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Advances in Pharmacology and Toxicology of Marine

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Abstract

The natural alkaloids extracted from Chinese herbal medicine have shown high medicinal value *in vivo* and *in vitro*, such as bacteriostasis, anti-virus, anti-tumor and anti-inflammation. This paper focuses on matrine and reviews its action mechanism and toxicological action. It is concluded that the medicinal prospect of matrine is very broad, but more basic research and clinical trials are needed for more comprehensive evaluation.

Keywords

Marine, Pharmacology, Toxicology, Antiviral Activity, Mechanism of Action

1. Introduction

Sophora flavescens is a kind of *Sophora alopecuroides* in Leguminosae. Compendium of Materia Medica and Classic of Shennong Materia Medica recorded that it clears heat, dryness, and dampness, kills insects, and dispels accumulation and diuresis. Matrine, isolated from *Sophora flavescens* Ait (Kushen), has been found to possess a variety of pharmacological effects, including anti-inflammation and immunity-regulation activity. Now, the research of matrine is most widely. Matrine has various medicinal properties. It acts as an antipyretic, analgesic and anticonvulsant. It also stabilizes the nervous system on the central nervous system. On the cardiovascular system, it has a negative frequency and positive inotropic effect, which can prevent atherosclerosis and reduce the role of myocardial injury. Matrine can also benefit the digestive system by providing anti-liver injury, anti-fibrosis, and elevated white blood cell properties. Additionally, it has anti-tumor and anti-liver cancer effects [1] [2].

Many kinds of literature have shown that the effects of matrine alkaloids include, but are not limited to, antivirus and inhibition of a variety of pathogenic bacteria in a variety of ways [3] [4]; anti-inflammatory effects can also be achieved by inhibiting the production of pro-inflammatory cytokines in macrophages and inhibiting the expression of TLR2 and the activation of downstream NF-kappa B [5] [6], analgesic effect [7] and anti-parasite effect [8]. In recent years, there have been many studies on its anticancer effect. Matrine can affect the proliferation of colon cancer cell HT_{29} by triggering the mitochondrial apoptosis pathway [9]. Some studies have shown that matrine extract has hepatotoxicity. *In vivo* experiments have found that matrine extract at the dose of 118 d and 154 mg/kg for 21 days will produce more significant toxicity to the liver of ICR mice [10].

The primary research, pharmacological action, and toxicity evaluation of matrine can provide vital information for future drug research. In this review, the biological characteristics and mechanism of matrine were discussed from the aspects of pharmacology and toxicity, and its therapeutic potential and safety in the clinical application were discussed.

2. Antiviral Activity

A virus is a kind of acellular organism that needs to be parasitic in living cells, which consists of genetic material and protein shell, The pathogenic basis of viruses to humans and animals is the proliferation of viruses in host cells, which can cause cell damage or changes [11]. Both the current epidemic of SARS-CoV-2 and the recent discovery of the porcine delta coronavirus that can infect humans in Haiti have shown the ability of the virus to adapt quickly to new hosts [12]. At the same time, viruses can infect host cells in many ways. This interaction is regulated by many host and virus products, so it is possible to use traditional Chinese medicine extract to achieve antivirus [13].

Both matrine and total alkaloids of *Scutellaria barbata* can directly inactivate porcine reproductive and respiratory syndrome virus (PRRSV) *in vitro*, and matrine can also interfere with some activities of the virus in cells to interfere with PRRSV replication [14] [15]. Further studies found that matrine blocked the expression of N protein in Marc-145 cells by inhibiting the activation of caspase-3 so as to inhibit PRRSV-induced apoptosis [16]. In addition, matrine could inhibit the DNA replication of porcine circovirus 2 (PCV2) in the porcine kidney cell line (PK-15) in a dose-dependent manner [17]. Some studies have shown that the anti-PCV2 mechanism of matrine may be related to the interference of PCV2Rep protein expression and/or interference with host cell p38/MAPK and JNK/SAPK signaling pathways, and matrine combined with osthol can inhibit the expression of Cap in Cap-transfected PK-15 cells, thus inhibiting Cap-induced PERK cell apoptosis [18] [19] [20]. In addition, matrine has the activity of anti-PRRSV/PCV2 co-infection *in vitro* by inhibiting the activation of TLR3 and 4 max NF-κB/TNF-α pathway [21]. In addition, matrine and its derivatives also have excellent anti-hepatitis B virus (hepatitis B virus, HBV) [22] [23] [24], anti-hepatitis

C virus (hepatitis C virus, HCV) [25], anti-human immunodeficiency virus, HIV, and other viruses [26].

