Anti-inflammatory, Bacteriostatic and Anticancer Effects of Madecassoside

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Abstract Madecassoside is a natural active component extracted from *Centella asiatica*. In recent years, a large number of studies have reported that madecassoside has a variety of biological activities, such as anticancer, anti-inflammatory and antibacterial effects, prevention and treatment of cardiovascular diseases, nerve damage, visceral damage and arthritis, and other pharmacological effects. In this paper, the pharmacological action and mechanism of madecassoside were reviewed to provide a theoretical basis for further research of madecassoside and drug development.

Key words Madecassoside, Pharmacological effect, Anti-inflammatory effect, Bacteriostasis, Anticancer effect, Arthritis

1 Introduction

Centella asiatica was first published in the *Sheng Nong's Herbal Classic* and was listed as a medium-grade drug. It is a perennial herb in Umbelliferae, and has multiple effects such as detoxification and detumification, promoting blood circulation and hemostasis[1]. Madecassoside ($C_{48}H_{78}O_2$) is the main active component of *C. asiatica*, and its molecular weight is 975.13. It is white crystal in appearance. A large number of studies have reported that madecassoside has a variety of biological activities in the field of biomedicine, including anticancer, anti-inflammatory, antibacterial, arthritis improvement, viscera protection and other pharmacological effects. In this paper, the pharmacological action and molecular mechanism of madecassoside were reviewed to provide a theoretical basis for further research of madecassoside and development of new drugs.

2 Anticancer effect of madecassoside

Cancer is a kind of disease that occurs when normal cells mutate, further evolve into cancer cells and proliferate due to the excessive secretion of carcinogenic factors under the long-term influence of various factors. Currently, commonly used antitumor drugs have many toxic side effects and adverse reactions, which seriously reduce the quality of life and survival rate of cancer patients. Therefore, to find a kind of efficient, safe and inexpensive natural anticancer drugs has become an urgent problem to be solved in the research and development of anticancer drugs. At present, research on the antitumor effect of Chinese herbal medicine and its mechanism have become a hot topic at home and abroad. Madecassoside is the main active substance of traditional Chinese medicine *C. asiatica*, and its anticancer effect has attracted much attention. Li Zexin *et al.*[2] found that madecassoside can inhibit the proliferation and invasion of hepatocellular carcinoma HepG2 and SMMC-77 cells by regulating the phosphorylation of corresponding receptor cMET, the phosphorylation of signal-regulated kinase 1/2 (ERK1/2), the activity of protein kinase C (PKC), and the expression levels of cyclocyase-2 (COX-2) and prostaglandin E2 (PGE2). Jiang Bin *et al.*[3] found that after the treatment of human cervical cancer C-33A/CaSki cells with madecassoside, the expression level of pro-apoptotic protein Bax increased, while the expression levels of anti-apoptotic protein B-lymphoblastoma-2 gene (Bcl-2) and recombinant human B-cell lymphoma factor xl (Bcl-xl) decreased, indicating that madecassoside induced apoptosis of C-33A/CaSki cells by regulating the expression level of apoptosis-related proteins. These results show that madecassoside can play an anticancer role by inhibiting the proliferation and invasion of cancer cells and inducing apoptosis of cancer cells.

3 Anti-inflammatory and bacteriostatic effects of madecassoside

Skin, which is composed of epidermis and dermis, can protect human body and prevent bacterial invasion, so it is an important protective barrier for human body. In recent years, a large number of studies have shown that madecassoside has significant therapeutic effects in moisturizing, antioxidant, antibacterial, anti-inflammatory, promoting wound healing and other aspects, and is widely used in the treatment of infectious wounds, burns, hypertrophic scars and other skin diseases. Jung *et al.*[4] found that madecassoside can inhibit the production of PGE2 and prostaglandin F2α (PGF2α) in keratinocytes to reduce the expression level of COX-2 and peroxisome proliferation factor activated receptor (PAR-2), and thus weaken the UV-induced melanin index and

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phagocytosis, finally inhibiting the synthesis and deposition of melanin. It indicates that madecassoside could improve the precipitation of skin melanin. From the western blotting analysis of proteins, Song Jie *et al.* [5] found that after the treatment of human earlobe keloid cells with madecassoside (10, 30, and 100 μmol/L), the phosphorylation levels of filin (cofilin), p38 mitogen activated protein kinase (p38 MAPK), phosphatidylinositol-3-hydroxykinase (PI3K), and serine kinase (AKT) in earlobe keloid cells were significantly reduced, but it had a small effect on the phosphorylation of matrix metalloproteinase 13 (MMP-13) and ERK1/2, revealing that madecassoside had a good effect on keloid. After treating the burn wound of burn model rats with madecassoside (0.5 g/L), Hou Qiang *et al.* [6] found that the wound of burn model rats gradually contracted and eventually crusted off. These results indicated that madecassoside has good antibacterial, anti-inflammatory and wound healing activities.

