Article

Matrine: Molecular mechanisms, pharmacological properties, pharmacokinetics, clinical applications, and challenges

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Abstract

Matrine is a tetracyclic quinolizidine alkaloid derived primarily from the dried roots of *Sophora flavescens* Aiton, a traditional Chinese medicinal herb with a history spanning centuries in East Asian medicine. In recent decades, matrine has emerged as a compound of significant scientific interest due to its broad spectrum of pharmacological activities and relatively favorable safety profile. This comprehensive review systematically examines the current state of knowledge regarding matrine, covering its discovery and historical background, physicochemical properties, extraction and purification methodologies, pharmacokinetic characteristics, and the molecular mechanisms underlying its major pharmacological effects. Particular emphasis is placed on the antitumor activities of matrine, which involve the regulation of core oncogenic signaling pathways including Wnt/β-catenin, MAPK/ERK, and PI3K/AKT/mTOR, as well as the induction of multiple programmed cell death modalities such as apoptosis, autophagy, pyroptosis, and ferroptosis. The anti-inflammatory mechanisms of matrine are explored in detail, with focus on its ability to suppress the TLR4/NF-κB/MAPK signaling axis and regulate macrophage polarization. Hepatoprotective effects are discussed in the context of matrine's bidirectional actions on the liver, mediated through Ca^{2+} homeostasis regulation and multiple downstream pathways including Nrf2 and NF-κB signaling. The wound healing potential of matrine is examined, highlighting its anti-inflammatory, angiogenic, and tissue-regenerative properties. Clinical applications of matrine, particularly in chronic hepatitis B and liver diseases, are reviewed alongside systematic evaluations of its efficacy and safety. Structural modification strategies aimed at improving the pharmacological profile of matrine are summarized, as are advances in nano-delivery systems designed to enhance its bioavailability. The review concludes with an assessment of current challenges and future research directions, including the need for high-quality clinical trials, the development of targeted delivery systems, and the exploration of combination therapies.

Keywords matrine; *Sophora flavescens*; antitumor; anti-inflammatory; hepatoprotective; pharmacokinetics; medicine.

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1 Introduction

Matrine (MT) is a naturally occurring alkaloid that constitutes one of the primary bioactive components of the traditional Chinese medicinal herb *Sophora flavescens* Aiton (Chen et al., 2024; Meng et al., 2025; Fig. 1). Over the past several decades, matrine has attracted increasing attention from the global scientific community due to its diverse pharmacological properties and therapeutic potential across a wide range of disease conditions (You et al., 2020). Emerging evidence has demonstrated that matrine possesses anticancer, anti-inflammatory, antioxidant, antiviral, antimicrobial, anti-fibrotic, anti-allergic, antinociceptive, hepatoprotective, cardioprotective, and neuroprotective activities (You et al., 2020; Chen et al., 2024). These pharmacological properties form the foundation for its application in the treatment of various diseases, including multiple types of cancers, hepatitis, skin diseases, allergic asthma, diabetic cardiomyopathy, pain, Alzheimer‘s disease, Parkinson’s disease, and central nervous system inflammation (You et al., 2020).

Fig. 1 *Sophora flavescens* (Source: https://www.flower-db.com/zh/flowers/sophora-flavescens).

The growing interest in matrine reflects a broader trend in contemporary pharmaceutical research, wherein natural products have emerged as important sources for new drug development (Zhang, 2017a-b; Meng et al., 2025). Natural products have demonstrated significant advantages in the comprehensive treatment of cancer, particularly in improving patients’ quality of life, prolonging survival, and reducing the toxic side effects associated with conventional chemotherapy (Meng et al., 2025). However, despite the considerable promise of matrine as a therapeutic agent, several challenges remain, including its low oral bioavailability, short half-life in vivo, and potential toxicity concerns, particularly hepatotoxicity and neurotoxicity at higher doses (You et al., 2020; Feng et al., 2024).

This comprehensive review aims to synthesize the current state of knowledge regarding matrine, from its discovery and historical use in traditional medicine to the latest advances in understanding its molecular mechanisms, pharmacokinetic properties, clinical applications, and formulation strategies. By integrating findings from preclinical studies, clinical trials, and systematic reviews, this article seeks to provide a thorough resource for researchers and clinicians interested in the therapeutic potential of this remarkable natural alkaloid.

2 Discovery and History

The use of *Sophora flavescens* in traditional medicine dates back centuries in East Asian countries, particularly China, Japan, and Korea, where the herb has been employed for the treatment of various conditions including

fever, dysentery, jaundice, and skin disorders (Baidu Baike, 2026). The root of *Sophora flavescens*, known as “Ku Shen” (苦参) in Chinese traditional medicine, has been documented in classical Chinese medical texts for its bitter and cold properties and its ability to clear heat, dry dampness, and expel parasites (Baidu Baike, 2026).

The isolation and chemical characterization of matrine as the primary alkaloidal constituent of *Sophora flavescens* represents a significant milestone in the modern scientific investigation of this traditional herb (Fig. 2). Matrine was first isolated and identified in the early twentieth century, and its molecular structure was subsequently elucidated as a tetracyclic quinolizidine alkaloid with the molecular formula $C_{15}H_{24}N_2O$ and a molecular weight of 248.36 g/mol (Baidu Baike, 2026; Fig. 2). The compound is also known by alternative names including sophocarpidine and matridin-15-one.

The discovery of matrine as a bioactive compound has since spurred extensive research into its pharmacological properties and therapeutic applications. In China, matrine has been developed into pharmaceutical preparations, including injections and oral formulations, for the treatment of viral hepatitis and liver diseases (Liu et al., 2003). The historical use of matrine-containing preparations in clinical settings, particularly for liver protection and antiviral therapy, has provided a foundation for subsequent systematic evaluations of its efficacy and safety (Feng et al., 2024).

