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Review Article

THERAPEUTIC VIABLE OF ASIATICOSIDE – A TRITERPENE OF *CENTELLA ASIATICA*: A REVIEW

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Abstract: ***The crude extract of a plant cures diseases through indistinct properties inherent in them, namely the phytochemicals. The active principle present in the crude extract plays a vital role in reducing the effects of disease condition. The active ingredient from Centella asiatica, the Asiaticoside a highly polyphenolic compound, is one of the major triterpene glycosides in Centella asiatica. Precedent research highlighted that asiaticoside ameliorates neurodisorders in cellular and animal models and revealed its clinical potentialities such as anti-oxidative, anti-inflammatory, anti-apoptosis of mitochondria, and inhibiting fibrillation of amyloid protein for enhanced therapeutic intervention. Asiaticoside possesses multi-therapeutic potential to recede cellular illness and senescence by its innate medicinal value, particularly neuroinflammation in Alzheimer's disease and Parkinsonism. Therefore, the objective of the review is to emphasise further interpretation on asiaticoside in the arena of drug discovery for mental illness and neurodegeneration. Further, it is obligatory to identify the complexity and needed investigation to consider asiaticoside as a potential therapy for neurodegeneration. Multi-targeted drug development is a superlative loom for neuronal disease. Since most of the neuronal diseases are interrelated with aging progression associated with cognitive deficits, the therapeutic potential for neurodegeneration should overwhelm all the concerns coupled with disease condition. This paper argues that asiaticoside could be the therapeutic choice for neurodegeneration. Further validation are needed in cellular signaling pathways, pharmacokinetic property, bioavailability, and biotransformation of AS.***

Key words: *Centella asiatica,* Asiaticoside, Neuronal disease

INTRODUCTION

Centella asiatica (L.) Urban (Umbelliferae), which is widely distributed in Asian countries, has been used as a folk medicine agent for the improvement of learning and memory ability and for treating neurological disorders [1]. Asiaticoside is a trierpenoid product derived from this plant possesses

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wound-healing properties [2], considering as liver-protecting agents [3] and enhancing cognitive functions [4]. Herbal medicines have been used to treat Alzheimer's disease and related neurodisorders [5]. Massive biological effects of asiaticoside have been established by researchers, which serve as a token for its therapeutic potential. Therefore, the objective of the review is to emphasise the therapeutic efficacy of asiaticoside to be a better drug and explore its potential to reduce the influence in neurodisorders.

Anti-neuroinflammation activity of asiaticoside: Neuroinflammation is the sign of an exacerbated disease condition of the brain. Microglia plays a vital role in protecting the tissue homeostasis in the central nervous system and regulates the normal physiological activities in the brain, such as identifying and invading the pathogens, maintaining the membrane integrity during signal transduction, immune response and neuroinflammation processes. Age-related neurodegenerative diseases such as Alzheimer's disease and Parkinson's are the outcomes of cellular senescence and altered features in neuronal cells [6]. Activated microglial cells start the synthesis of pro-inflammatory cytokine tumor necrosis factor-alpha, which stimulates the adjacent glial cells to augment the inflammation process.

