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ASIATIC ACID: A PENTACYCLIC TRITERPENOID OF THERAPEUTIC POTENTIAL

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ABSTRACT

In triterpenoids, Asiatic acid, a pentacyclic triterpenoid, has gained enormous attention due to its polypharmacological properties and therapeutic potential in numerous diseases. Asiatic acid possesses numerous pharmacological activities such as antioxidant and anti-inflammatory and regulates apoptosis that attributes its therapeutic effects in numerous diseases. Asiatic acid showed potent antihypertensive, nootropic, neuroprotective, cardioprotective, antimicrobial, and antitumor activities in preclinical studies. In various in vitro and in vivo studies, asiatic acid is found to affect many enzymes, receptors, growth factors, transcription factors, apoptotic proteins, and cell signalling cascades. Asiatic acid showed favourable pharmacokinetics and was found bioavailable following oral or intraperitoneal administration. The present review targets to represent the available scientific reports on therapeutic potential and underlying pharmacological and molecular mechanisms of asiatic acid.

KEYWORDS: Asiatic acid, Pentacyclic Triterpenoid, nanoformulations, nanocarriers, anticancer activity.

1. INTRODUCTION

Natural substances have been used in medicine for ages. Over the past few years, there has been a growing interest in natural triterpenoids, specifically focusing on the scientific aspects of extraction, isolation, structural analysis, and a wide spectrum of biological activities. Pentacyclic triterpenoids are phytoconstituents with promising therapeutic potentials. They are well reported to possess potent antioxidant, organ protective, anticancer activities. They are known sensitizers of cancer cells to chemotherapy. They are non-toxic and have been

used in diets since history. Pentacyclic triterpenes are ancillary plant elements broadly spread in stem, leaves, bark and fruit peel. Specifically, the ursane, lupane and oleanane pentacyclic triterpenes show different pharmacological impacts. Subsequently, these triterpenes are offering key components for the improvement of novel multi-targeted bioactive agents.[1]

Asiatic acid has been patented as a food supplement that prevents skin ageing, enhances wound-healing properties and has anticancer properties. Asiatic acid is the major constituent of Centella asiatica, a plant that is widely used as food and cultivated in India, China, Sri Lanka and Africa as a vegetable or spice. Asiatic acid is a pentacyclic triterpenoid that has been evaluated for anticancer, antidiabetic anti-inflammatory, organotropic and antioxidant effects in suitable animal models.[2]

2. Physicochemical Properties and Pharmacokinetic of Asiatic Acid[3,4,5]

In plants, asiatic acid is biosynthesized by cyclization of squalene and abundantly present in the leaves, flowers and aerial parts with traces in bark, stem, roots, and rhizomes. The extraction of the bioactive compounds from plants is critical to establish standardization and quality control in the pharmaceutical and chemical industry along with ensuring safety, efficacy of the products for human use. Asiatic acid is poorly soluble or miscible in water. It is stable in saline and dissolves at the concentration of 0.1583 mg/mL in saturated saline. Asiatic acid undergoes rapid metabolism that makes it less bioavailable. The CMC and surface tension of asiatic acid were 15 ± 2M and 64.1 mN/m, respectively. The aggregation numbers and molecular association were between 5 and 7 molecules in solution 5 to 7.

Numerous bioactive asiatic acid derivatives were synthesized by modifications at C-11 and C-28 positions. The modified derivatives appear more potent, have a higher bioavailability and exhibit improved activity against key signalling pathways regulating inflammation. Based on numerous findings, the derivatives were found to be more potent with optimal efficacy and minimal toxicity. Till date, a large number of derivatives of asiatic acid have been synthesized and their structures were confirmed using analytical instrumentation such as infrared spectroscopy, Proton Nuclear magnetic resonance Spectroscopy, High Resolution Mass Spectrometry and Carbon 13 Nuclear magnetic resonance Spectroscopy.

Numerous experimental studies demonstrated the pharmacological effects and therapeutic benefits of asiatic acid against many diseases, but non-availability of pharmacokinetic data was the major factor limiting its clinical use. In modern medicine, randomized clinical trials

are vital steps in establishing the safety and efficacy of asiatic acid as a potential agent for use in therapeutics in numerous diseases. Not only asiatic acid, but also many natural molecules such as resveratrol, curcumin, epigallocatechin gallate, and baicalein found promising drug candidates in preclinical models but due to their limited bioavailability and physicochemical properties, clinical development, and usage for therapeutic benefits were limited. The available preclinical data on asiatic acid positively suggest a promising future for clinical studies.

Rats and dogs were used to characterise pharmacological data for asiatic acid. Asiatic acid appears to be a potent inhibitor of CYP2C9 (Ki = 9.1 mg/ml) isoform of P450 enzymes. The potent inhibitory effect of Asiatic acid on CYP2C9 showed its potential to cause drug-herb interactions especially for the drugs metabolized by this isoform determined pharmacokinetics of orally administered asiatic acid in beagle dogs. Oral bioavailability is a vital parameter to attain the effective therapeutic levels of the drug and it represents the most optimal route of drug administration. In the majority of the preclinical studies, asiatic acid was efficacious when administered orally or intraperitoneally. This is noteworthy since oral bioavailability is physiologically and clinically relevant to maximize therapeutic utility.

