

Review

# Actions and Therapeutic Potential of Madecassoside and Other Major Constituents of *Centella asiatica*: A Review

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**Abstract:** *Centella asiatica* is a popular herb well-known for its wide range of therapeutic effects and its use as a folk medicine for many years. Its therapeutic properties have been well correlated with the presence of asiaticoside, madecassoside, asiatic and madecassic acids, the pentacyclic triterpenes. The herb has been extensively known to treat skin conditions; nevertheless, several pre-clinical and clinical studies have scientifically demonstrated its effectiveness in other disorders. Among the active constituents that have been identified in *Centella asiatica*, madecassoside has been the subject of only a relatively small number of scientific reports. Therefore, this review, while including other major constituents of this plant, focuses on the therapeutic potential, pharmacokinetics and toxicity of madecassoside.

**Keywords:** madecassoside; *Centella asiatica*; asiaticoside; asiatic acid; madecassic acid



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## 1. Introduction

*Centella asiatica* (L.) Urb., is an ethnomedical tropical plant that belongs to the Apiaceae family. Locally known as pegaga, or more commonly known as 'Indian pennywort', it is a lightly aromatic, slender and perennial creeper that blooms in shady, marshy and humid areas in tropical and subtropical Asian countries such as Malaysia, India and China [1,2]. The plants have a creeping stem, rooting at the nodes, producing tufts of leaves and white or pink flowers [3]. This plant is widely consumed as a health drink, while also used as a vegetable in a variety of cuisines and traditional food recipes in Asian countries [4]. *C. asiatica* (CA) has been used extensively in Ayurvedic and Chinese traditional medicine for hundreds of years to treat dermatological diseases, including bacterial infections, psoriasis, scleroderma, ulcer, leprosy and also skin inflammation due to wounds and burns [5–9]. Moreover, *C. asiatica* has also been reported to have neurological actions, including neuroprotective, memory-enhancing, antidepressant and anxiolytic effects [4–6,8,10,11]. Due to the outcome of in vitro and in vivo studies, as well as their cost effectiveness, easy access and low observed toxicity, *C. asiatica* extracts have been investigated clinically in various fields. A study found that CA lowered stress, attenuated anxiety, negated depression and enhanced adjustment and attention in patients with general anxiety disorder without any adverse effects [12]. CA was also reported to exert anxiolytic activity [13], as well as improve mood, behavior and cognitive functions [14–16]. Furthermore, CA has been used widely in treating vascular diseases, such as venous hypertensive microangiopathy [17–20], diabetic microangiopathy [21,22] and chronic venous insufficiency [23,24]. Clinical trials of CA have also been undertaken in other conditions, including leprosy [25], chronic hepatic disorder [26] and gastric ulcers [27–29]. With the abundant literature available on therapeutic effects of CA, it is worthwhile to explore into the compounds that is/are responsible for the effects.

The novelty of this review is it highlights the compound madecassoside, as it's potential have not been tapped into vastly. This review also compiles the pharmacological activities of the main constituents, that has not been published previously.

## 2. Methodology

An extensive literature search was performed to identify the major constituents responsible for the reported pharmacological properties of *C. asiatica*. Furthermore, an attempt to summarize the common mechanism was made. Various electronic databases, such as Science Direct, PubMed, Taylor and Francis, Wiley, along with Google Scholar search engine were used for the literature survey. Papers with information on phytochemicals, medicinal properties, traditional practices and clinical trials were included. The literature cited in this review paper consists of 261 references which includes research and review papers. The search terms used in combination were *Centella asiatica*, madecassoside, asiaticoside, madecassic acid, asiatic acid, pharmacokinetics, toxicity profile and pharmacological properties. Studies or trials that did not include basic details were excluded. The results were compared, correlated and discussed to help researchers to further explore the possibilities of using the compounds in other research areas as well as clinical trials. The summary of the methodology adopted in the development of this review is illustrated in Figure 1.

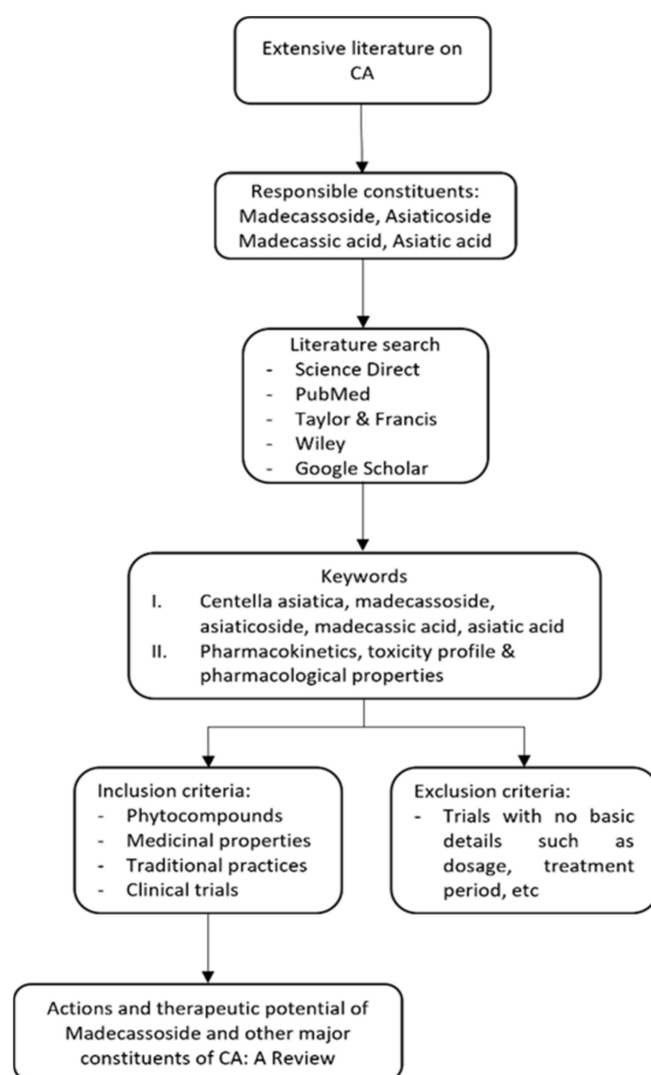
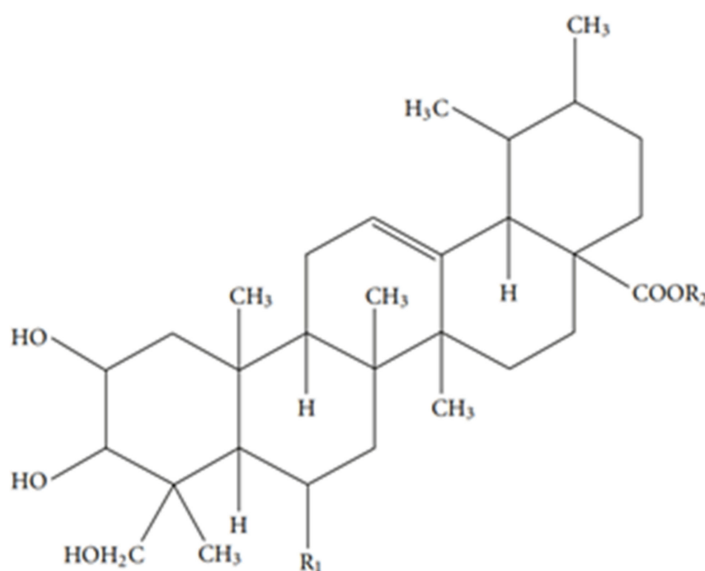


Figure 1. Summary of methodology.

### 3. Active Constituents of *C. asiatica*

Inconsistent pharmacological activities of *C. asiatica* extracts harvested from various origins were reported; these extracts displayed substantial variations in the quality and quantity of their bioactive compounds [11]. Previous analytical studies showed *C. asiatica* to contain triterpenoids, amino acids and essential oils. The most important bioactive compounds are triterpene glycosides (saponins), such as asiaticoside and madecassoside, along with their respective aglycones (sapogenins), asiatic acid and madecassic acid [5,8,10,30–32]. These four major compounds, also known as pentacyclic triterpenes, are claimed to be responsible for the biological effects of *C. asiatica* extracts (Figure 2). Other constituents include oxyasiaticoside, centelloside, brahmoside, brahminoside, thankunside, isothankunside, brahmic acid, isobrahmic acid, betulic acid,  $\beta$ -sitosterol, hexacosanol octanoate, kaempferol, quercetin, daucosterol, vanillic acid and succinic acid [2,7,9,33,34]. Madecassoside and asiaticoside are identified as the biomarker components of this plant extract, due to their high contents relative to other constituents, with the content of madecassoside ( $C_{48}H_{78}O_{20}$ ) being the highest [35].