To sum up, matrine and its derivatives have great potential in antiviral applications. In addition to matrine, many alkaloids and their derivatives have good antiviral value [27].

3. Bacteriostatic and Antibacterial Activity

In recent years, antibiotics' effectiveness in treating common infections has been declining, and alkaloids can reduce the pressure and dependence on antibiotic selection [28] [29]. Intestinal pathogenic *Escherichia coli* can cause disease in poultry, thus causing huge economic losses to animal production [30]. The total alkaloids of *Sophora alopecuroides* (including matrine) have antibacterial activity. When combined with ciprofloxacin, the AcrAB-ToLC efflux pump can be down-regulated to improve the sensitivity of multidrug-resistant Escherichia coli [31] [32]. *Staphylococcus aureus* can adhere to the infected site and proliferate, producing a variety of toxins and invasive enzymes, resulting in inflammation and apoptosis of host cells [33]. Matrine can prevent the formation of biofilm of Staphylococcus epidermidis infection mediated by quorum sensing (Quorum-sensing, QS) by inhibiting the activity of self-inducible molecule 2 (auto-inducer 2) [4]. At the same time, matrine could down-regulate the expression of endogenous and exogenous cleaved caspase-3, cleaved caspase-8, and cleaved caspase-9 in BMEC to inhibit PVL-producing *Staphylococcus aureus*.

The discovery and development of antibiotics are inseparable from natural products [34]. In addition to the above, matrine has the effect of anti-Candida albicans, *Bacillus subtilis*, and other bacteria. Generally speaking, matrine is a potential antibacterial agent worthy of further research and development.

4. Anticancer Activity

In recent years, the anticancer and anticancer mechanism of matrine has been widely reported. Many studies have shown that matrine can inhibit tumor cell proliferation by accelerating apoptosis [35], inhibiting tumor metastasis [36], inducing cell cycle block [37], inhibiting angiogenesis, inhibiting malignant cell differentiation [38], reversing multidrug resistance [39], and in combination with other chemotherapeutic drugs. Prevent or reduce toxicity caused by chemotherapy or radiotherapy [40].

Apoptosis is a ubiquitous, autonomous, programmed physiological process of cell death, which is used to remove malignant cells, such as cancer cells, without causing damage to normal cells or surrounding tissues [41]. Destroying the mitochondrial membrane potential of cancer cells is one of the ways for matrine to promote apoptosis by inducing mitochondria to release cytochrome C and targeting caspase-dependent signaling pathways to interact with critical proteins [42]. Still, a recent study also pointed out that cancer cells can use nanotubes to pull mitochondria from T cells into their bodies. Whether this will affect the ef-

