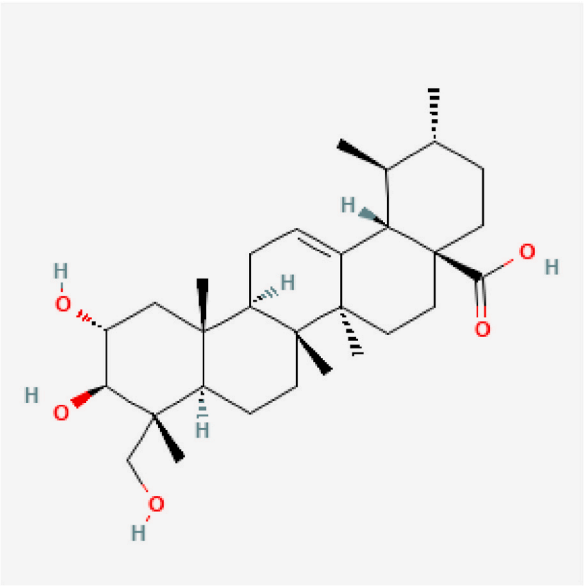

Fig. 1. The chemical structure of Asiatic acid.

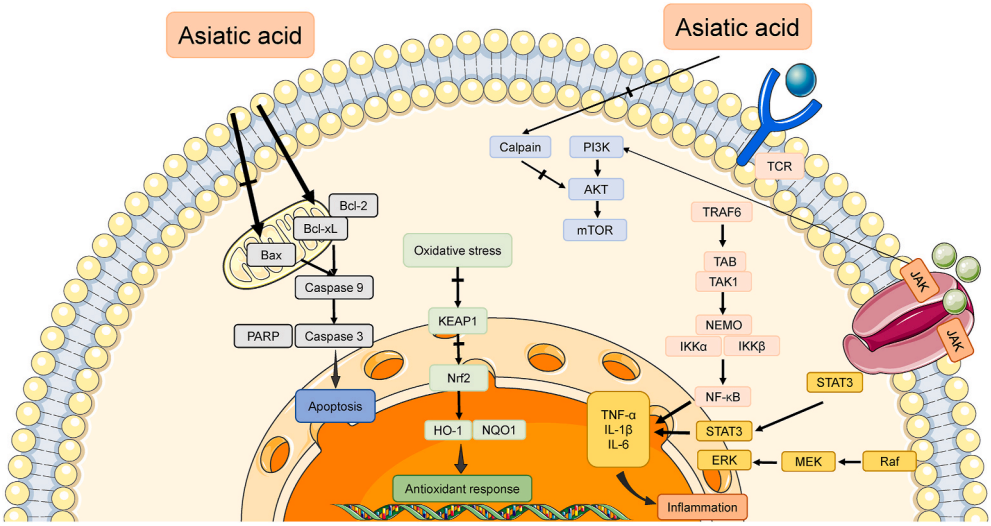

Fig. 2. The neuroprotective mechanism of AA.

effects in SCI models [35–37]. Furthermore, this study observed the neuroprotective effects of AA against SCI via inhibition of oxidative and inflammatory stress, indicating the potential of AA in SCI therapy.

4. Cerebral ischemia

Cerebral ischemia is a severe cerebrovascular disease with high disability and mortality rates, seriously threatening the public health and life of patients [38].

The study by Krishnamurthy et al. [39] utilized AA (3, 10, 20 mg/kg) to treat cerebral ischemia in mice. It was observed that AA substantially decreased cerebral infarct volume by 60% on day one and 26% on day seven and enhanced neurological outcomes 24 h after ischemia. Therefore, the neuroprotective characteristics of AA can be facilitated through limited blood-brain barrier permeability and attenuated mitochondrial damage, suggesting that it can be utilized for cerebral ischemia treatment. Lee et al. [40] administered increasing doses of AA intravenously to stroke mice and measured serum concentrations at various intervals. Pharmacokinetic studies revealed that the half-life of AA (75 mg/kg) was around 2 h. It substantially decreased infarct volume and enhanced neurological outcomes even when administered within 12 h of the ischemia onset. Moreover, AA impacts various models of focal ischemia with an extended therapeutic time.