Madecassoside	R <sub>1</sub> = OH	R <sub>2</sub> = Glu-Glu-Rha
Asiaticoside	R <sub>1</sub> = H	R <sub>2</sub> = Glu-Glu-Rha
Madecassic acid	R <sub>1</sub> = OH	R <sub>2</sub> = H
Asiatic acid	R <sub>1</sub> = H	R <sub>2</sub> = H

**Figure 2.** Chemical structures of madecassoside, asiaticoside, madecassic acid and asiatic acid (Glu: glucose, Rha: rhamnose).

Several methods have been used to quantify the triterpene content of *Centella* extracts. These include thin-layer chromatography and mass spectrometry (TLC-MS) [36], TLC coupled to high-speed counter-current chromatography [37,38], ultraviolet-visible spectroscopy (UVS) [39], high performance liquid chromatography (HPLC) [40–42], HPTLC [37,42–45], HPLC–electrospray ionization–mass spectrometry (HPLC–ESI–MS) [6], HPLC–ultraviolet (HPLC–UV) [5,41,46], and HPLC–paired with evaporative light scattering detector (HPLC–ELSD) [5,42]. Among these methods, some are comprised of multiple-step extraction and/or purification processes. These techniques have limited sensitivity and specificity, while necessitating long analysis cycles to acquire satisfactory chromatographic separation. High-performance anion-exchange chromatography combined with pulsed amperometric detection (HPAEC–PAD) is often used to quantify carbohydrates in plant extracts, allowing absolute detection of carbohydrates with great sensitivity [5]. Glycosides have previously been analyzed using reversed phase HPLC–PAD, where the compounds

were detected following chromatographic separation. For example, madecassoside and asiaticoside were detected within 5 min of sample pre-treatment by combination with a post-column sodium hydroxide solution using the reversed phase HPLC-PAD method [5].

Although the quantification of *C. asiatica* triterpenes have been corroborated by numerous researchers using HPLC-UV and HPTLC, variations in the triterpene content of extracts were found, depending on the location and the diverse environmental conditions for the growth of the plant. An investigation of the chemotypic variations of active biomarkers in relation to morphotypic changes in *C. asiatica* found no distinct disparity in botanical descriptors, physicochemical parameters or in bioactive metabolites quantified through HPTLC; this led the team to conclude that morphotypic variations do not always lead to chemotypic variations in *C. asiatica* [33].

A different approach using a polyclonal antibody against madecassoside, ELISA and Eastern blotting was used to quantitatively analyze triterpene glycosides in *C. asiatica*. ELISA was used to determine total madecassoside and asiaticoside content, whereas Eastern blotting was used to separate and quantify madecassoside and asiaticoside. These methods are faster, more straightforward and cost effective compared to HPLC [4].

#### 4. Pharmacokinetics of *C. asiatica* Constituents

Over the years, countless small molecules derived from natural products have failed to progress to clinical studies, due to poor pharmacokinetic properties. Pharmacokinetics and bioavailability are major barriers in drug development. Oral bioavailability is an important factor to achieve the efficacious therapeutic concentrations of the drug, as it also denotes the most ideal route of drug administration [47].

Several studies have examined the pharmacokinetics of asiatic acid in rats and dogs [48–50]. With oral dosing, asiatic acid achieves a maximum plasma concentration ( $c_{max}$ ) after 30 min, indicating rapid gastrointestinal absorption. However, it is absorbed poorly and follows passive diffusion, with a major site of absorption in the jejunum, followed by rapid metabolism in the liver by cytochrome P450 enzymes [50]. Bioavailability studies have shown that asiatic acid may cross the blood–brain barrier (BBB), as the concentration of asiatic acid attained in the brain appears to be adequate to elicit neuroprotection [51–54]. The pharmacokinetics of asiatic acid present in a total triterpenic fraction of *C. asiatica* were studied in a randomized crossover design, administering a single oral dose or repeated oral doses to healthy volunteers. Difference in dosage or treatment schemes did not affect the time taken to achieve peak plasma concentration. However, a chronic treatment protocol demonstrated increased half-life ( $t_{1/2}$ ),  $AUC_{0-24}$  (area under the plasma concentration–time curve from zero to 24 h) and  $c_{max}$  [55]. The pharmacological effects and therapeutic benefits of asiaticoside are mediated by its in vivo metabolic conversion to asiatic acid [56]. Following intravenous administration of asiaticoside to rats, it is widely distributed in several organs and metabolized extensively, then finally recovered as asiatic acid in feces [10]. Asiatic acid is a non-toxic compound with an  $LD_{50}$  value of 980 mg/kg in rats [57].

Pharmacokinetic studies of madecassoside in rats have shown a  $c_{max}$  of  $303.75 \pm 28.53$  ng/mL after a single-dose oral administration of 100 mg/kg [6]; it was hypothesized that madecassoside could be metabolized to madecassic acid by intestinal bacteria [6,35]. Another pharmacokinetic study conducted using collagen-induced arthritic (CIA) rats showed the  $c_{max}$  and AUC of madecassoside to be notably reduced, while the  $V_d/f$  was augmented during the initial seven days of dosing. On the other hand, the  $T_{1/2}$ ,  $c_{max}$  and AUC of madecassic acid were prominently elevated, with a significant reduction of elimination rate constant ( $K_e$ ) in CIA rats compared with normal rats. This study showed that the pharmacokinetic parameters of both madecassoside and madecassic acid in rats were substantially altered by arthritis status [58]. Another study compared pharmacokinetic changes of madecassoside and asiaticoside following the administration as pure compounds and ECa 233, a standardized extract of *C. asiatica* with madecassoside (51%) and asiaticoside (38%) in male Wistar rats. The  $AUC_{0-\infty}$  of madecassoside from ECa

233 was 2-fold higher than that of pure madecassoside. Furthermore, the elimination half-life of madecassoside and asiaticoside as pure compounds were approximately 4 h, while the elimination half-life of madecassoside and asiaticoside as ECa 233 were prolonged. The study suggested that the pharmacokinetic behavior of madecassoside and asiaticoside was improved when administered as ECa 233 compared to pure compounds [10].

## 5. Toxicity Profile of *C. asiatica* Constituents

There is a scarcity of literature relating to the adverse effects and toxicity of *C. asiatica*. In a recommended dosage in humans *C. asiatica* is not toxic and side effects are rare, although it may cause skin allergy and burning sensations with external use, and in high doses, headache, upset stomach, nausea, dizziness and drowsiness were observed [59]. Contact dermatitis cases were reported on a few occasions from using topical preparations that contained *C. asiatica* [60–65]. The median lethal dose of dried powder of *C. asiatica* given orally to mice was greater than 8 g/kg, attesting to the lack of acute toxicity of the dried plant [66]. In a chronic toxicity study, 20, 200, 600 and 1200 mg/kg/day of *C. asiatica* were given to Wistar rats for six months. At the end of the study, treated animals showed no significant changes in body weight, blood chemistry, clinical chemistry and histopathology when compared to the control group [67]. However, in contrast, oral administration of dried *C. asiatica* at a dose of 1000 mg/kg/day for 30 days to albino rats produced hepatic damage [68]. Furthermore, there is also a report on the risk of hepatotoxicity in humans treated with *C. asiatica* for 20–60 days [69]. Although *C. asiatica* was rarely reported to cause any adverse effects, it is advised not to be consumed by women during pregnancy and lactation, as it may have emmenagogue effects [70]. Extended treatment with high doses appears to reduce the metabolism of active constituents, which may increase the risk of toxicity; this should be considered during pharmacotherapy [55].

There are few studies on the toxicity of individual constituents of *C. asiatica*. One study reported that asiaticoside did not exhibit any signs of toxicity after oral administration of 1 mg/kg. However, intramuscular injection of asiaticoside caused toxicity in mice and rabbits at 40–50 mg/kg [71]. Asiaticoside was also implicated as a weak carcinogen after repeated topical application on hairless mice [72]. Drug–drug interactions are possible with asiaticoside and/or madecassoside, as they were shown to inhibit human cytochrome P450 enzymes that are responsible for drug metabolism [73].

## 6. Therapeutic Actions of Madecassoside and Other Major Compounds in *C. asiatica*

Despite the extensive use of *Centella asiatica* as a traditional remedy, there have been few clinical studies because the drug delivery of a whole plant extract is more challenging compared to individual compounds. Therefore, attention has been focused on the isolation, production and medicinal efficacy of its bioactive compounds. This review focuses on madecassoside, asiaticoside, asiatic acid and madecassic acid, which have been researched considerably in recent years. A summary of the recent findings (from year 2015 to 2021) for the various conditions discussed below is presented in Table 1.

