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Review Article

The Multifaceted Therapeutic Profile of Madecassoside: A Scholarly Review

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Abstract

Medicinal plants are indispensable in both modern and traditional healthcare, offering a diverse array of bioactive compounds with therapeutic properties, including anti-inflammatory, antimicrobial, and anticancer effects. They provide accessible and affordable treatment options and play a crucial role in drug discovery, enhancing holistic health and promoting biodiversity conservation. Ongoing scientific research continues to validate and expand their applications in contemporary medicine, underscoring their enduring significance. *Centella asiatica*, a medicinal plant known for its therapeutic properties in traditional medicine and increasingly recognized in modern pharmacology for various health benefits. Madecassoside, stands out as a phytoactive constituent of *Centella asiatica,* renowned for its wide-ranging pharmacological properties, encompassing anti-inflammatory, antioxidant, wound-healing, and skin-protective effects. The present review illuminates madecassoside's pharmacological properties and its mechanistic roles, as documented by various researchers.

Keywords: Madecassoside, *Centella asiatica,* anti-inflammatory, antioxidant, wound-healing

Introduction

Plants have served as medicinal treatments for millennia, rooted in both empirical knowledge and traditional remedies. They continue to garner significant attention for their efficacy in managing a spectrum of mild to chronic ailments. Among these, *Centella asiatica*, a traditional Chinese herb widely utilized across Southeast Asia, stands out for its profound medicinal properties. Madecassoside, a triterpenoid saponin obtained from *Centella asiatica*, demonstrates a wide-range of pharmacological activities such as neuroprotective, cardioprotective, and hepatoprotective effects, as well as wound healing, anti-inflammatory, and antioxidant properties. Additionally, it exhibits anti-allergic, antidepressant, anxiolytic, antifibrotic, and antibacterial activities. Madecassoside also has anti-arthritic, anti-tumor, and immunomodulatory effects. Figure 1 illustrates the chemical structure of madecassoside.[1-3]

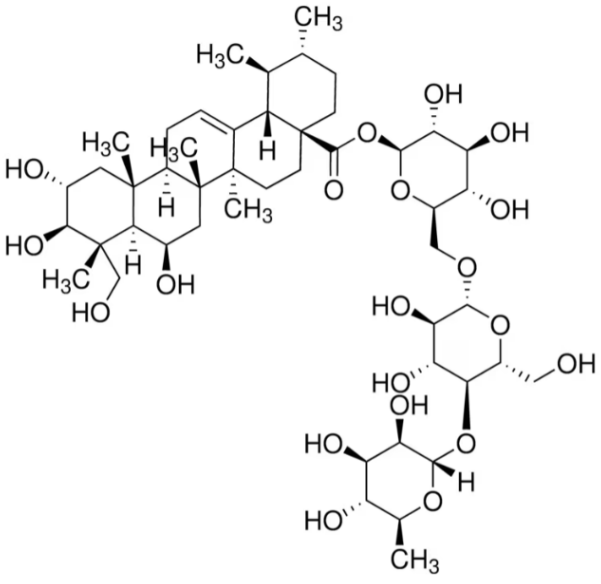

Figure 1: Structure of Madecassoside

Materials and methods

The information presented here is sourced from PUBMED databases, google scholar, Web of science, previous published articles, and pertinent citations, providing a comprehensive exploration of madecassoside's therapeutic capabilities.