fect of matrine needs to be further studied [43] [44] [45]. In an *in vitro* experiment, it was confirmed that matrine inhibited osteosarcoma cells in a dose-dependent manner by inducing the activation of Caspase-3,-8 and-9, and up-regulating the expression of apoptotic factors Bax and Fas/FasL and down-regulating the expression of anti-apoptotic factor Bcl-2 [46]. Matrine can induce down-regulation of phosphorus-Aktser473 to activate p21 and Bax, leading to melanoma cell apoptosis. In some studies on retinoblastoma cells, lung cancer A549 cells, and liver cancer SMMC-7721 cells, it has also been found that matrine can promote apoptosis by up-regulating the expression of Bax and down-regulating the expression of Bcl-2 [47]. In the experiment of the inhibitory effect of matrine on chronic myeloid leukemia cells (chronic myeloidleukemia cells, CML), it was observed that matrine could regulate JAK2/STAT3 signaling pathway-related genes to induce apoptosis and inhibit the proliferation of CML cells by inhibiting IL-6 [48]. In addition, matrine can trigger apoptosis of pancreatic cancer cells by reducing the expression of PCNA [49]. Cancer cell metastasis is a significant cause of death in cancer patients, and matrine has an excellent inhibitory effect on cancer cell metastasis. HeLa cells are commonly used in cancer-related research. Matrine can significantly reduce the average migration rate of HeLa cells, which may be due to the inhibition of cAMP-dependent protein kinase (PKA) activity during adhesion and migration of HeLa cells, thus reducing the phosphorylation of vasodilator-stimulated phosphoprotein (VASP) [36]. Matrix metalloproteinases (Matrixmetalloproteinases, MMPs) play an important role in promoting tumor metastasis, while matrine can reduce the expression of MMP-9, MMP-2 and VEGF in astrocytoma cells to inhibit their metastasis [50] [51]. In addition, matrine can inhibit the expression of MMP-9 by down-regulating the NF-κB signal pathway, thus reducing the metastatic ability of hepatocellular carcinoma cells [52]. And down-regulate the face of heparanase to inhibit the metastatic capacity of human malignant melanoma cells [53]. There are many ways of tumor cell metastasis, and the complex relationship between tumor cells and the body is an excellent strategy to inhibit their metastatic ability [54].

The regulation of the cell cycle is controlled by the expression of cyclin-dependent cyclin, cyclin-dependent kinase (CDK), and CDK inhibitor [55]. Matrine can block human retinoblastoma cells (Y79, WERI-RB1, and SO-RB50) and melanoma in G0/G1 phase by inducing up-regulation of CDK inhibitors p21 and p27 and down-regulation of cyclin D1 [56]. In addition, other studies have shown that matrine can up-regulate the expression of p53 and p21, and down-regulate the word of CDK2, CDK4, cyclin D1, cyclin E, and phosphorylated Rb, which leads to the arrest of vascular smooth muscle cells and gallbladder carcinoma GBC-SD cells in G0/G1 stage and induce apoptosis [57] [58].

Multidrug resistance (MDR) is cancer patients' leading cause of chemotherapy failure. Matrine can mediate the reversal of paclitaxel resistance in the NCI-H520/TAX25 cell line, which may be due to the decreased expression of mRNA and protein in survivin, Oct-4, and Sox-2 [59]. In addition, studies have shown

that matrine can increase the intracellular accumulation of adriamycin (DOX) and induce its apoptosis in drug-resistant K562/DOX cells by reducing the expression of P-gp [60]. It can also reverse the resistance of human nasopharyngeal carcinoma cell line HONE1 to cisplatin (DDP) [61].

Anti-angiogenesis is one of the primary ways of cancer treatment. Matrine can inhibit the growth and survival of lung cancer (NSCLCA549 cell) and pancreatic cancer (PANC-1 cell) by down-regulating the expression of vascular endothelial growth factor (VEGF), NF-κB and NF-κBp-65 protein [62] [63]. Angiogenesis plays a vital role in tumor growth and diffusion. Therefore, the anti-angiogenic potential of matrine may be of great value in cancer treatment.

The aforementioned does not fully cover all the anticancer pathways of matrine, for example, matrine can also cause cells to autophagy by promoting the accumulation of autophagy vesicles [64]. The complicated relationship between the average body and cancer cells allows matrine to realize anticancer in many aspects. Although the mechanism of its anti-tumor activity has been explained from the point of view of molecular biology, there still needs to be a large sample, multi-control, double-blind and random clinical trials to verify its safety and effectiveness.