### 6.1. Skin Related Disease or Wound

*C. asiatica* has been used extensively in traditional medicines for treating skin related wounds and diseases, such as ulcerous skin abnormalities, lupus, scleroderma, leprosy [74]; a small number of studies have suggested that the beneficial effects are due to madecassoside, the most abundant triterpene present in extracts of *C. asiatica* [75]. Many studies suggested that madecassoside is beneficial in a variety of skin disorders, in which it may prevent skin aging and promote wound healing, as well as exerting anti-inflammatory and anti-psoriasis effects [76]. These effects of madecassoside may be due to its ability to protect against lipid peroxidation, and intensify collagen synthesis and expression while stimulating angiogenesis [77].



The most widely studied effects of *C. asiatica* extract and madecassoside have been in the context of burn wound healing. Burn wounds are categorized as tissue injury caused by external triggers, such as heat, chemicals, radiation and electricity [74]. Burn wounds could be classified into three degrees, predominantly based on the complexity of the wound incurred; these are superficial (first degree), partial thickness (second degree) and full thickness (third degree). Burn wound healing is complex, comprising an array of processes. It commences with inflammation that interrupts blood vessels and stimulates blood constituents to be released to the target area to stimulate re-epithelialization; followed by the formation of granulation tissue consisting of macrophages and fibroblasts that are responsible for extracellular matrix recovery; neo-vascularization towards the target area; in addition to mitogenic stimulation and migration of cells of endothelial origin. Finally, communication between extracellular matrix cells and cytokines results in wound contraction [74]. In rats, madecassoside and asiaticoside were reported to possess wound healing properties [74]. Madecassoside was shown to augment inflammatory cell infiltration, and to nurture re-epithelialization to achieve an almost complete wound closure with an improved healing pattern in the burned skin on mice [78]. Furthermore, in vitro studies have demonstrated the ability of madecassoside to promote type I and III collagen synthesis and to stimulate the proliferation of cultured human fibroblasts [78]; similar findings were also reported for asiaticoside [79]. Madecassoside was shown to augment endothelial cell growth in rat aortic rings in vitro, and to markedly increase angiogenesis in mouse burn wounds; it was hypothesized that madecassoside expedites burn wound healing through increased antioxidative activity, enriched collagen synthesis and angiogenesis [78]. In a separate study, madecassoside was shown to protect human umbilical vein endothelial cells (HUVECs) against hydrogen peroxide-induced lipid peroxidation and apoptosis via protecting the mitochondrion membranes, and inhibiting the activation of caspase-3 and p38 MAPK [80]. Similar studies have also been conducted to test the efficacy of asiaticoside in wound healing. Asiaticoside treatment increased migration rates and initial attachment of skin cells, while promoting normal human dermal fibroblast proliferation [81]. Asiaticoside also exhibited significant wound healing activity in normal as well as delayed healing models [82]. A study suggested that the enhancement of burn wound healing by asiaticoside could be due to the promotion of angiogenesis as a result of stimulation of the production of vascular endothelial growth factor (VEGF), caused by an increased expression of monocyte chemoattractant protein-1 (MCP-1) in keratinocytes, even at very low doses of asiaticoside (10 pg, 1 ng and 100 ng per mouse) [83]. Furthermore, the augmented healing produced by asiaticoside could be due to its capacity to enhance tissue antioxidant levels [84]; this study also suggested that asiaticoside would be helpful in wound repair only if applied during the active/initial phase of healing [84]. Asiaticoside has also showed potential in accelerating wound healing in a fish model via increased cellular proliferation and suppressed apoptosis [85].

Skin aging is a multifaceted biological process molded by a combination of endogenous or intrinsic (genetics, cellular metabolism, hormone and metabolic processes) and exogenous or extrinsic (chronic light exposure, pollution, ionizing radiation, chemicals, toxins) factors. It is characterized by features, such as wrinkling, loss of elasticity, laxity and a rough textured appearance. Madecassoside showed protective effects against oxidative stress and UVB radiation. It significantly inhibited UV-induced melanin synthesis and melanosome transfer in a co-culture system of keratinocytes and melanocytes, by suppressing PAR-2 expression and its signaling pathway involving COX-2, PGE2 and PGF2 $\alpha$  in keratinocytes [86]. Several traditional Chinese medicine practitioners have shown a therapeutic effect of madecassoside in the re-pigmentation of vitiligo and post-inflammatory hyperpigmentation. For example, madecassoside showed an anti-oxidative effect in human melanocytes exposed to hydrogen peroxide; here, it attenuated mitochondrial damage and promoted autophagy [87]. Madecassoside was also reported to impede the proliferation of SVK-14 keratinocytes, a cell line useful for investigating psoriasis [88]. In an in vivo mouse model of psoriasis-like inflammation induced by the immune response modifier

imiquimod (IMQ), topically applied madecassoside decreased dermal inflammation and reduced keratinocyte proliferation. These effects were associated with a reduction in the elevated expression of IL-22, IL-17 and IL-23, and a reduction in the number of Th17 cells in the spleen and cervical lymph nodes [89]. Such observations suggest that madecassoside could be a novel treatment for psoriasis. Skin aging is primarily associated with reduction in type I collagen levels. As mentioned above, asiaticoside was reported to induce type I collagen; thus, it was hypothesized that asiaticoside induces an anti-wrinkle effect by elevating type I collagen levels through T $\beta$ RI kinase-independent Smad signaling pathway [90]. Microphthalmia-associated transcription factor (MITF) regulates key enzymes in melanocytes, which is important for hyper- or hypopigmentation diseases. Asiaticoside was shown to be a novel candidate for melanogenesis inhibition through repression of DNA binding to MITF [91]. Advanced glycation end-products (AGEs) accumulate in skin and cause overproduction of free radicals and inflammatory cytokines that enhance skin aging. Pre-treatment with asiatic acid protected HaCaT cells against AGE-induced injury. Asiatic acid exhibited antioxidative, anti-inflammatory and antiapoptotic effects by reducing ROS production and decreasing caspase activity [92]. Moreover, asiatic acid also prevented UVA irradiation-induced ROS production, lipid peroxidation and induction of MMP-2, as well as preventing UVA-enhanced expression of p53 in HaCaT cells [93].

Keloids result from an anomalous wound healing process: they are regarded as benign dermal tumors, as they proliferate beyond the boundaries of the original wound without regressing spontaneously [94]. Keloids cause substantial cosmetic defects and deformities, and can sometimes limit joint mobility. Although there are no reports of keloids transforming into malignant tumors, the invasion activity of keloid fibroblasts (KF) is comparable to some extent to that of malignant cells [94]. Treatment of human keloid-derived fibroblasts with madecassoside (10, 30 and 100  $\mu$ M) for 48 h inhibited their proliferation and migration in a time- and concentration-dependent manner, while inducing KF to undergo apoptosis [94]. Additionally, madecassoside depolarized the mitochondrial membrane, activated caspase-9 and caspase-3 and regulated the expression of Bcl-2 family members in KFs, implying that madecassoside induced KF apoptosis through a mitochondrial-dependent pathway. These effects were associated with a marked attenuation of phosphorylation of cofilin, and p38 MAPK of phosphatidylinositol-3-kinase (PI3K)/AKT signaling. This study provided an explanation for the mechanism whereby madecassoside attenuates the formation of keloid scars and suggests that madecassoside could be of immense benefit for treating and/or preventing hypertrophic scars or keloids [94]. While madecassoside was proposed to exert its effects through a mitochondrial-dependent pathway, asiaticoside was suggested to hinder the invasive growth of KFs by inhibiting the growth differentiation factor-9 (GDF-9)/MAPK/Smad pathway [95]. Another study suggested that asiaticoside inhibited keloid-derived fibroblast proliferation and collagen synthesis. This study demonstrated that asiaticoside could negatively regulate the expression of both TGF- $\beta$ RI and TGF- $\beta$ RII while increasing inhibition of Smad7 expression, thereby altering fibroblast proliferation and collagen production [96]. Similar findings were also reported in separate studies [97–99]. Likewise, asiatic acid also inhibited TGF- $\beta$ I-induced collagen type I and plasminogen activator inhibitor-1 (PAI-1) expression, while increasing Smad7 protein level in KFs via activation of PPAR- $\gamma$  [100].