Anticancer effect of madecassoside

Madecassoside has been shown to exhibit significant anticancer properties, including the ability to induce apoptosis, inhibit cell proliferation, and suppress metastasis across various cancer types. Glioma, a predominant form of primary malignant brain tumor, is distinguished by its abnormal proliferation and resistance against conventional therapeutic approaches. Renju et al.,[4] conducted a study to explore the antiproliferative properties of madecassoside encapsulated alginate-chitosan nanoparticles (MACNPs) against C6 glioma cells. Their research demonstrated that MACNPs achieved superior uptake and intracellular distribution within C6 glioma cells, effectively inhibiting their proliferation via increased intracellular ROS production. The study indicated that MACNPs have considerable potential as a therapeutic agent for treating glioma. Li et al.,[5] provided compelling evidence that madecassoside markedly attenuates HGF-induced proliferative and invasive responses in HepG2 and SMMC-77 cells. Their findings revealed that treatment with madecassoside led to a significant down-regulation of COX-2 and PGE2 expression in these cells under HGF stimulation, underscoring the compound's potent anti-tumor and anti-invasive effects.

Antioxidant effect of madecassoside

Research has consistently highlighted that *Centella asiatica* extracts exhibit a broad spectrum of health benefits, largely attributed to their antioxidant capabilities. The triterpene constituents, including asiatic acid, asiaticoside, and madecassoside, found in *Centella asiatica,* have demonstrated potent free radical-scavenging activities and strong reducing properties.[6] Xu et al.,[7] evaluated the antioxidant potential of madecassoside by measuring glutathione levels in the substantia nigra. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treatment significantly reduced GSH levels, but madecassoside administration notably restored GSH concentrations compared to the MPTP-treated group. Ling et al.,[8] illustrated that madecassoside exhibited significant antioxidative properties in human melanocytes experiencing oxidative stress, primarily by triggering autophagy. Additionally, they posited that madecassoside holds potential as an effective treatment for vitiligo, a condition predominantly driven by oxidative stress.

Neuroprotective effect of madecassoside

Ling et al.,[9] explored the neuroprotective effects of madecassoside, a compound derived from *Centella asiatica*, in the context of neurodegeneration induced by protein L-isoaspartyl methyltransferase (PIMT) deficiency. Their findings suggest that madecassoside not only enhances circadian rhythm regulation, particularly in the sleep-wake cycle, but also promotes synaptic plasticity in PIMT-deficient mice. These effects hold potential for alleviating anxiety-related symptoms and cognitive impairments associated with neurodegenerative conditions. Li et al.,[10] demonstrated the neuroprotective effects of madecassoside in GT1-7 cell lines, revealing that this compound possesses significant protective properties against hypoxia-induced cellular damage. Luo et al.,[11] explored the neuroprotective potential of madecassoside in a rat model subjected to focal cerebral ischemia-reperfusion (I/R) injury. Their findings demonstrated that madecassoside notably mitigated inflammation and alleviated oxidative stress in the brain following I/R injury. Treatment with madecassoside resulted in a significant reduction in pro-inflammatory cytokines and the activation of NF-κB p65. These findings indicate that madecassoside exhibits significant neuroprotective potential and could serve as an effective therapeutic agent in reducing damage caused by strokes. Xu et al.,[7] demonstrated that madecassoside effectively mitigated early symptoms of MPTP-induced parkinsonism through its neuroprotective properties. These effects included restoring dopamine levels, enhancing the Bcl-2/Bax ratio, and upregulating the expression of BDNF. Sasmita et al.,[12] explored the neuroinflammatory properties of madecassoside in BV2 microglial cells, demonstrating its potential as a potent natural anti-neuroinflammatory agent. Viswanathan et al.,[13] evaluated the neuroprotective properties of *Centella asiatica* methanol extract (CAM), which is rich in triterpenoid saponins, including asiaticoside and madecassoside. Their study offered substantial pharmacological evidence that *Centella asiatica* methanolic extract served as an effective antioxidant and anti-inflammatory agent, validating its traditional use in ethnomedicine for managing oxidative stress and inflammation.