Research has shown that deterioration of memory begins prior to the onset of old age in animals, including humans [7]. Inflammation of the brain is the hallmark in the development of Alzheimer's disease, and β-amyloid peptide is one of the causes of inflammatory response blending with mitochondrial-induced apoptosis or necrosis of neuronal cells [8]. The fibrillar deposition of β-amyloid peptides takes place in the brain and cerebro-spinal fluid are still a mystery. Several key events are taking place, including the mechanism by which Aβ-1-42 also, called amyloid A4 protein abandon its random coil-alpha helix conformation and acclimatized a β-sheet conformation, leading to oligomerisation. These α-helix to β-sheet conformational transitions are the clue events in understanding the mechanisms of fibre formation, further asiaticoside has been found to inhibit early stages of fibrillogenesis through interactions with 'nucleating' amyloid species and decelerating the growth [9]. The Autogenic senile strain of mice produces increased amounts of amyloid precursor protein, Which is similar to β-amyloid protein those observed in Alzheimer's disease patients [10]. Extreme accumulation of β-amyloid oligomers in the hippocampus of brain enhances disease pathogenesis, such as cognitive defi-cits such as learning and memory. Asiaticoside minimized the deposit of β-amyloid in the hippocampus and increased the learning and memory function, and re-establishing sub cellular structures [11]. The Morris water maze is a spatial learning test is typically used for evaluation of rodent models for cognitive disorders and possible treatments [12,13]. The results from one study has been suggested that asiaticoside improving the learning and memory deficit in rats with β-amyloid protein [4]. The hippocampus of Alzheimer's disease patients exhibits enhanced expression of tumor necrosis factor-α [14]. Neutrophils and lymphocytes were activated by tumor necrosis factor-alpha, which altogether increases the permeability of vascular endothelial cells, regulates the metabolic activity of tissues, and promotes the synthesis and release of other cytokines [15]. Also, induce phosphorylation of nuclear factor-kappaB p65 protein. The activated nuclear factor-kappaB translocates from the cytoplasm into the nucleus of cell to enhance the gene expressions and promotes the synthesis of cytokines, leading to cell apoptosis [16]. Fong et al. [17], has shown that asiaticoside inhibited tumor necrosis factor and suppressing fiber formation. Pro inflammatory cytokines released by activated microglia including interleukins and tumor necrosis factor α which have been of great concern in neurodegeneration has been decreased by the healing quality of asiaticoside [18]. Pre-treatment of asiaticoside (25, 50, and 100 Milli Molar) for 12 hrs could reverse the effect of p65 nuclear translocation induced by β-amyloid treatment. In addition, more expression of adapter proteins LR4, MyD88, Signaling protein TRAF6, phosphorylated nuclear factor-kappaB and p65 proteins were down regulated by asiaticoside. Therefore, targeting translocator protein signaling pathway may afford a novel approach for the treatment of diseases such as inflammation, neurodegenerative disease, and cancer [19]. The expression of peroxisome proliferator-activated receptor gamma is low in normal brain and during the progression of Alzheimer's disease, the level is much increased [20] and inhibits the inflammatory responses caused by β-amyloid protein. In addition, the level of peroxisome proliferator-activated receptor gamma stops increasing at certain stages and inflammatory lesions are aggravated [21]. The incidence of asiaticoside further increases the expression of Peroxisome proliferator-activated receptor gamma protein and exerts its anti-

inflammatory effect [22]. Neuroinflammation is a sign of Alzheimer's disease and probably the therapies holding anti-inflammatory effect may attest for therapeutic intervention [23,24]. Thus, it is essential to formulate an effective treatment that can put off or slow down Alzheimer's disease related memory decline and explore preventive mechanisms to delay the onset of memory deterioration [25]. Mitochondria affect gene expression and are central nodes in the apoptotic route. The load of mitochondria in the cells determines the fate of the cell toward apoptosis or necrosis and this could be a good marker for apoptotic cell fate [26]. Evidence shows that the excessive accumulation of β-amyloid peptides in mitochondria may induce mitochondrion-mediated toxicity [27]. Obviously, asiaticoside has neurosheilding effective against β-amyloid induced pathology and the mechanism are associated with lessening the mitochondrial injuries, anti inflammatory activities, and controlling the expression levels of apoptosis-associated proteins. Recent transmission electron microscopy studies revealed that the damaged sub cellular structure of nuclei and mitochondria in the hippo-campus have been renovated upon asiaticoside treatment [28]. The cholinergic system plays a vital role in a number of neuropsychic functions, such as learning, memory, and sleep [29]. The enzyme acetylcholine esterase converts acetylcholine to acetate and choline in the synaptic cleft. Acetylcholine plays a primary role in amending neuropsychic functions [30]. Prolonged treatment of asiaticoside restored the activity of acetylcholine esterase and increased the level of acetylcholine in the brain. Thus, asiaticoside possesses the therapeutic potential to restore the function of the cholinergic system [12]. Asiaticoside diminished the calcium influx during excitotoxicity induced by N-methyl-D-aspartate in cultured cortical neurons. Thus, asiaticoside reduces the calcium burden and diverts the neuronal cells toward apoptosis cascade events and it has been proved as a neuroprotective agent [31].