## 6.2. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic disease distinguished by chronic inflammation, synovial hyperplasia with concomitant joint destruction, deformity and loss of function [101]. Collagen II (CII) is the core constituent protein of the cartilage in the diarthrodial joint, which is the principal site affected in RA [102]. The presence of heterologous CII species in the articular cartilage of joints initiates an immune response and Type II collagen-induced arthritis (CIA) is a well-established in vivo model for assessing the effects of anti-inflammatory or anti-rheumatic drugs, as it expresses similar immunological and pathological traits to human RA [103]. Oral administration of madecassoside to

mice with CIA produced a dose-dependent reduction in paw inflammatory swelling and erythema, but did not modify the disease-associated body weight loss. Moreover, it also radically ameliorated the pathological indicators, including infiltration of inflammatory cells into the joint cavity, synovial hyperplasia, pannus formation and erosion of bone and cartilage [104]. It was hypothesized that madecassoside downregulated the abnormal humoral and cellular immunity, such as the overproduction of auto-antibodies and the excessive activation of T lymphocytes as well as joint destruction [104]. Another study suggested that the anti-inflammatory effect of madecassoside in mice with CIA may be associated with the inhibition of the production of TNF- $\alpha$ , IL-6, PGE<sub>2</sub> and the expression of COX-2, as well as the upregulation of the expression of the anti-inflammatory cytokine IL-10 [105]. Systemic levels of IL-10 were shown to be increased in rats with CIA receiving madecassoside, although the secretion of IL-10 from peripheral mononuclear cells was not enhanced [106]. Furthermore, madecassoside treatment led to a prominent increase in Foxp3<sup>+</sup> lymphocytes in the intestinal lamina propria, one of the major sources of IL-10. This study suggested that the anti-arthritic effects of madecassoside in rats were mediated primarily through intensifying the secretion of IL-10 from Foxp3<sup>+</sup> lymphocytes in the intestinal lamina propria and the mobilization of IL-10 to the circulation, rather than by a systemic anti-inflammatory action [106].

Cytokines are acknowledged to stimulate fibroblast-like synoviocytes (FLS) to produce MMPs, which damage the collagen component of cartilage and bone, contributing to the joint deformity and pain in RA patients [107]. MMP-13 is one of the most important collagenases responsible for damaging the articular cartilage and is often found in higher levels in the synovial fluids of RA patients [108]. The chief inducer of MMP-13 is IL-1 $\beta$ , mainly through pathways involving NF- $\kappa$ B [109]. Madecassoside reversed the histological lesions in adjuvant-induced arthritis rats and suppressed IL-1 $\beta$ -induced invasion and migration of FLS, as well as inhibited the expression of MMP-13 in FLS but with little effect on the expression of other MMPs. Additionally, madecassoside attenuated IL-1 $\beta$ -stimulated p65 phosphorylation and translocation. These data suggested that madecassoside inhibited MMP-13 by preventing NF- $\kappa$ B translocation and phosphorylation [110].

As described earlier, the pharmacokinetics of madecassoside may be influenced by the presence of arthritis. Thus, the metabolism of madecassoside and the absorption of its metabolite madecassic acid were amplified in rats with CIA. This may be related to arthritis-induced changes in the levels of inflammatory cytokines, the activity of intestinal bacteria and the expression of hepatic drug metabolizing enzymes [58]. No studies appear to have been reported on the anti-arthritic effects of asiaticoside, asiatic acid and madecassic acid.

### 6.3. Neurodegenerative Diseases

Neurodegeneration entails numerous cellular processes whereby neuronal cells gradually deteriorate, lose functionality and eventually die [111]. Neurons are susceptible to ROS-induced oxidative damage resulting from ROS-induced oxidation of various biological macromolecules, causing homeostatic disturbances within neurons leading to cell death. Neuroinflammation is one of the key risk factors of progressive neurodegeneration [112]. The accumulation of ROS and protein misfolding associated with neuroinflammation could be one of several triggers of neurodegeneration [111]. Some studies have implicated neuroinflammation in aggravating Alzheimer's disease (AD) and Parkinson disease (PD), by stimulating excessive production of amyloid  $\beta$  plaques and the destruction of dopaminergic neurons [111]. Several studies have suggested the potential of *C. asiatica* extract to mitigate symptoms of various neurodegenerative diseases, such as memory impairment, anxiety and locomotive dysfunction [113]. It has been used extensively as a memory-enhancing drug in Asian countries, such as India, China and Malaysia, and has been shown to have some pharmacological activities in the central nervous system [114]. Additionally, *C. asiatica* extracts were also reported to possess anticonvulsant and central nervous system depressant actions [59].



Purified madecassoside was shown to inhibit *in vitro* A $\beta$ <sub>1–42</sub> fibril formation and to markedly inhibit A $\beta$ <sub>1–42</sub> induced apoptosis in SHSY5Y cells [115]. Long-term oral administration of madecassoside protected against spatial memory impairment in A $\beta$ <sub>1–42</sub>-infused rats, a model of AD, as well as inhibiting the formation of A $\beta$ <sub>1–42</sub> fibrils [116]. Madecassoside also diminished the brain A $\beta$ <sub>1–42</sub> burden, oxidative stress, TNF $\alpha$  and cathepsin D levels, along with a parallel increase in BDNF and postsynaptic density protein (PSD-95) levels in the hippocampus. The interaction of madecassoside with A $\beta$ <sub>1–42</sub> by molecular docking was examined to further assess the anti-A $\beta$ <sub>1–42</sub> fibrillation effect of madecassoside. Computational modeling studies showed effective molecular docking of madecassoside onto A $\beta$ <sub>1–42</sub>, consistent with the inhibitory effects of madecassoside on *in vitro* fibril formation and memory impairment in a rat model of AD [116]. In agreement with these findings, madecassoside was found to markedly improve D-galactose-induced cognitive impairment in mice; this may be mediated by reducing oxidative damage via the inhibition of the NF- $\kappa$ B and ERK/p38 MAPK pathways, and diminishing the deposition of A $\beta$ , thus ameliorating the synaptic plasticity dysfunction with amplified BDNF and PSD-95 expressions in the hippocampus. Furthermore, madecassoside notably enhanced acetylcholine levels while diminishing cholinesterase activity [112]. In another study, madecassoside significantly reduced A $\beta$ <sub>25–35</sub>-induced autophagosomes in neural cells and increased neural cell viability, as well as reducing the production of inflammatory cytokines such as TNF- $\alpha$ , IL-10, IL-6 and COX-2, blocking the conversion of light chain 3-I (LC3-I) to light chain 3-II (LC3-II) and decreasing the level of Beclin-I level. All of the above findings suggest that madecassoside could be a potential agent for treating AD [112]. Asiaticoside also has been researched considerably as a therapeutic agent for AD. In an AD rat model induced by intracerebroventricular injection of A $\beta$ <sub>1–42</sub> oligomers, asiaticoside diminished learning and memory function impairment, reduced A $\beta$  build-up in the hippocampus and reinstated subcellular structure damages. Asiaticoside also decreased levels of IL-6 and TNF- $\alpha$  as well as caspase-3 expression, while amplifying Bcl-2 expression [117]. Moreover, asiaticoside attenuated A $\beta$ <sub>1–42</sub>-induced cytotoxicity and apoptosis, restored declined mitochondrial membrane potential and significantly downregulated TNF- $\alpha$ , IL-6, TLR4, MyD88 and TRAF6 expressions in human brain microvascular endothelial cells (hBMECs) [118]. Administration of asiaticoside to senescence-accelerated mice (SAMP) averted spatial learning and decline by scavenging free radicals, increasing antioxidant enzymes activities, reducing A $\beta$  load, ameliorating synaptic plasticity dysfunction and keeping ACh levels and AChE activity in check [119]. Furthermore, asiaticoside effectively protected HUVECs against impairment elicited by aggregated A $\beta$ <sub>1–42</sub>, by promoting cell proliferation, apoptosis inhibition and the elevation of the Bcl-2/Bax ratio [120]. An *in silico* study deduced that asiaticoside hinders early phases of fibrillogenesis via interactions with nucleating amyloid species and slowing the growth phase [121]. Unlike madecassoside and asiaticoside, asiatic acid can cross the BBB to exert rapid neuroprotective actions. Administration of asiatic acid reduced aluminum-stimulated cell death by diminishing mitochondrial dysfunction, oxidative stress and signaling pathways [122] in *in vitro* and *in vivo* AD models, moderating the aluminum load, AChE activity, behavioral performance, A $\beta$  levels and neuroinflammation [123]. Furthermore, asiatic acid exerted a neuroprotective effect against AlCl<sub>3</sub>-induced cognitive impairments, oxidative stress, cholinergic deficits, tau pathology, A $\beta$  burden, neuroinflammation and apoptosis [124]. Asiatic acid also demonstrated protective effects against A $\beta$ <sub>25–35</sub>-induced tau protein hyperphosphorylation [125], C<sub>2</sub>-ceramide-induced neuronal cell injury [126], cholesterol-induced cytotoxicity [127], in addition to positively moderating various targets related to A $\beta$  pathways, thus, mitigating A $\beta$  levels in AD brain by diminishing A $\beta$  production and escalating A $\beta$  degradation [128]. Asiatic acid treatment also showed protection against apoptosis, oxidative and glycativ stress by reducing ROS and AGE, and downregulating the expression of Bax, NADPH oxidase, RAGE and MAPK [53]. Furthermore, asiatic acid intake was shown to be effective in enhancing memory and learning, as measured by the passive avoidance test [129]; it increased cell pro-

liferation in the hippocampus and stimulated spatial working memory [130,131], as well as prevented impairment of neurogenesis and spatial memory caused by valproic acid [132].