Additionally, AA can regulate neuroprotection by protecting mitochondria and inhibiting matrix metalloproteinase-9 induction. Lee et al. conducted a rat model study of focal embolic stroke [41]. They observed that combination therapy with AA (75 mg/kg) and low-dose t-PA for 3 h after embolic stroke reduced infarct volume, improved neurological function, and provided neuroprotection benefits. The neuroprotective effects of AA are regulated by decreasing the release of cytochrome *c* and apoptosis-inducing factor (AIF) in the mitochondria of the brain.

The growing research on the anti-ischemic effect of Chinese medicine has brought much attention to the neuroprotective effect of AA due to its significant impact on neuronal protection.

5. Epilepsy

Epilepsy is a chronic disease that affects approximately 65 million people worldwide, and it can increase physical injuries and mortality if not optimally treated [42]. Antiepileptic drugs are the primary therapy for epilepsy, and natural products from herbal medicine have contributed significantly to the discovery and development of novel antiepileptic drugs [43–45].

Inhibition of glutamate release reduces neuronal excitability and is a vital mechanism of antiepileptic drugs. AA administration in rat hippocampal synaptosomes inhibited the release of glutamate in a concentration-dependent manner [46]. Moreover, AA significantly reduced inward calcium flow by activating the calcium channels of N- and P/Q-types to inhibit the activity of protein kinase C, ultimately decreasing glutamate release, thus producing promising results in individuals with epilepsy. Wang et al. [47] observed that AA (20, 40 mg/kg) reduced the production of inflammatory factors, i.e., IL-1β, IL-6, TNF-α, and prostaglandin E2 in a mouse model of epilepsy induced by kainic acid (KA). AA preadministration enhanced glutamine synthetase activity in the hippocampus of KA-treated mice, reduced levels of glutamate, and improved glutamine levels. Thus, AA improved epileptic seizure-like behaviour and attenuated hippocampal inflammatory, oxidative, and apoptotic damage. *In vitro* findings revealed that the pretreatment with AA increased the viability of KA-treated nerve growth factor (NGF)-differentiated PC12 cells, reduced plasma membrane damage, and decreased KA-induced calcium release in NGF-treated PC12 cells. Therefore, AA is an effective drug for epileptic seizure relief.

Cognitive impairment is not only associated with seizures but is also one of the side effects of antiepileptic drugs [48,49]. A study by

Lu et al. [50] suggested that AA (30 mg/kg) can prevent KA, treat seizures, and improve cognitive impairment in rats by inhibiting calpain activation, elevating activated AKT levels, and increasing synaptic and mitochondrial function to reduce hippocampal neuronal damage (Fig. 2). Jariya et al. [51] confirmed that AA (30 mg/kg) prevents spatial working memory deficits and sodium valproate-stimulated cell proliferation and survival. Therefore, AA might help prevent memory deficits in patients taking sodium valproate.

In summary, the mechanism of action of AA in the brain can help explain its antiepileptic effect, but further studies and clinical trials are necessary for a thorough understanding.

6. Parkinson's disease

Parkinson's disease (PD) is a chronic, progressive, degenerative brain disease commonly observed in the elderly. Considering the social treatment requirements of PD and the economic burden on affected families, neurobiologists should urgently identify and develop neuroprotective therapeutic agents with antioxidant properties. Evidence shows that herbal extracts may positively affect PD [52]. According to the study by Chen et al. [53], 1-methyl-4-phenyl-pyridine (MPP +) was utilized to stimulate SH-SY5Y cells to establish a PD model *in vitro*. Their study revealed that AA (0.1, 1.0, 10 nM) decreased intracellular production of mitochondrial ROS, changed mitochondrial membrane potential for regulating mitochondrial dysfunction, and caused the inhibition of NLRP3 inflammasome activation in BV2 microglia via the downregulation of mitochondrial ROS, thereby protecting dopaminergic neurons.

Additionally, AA played a significant role in protecting BV2 microglia from lipopolysaccharide (LPS)-induced toxic impacts, improved cell viability to a great degree, and reduced MPP + -induced mitochondrial dysfunction in SH-SY5Y cells. Another study by Xiong et al. [54] observed that AA (0.01–100 nM) pretreatment protected cells against toxicity induced by rotenone or H2O2 in SH-SY5Y cells. In addition, AA preadministration protects neuronal cells from mitochondrial dysfunction injury. Therefore, AA has a certain potential to prevent and treat PD.