4 Protective effect of madecassoside on heart and cerebral vessels

Cardiovascular and cerebrovascular diseases are ischemic or hemorrhagic diseases of the heart, brain and systemic tissues caused by hyperlipidemia, blood viscosity, atherosclerosis, hypertension, *etc.*, and seriously harm human health and life. In recent years, a large number of studies have shown that madecassoside has a remarkable effect on the prevention and treatment of cardiovascular diseases. Bai Jihong *et al.* [7] found that after the treatment of hypertensive model rats with madecassoside, the systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) of hypertensive model rats significantly reduced, but it had no significant effect on the blood pressure and heart rate of normal rats. Cao Wei *et al.* [8] believed that madecassoside (20 mg/kg) could inhibit the production of tumor necrosis factor in rat cardiomyocytes and delay the decline of mean arterial blood pressure, showing that madecassoside had a good effect on lowering blood pressure. Li Guigui *et al.* [9] found that after the treatment of ischemia reperfusion injury (MIRI) model rabbits with madecassoside, the expression level of C-reactive protein (CRP) in serum of MIRI model rabbits significantly declined, and the activity of superoxide dismutase (SOD) and the expression level of Bcl-2 increased, while malondialdehyde (MDA) content decreased, thereby inhibiting myocardial apoptosis induced by MIRI, and finally playing a preventive and protective role in myocardial ischemia reperfusion injury. These results reveal that madecassoside can dilate coronary artery and protect vascular endothelial cells.

5 Protective effect of madecassoside on nerves

Nervous system is the regulating center of organism organ activity. With the aggravation of ageing population of society, the incidence of nervous system diseases is increasing year by year. An inflammatory response occurs when degenerative changes occur in the nervous system, and excessive neuroinflammation can cause greater damage to surrounding tissues. In recent years, a large number of studies have shown that madecassoside has a significant effect on inhibiting inflammation, protecting nerve cells and improving nerve dysfunction. Zhang Sisi *et al.* [10] pointed out that after the treatment of LPS-induced microglia cells with madecassoside for 48 h, the expression levels of pro-inflammatory cytokines TNF-α and interleukin-6 (IL-6) in microglia cells were significantly reduced, and the cycle of microglia cells was arrested in the G_2 phase, thus inhibiting the proliferation of microglia cells. Du Baoshun *et al.* [11] found that after the treatment of nerve cells with madecassoside for 24 h, cell vitality increased and lactate dehydrogenase leakage in nerve cells induced by Aβ25-35 decreased. In addition, western blotting showed that madecassoside could block the transformation from light chain 3-I (LC3-I) to light chain 3-II (LC3-II), reduced the expression level of Beclin-1, and increased the expression level of anti-apoptotic protein Bcl-2. Madecassoside protects nerve cells by blocking the inflammatory response and autophagy induced by Aβ25-35. Jia Yanfeng *et al.* [12] proposed that madecassoside could reduce the apoptosis of cortical neurons by inhibiting the activation of NR2B, an important inducer of excitatory neurotoxic damage. These results indicate that madecassoside can inhibit inflammation, protect nerve cells and improve nerve dysfunction.

6 Therapeutic effect of madecassoside on rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease characterized by chronic, symmetrical, polysynovial arthritis and extraarticular lesions. Persistent recurring synovitis can lead to intraarticular cartilage and bone destruction, joint dysfunction, and even disability, seriously affecting the quality of life of patients. In recent years, many studies have shown that madecassoside has good pharmacological activity in improving rheumatoid arthritis. Wang Ting *et al.* [13] found that after the treatment of small intestinal epithelial cells of collagen-induced arthritis model rats with madecassoside, the expression levels of secreted immunoglobulin and interferon-γ in small intestinal epithelial cells decreased, and the ratio of CD^{4+} to CD^{8+} in T cells of small intestinal epithelium decreased; the expression levels of CD80, CD86, IL-6 and interleukin-12 (IL-12) mRNA in the small intestine declined, which inhibited the immune response of the intestinal mucosa of arthritis model rats, and finally formed the immune tolerance of the intestinal mucosa. Yu Weiguang *et al.* [14] found that after the treatment of primary rat fibroblast-like synovial cells (FLS) with madecassoside, the expression level of MMP-13 in FLS reduced, which hindered the transcription process of MMP-13 and then inhibited the migration and invasion of FLS. Further studies showed that madecassoside can reduce the translocation and phosphorylation of NF-κB in rat FLS, suggesting that madecassoside may play a role in the prevention and treatment of rheumatoid arthritis by regulating the NF-κB/MMP-13 pathway. Zhang Li *et al.* [15] proposed that after the treatment of arthritis model rats with madecassoside, the secre-