Asiaticoside as a anti-parkinsonism agent: A few evidences have been established in this review that asiaticoside can reduce parkinsonism insult in both in-vivo and in-vitro models. Parkinson's disease is a neuro disorder and the causative factors are genetic factors, glial cell activation, inflammation, oxidative stress, mitochondrial dysfunction mediated by oxidative stress, and toxins such as rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [32]. The reactive oxyradicals produced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine are capable of damaging a number of biological molecules such as DNA, RNA, fatty acids, and proteins [33]. Decreased cholesterol synthesis takes place in the skin fibroblast of Parkinson disease patients [34] with lower levels of total cholesterol [35,36]. Asiaticoside holds the potential of retaining the levels of lipids [34]. The neuronal cells have a high content of enzyme tyrosine hydroxylase which converts the amino acid L-tyrosine to dihydroxy phenylalanine [37]. Tyrosine hydroxylase immunoreactive neuron of substantia nigra and neostriatum were markedly reduced by the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. The specific activity of the enzyme has upturned by asiaticoside [38]. Inhibition of Na^+ K^+ - ATPase activity, is found in various neuropathological conditions, including cerebral ischemia [39]. Enzyme activity was significantly increased subsequent treatment of asiaticoside [40]. Astrocytes secrete various neurotoxic substances and express an enhanced level of Glial fibrillary acidic protein, which is considered a marker protein for astrogliosis. Asiaticoside minimise the astroglial activation by diminishing glial fibrillary acidic protein expression [41]. More recently, it has been shown that the ratio of Bcl-2/Bax in the cell determines to a large extent whether the cell initiates apoptosis or not [42]. Chang-Liang Xu et al. [43] demonstrated that asiaticoside increased the expression of Bcl-2, decreased the expression of Bax (hence, a higher Bcl-2/Bax ratio), and increased the resistance of substantia nigra to the damage caused in Parkinsonism. Another study exhibited that asiaticoside could minimise the cell fate apoptosis [33]. Few studies have shown that the combined effect of microtubule dysfunction and Vesicular monoamine transporter 2 reduction could effectively increase the cytosolic dopamine on rotenone exposure and affecting the translocation of monoamines to create oxidative burden leading to cell death [44]. Asiaticoside can claimed to abrogate rotenone-infused presynaptic irregularities to protect against dopamine toxicity [45] and normalize the level of dopamine and rescuing neuronal cell death by upholding the levels of phosphoinositides for normal synaptic functions [46]. Asiaticoside has been patented as a dementia-treating agent and cognitive enhancer [47]. From the above debate, asiaticoside has the potential to reach the molecular level and cascades its anti parkinsonism effect.

Asiaticoside enhances the cognition features: A few studies have confirmed that treatment with asiaticoside might induce antidepressant-like effects [48] such as, attenuate neurotoxicity induced by 1-methyl- 4-phenyl-1, 2, 3, 6-tetrahydropyridine in a rat model of Parkinsonism [49]. The elevated plus-maze test is usually being used to explore and find the anxiety and fear-like behaviour in animals. Rats exposed with rotenone to the elevated plus-maze apparatus avoid open arms [50] and display fear-like behaviour [51]. Treatment with asiaticoside improved the movement dysfunction induced by 1-methyl- 4-phenyl-1, 2, 3, 6-tetrahydropyridine in the open field tests as well as in the ladder walking test, increasing the level of dopamine and 3,4-Dihydroxyphenylacetic acid contents in the striatum of the brain. These results pointed out that asiaticoside might change motor deficits and the depleted levels of dopamine in rats [43]. At the cellular level, asiaticoside can inhibit C6 glioma cell proliferation, migration, and invasion depending on the dose and restored the cognitive functions to uphold the functional plasticity of long-term potentiation in glioma [52].