The pathogenesis of PD is also associated with alterations in mitochondrial complex I, typically promoting the α-synuclein (α-syn) bonding to mitochondria [55]. Moreover, α-syn overexpression leads to the generation of oxidative free radicals in mitochondria, resulting in abnormal mitochondrial structure and function. Through its antioxidant properties, AA reduces oxidative stress and apoptosis in mitochondria while preserving the integrity of the membrane and ATP synthesis. In addition, AA prevents the α-synuclein translocation to mitochondria at the molecular level. The potential of AA as a preventive and therapeutic agent for PD is highly intriguing, especially in light of the significant role of mitochondria in the initiation and progression of PD. In a study carried out by Nataraj et al. [56] *in vitro*, it was observed that inducing Parkinson's disease with rotenone resulted in a significant increase in ROS, mitochondrial dysfunction, and apoptosis in SH-SY5Y cells. However, AA (0.01, 0.1, 1.0, 10, 100 nM) pretreatment reversed these changes, which can be credited to its antioxidant, mitosis-protective, and anti-apoptotic characteristics. Taking into account the important function performed by mitochondria in the development and progression of PD, AA can prevent and play a significant role in the treatment of PD. Furthermore, Nataraj et al. [57] evaluated the protective effects of AA (25, 50, 100/kg) on dopamine-GIC neurons in a mouse model of chronic PD, suggesting that AA, through activation of the ERK and PI3K/Akt/mTOR/GSK-3β pathways, exerts effective neuroprotective effects in neuronal loss caused by MPTP/P. These findings suggest a neurotrophic mechanism for AA treatment in PD. CHAO et al. [58] modeled mice with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and AA administration at doses of 40 and 80 mg/kg BW/day resulted in reduced striatal expression of α-synuclein and TLR4 and increased striatal expression of dopamine, brain-derived nerve growth factor, and glial cell-derived neurotrophic factor in mice. The results indicate that AA is an effective trophic agent that can inhibit the development of Parkinson's disease.

Various *in vivo* and *in vitro* experiments revealed AA has anti-PD effects. Therefore, AA is expected to be a new potential treatment for PD. However, more clinical investigations are needed to validate the findings of this study.

7. Alzheimer's disease

Alzheimer's disease (AD) is classified as a progressive neurodegenerative disease and is linked with disabilities of memory, language, and other cognitive impairments in the elderly. An *in vitro* study conducted by Xu et al. [59] demonstrated that AA (at doses of 50 and 100 mg/kg) plays a crucial role in various processes, including protecting SH-SY5Y cells from glutamate-induced apoptosis, reducing ROS production, stabilizing mitochondrial membrane potential (MMP), and regulating the expression of Sirt1 and PGC-1α. *In vivo* study suggested that AA reduced glutamate-induced cognitive deficits in mice and restored lipid peroxidation, SOD, and glutathione activities to normal levels in the cortex and hippocampus. The findings from both *in vivo* and *in vitro* experiments suggest that protecting mitochondria with AA may be useful in developing new strategies for preventing and/or treating neuronal injury and degenerative diseases. Aluminum (Al) is associated with neurotoxicity [60,61] and is considered a possible causative or contributing factor in neurodegenerative diseases, particularly in AD [62]. Ahmad et al. [63] found in an *in vitro* model of AD that AA protected SH-SY5Y cells from aluminum-induced toxicity, significantly enhanced cell viability, and increased cellular activity via the AKT/GSK-3β signaling pathway to attenuate rotenone-induced ROS production, mitochondrial membrane dysfunction, and apoptosis. Moreover, one of the crucial neurotransmitters involved in learning and memory processes is Acetylcholine (Ach), and the leading cause of neurochemical changes in AD is the modification in cholinergic activity [64]. Acetylcholinesterase (AChE), the marker enzyme which regulates cholinergic activity, plays an important role in reducing the physiological impacts of Ach. Ahmad et al. [65] reported that AA administration substantially decreased AChE activity in the cortical and hippocampal regions.