tion of inflammatory factor IL-6 in the FLS of arthritis model rats reduced, and the phosphorylation level of reaction element binding protein (CREB) induced by ERK, p38, PKC and interleukin-1β (IL-1β) declined. Moreover, the activation of FLS in arthritis rats was inhibited. These results indicate that madecassoside has a good effect on improving rheumatoid arthritis.

7 Protective effect of madecassoside on visceral organs

Viscera is an important system for providing energy, maintaining vital signs and life reproduction. It is responsible for the circulation, absorption, excretion and reproduction of the human body and plays an important role in the health and normal function of the body. Visceral injury mainly includes trachea injury, heart injury, stomach injury, liver injury and kidney injury. In recent years, a large number of studies have shown that madecassoside has a good effect on the protection of viscera.

Wang Wei *et al.* [16] found that madecassoside can reduce the expression levels of inflammatory cytokines such as TNF-α, IL-1β and IL-6, and restore the protein activities of antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase), thus alleviating liver injury induced by LPS/D-Galn. In addition, madecassoside can improve acute liver failure in mice by decreasing the phosphorylation of p38, MAPK and NF-κB and reducing LPS levels of inducable nitric oxide synthase (iNOS) and COX-2. Su Zhonghao *et al.* [17] pointed out that after 24-h treatment of human renal tubular epithelial cells (HK-2) with madecassoside, madecassoside can reduce the expression level of Bax, phosphorylated ERK1/2, NF-κB and iNOS, increase the expression level of Bcl-2 protein, and reduce the expression level of caspase-3 by restoring the activity of antioxidant enzymes. It indicates that madecassoside had a significant inhibitory effect on adriamycin induced apoptosis and inflammatory reaction. Lu Guoxun *et al.* [18] found that madecassoside could raise the expression level of human growth factor receptor (HGF) in colon tissues. Further studies showed that madecassoside could also improve the ratio of matrix metalloproteinase 1 to metalloproteinase inhibitor 1 in the lung tissue of mice with pulmonary fibrosis by reducing the expression level of tissue inhibitor 1, and finally improve the pulmonary fibrosis of mice by inhibiting extracellular matrix deposition. These results show that madecassoside had a good alleviating and therapeutic effect on visceral injury.

8 Therapeutic effect of madecassoside on spinal cord injury

Acute spinal cord injury is a kind of disease that seriously endangers human health, and free radical and lipid peroxidation are the main causes of secondary injury. MDA and SOD are important indicators reflecting the degree of oxygen free radical and lipid peroxidation. Zhao Gang *et al.* [19] treated acute spinal cord injury model rats with madecassoside, and found that madecassoside could increase the behavioral score index of acute spinal cord injury model rats, improve the pathological injury, reduce MDA content, increase SOD activity and increase the expression level of neuron-specific enolase (NSE), so as to alleviate the acute spinal cord injury in the model rats. The results reveal that madecassoside had an obvious repairing effect on spinal cord injury.

9 Conclusions and prospects

As the triterpenoid saponins extract and the highest secondary metabolite of the pure natural Chinese herb *C. asiatica*, madecassoside has good pharmacological activity in anti-cancer, anti-inflammatory, antibacterial and other aspects, and has high commercial value and development potential. Although there are many reports on madecassoside, most of them are confined to the characterization of pharmacological action, and there is a lack of comprehensive and systematic studies on molecular mechanism of action and related clinical application. Therefore, it is necessary to use the multidisciplinary knowledge of biology, traditional Chinese medicine, pharmacology, basic medicine and clinical medicine to carry out more in-depth basic and applied research at the molecular, cellular and animal levels, so as to provide a theoretical basis for the drug development and clinical application of madecassoside.

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gene, it lays a foundation for exploring the regulation mechanism of its protein on bacterial virulence in the future.

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