The neuroprotective effects of madecassoside have also been investigated in a rat model of early-phase Parkinsonism, comprising the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a potent neurotoxin that is known to cause dopaminergic neurodegeneration by producing free radicals, leading to oxidative stress. In this model, madecassoside reduced locomotor dysfunction and preserved dopaminergic neurons. Furthermore, madecassoside markedly attenuated the MPTP-induced reduction of striatal dopamine. The MDA content was significantly reduced, while GSH levels, Bcl-2/Bax ratio and expression of BDNF protein were substantially increased in madecassoside-treated groups. These results implied that madecassoside is effective in reducing the early signs of MPTP-induced Parkinsonism [133]. Similar findings were observed in the neuroprotective effect of asiatic acid and asiaticoside against MPTP-induced neurotoxicity [54,134–136]. In a rotenone-induced Parkinson model, asiatic acid protected against mitochondrial injury [137,138] and exerted antiapoptotic effects through a reduction in oxidative stress, maintenance of mitochondrial membrane potential and regulation of expressions of Bcl-2, Bax and caspases [139]. Additionally, the anti-Parkinson effect of asiaticoside was accompanied by an increased expression of proteins involved in phosphoinositide signaling [140].

Neurite formation is considered to be one of the essential steps in neuro-regeneration, particularly for memory enhancement [113]. The pentacyclic triterpenoids madecassoside, asiaticoside, madecassic acid and asiatic acid are among various natural products that exhibited positive neuroactivity. Immunofluorescent staining studies using the cell line neuro2 $\alpha$  showed madecassoside and asiaticoside to produce a significant elevation in the percentage of neurite-bearing cells and in neurite length; madecassoside and asiaticoside were more potent than madecassic acid and asiatic acid. The activity of the glycosides in promoting neurite outgrowth required sustained activation of ERK1/2 leading to CREB phosphorylation, while neurite lengthening required activation of protein kinase B (Akt) [113].

Neuroinflammation is not only involved in neurodegenerative diseases, but also implicated as a key player in the pathology of cerebral ischemia-reperfusion (I/R) injury [141]. Madecassoside significantly reduced the brain infarct area, resolved the neurological deficit and ameliorated neuronal apoptosis in rats subjected to cerebral I/R. Furthermore, it substantially diminished the MDA and NO levels and heightened antioxidant activity in these animals, as well as decreased the levels of pro-inflammatory cytokines and of NF- $\kappa$ B p65 [141]. In an in vitro ischemic model of oxygen-glucose deprivation followed by reperfusion (OGD/R) in BV2 microglia, madecassoside not only significantly rescued OGD/R-induced cytotoxicity, but also suppressed the secretion of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-1 $\beta$  and IL6. This study concluded that the significant neuroprotective effect of madecassoside against I/R injury both in vivo and in vitro was produced by the attenuation of microglia-mediated neuroinflammation through inhibition of the TLR4/MyD88/NF- $\kappa$ B signaling pathway [142]. In an in vitro ischemia-hypoxia model asiaticoside increased the neuronal survival rate in a concentration-dependent manner, modulating the expression of apoptotic factors such as Bcl-2, Bax and caspase-3 [143]. Asiaticoside also had a neuroprotective effect against transient cerebral ischemia and reperfusion in a mouse model, by reducing microglial activation, iNOS activity and the level of NO. It also reduced the gene expression of inflammatory cytokines, such as TNF- $\alpha$ , IL-1 $\beta$  and IL6 by inhibiting the p38 MAPK signaling pathway [144]. Asiatic acid attenuated cerebral infarction, mitochondrial dysfunction and the induction and activation of matrix metalloproteinase-9 produced by middle cerebral artery occlusion in the rat [51]; similarly, it reduced infarct size, and improved neurological outcome in a mouse model of focal cerebral ischemia, these effects being accompanied by a reduction in BBB permeability [145].

As neuroinflammation is a major factor underlying neurodegenerative diseases, attenuating neuroinflammation is an important target of any therapy [111]. In a model of neuroinflammation induced by lipopolysaccharide (LPS), which triggers toll-like receptor 4 activation on the microglia surface, madecassoside markedly reduced the production of ROS, while also concentration-dependently downregulating the gene and protein expression of pro-inflammatory components such as iNOS, COX-2, STAT1 and NF- $\kappa$ B, and increasing the anti-neuroinflammatory heme oxygenase 1 [111]. Likewise, asiatic acid protected against methamphetamine-stimulated neuroinflammation and neurotoxicity via inhibition of NF- $\kappa$ B/STAT3/ERK and mitochondria-mediated apoptosis pathway [146]. Mass accumulation of the endogenous neurotoxin quinolinic acid (QA) causes excessive oxidative stress that leads to neuroinflammation. Treatment with asiatic acid prevented quinolinic acid-induced spatial memory loss and alleviated oxidative stress; these effects were accompanied by improved antioxidant status and a reduction in the dysfunction in mitochondrial oxidative phosphorylation [147].

Beneficial effects have also been reported in other experimental neurological conditions. Asiaticoside and asiatic acid were reported to exhibit antidepressant-like action [148–151], anxiolytic activity [151–153] and antinociceptive effects [154], as well as protection against glutamate-induced excitotoxicity [155,156], kainite-induced seizure [157] and diabetes-induced cognition deficits [158].

#### 6.4. Cardiovascular Diseases

Acute myocardial infarction (MI) produces irreversible myocardial injury, resulting in necrosis of a significant portion of the myocardium. Acute MI may be either the non-perfusion type, where the obstruction to blood flow is permanent, or the reperfusion type, in which the obstruction or lack of blood flow is long enough in duration but can be reversed or restored after myocardial cell death occurs. There is a direct correlation between infarct size and prognosis [159]. Since reperfusion is the keystone of treatment for acute MI, there is a need for the advancement of adjunct therapies, which may possibly diminish reperfusion injury and thereby intensify the benefits of reperfusion [160]. Madecassoside showed anti-ischemic effects *in vitro* and protected rabbit isolated hearts and cardiomyocytes against reperfusion injury [161]. It also protected against vascular endothelial cell injury and increased the coronary flow in the rat isolated heart. The protective effect of madecassoside against myocardial ischemia-reperfusion injury was investigated further *in vivo* in rats. Madecassoside significantly reduced infarct size in rats subjected to coronary artery ligation followed by reperfusion. The serum levels of CK and LDH, indicators of myocardial injury, were significantly reduced in madecassoside-treated rats, suggesting a protective effect of madecassoside on myocardial cells. There was also improved post-ischemic ventricular function in rats receiving a high dose of madecassoside. Moreover, madecassoside-treated animals exhibited significantly lower MDA levels, increased SOD activity and lower serum CRP levels compared to the control group [162]. These findings are exactly in accordance with those in a rabbit model of ischemia-reperfusion [161]. Myocardial TNF- $\alpha$  is an autocrine contributor to myocardial contractile dysfunction and cardiomyocyte death in sepsis [163]. Pre-treatment of neonatal rat cardiomyocytes with madecassoside inhibited LPS-induced TNF- $\alpha$  production in a concentration-dependent manner, and, *in vivo*, significantly reduced the elevation of plasma TNF- $\alpha$  induced by LPS in rats. Investigation of the underlying mechanism showed that madecassoside prevented LPS-induced NF- $\kappa$ B translocation from cytoplasm into nucleus, and inhibited LPS-induced phosphorylation of ERK1/2 and p38. *In vivo* studies showed that madecassoside pre-treatment delayed the reduction in mean arterial blood pressure, and attenuated the tachycardia induced by LPS [163]. Asiatic acid was also reported to protect against myocardial ischemia/reperfusion injury in an H9c2 cell model, partly via the Akt/GSK-3 $\beta$ /HIF-1 $\alpha$  pathway [164]. Asiatic acid, among two other triterpenes, protected H9c2 cardiomyocytes against high glucose-induced injury by obliterating oxidative stress and apoptosis [165]. Other studies also reported that the antioxidant and anti-inflammatory properties of asi-