Nephroprotective effect of madecassoside

Yuan et al.,[14] assessed the protective potential of madecassoside in countering nephrotoxicity caused by cisplatin and found that it significantly alleviated renal tubular damage, likely by inhibiting MAPK signaling pathway activation, suggesting its potential as a therapeutic agent for acute kidney injury. Su et al.,[15] carried out an in-depth study on how madecassoside alleviates nephrotoxicity caused by doxorubicin, utilizing both in vivo and in vitro methods by exposing HK-2 cells and a murine model to the compounds. Their findings demonstrated that madecassoside treatment effectively mitigates renal toxicity in tumor bearing animals undergoing doxorubicin therapy. This is achieved through the preservation of renal function, restoration of antioxidant enzyme activity, and suppression of apoptotic and inflammatory markers.

Anti-diabetic effect of madecassoside

The progressive decline in β cell function and mass is a critical factor in type 2 diabetes mellitus. Tan et al.,[16] explored the anti-hyperglycemic effects of madecassoside in experimentally induced diabetic rats, demonstrating that madecassoside has an antidiabetic effect linked to the preservation of β-cell structure and function. Further investigations by Tan et al.,[17] revealed that madecassoside directly protects a β cell line (INS-1E) from various harmful agents, enhancing cell viability and function under conditions typically associated with type 2 diabetes. Elhassan et al.,[18] explored the effects of madecassoside and catalpol on insulin sensitivity in pancreatic INS-1E cells, suggesting that both compounds markedly increased the expression of p-IRS-1, Akt, and p-Akt proteins, while also significantly enhancing insulin secretion in response to high glucose levels.

Anti-inflammatory effect of madecassoside

Li et al.,[19] elucidated that madecassoside exhibited a powerful anti-inflammatory effect in models of collagen-induced arthritis, primarily by inhibiting the expression of key pro-inflammatory mediators such as COX-2 and IL-6, while concurrently enhancing IL-10 expression. Won et al.,[20] investigated the anti-inflammatory effects of madecassic acid and madecassoside, compounds derived from *Centella asiatica*, in lipopolysaccharide stimulated RAW 264.7 murine macrophage cells. Their research revealed that both compounds significantly inhibited the production of key inflammatory mediators, including nitric oxide (NO), prostaglandin E2 (PGE2), tumor necrosis factor-alpha (TNF-

alpha), interleukin-1 beta (IL-1beta), and IL-6. Moqbel et al.,[21] examined the protective properties and underlying mechanisms of madecassoside in the treatment of osteoarthritis, revealing that madecassoside inhibited the NF-κB signaling pathway. This inhibition reduces IL-1β induced inflammation in chondrocytes, highlighting its promising therapeutic potential for managing osteoarthritis. Lu et al.,[22] investigated the clinical effectiveness of madecassoside in the treatment of gouty arthritis and hyperuricemia, finding that it significantly alleviates paw swelling and joint inflammation in murine models of gouty arthritis. Additionally, madecassoside significantly reduced the expression of neutrophil cytosolic factor 1, caspase-1, and NLRP3 in models of peritoneal inflammation triggered by MSU. Shen et al.,[23] investigated the anti-inflammatory and skin hydration properties of madecassoside. Their findings showed that madecassoside effectively reduced the expression of IL-1β and TLR2, and also inhibited the nuclear translocation of NF-κB in P. acnes-stimulated THP-1 human monocytic cells. These effects are crucial for maintaining skin homeostasis and barrier function. Lu et al.,[24] explored a novel transdermal delivery system using a nanoemulsion to co-deliver Paeonol and madecassoside, demonstrating its potential to enhance skin barrier repair and anti-inflammatory efficacy, thereby offering a promising new strategy for developing advanced skincare products for sensitive skin. Du et al.,[25] investigated the ability of madecassoside to prevent Aβ25-35-induced inflammation and autophagy, finding that it significantly reduced the production of inflammatory cytokines like TNF-α and IL-6. Their results suggested that madecassoside protected neural cells from these effects through the class III PI3K/Beclin-1/Bcl-2 pathway. Jung et al.,[26] examined the impact of madecassoside on ultraviolet-induced inflammation through a co-culture model of keratinocytes and melanocytes. Their study revealed that Madecassoside markedly reduced UV-induced melanogenesis by inhibiting PAR-2 expression and its related signaling pathways, including COX-2, PGE2, and PGF2α, in keratinocytes.