The lipophilicity, physicochemical properties and availability in brain tissues after administration reasonably supports the neuroprotective potential of asiatic acid. Bioavailability in the brain has indicated that asiatic acid may cross the blood-brain barrier (BBB) and the attained concentration of asiatic acid appear adequate to elicit neuroprotection against neurodegenerative diseases.

The available preclinical and clinical pharmacokinetic data suggest that asiatic acid is bioavailable in almost every tissue. It's distributed to many components of the body by binding with albumin. Following intravenous injection, asiaticoside gets widely distributed in several organs and is metabolized extensively and recovered as asiatic acid in the feces. However, for determining first dose size and optimal therapeutic dose, there is an urgent need of studies to optimize the pharmacokinetics in humans, taking support from preclinical efficacy and safety results.

3. Potential Role of Asiatic Acid in the Prevention and Treatment[5,6,7,8]

Asiatic acid is a naturally occurring aglycone of ursane type pentacyclic triterpenoids. Asiatic acid possesses numerous pharmacological activities such as antioxidant and anti-

inflammatory and regulates apoptosis that attributes its therapeutic effects in numerous diseases. Asiatic acid showed potent antihypertensive, nootropic, neuroprotective, cardioprotective, antimicrobial, and antitumor activities in preclinical studies. In various in vitro and in vivo studies, asiatic acid is found to affect many enzymes, receptors, growth factors, transcription factors, apoptotic proteins, and cell signalling cascades.

3.1 Asiatic Acid as Antioxidant

Asiatic acid showed to elicit potent antioxidant and free radical scavenging properties involving various pathways. Asiatic acid produced dose-dependent free radical scavenging activity by countering hydroxyl radicals and superoxide anions. The antioxidant mediated organo-protective effects of asiatic acid demonstrated in various experimental models of human diseases. Asiatic acid is a highly effective chain-breaking antioxidant, which acts against reactive oxygen species (ROS). Asiatic acid showed to attenuate myeloperoxidase activation and inhibit lipid peroxidation. The inhibitory capacity on lipid peroxidation appears higher than several well-known antioxidants such as probucol, ascorbic acid, and α-tocopherol. Asiatic acid is also found to augment activities/levels of both enzymatic and non-enzymatic antioxidants.

3.2 Asiatic Acid as Anti-Inflammatory

Effect of asiatic acid in inflammatory conditions in several experimental studies showed due to its capacity to regulate pro-inflammatory cytokines and preventing the development and progression of immune-inflammatory disorders. Asiatic acid ameliorated NF-κB expression in LPS-stimulated RAW264.7 cells, inhibited IKKα/β phosphorylation and interferon-gamma (IFN-γ) activation. Docking studies for the prediction of NF-κB inhibitory activity were carried out using PASS (prediction of activity spectra of substances) software followed by docking of the NEMO/IKKβ association complex (PDB: 3BRV). The compliance was tested with the softened Lipinski's Rule of Five that showed asiatic acid has promising potential to be developed as an anti-inflammatory drug against various inflammatory diseases.

Asiatic acid showed potent immunomodulation due to its inhibitory effect on both Th1/Th2 cytokines that indicates the potential benefits of asiatic acid in several autoimmune diseases. Owing to the multimodal anti-inflammatory mechanisms, asiatic acid appears an important agent to treat diseases where immune-inflammatory alterations are a common accompaniment in pathogenesis.

3.3 Antibacterial Activity

Asiatic acid suppresses growth, cell morphology, virulence factors, and biofilm formation by Enterococcus faecalis strains. It showed potent anti-biofilm activity without affecting hydrophobicity of bacteria and reduced survival as well as virulence. Asiatic acid isolated from Melastoma malabathricum L. showed antibacterial activity against numerous microbes in agar diffusion method. Asiatic acid isolated from Symplocos lancifolia showed antibacterial against Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, and several Gram-positive bacteria.

Asiatic acid examined on silicone catheters and polystyrene microtiter plates was found to inhibit biofilm formation in uropathogenic Escherichia coli. Asiatic acid synergistically enhances the bactericidal activity of ciprofloxacin, a fluoroquinolone antibiotic used in the treatment of recurrent urinary tract infections caused by Escherichia coli. Asiatic acid favourably influenced morphology, hydrophobicity and adhesion of uropathogenic Escherichia coli strain to the epithelial cells to reduce antibiotic resistance and thus reduced chances of recurrent infections. Asiatic acid also exhibited anti-biofilm activity in combination with tobramycin and ciprofloxacin.

3.4 Role of Asiatic Acid in Epilepsy, Depression, and Associated Complications

Asiatic acid was found to reduce severity and frequency of seizures. Asiatic acid has been shown to reduce the production of inflammatory cytokines and mediators such as cyclooxygenase-2 and NF-κBp50/65 in the hippocampus. Also prevented neuronal damage of the pyramidal layer in the CA1 and CA3 regions of hippocampus, restored antioxidants and attenuated cognitive deficits in mice. Asiatic acid and its derivatives are promising for memory and cognition enhancement. Thus, asiatic acid can be used either alone or as an adjuvant in neuropsychiatric diseases including epilepsy as well as learning and memory impairment.