Moreover, elevated levels of Al were observed in the cortex and hippocampus regions of AlCl3-treated rats, and AA provided neuroprotection in AD animals by reducing Al levels. Ahmad et al. suggested that AA treatment attenuated AlCl3-induced AD-related

pathology, including Al overload, AChE hyperactivity, behavioral disturbances, Aβ burden, and inflammation, which may be attributed to its multiple pharmacological effects. To completely understand the beneficial effects of AA, Ahmad et al. [66] further confirmed that AA (75 mg/kg) was involved in inhibiting AlCl3-induced enhancement of Bax, cystathionin expression, and cytosolic cyto-c, decreased Bcl 2 expression and blocked the mitochondrial cyto-c release. Moreover, AA reduced the oxidant-mediated neuronal apoptosis by activating the Akt/GSK-3β/caspase-3 signaling pathway (Fig. 2).

Thus, AA attenuates Al-induced cognitive impairment, Tau pathology, cholinergic deficits, inflammation, Aβ burden, oxidative stress, and apoptosis. Additionally, different pharmacological characteristics indicate that AA can be a potential therapeutic compound for treating AD.

8. Brain tumor

Glioblastoma multiforme (GBM) is a malignant tumor that adversely affects the healthy cells of the brain, thus causing impairment of various body functions. Moreover, the available therapeutic options are insufficient, and multiple studies are being conducted for its efficient treatment. A mechanistic study [67] has revealed that AA induces apoptosis by regulating the protein expression of some apoptosis regulators, such as caspase, Bcl2 family members, and survivin in GBM cells (Fig. 2). Furthermore, in GBM cells, AA was found to induce ER stress, characterized by an increase in the expression of Calpain and GRP78 and a decrease in the expression of IRE1α and Calnexin. This resulted in an elevation of intracellular free calcium and disruption of cellular organization. The findings reveal the efficacy of AA in GBM treatment. Therefore, further AA-based preclinical and clinical evaluation of GBM should be performed. THAKOR et al. [68] highlighted that AA (40 μmol/L) inhibits cell proliferation and viability of fetal neurogliocytes (SVG p12) and grade IV glioblastoma cells, and its efficacy is comparable to that of the standard chemotherapeutic agent cisplatin.

Moreover, AA and other anti-angiogenic agents can improve the condition of patients with glioma [67]. AA holds promise in treating malignant gliomas by inhibiting glioma cells via anti-angiogenic mechanisms [69–71]. According to CHAISAWANG et al. [72], AA (30 mg/kg) can also prevent neurological damage caused by chemotherapeutic drugs. The above study established a rat model of neurological injury caused by 5-Fu chemotherapy, and AA was administered simultaneously. It was observed that the nerve damage in the combined AA treatment group could be restored to normal levels. This finding suggests that AA can be used as an adjuvant chemotherapeutic agent in clinical practice to achieve better therapeutic results. However, further in-depth studies are still needed.

The understanding of the antineoplastic mechanism of AA is still not comprehensive. In addition, the molecular mechanisms acting on tumor cells are unclear, and there is a lack of preclinical and drug toxicity tests. Therefore, the large-scale application of AA in the clinic still requires more effort.

9. Demerits of AA

AA has not been used in clinical trials, and its effectiveness has only been demonstrated in some zoological experiments. Several important indicators must be further determined before they can be applied to human studies. First, the toxicity and safety of AA need to be determined [8]. Current data are limited to the safety and toxicity of extracts of *Centella asiatica* containing AA. Second, AA may have side effects. For example, extracts of *Centella asiatica* have shown weak sensitization in zoological experiments and have caused contact dermatitis [8,73]. Finally, the size of AA doses to treat different diseases in humans is still unknown.

10. Prospect

This review has comprehensively described the *in vitro* and *in vivo* research on the possible neuroprotective benefits of AA and thoroughly summarized the present state of clinical investigations. The results of various experimental data confirm the neuroprotective role of AA in central nervous system disorders. Despite promising data, more detailed research is needed to clarify the pharmacological impacts and molecular mechanisms of AA to establish it as a therapeutic agent for various diseases of the central nervous system. Currently, therapeutic data for AA in central nervous system (CNS) diseases are primarily derived from *in vivo* and *in vitro* models. Therefore, it is necessary to perform extensive human trials to determine the ideal dose concentration and route of administration. In addition, extensive structural modifications should be conducted on AA to improve its bioavailability. Overall, the results of this review present a theoretical basis for developing more efficient and less toxic drugs.

Production notes

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data included in article/supplementary material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15853.

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