5. Anti-Inflammatory Activity

Matrine can exert its anticancer activity by inhibiting NF-κB and regulate inflammatory response through this pathway. Inhibition of airway inflammation in airway epithelial cells and asthmatic mice by suppressing the expression of cytokine signal 3 down-regulated by NF-κB signal transduction. Staphylococcus aureus lipoteichoic acid-induced endometritis can also be protected by the use of matrine to inhibit TLR2-mediated NF-κB pathway [6]. The potential to prevent atherosclerotic progression also seems to be the potential use of matrine. The molecular mechanism can significantly inhibit the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) in vascular smooth muscle cells stimulated by TNF-α by inhibiting the activation of NF-κB and MAPK pathways [65]. Studies have shown that matrine can reduce inflammation-related diseases, including osteoarthritis, by inhibiting the activation of NF-κB and MAPK signal pathways to inhibit the expression of MMP-3 and MMP-13 in human articular chondrocytes induced by IL-1b. In addition to NF-κB pathway [66], matrine can also inhibit mouse ovalbumin (OVA)-induced airway hyperresponsiveness (AHR) by reducing the production of IL-4 and IL-13 and increasing the expression of IFN-γ. By reducing the production of IL-1b, IL-17, and malondialdehyde (MDA) and increasing the expression of chemokine receptor 7 (CCR7), matrine can reduce LPS-induced inflammation and oxidative stress [67].

Interestingly, matrine also seems to protect mice from TNBS-induced colitis by improving intestinal microbiota [68]. The anti-inflammatory effect of matrine has been fully confirmed. This effect is achieved by regulating the expres-

sion of inflammatory cytokines and chemokines and even improving the intestinal microbial community, which provides a new direction and reference for the development of matrine.

6. Toxicological Effect

Drug toxicity is one of the first factors to be considered in evaluating drug treatment, and the hepatotoxicity of matrine has been widely concerned. The results show that the hepatotoxicity induced by oxymatrine may be mainly through its metabolite matrine in mice. Compared with the single component, the combined effect of oxymatrine and oxymatrine is more toxic [69]. Matrine can induce apoptosis of zebrafish hepatocytes and down-regulate oxidative stress related gene zgc: 136383 and anti-apoptosis gene EIF4BP3 [70], and has teratogenic and lethal effects on zebrafish eggs [71]. It pointed out that matrine may inhibit the viability of liver (HepaRG; HL-7702) cells and induce cell cycle arrest and apoptosis by inhibiting the Nrf2 pathway and activating ROS [72] [73]. Recent studies have shown that matrine can inhibit cell viability, increase cytotoxicity, induce apoptosis, change the expression of apoptosis-related proteins, activate caspase-3 and caspase-9, and inhibit mitochondrial membrane potential and ATP levels in NCTC cells [74].

In addition to hepatotoxicity, matrine can also cause cardiac side effects and neurological abnormalities through large doses of oral or injection [75]. An experiment in Kunming mice found that matrine can cause the formation of small softening foci in the brain tissue of mice, as well as necrosis or even rupture of some nuclei [76]. Matrine can damage mice's central nervous system and their balance [77]. In addition, matrine has reproductive toxicity by inhibiting ERK1/2 phosphorylation and inhibiting mouse sperm function through CatSper channel-related mechanisms [78]. At present, there are relatively few studies on the pharmacokinetics of matrine *in vivo*. It is recommended to strengthen this research in the future in order to better exert its pharmacological effects, effectively prevent its toxic reactions, and ensure drug safety.

7. Conclusions

Matrine has considerable medicinal value. Its excellent antiviral, antibacterial, anticancer, and anti-inflammatory effects have potential pharmacological effects in the prevention and treatment of cancer, hepatitis, skin diseases, and allergic asthma. However, the molecular mechanism of these actions has not been fully elucidated, and there are still many gaps. And most of the studies are limited to *in vitro* experiments, so there is still a lot of uncertainty about its effect *in vivo*. At the same time, although matrine can affect the disease progression through multiple pathways and multiple targets, it is rare in modern clinical applications. In addition, the severe side effects of matrine may also limit its clinical value. In recent years, some studies have shown that matrine has a protective effect on the liver and kidney [79]. Therefore, the toxicity of matrine may be related to time

and concentration. Moreover, the poor liposolubility of matrine seriously restricts its clinical efficacy.

Because of the current scattered research, systematic integration should be carried out in the future, its molecular mechanism should be further explored, and *in vivo* experiments should be carried out as the basis of its clinical application. At the same time, it can enhance its clinical efficacy and reduce its side effects by modifying its chemical structure.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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