Hepatoprotective effect of madecassoside

Choi et al.,[27] explored the impact of madecassoside on primary hepatocytes subjected to palmitate and in the livers of mice fed a high-fat diet, revealing that madecassoside effectively decreased lipogenic lipid accumulation, apoptosis, and endoplasmic reticulum stress in hepatocytes. This suggests that madecassoside may alleviate obesity-related hepatic steatosis via an AMPK/autophagy-dependent mechanism, highlighting its potential as a promising treatment for hepatic steatosis. Wang et al.,[28] conducted a study to explore the protective role of madecassoside in acute liver failure triggered by lipopolysaccharide and D-galactosamine in mouse model. Their research demonstrated that madecassoside notably elevated the levels of heme oxygenase and antioxidants by enhancing the activity of nuclear factor E2-related factor 2 in response to LPS-induced liver damage. These results suggest that madecassoside could be a promising therapeutic candidate for treating lipopolysaccharide and D-galactosamine-induced liver injury, with the potential to be developed into a hepatoprotective drug for acute liver failure. Li et al.,[5] revealed that madecassoside profoundly inhibited proliferation and invasion in liver cancer cells. This suppression was orchestrated through the PKC-cMET-ERK1/2-COX-2-PGE2 signaling axis, highlighting the compound's potent regulatory effects on these pathways.

Wound healing effect of madecassoside

Liu et al.,[29] explored the impact of madecassoside on the healing of burn wounds, proposing that its effectiveness in wound repair is a key reason for the traditional use of *Centella asiatica* in treating burns. Their findings suggested that madecassoside's wound-healing property is attributed to its antioxidant activity, promotion of collagen production, and enhancement of angiogenesis. Hou et al.,[30] evaluated the wound healing capability of madecassoside, revealing that madecassoside stimulated collagen synthesis, reduced oxidative stress in wounds, and promoted vasodilation. They also noted that madecassoside supported cell proliferation and growth in animal models. Rachpirom et al.,[31] explored the wound healing potential of madecassoside. Their study highlighted the extract's strong anti-inflammatory properties, including the inhibition of nitric oxide, and its ability to promote wound healing through processes like cell proliferation, migration, and collagen synthesis in human dermal fibroblast cells. Kim et al.,[32] highlighted the synergistic protective effects of madecassoside combined with rosmarinic acid in Hs68 cells against UVB-induced photoaging. Their findings propose that these natural compounds are promising candidates for anti-aging and skin care interventions, with significant potential applications in both the cosmetic and pharmaceutical industries. Park[33] reported that *Centella asiatica* and its triterpene, madecassoside, showed therapeutic effects on dermatological conditions like acne, burns, atopic dermatitis, and wounds. These effects are mediated through NF-κB, TGF-β/Smad, MAPK, Wnt/β-catenin, and STAT pathways. Liu et al.,[34] observed that PECE-modified madecassoside liposomes significantly improved wound healing in second-degree burns in a rat model compared to unmodified madecassoside liposomes. Their study suggested that the modified liposomes exhibited superior surface adhesion and healing performance. Li et al.,[35] carried out a split-face, double-blind, randomized controlled trial to evaluate the efficacy and safety of a novel non-steroidal cream in comparison to a hospital-made emollient for aiding wound healing post-fractional CO2 laser treatment. Their study revealed that a B5 cream, formulated with madecassoside, 5% panthenol, and copper-zinc-manganese, significantly expedited the healing of minor laser-induced wounds, while only producing mild and transient side effects. Li et al.,[36] ingeniously developed madecassoside-loaded liposomes using a double-emulsion technique, significantly enhancing transdermal delivery and optimizing wound healing efficacy. Their research suggests that this advanced liposomal formulation offers a promising pharmaceutical strategy for enhancing the therapeutic potential of madecassoside in wound care applications. Changsan et al.,[37] investigated the clinical effectiveness of a polymeric spray film formulated with *Centella asiatica* extract, which includes triterpenes such as asiatic acid, madecassic acid, asiaticoside, and madecassoside, in treating acute wounds. Their findings indicated that the polymeric spray film was advantageous as a treatment for acute wounds, as it significantly accelerated the healing process without causing any adverse effects. Swatdee et al.,[38] conducted a comprehensive assessment of a topical spray specifically formulated with *Centella asiatica* extract, focusing on its effectiveness in treating excision wounds in rats. The triterpene content analysis of the extract revealed concentrations of asiatic acid (0.12%), madecassic acid (0.54%), asiaticoside (0.25%), and madecassoside (1.02%). The results demonstrated that the formulation was non-irritating in the rat model and led to complete wound closure within 14 days in an in vivo excision wound healing model.