atic acid were responsible for attenuation of isoproterenol-induced cardiotoxicity [166] and lactate-induced cardiomyocyte apoptosis [167]. Furthermore, asiatic acid augmented survival of AC16 cardiomyocytes against hypoxia-induced apoptosis by regulation of miR-1290/HIF3A/HIF-1 $\alpha$  axis [168]. In a model of heart failure, treatment with asiatic acid preserved cardiac function and inhibited left ventricular remodeling, alleviated cardiomyocyte apoptosis, and reduced interstitial fibrosis and inflammatory responses by inhibiting the mitochondria-dependent apoptotic pathway [169]; it also inhibited phosphorylation of p38 MAPK and ERK 1/2 [170] and reduced NF- $\kappa$ B binding activity [171]. A role for AMPK in asiatic acid-mediated protection against cardiac hypertrophy and fibrosis was suggested by the loss of this protective effect following the depletion of AMPK $\alpha$  [172]. A study also highlighted the efficacy of asiatic acid in blocking IL-1 $\beta$  activated NF- $\kappa$ B signaling in *in vitro* and *in vivo* models [173]. Asiatic acid was also shown to reduce blood pressure and improve vascular function in L-NAME-induced hypertensive rats by enhancing NO bioavailability [174], possibly via upregulation of eNOS protein expression and suppression of inflammation and oxidative stress [175]. In a rat model of the metabolic syndrome (MS) induced by a high-carbohydrate-high-fat (HCHF) diet, asiatic acid supplementation improved the metabolic and cardiovascular complications [176], as well as improved vascular function and reduced activation of the renin-angiotensin system [177]. Asiatic acid could also protect the heart in experimental diabetes in the mouse by attenuating glycation injury and coagulatory disorders [178]. Atherosclerosis, chiefly in coronary artery disease (CAD) or carotid stenosis, is the leading cause of myocardial infarction and stroke, which together are responsible for more than 50% deaths worldwide [179]. Asiaticoside was shown to impede endothelial hyperpermeability [180], thus possibly disrupting development of early atherosclerotic events [181]. Similar observations were found in studies testing the efficacy of asiatic acid in protecting human aortic endothelial cells [182,183].

### 6.5. Lung Diseases

Pulmonary fibrosis (PF) is a chronic, progressive, irreversible and fatal lung disease [184]. As described above, madecassoside exhibits significant antioxidant and anti-inflammatory activities, which are also implicated in PF. An analogue of madecassoside, asiaticoside, was shown to suppress septic lung injury induced by cecal ligation and puncture in mice [185], as well as to inhibit collagen expression and TGF- $\beta$ /Smad signaling pathway activation in keloid fibroblasts [96]. These findings led to an investigation of the effect of madecassoside on bleomycin (BLM)-induced PF in a mouse model. In this study, madecassoside improved pathological changes in the lung and decreased collagen deposition. Expression of  $\alpha$ -smooth muscle actin and TGF- $\beta$ 1 were reduced while phosphorylation of Smad2 and Smad3 (major factors in TGF- $\beta$ 1 signaling [96]) in the lung tissues were inhibited. Furthermore, madecassoside attenuated the oxidative damage and inflammation present at the early stage of PF; this was evidenced by a reduction in total leukocytes in the bronchoalveolar lavage fluid, the reduced myeloperoxidase activity and MDA levels, as well as the increased SOD activity and GSH level in the lung tissues [186]. The anti-PF of madecassoside in a bleomycin mouse model was suggested to be mediated by activation of PPAR $\gamma$ , leading to subsequent generation of hepatocyte growth factor (HGF) in the colon, from where the upregulated HGF perhaps enters the circulation to reach the lung and impede PF; antagonism of PPAR $\gamma$  almost completely prevented the madecassoside-induced HGF production and its ability to reduce PF [187]. Other studies have shown the effectiveness of HGF in attenuating the fibrotic remodeling in both a rat and mouse PF model [188,189]. On the other hand, asiatic acid was reported to ameliorate lung fibrosis and inflammation in BLM-induced PF in mice via TGF- $\beta$ 1-induced Smad2/3 and ERK 1/2 signaling pathway inhibition and NLRP3 inflammasome inactivation [190].



Acute lung injury (ALI) is an acute inflammatory disorder that causes disruption of the lung endothelial and epithelial barriers [191]. Asiaticoside exhibited protective effects against LPS-induced ALI by lowering the load of IL-6 and TNF- $\alpha$  while elevating IL-10 secretion [192]; this protective effect was mediated by inhibiting inflammatory cell infiltration and downregulating the NF- $\kappa$ B signaling pathway [193]. Similar findings were obtained in a study investigating the effect of asiatic acid on LPS-induced ALI, where the anti-inflammatory mechanism of asiatic acid was associated with the inhibition of the LPS-induced TLR4 signaling pathway [194]. In a model of ALI produced by spinal cord injury, asiatic acid was reported to activate Nrf2 and inhibit the NLRP3 inflammasome pathway [195]. Asiatic acid was also suggested to have the potential to treat chronic obstructive pulmonary disease (COPD), due to its ability to hinder the pulmonary inflammatory response via suppression of inflammatory mediators and induction of HO-1 [196].

#### 6.6. Kidney Diseases

Doxorubicin (DOX) is a chemotherapeutic agent used to treat malignant neoplasms; its use is limited by serious adverse effects, such as nephrotoxicity [197], cardiotoxicity [198] and hepatotoxicity [199], which are in part mediated through free radical formation, oxidative damage and membrane lipid peroxidation [200]. In view of the demonstrated ability of madecassoside to reduce oxidative damage while improving the anti-oxidative enzymes status in various disease models, the effect of madecassoside on DOX-induced renal toxicity was examined in vitro and in vivo. Treatment with madecassoside significantly and concentration-dependently attenuated DOX-induced apoptosis in human proximal tubule cells (HK-2 cells). This effect was associated with the inhibition of DOX-induced ERK phosphorylation, reductions in apoptotic factors (cleaved caspases, apoptotic protease activating factor1, BAX) and an inhibition of iNOS [201]. Moreover, concomitant treatment with madecassoside markedly reduced DOX-induced renal injury in mice, as evidenced by the reduction in serum creatinine and BUN and the preserved structural integrity of the kidneys. These observations suggest that madecassoside could be valuable in preventing/ameliorating DOX-induced toxicity in chemotherapy patients [201].

In a mouse model of obstructive nephropathy, asiatic acid intake significantly ameliorated tubulointerstitial fibrosis by suppressing tubular injury, fibroblast activation and ECM accumulation mediated via Smad7-dependent TGF- $\beta$ 1 signaling [202]. Asiatic acid was identified to function as a Smad7 agonist that inhibits Smad3 signaling [203]. Moreover, pre-treatment with asiatic acid inhibited NF- $\kappa$ B activation and inflammatory responses, possibly from Smad7 upregulation, in cisplatin-induced acute kidney injury [204].

#### 6.7. Liver Diseases

Acute liver failure (ALF) is a life-threatening condition with a high mortality rate worldwide. It is manifested by hepatic dysfunction, abnormal liver biochemical parameters and coagulopathy [205]. The onset of ALF is an inflammation mediated by hepatocellular injury process that closely resembles the innate immune response induced by exposure to LPS (endotoxin). LPS combined with D-GalN acts as a hepatotoxic or liver damaging agent that is typically used to induce ALF in experimental models [206]. Pre-treatment of mice with madecassoside markedly suppressed the LPS/DGalN-induced increases in the serum concentrations of ALT and AST, and preserved hepatic integrity, protecting against hemorrhage and cellular necrosis. Madecassoside pre-treatment significantly reduced the LPS/DGalN-mediated increase in the hepatic levels of the inflammatory cytokines IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , while increasing levels of the antioxidant enzymes SOD, catalase and glutathione peroxidase. These effects were associated with inhibition by madecassoside of the phosphorylation of p38 MAPK and NF- $\kappa$ B [207]. The effects of asiaticoside on ALF were also tested in a similar model. Treatment with asiaticoside improved liver function, alleviated liver injury and attenuated apoptosis induced by LPS/DGalN, possibly via the inhibition of the expression of TNF- $\alpha$  and MAPKs [208]. The protective effects of asiatic



acid against LPS/DGalN-induced injury was associated with the inhibition of the cellular redox-regulated LTC<sub>4</sub>S expression pathway [209].

Liver fibrosis occurs when excessive collagen and extracellular matrix deposit in the liver. Liver fibrosis can advance to liver cirrhosis, eventually causing liver failure and ultimately death [210]. Asiatic acid was discovered to protect against carbon tetrachloride (CCl<sub>4</sub>)-induced liver fibrosis via multiple mechanisms; these include the inhibition of TGF- $\beta$ /Smad signaling pathways in in vivo and in vitro models [211], regulation of the PI3K/AKT/mTOR and Bcl-2/Bax signaling pathways [212] and suppression of NF- $\kappa$ B/I $\kappa$ B $\alpha$  and JAK1/STAT3 signaling [213].