The mechanism of neurodegeneration is elusive at the cellular level, and the current therapies are inadequate to carry out all the issues in the healing process. Thus, there is an urgent need to develop drugs with multifactorial target and prevent recurrence of the disease. The major active compounds of *Centella asiatica* are asiatic acid, madecassic acid, asiaticoside, madecassoside, madasiatic acid, betulinic acid, thankunic acid, and isothankunic acid [53]. Asiaticoside reduces the fibre formation and prevents amyloidogenesis and it has been proved that it holds the inherited anti-fibrillation spirit. After intragastrical administration of asiaticoside, enhances the antioxidant defense systems and alleviates the harmful effects of free radicals in Senescence Accelerated Mouse Prone 8 mice characterized by age-related deteriorations [12]. Brain-derived neurotrophic factor is a powerful modulator of neuronal excitability and synaptic transmission and plays a role in hippocampal-dependent learning and memory and the synaptic plasticity is recuperated by asiaticoside [54]. This will be a token of therapeutic strategies to design an appropriate inhibitor for Alzheimer's disease. The aggregation of a-synuclein is the primary event in the pathogenesis of Parkinson's disease [55]. Methanolic extract of *Centella asiatica* containing asiaticoside could improve the active movement in rotenone-induced zebrafish Parkinson's disease model through the stability of dopamine neurotransmitter and decrease of a-synuclein aggregation [56]. The neuroprotective effect of asiaticoside can mediated by maintaining redox balance and up-regulating the ratio of Bcl-2/Bax [44]. Asiaticoside showed more potent in maintaining the redox balance by decreasing the apoptic activity of Bax and increasing antiapoptic activity of Bcl-2. Our previous results confirmed that asiaticoside improved ATPases activity by influencing the translocation of transmitters, nutrients, ions, and cellular components between different cellular compartments which could benefit for neuronal integrity shown from the results [40]. Overall, data obtained from clinical and basic research indicate a strong involvement of tumor necrosis factor-alpha in the signaling event of Parkinson's disease and Lewy body dementia [6]. Asiaticoside has the potential of curbing the activation of tumor necrosis factor-alpha reducing cytokine cascade to forfeit the inflammation pathway. Any shortcomings of asiaticoside are yet to be explored for further clinical use, particularly in brain disorder. The solubility of asiaticoside in water is the lowest and is less sensitive to temperature [57]. Being a high molecular weight 959.1 g/Mol asiaticoside the possibility of crossing the blood brain barrier is less viable. Therefore, in most of the experiments, oral administration of asiaticoside was utilized and the metabolites may have the potential to reach the target by crossing the blood brain barrier. Proton emission technology studies using selective radioligands clearly showing that the compound enters the brain and occupies its receptor or target [58]. Yet, there is no available data on asiaticoside metabolomics. Hence, it need further studies in pharmacokinetics and bioavailability. It is essential to conduct clinical trials based on human studies to confirm the efficacy of asiaticiside for clinical usage, particularly in neurodegeneration diseases. Obviously, High Throughput Screening as a drug discovery tool may utilised to study the clinical efficacy. Also, need to study the effect of asiaticoside on neurodegeneration connected with hormonal regulation. Asiaticoside has not shown much nephrotoxic and hepatotoxic effects related to in vivo and in vitro studies, and our previous observations highlighted that the usage of asiaticoside is safe up to 500 mg/kg body weight. Non-toxic dose level of asiaticoside possesses many potential effects and thus provides a supporting evidence for safe

intervention in the disease models [59]. It has been established that the diabetic cutaneous ulcer wounds are healed by the combined effect of asiaticoside and nitric oxide gel by inhibiting the growth of bacteria and alleviate the inflammatory reaction of wounds, and increases the expression of cluster of differentiation protein, endothelial nitric oxide synthase, inducible nitric oxide synthase and vascular endothelial growth factor [60]. Now the task before the researchers is to amend target validation for asiaticoside both *in vitro* and *in vivo* studies.

Conclusion and future perspectives

Based on the available literature this review conveyed the possibilities of asiaticoside be a potential therapy for neurodisorders. Also, it has the potential of restoring the plasticity function which in turn will impact the long-term potentiality of the hippocampus. Many studies authenticated that asiaticoside has the efficacy of restoring the alterations at the cellular level after the insult of neurotoxins, mitochondrial stress, and cell-mediated apoptosis. This review will persuade future researches to design further experiments on asiaticoside metabolomics to analyse the drug target of its metabolites. Although enough evidences are available about molecular studies, a mechanism for the same is lagging with unresolved cellular signaling pathways, biotransformation, bioavailability, and pharmacoknetics. Thus, asiaticoside could be therapeutically potential candidate for neuro degeneration subsequent to make clear the above mentioned issues.

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