Cardioprotective effect of madecassoside

Li et al.,[39] explored the potential of madecassoside to mitigate myocardial reperfusion injury in a rabbit heart model. They found that pretreatment with madecassoside significantly attenuated the reduction in superoxide dismutase activity, notably lowered levels of malondialdehyde, C-reactive protein, and cardiomyocyte apoptosis, while also upregulating Bcl-2 expression. These findings indicate that madecassoside confers

protection against myocardial ischemia-reperfusion injury, primarily by inhibiting lipid peroxidation, enhancing superoxide dismutase (SOD) activity, and exerting potent anti-inflammatory and anti-apoptotic effects. Similarly, Biian et al.,[40] investigated madecassoside's protective role against myocardial ischemia-reperfusion injury in vivo. Their study corroborated that madecassoside offers cardioprotection, likely attributed to its apoptotic and anti-inflammatory functions, along with its ability to enhance SOD activity. Cao et al.,[41] assessed the therapeutic impact of madecassoside on cardiac dysfunction in a rat model of sepsis induced by lipopolysaccharide (LPS). Their findings indicated that madecassoside inhibited LPS-induced production of tumor necrosis factor-alpha (TNF-α) by blocking the ERK1/2, p38, and NF-κB pathways in cardiomyocytes. This suggests that madecassoside may possess cardioprotective effects in the context of LPS-mediated sepsis.