Intragastric administration of asiatic acid was shown to protect the liver against ethanol-induced hepatotoxicity by ameliorating oxidative stress and inhibiting Kupffer cell activation, via diminishing the expression of TLR4, CD14 and MyD88 [214]. In addition, supplementation with asiatic acid improved insulin resistance and attenuated hepatic oxidative and inflammatory injury in mice fed a high-fat diet [215]. Pre-treatment with asiatic acid reportedly can protect against I/R-induced liver injury in rats and anoxia/reoxygenation (A/R)-induced injury in isolated rat liver mitochondria [216]. This is in agreement with a previous study demonstrating that treatment with asiatic acid induced partial uncoupling of mitochondria and thus protected mitochondrial function [217]. Moreover, asiatic acid may alleviate hepatic I/R injury through mitigation of Kupffer cells activation via the PPAR $\gamma$ /NLRP3 inflammasome signaling pathway [218]. On the other hand, asiatic acid demonstrated a protective effect against DOX-induced liver toxicity in a rat model in a dose-dependent manner through the modulation of Nrf2 translocation, suggesting its use as an organ-protective adjuvant in DOX treatment [219].

#### 6.8. Anticancer Actions

Cancer chemoprevention is presently the favored area in current research trends [220]. Dysregulation of growth factor pathways is a known contributor to the development of hepatocellular carcinoma (HCC) [221]. Binding of HGF to its receptor promotes proliferation, survival and migration in a variety of cancer cells, including HCC [222]. Treatment of HGF-induced hepatocellular carcinoma (HCC) cell lines (HepG2 and SMMC-77 cells) with madecassoside significantly reduced HGF-induced proliferative and invasive responses. These effects of madecassoside were associated with the downregulation of the expression of COX-2 and PGE<sub>2</sub>, and inhibition of p-cMET, p-ERK1/2 and PKC activity. This suggested that madecassoside could be an effective therapeutic drug to reduce HGF-induced tumor growth and metastasis in HCC [223]. Meanwhile, madecassic acid has been showed to exert antitumor activity by inducing cancer cell apoptosis and improving immunomodulation in a mouse colon cancer model [224]. Asiaticoside has demonstrated effectiveness in both in vitro and in vivo breast cancer models, significantly reducing TNF- $\alpha$  and IL-1 $\beta$  expressions, inducing apoptosis and enhancing antitumor activity [220,225]. In addition, asiaticoside counteracted proliferation, migration and invasion of drug-resistant multiple myeloma cells by triggering autophagy via STAT-3 pathway inhibition [226]. Unlike madecassoside, madecassic acid and asiaticoside, asiatic acid has been researched extensively for its antitumor effect. For instance, asiatic acid has been successively reported to possess strong cell growth inhibition in hepatoma [227–229], melanoma [230,231], glioblastoma [232–234], multiple myeloma [235], colon [236–240], in ovarian [241], breast [242], lung [243,244], and prostate cancer [245], as well as in leukemia [246].

#### 6.9. Diabetes

Diabetes mellitus (DM) is a widespread disease worldwide, especially in Asia [247]. *Centella asiatica* has been used as a remedy for DM in Ayurvedic traditional medicine [248,249]. A study reported that asiaticoside exhibited significant antidiabetic activity in alloxan-induced diabetic mice, most likely by stimulating pancreatic  $\beta$  cells to secrete insulin [247]. In streptozotocin (STZ)-induced diabetic rats, asiatic acid exhibited antihyperlipidemic and antidiabetic effects; here, it decreased blood glucose, increased plasma

insulin concentrations and reversed changes in key carbohydrate-metabolizing enzyme levels [250], as well as prevented lipid peroxidation and increased antioxidant status [251,252]. Asiatic acid was postulated to exert its antihyperglycemic activity by enhancing glucose uptake into skeletal muscle in insulin-deficient STZ diabetic rats via the PI3K-Akt signaling pathway [253]. Asiatic acid also demonstrated lipid and glucose lowering effects in db/db mice via PI3K/Akt/GSK-3 $\beta$  to accelerate glycogen synthesis [254]. Asiatic acid was also proposed to mitigate hyperglycemia by preserving and restoring beta cell mass and function [255], reducing islet fibrosis formation and reversing the over-expression of fibronectin [256]. Madecassic acid was shown to improve glycemic control, lower plasma lipids and attenuate oxidative and inflammatory stress in streptozotocin-induced diabetes in mice [257]. Madecassic acid also reduced insulin resistance and endothelial dysfunction in mice made obese using a high-fat diet [258]. A study conducted recently in our laboratory has demonstrated the efficacy of madecassoside in protecting  $\beta$  cells both in vivo in STZ-diabetic rats and in vitro [259].

Asiatic acid and asiaticoside may also be effective in ameliorating the complication of diabetes. Asiatic acid could protect against diabetic nephropathy in rats with STZ-induced diabetes [260]. In vitro, asiaticoside was shown to protect cochlear hair cells from high glucose-induced injury by increasing antioxidative activity and suppressing the AGEs/RAGE/NF- $\kappa$ B pathway [261].

**Table 1.** A summary of pharmacological activities of all compounds published from year 2015 to 2021.

Condition	Compound	Outcome	Reference	
Skin related conditions	Asiaticoside	Promote cell proliferation and collagen synthesis	[79]	
		Accelerate wound healing, suppress apoptosis	[85]	
Hinder keloid fibroblast's invasive growth		[95]		
	Madecassoside	Anti-oxidative, attenuate mitochondrial damage, promote autophagy Decrease dermal inflammation, reduced keratinocyte proliferation	[87] [89]	
Rheumatoid arthritis	Madecassoside	Increase systemic levels of IL-10	[106]	
		Prevent NF- $\kappa$ B translocation and phosphorylation	[110]	
Neurodegenerative diseases	Asiaticoside	Reduce learning and memory function impairment, A $\beta$ build-up, IL-6 and TNF- $\alpha$ levels	[117]	
		Attenuate A $\beta$ <sub>1-42</sub> -induced cytotoxicity and apoptosis	[118]	
		Promote cell proliferation, inhibit apoptosis	[120]	
		Hinder early phase of fibrillogenesis	[121]	
		Modulate expression of apoptotic factors	[143]	
		Antidepressant-like action	[149,150]	
		Antinociceptive effects	[154]	
	Attenuate diabetes induced cognitive deficits	[158]		
			Diminish mitochondrial dysfunction, oxidative stress	[122]
			Regulate aluminium load, AChE activity, behavioural performance, A $\beta$ levels and neuroinflammation	[123]
			Protect against oxidative stress, cholinergic deficits, tau pathology, apoptosis	[124]
			Protect against A $\beta$ <sub>25-35</sub> induced tau protein hyperphosphorylation	[125]
			Protect against cholesterol-induced cytotoxicity	[127]
		Asiatic acid	Increase hippocampal cell proliferation, stimulate spatial working memory	[130,131]
			Prevent neurogenesis and spatial memory impairment	[132]
			Reduce MDA, increase GSH content	[136]
			Protect against mitochondrial injury	[138]
	Reduce oxidative stress, maintain mitochondrial membrane potential		[139]	
	Increased proteins expression involved in phosphoinositide signalling		[140]	
	Protect against neuroinflammation and neurotoxicity		[146]	
	Prevent spatial memory loss and alleviate oxidative stress	[147]		
		Antidepressant-like action, anxiolytic activity	[151]	
		Decrease hippocampal inflammatory and oxidative stress	[157]	
	Madecassoside	Reduce ROS production, downregulate pro-inflammatory components gene and protein expression	[111]	
		Attenuate microglia-mediated neuroinflammation	[142]	

Table 1. Cont.