3.5 Asiatic Acid in Cancer

To minimize the multi organ toxicities of cancer chemotherapy, organ protective adjuvants are also prescribed. Organ protectants are under clinical investigation and few drugs including amifostine are FDA adjuvants to cancer chemotherapy. Numerous pre-clinical and clinical studies demonstrated the anticancer potential of Asiatic acid Asiatic acid itself and validated the traditional claims of anticancer potential of many plants containing asiatic acid as a major ingredient used in traditional medicines. The anticancer and chemo preventive

efficacy of several medicinal plants is attributed mainly to the presence of asiatic acid. The effects of AA on the PI3K/Akt/mTOR pathway were also examined in ovarian cancer cells. AA significantly reduces lung cancer cell growth both in vitro and in vivo, and the associated apoptosis is mediated through mitochondrial damage.

3.6 Asiatic Acid in Malaria

Asiatic acid found to elicit chemoprophylactic effects by diminishing parasitemia and anemia associated with murine malaria in rats. The authors further showed the antimalarial effect of transdermal formulation of asiatic acid applied as on the shaven dorsal neck region of Sprague Dawley rats infected with Plasmodium berghei.

Asiatic acid has been suggested to be a novel agent for malaria treatment as well as an adjuvant in countering hypoglycaemia, which occurs during malaria or synergizes with the action of antimalarial drugs.

3.7 Activity of AA in Neuroprotective Effects

Neuroprotection refers to the preservation of brain function and structure. Administration of AA has clearly demonstrated an improvement in learning and memory in animal models, an effect that was correlated with the amplification in hippocampal neurogenesis. AA can be regarded as a reasonable therapeutic candidate for Alzheimer's disease, that is, a drug that protects neurons from β-amyloid toxicity. AA was used to describe the inhibitory effect on acetylcholinesterase (AChE) properties, excitatory postsynaptic potential (EPSP), and locomotor activity.

3.8 Activity of AA in Cardiovascular Diseases

Cardiovascular disease includes various coronary artery diseases, such as stroke, heart failure, hypertensive heart disease, angina and myocardial infarction, rheumatic heart disease, heart arrhythmia peripheral artery disease, and venous thrombosis. It is well established that L-NAME-induced hypertension produces not only cardiovascular alterations, but also inflammation and an increase in oxidative stress. Chronic inhibition of NOS with L-NAME induces pro-inflammatory phenotypic changes of the vascular wall, including an increase in the expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and inducible nitric oxide synthase. AA plays an important role in the inhibition and treatment of cardiac hypertrophy. AA plays an important role in the inhibition and treatment of cardiac hypertrophy.

3.9 Activity of Asiatic acid in Diabetes

Diabetes mellitus is a group of metabolic disorders in which blood sugar levels are affected; over a prolonged period, diabetes can cause many complications. Asiatic acid and its derivatives are promising agents in the prevention of diabetic complications. As Asiatic acid has strong antioxidant activity, which can inhibit or slow the formation of advanced glycation end products, it is implicated in the pathogenesis of diabetic nephropathy, embryopathy, and neuropathy.

4. Toxicity and Safety of Asiatic Acid[8,9,10]

The safety and toxicity of asiatic acid is based on the evidence arisen from toxicity studies with the extract only. Therefore, efficacy evidence, regulatory toxicology data is essential to evaluate the drug in humans.

There is no clinical study wherein the safety and toxicity of asiatic acid have been reported as it has not been tested for its efficacy in humans yet. In animal studies, the doses studied for pharmacological effects are in the dose range of 20 to 500 mg/kg. In the majority of the preclinical studies, asiatic acid was administered orally or intraperitoneally and was found pharmacologically effective. Many preclinical studies showed the organo-protective effects of asiatic acid where asiatic acid was devoid of general, behavioral and systemic toxicity. In future, systematic regulatory toxicology studies are warranted to determine the safety parameters and further translate the beneficial effects in humans. The LD50 and no observed adverse effect level (NOAEL) should be investigated with different routes of administration in acute and chronic settings in the most appropriate animal species following the US FDA guidelines. The preclinical data including dose-response relationship, pharmacokinetics, and regulatory toxicity data are vital to determine the first dose size in humans and clinical drug development of asiatic acid.

5. CONCLUSION

Asiatic acid has high potential to be developed for wound healing, neurodegenerative diseases and cancer. The main anticancer mechanisms of action of AA include inhibition of proliferation, angiogenesis, metastases, migration, tumorigenesis along with induction of apoptosis and activation of carcinogen-metabolizing enzymes. However, more in vivo studies are still needed to confirm in vitro findings and reconfirm the reported findings with pharmacological and molecular mechanisms. This review provides important evidence that AA and its derivatives have promising therapeutic applications for the treatment of various

chronic disorders. Because of its pharmacological activities, low toxicity, and commercial availability, AA has been receiving greater consideration in molecular biology.

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