Other pharmacological effect of madecassoside

Mando et al.,[42] conducted an in-depth investigation into the antidepressant properties of principal compounds found in *Centella asiatica*, specifically focusing on its triterpene including madecassoside. Their research underscores the potential of madecassoside and asiaticoside to alleviate depressive symptoms by positively influencing behavior and modulating the hypothalamic-pituitary-adrenal (HPA) axis in a zebrafish model subjected to chronic unpredictable stress. Additionally, in silico analysis further corroborated these findings. Liu et al.,[43] assessed the impact of madecassoside (MC) on depressive behavior in mice and its effects on monoamine oxidase (MAO) activity across different brain regions in rats. Their findings substantiate the hypothesis that madecassoside exerts its antidepressant effects by inhibiting MAO activity, with a more pronounced effect observed following acute administration compared to chronic use, although the underlying mechanisms warrant further exploration. Cho et al.,[44] explored the role of madecassoside in modulating lipid metabolism within visceral adipocytes, focusing on its potential for obesity treatment through mechanisms of browning, lipolysis, and lipogenesis. Their results demonstrated that madecassoside promoted thermogenic browning and enhances lipolysis while suppressing adipocyte lipogenesis, indicating its potential as a therapeutic agent for obesity management. Sun et al.,[45] investigated the anti-obesity effects of madecassoside and its underlying mechanisms. Their study revealed that madecassoside inhibited weight gain in obese diabetic mice, reduced triglyceride levels, suppressed mesenteric fat lipogenesis, promoted epididymal fat lipolysis, and enhanced fatty acid oxidation. Additionally, madecassoside appeard to facilitate mesenteric fat browning and activate mitochondrial function in both brown and mesenteric fat tissues. Shan et al.,[46] demonstrated the protective effect of madecassoside in vitro against cisplatin- and hypoxia-reoxygenation-induced injury in renal tubular epithelial cells, and in vivo in a model of acute kidney injury (AKI) in mice. Their results suggested that madecassoside served as a potential therapeutic agent for AKI, possibly through the JNK/c-JUN signaling pathway. Arora et al.,[47] analyzed the impact of triterpenes in *Centella asiatica* extract on antioxidant properties, cholinesterase inhibition and anti-amnesic effects. Their study revealed that the methanolic extract (CAE) demonstrated exceptional efficacy in scavenging free radicals, inhibiting cholinesterase activity, and ameliorating scopolamine-induced amnesia. Interestingly, the triterpene-free fraction (CAE-FF) displayed stronger antioxidant activity compared to the triterpene-enriched fraction (CAE-EF), indicating that triterpenes alone do not account for the extract's full range of bioactivities. Wang et al.,[48] discovered that madecassoside prevented osteoporosis caused by estrogen deficiency by inhibiting RANKL-induced osteoclastogenesis. Their study showed that madecassoside inhibited the formation and function of osteoclasts in a dose-dependent manner without causing cytotoxicity. Madecassoside achieved this by blocking Ca2+ oscillations and the NF-κB and MAPK pathways, and its efficacy in preventing bone loss was confirmed in an ovariectomized mouse model, highlighting its potential as a treatment for osteolytic bone diseases. Yu et al.,[49] found that madecassoside significantly reversed histological damage in rats with adjuvant-induced arthritis, showcasing its remarkable therapeutic potential. Their findings suggested that madecassoside exerted anti-rheumatoid arthritis (RA) activity through suppression of NF-κB/MMP-13 pathway. Dou et al.,[50] explored how adrenergic and cholinergic nerves affect the impact of madecassoside in the context of rheumatoid arthritis. Their research concluded that madecassoside potentially ameliorated collagen-induced arthritis through a partial modulation of the peripheral cholinergic system. Lin et al.,[51] examined the protective effects of madecassoside from Hydrocotyle sibthorpioides against cognitive impairment induced by D-galactose in mice. They found that madecassoside mitigated cognitive decline primarily by reducing oxidative stress, improving synaptic plasticity, and restoring cholinergic function, suggesting its potential as a preventive agent for cognitive impairment. Lu et al.,[52] performed an extensive analysis of the protective function of madecassoside in experimental pulmonary fibrosis. Their study demonstrated that madecassoside ameliorated oxidative damage and inflammation in the early stages following bleomycin (BLM) instillation, suppressing TGF-β1 overexpression and collagen synthesis while promoting collagen degradation through an enhanced MMP1/TIMP1 ratio. Consequently, madecassoside shows promise as a candidate for pulmonary fibrosis treatment. Bian et al.,[53] showed the protective efficacy of madecassoside against oxidative stress-induced injury in endothelial cells. Their study indicated that madecassoside shielded HUVECs from oxidative damage, likely by inhibiting cell apoptosis through the preservation of mitochondrial membrane integrity and downregulation of caspase-3 and p38 MAPK activation.

Conclusion

In conclusion, the longstanding use of plants in medicine, founded upon empirical knowledge and traditional practices, continues to be a focal point in healthcare due to their demonstrated effectiveness across a wide range of ailments. Madecassoside emerges as a noteworthy triterpenoid saponin, showcasing a plethora of pharmacological activities. Its documented neuroprotective, cardioprotective, and anti-inflammatory properties, among others, underscore its potential therapeutic value. As research expands, madecassoside holds promise for future therapeutic applications, further validating the rich legacy of plant-based medicines in modern healthcare.

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