Condition	Compound	Outcome	Reference
Cardiovascular diseases	Asiatic acid	Attenuate isoproterenol-induced cardiotoxicity	[166]
		Attenuate lactate-induced cardiomyocyte apoptosis	[167]
		Protect against hypoxia-induced apoptosis	[168]
		Preserve cardiac function, inhibit left ventricular remodelling, alleviate cardiomyocyte apoptosis	[169]
		Inhibit p38 MAPK and ERK 1/2 phosphorylation	[170]
		Protect against cardiac hypertrophy and fibrosis	[172]
		Block IL-1 $\beta$ activated NF- $\kappa$ B signaling	[173]
		Suppress inflammation and oxidative stress	[175]
		Improve vascular function	[177]
		Attenuate glycolytic injury and coagulatory disorders	[178]
		Protect human aortic endothelial cells	[182,183]
	Asiaticoside	Impede endothelial hyperpermeability	[183]
		Disrupt development of early atherosclerotic events	[181]
Lung diseases	Madecassoside	Activate PPAR $\gamma$ , generate HGF, impede pulmonary fibrosis	[187]
	Asiatic acid	Ameliorate lung fibrosis and inflammation	[190]
		Inhibit TLR4 signaling pathway	[194]
		Activate Nrf2 and inhibit NLRP3 inflammasome pathway	[195]
		Suppress inflammatory mediators and induction of HO-1	[196]
Asiaticoside	Inhibiting inflammatory cell infiltration and downregulate the NF- $\kappa$ B signaling pathway	[193]	
Kidney diseases	Madecassoside	Inhibit ERK phosphorylation, reduce apoptotic factors, inhibit iNOS	[201]
	Asiatic acid	Inhibits Smad3 signaling	[203]
		Inhibit NF- $\kappa$ B activation and inflammatory responses	[204]
Liver diseases	Madecassoside	Reduce inflammatory cytokines, increase antioxidant enzymes	[207]
	Asiatic acid	Regulate PI3K/AKT/mTOR and Bcl-2/Bax signaling pathways	[212]
		Suppress NF- $\kappa$ B/I $\kappa$ B $\alpha$ and JAK1/STAT3 signaling	[213]
		Protect mitochondrial function	[216–218]
		Organ protective adjuvant	[219]
Cancer	Madecassoside	Downregulate expression of COX-2 and PGE $_2$	[223]
	Asiaticoside	Autophagy induction, inhibit cell migration and invasion	[226]
	Asiatic acid	Inhibit cancerous cell growth in glioblastoma	[232,234]
		Reduce inflammation, cell proliferation and induce apoptosis in colon cancer	[236,237,239]
		Suppress PI3K/AKT/mTOR signaling	[241]
	Inhibits lung cancer cell growth	[243]	
	Apoptosis of human leukemia cells	[246]	
Diabetes	Asiatic acid	Enhance glucose uptake into skeletal muscle	[253]
		Lower lipid and glucose levels	[254]
		Reduce islet fibrosis formation	[256]
		Protect against diabetic nephropathy	[260]
	Madecassic acid	Improve glycemic control, lower plasma lipids, attenuate oxidative and inflammatory stress	[257]
		Reduce insulin resistance and endothelial dysfunction	[258]
	Asiaticoside	Protect cochlear hair cells	[261]

## 7. Conclusions

The use of natural compounds extracted from plants has attracted the interest of scientific and medical communities, due to their accessibility as well as their lower cost in comparison with synthetic drugs. *Centella asiatica* has been widely used in Ayurvedic and Chinese traditional medicines for a century as a therapy in many cases, such as skin diseases, neurological disease, cardiac disease, diabetes, cancer and many more. The bioactive pentacyclic triterpenoid compounds of *C. asiatica* have been widely studied and reported to possess various biological properties. Among them, madecassoside, the main bioactive saponin of *C. asiatica* has been shown experimentally to have wound healing, scar healing, cell growth-promoting, neuroprotective, cardioprotective, anti-oxidative and

anti-inflammatory properties. There are many more niche areas that can be investigated for its therapeutic effect, given its consistent anti-oxidative and anti-inflammatory properties. Madecassoside exerts its therapeutic effect through various mechanisms and cell signaling pathways. Recognition and understanding of the pathways and mediators involved are fundamental in illuminating the therapeutic potential, along with determination of the drug's toxicity. In summary, this review demonstrates that madecassoside could be a significant complementary medicine for the prevention and treatment of various disorders, owing to its natural origin and affordable cost compared to synthetically produced drugs. Further studies of this triterpenoid are warranted.

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## Abbreviations

CA	Centella asiatica
TLC	Thin layer chromatography
TLC-MS	Thin layer chromatography-mass spectrometry
UVS	Ultraviolet-visible spectroscopy
HPLC	High performance liquid chromatography
HPTLC	High performance thin layer chromatography
HPLC-ESI-MS	HPLC-electrospray ionisation-mass spectrometry
HPLC-UV	HPLC-ultraviolet
HPLC-ELSD	HPLC-paired with evaporative light scattering detector
HPAEC-PAD	High-performance anion-exchange chromatography combined with pulsed amperometric detection
HPLC-PAD	HPLC- pulsed amperometric detection
ELISA	Enzyme-linked immunosorbent assay
c <sub>max</sub>	Maximum plasma concentration
BBB	Blood brain barrier
t <sub>1/2</sub>	Half-life
AUC <sub>0–24</sub>	Area under plasma concentration-time curve from 0–24 h
LD <sub>50</sub>	Median lethal dose
V <sub>d/f</sub>	Apparent volume of distribution
K <sub>e</sub>	Elimination rate constant
CIA	Collagen-induced arthritis
HUVEC	Human umbilical vein endothelial cell
MAPK	Mitogen activated protein kinases
VEGF	Vascular endothelial growth factor
MCP-1	Monocyte chemoattractant protein-1
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
PAR-2	Protease activator receptor 2
COX-2	Cyclooxygenase 2
PGE <sub>2</sub>	Prostaglandin E <sub>2</sub>
PGF <sub>2α</sub>	Prostaglandin F <sub>2</sub> alpha

IMQ	Imiquimod
IL	Interleukin
TGF $\beta$	Transforming growth factor beta
T $\beta$ RI	TGF $\beta$ receptor type I
T $\beta$ RII	TGF $\beta$ receptor type II
MITF	Microphthalmia-associated transcription factor
DNA	Deoxyribonucleic acid
AGE	Advanced glycation end-products
ROS	Reactive oxygen species
MMP-2	Matrix metalloproteinase-2
KF	Keloid fibroblasts
Bcl-2	B-cell lymphoma 2
PI3K	Phosphatidylinositol-3-kinase
AKT	Protein kinase B
GDF-9	Growth differentiation factor-9
PAI-1	Plasminogen activator inhibitor-1
PPAR- $\gamma$	Peroxisome proliferator-activated receptor gamma
RA	Rheumatoid arthritis
CII	Collagen II
TNF- $\alpha$	Tumor necrosis factor alpha
FLS	Fibroblast-like synoviocytes
NF- $\kappa$ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
AD	Alzheimer's disease
PD	Parkinson disease
A $\beta$	Amyloid $\beta$
BDNF	Brain-derived neurotrophic factor
PSD	Postsynaptic density protein
ERK	Extracellular signal-regulated kinases
LC 3-I	Light chain 3-I
LC 3-II	Light chain 3-II
TLR4	Toll-like receptor 4
MyD88	Myeloid differentiation primary response 88
TRAF6	TNF receptor associated factor 6
hBMEC	Human brain microvascular endothelial cells
SAMP8	Senescence accelerated Mouse-Prone 8
ACh	Acetylcholine
AChE	Acetylcholine esterase
AlCl <sub>3</sub>	Aluminium chloride
NADPH	Nicotinamide adenine dinucleotide phosphate
RAGE	Receptor for advanced glycation end products
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MDA	Malondialdehyde
GSH	Glutathione
CREB	cAMP response element-binding protein
I/R	Ischemia-reperfusion
NO	Nitrogen oxide
OGD/R	Oxygen-glucose deprivation/reperfusion
iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
STAT	Signal transducer and activator of transcription
QA	Quinolinic acid
MI	Myocardial infarction
CK	Creatine kinase
LDH	Lactate dehydrogenase
SOD	Superoxide dismutase
CRP	C-reactive protein
GSK-3 $\beta$	Glycogen synthase kinase 3 beta



HIF-1 $\alpha$	Hypoxia-inducible Factor 1-alpha
HIF3A	Hypoxia-inducible Factor 3-alpha
AMPK	5' adenosine monophosphate-activated protein kinase
L-NAME	N(gamma)-nitro-L-arginine methyl ester
eNOS	Endothelial nitric oxide synthase
MS	Metabolic syndrome
HCHF	High carbohydrate high fat
CAD	Coronary artery disease
PF	Pulmonary fibrosis
BLM	Bleomycin
HGF	Hepatocyte growth factor
ALI	Acute lung injury
COPD	Chronic obstructive pulmonary disease
HO-1	Heme oxygenase-1
DOX	Doxorubicin
HK-2	Human proximal tubule cells
BUN	Blood urea nitrogen
ECM	Extracellular matrix
ALF	Acute liver failure
D-GalN	D-galactosamine
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
LTC4S	Leukotriene C4 synthase
CCl4	Carbon tetrachloride
mTOR	Mammalian target of rapamycin
I $\kappa$ B $\alpha$	Inhibitor of nuclear factor kappa B
CD14	Cluster of differentiation 14
A/R	Anoxia/reoxygenation
Nrf2	Nuclear transcription factor
HCC	Hepatocellular carcinoma
PKC	Protein kinase C
DM	Diabetes mellitus
STZ	Streptozotocin

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