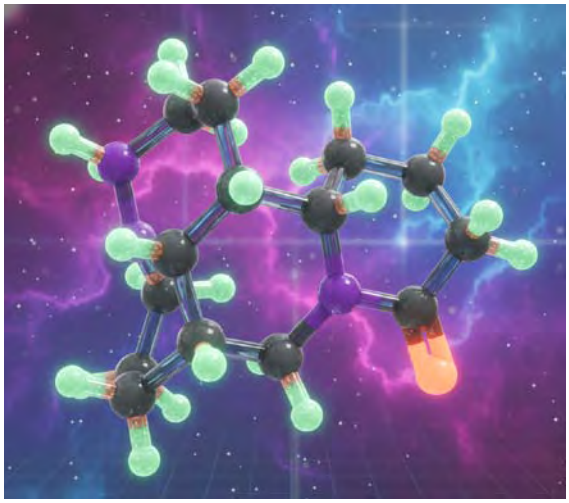

Fig. 2 Matrine molecule.

3 Physicochemical Properties and Natural Sources

3.1 Chemical Structure

Matrine belongs to the class of quinolizidine alkaloids and possesses a unique tetracyclic ring system. Its chemical structure consists of two fused quinolizidine rings, forming a characteristic tetracyclic framework with a lactam functionality at the D-ring (Xiong and Pu, 2025). The molecular formula of matrine is $C_{15}H_{24}N_2O$ (Fig. 2), with an exact molecular weight of 248.36 g/mol (Plant Hormanes, 2019). The compound contains two nitrogen atoms and one oxygen atom, with the lactam carbonyl group contributing to its polarity and hydrogen-bonding capacity. The tetracyclic skeleton of matrine is relatively rigid, which influences its interactions with biological targets and its overall pharmacological profile (Qiu et al., 2024).

The stereochemistry of matrine is an important consideration for its biological activity. Matrine is a chiral molecule, and research on chiral matrine derivatives has revealed that differences in drug configuration can

lead to significant variations in therapeutic efficacy (Qiu et al., 2024). Since the thalidomide incident, research on chiral drugs has escalated immensely, and the investigation of chiral matrine derivatives represents an important direction for optimizing its pharmacological properties (Qiu et al., 2024).

3.2 Physicochemical Characteristics

Matrine is characterized by good water solubility, a property that distinguishes it from many other natural product alkaloids and contributes to its favorable pharmaceutical properties (Qiu et al., 2024). The compound is a white to off-white crystalline powder with a bitter taste, consistent with the traditional description of *Sophora flavescens* root. Matrine is stable under normal storage conditions and can be analyzed using various chromatographic techniques, with high-performance liquid chromatography (HPLC) being the most commonly employed method for its quantification and purity assessment (Liu et al., 2010).

The physicochemical properties of matrine have been systematically characterized. The compound exhibits good permeability across biological membranes, as demonstrated by studies using Caco-2 cell monolayers, which serve as an in vitro model of intestinal epithelial absorption (Bui et al., 2021). At a concentration of 10 μM, matrine was shown to have good permeability of 42.5×10^{-6} cm/s across t he Caco-2 cell monolayer, with the ratio of permeability from apical to basolateral versus basolateral to apical being approximately equal at both 1 and 10 μM concentrations, suggesting that passive diffusion is the primary mechanism of intestinal absorption (Bui et al., 2021).

3.3 Natural Sources

Matrine is primarily derived from plants belonging to the genus Sophora, which is part of the legume family (Fabaceae) (Baidu Baike, 2026). The most important commercial source of matrine is *Sophora flavescens* Aiton, the dried roots of which have been used in traditional Chinese medicine for centuries (Chen et al., 2024). Additional sources of matrine include *Sophora alopecuroides* L. and *Euchresta japonica* Benth. ex Oliv. (Yang et al., 2025). The content of matrine in these plant materials varies depending on factors such as geographical origin, growing conditions, harvest time, and processing methods, which has implications for quality control and standardization of matrine-containing products.

4 Extraction and Purification Methodologies

4.1 Conventional Extraction Methods

The extraction of matrine from plant materials typically involves the use of solvents such as ethanol, methanol, or aqueous acid solutions to solubilize the alkaloidal components. Traditional extraction methods include maceration, percolation, and reflux extraction, which are simple and cost-effective but may be time-consuming and relatively inefficient (He et al., 2024). The process of separating and purifying matrine poses challenges due to its low concentration and frequent presence in mixtures with other structurally similar alkaloids during raw extraction (He et al., 2024).

4.2 Advanced Extraction Technologies

Several advanced extraction technologies have been developed to improve the efficiency and selectivity of matrine extraction. Ultrasonic-assisted extraction has been shown to enhance the extraction yield of matrine while reducing extraction time and solvent consumption (He et al., 2024). After optimization by response surface methodology, the extraction yield of matrine was found to be 2.03%, substantially higher than the yield obtained through traditional extraction methods (Cao et al., 2018).

Reverse micellar extraction represents another innovative approach for matrine isolation. Using reverse micelles of a non-ionic trialkyl phosphine oxide (TRPO) surfactant, the extraction of matrine can be achieved with high selectivity (Zhou et al., 2007). Theoretical analysis and experimental results showed that the driving forces for the extraction are the coordination forces between matrine and TRPO molecules. Under optimum

operating conditions determined by orthogonal experiments, the yield of matrine from raw matrine solution can reach 70%, with purity exceeding 90%.

4.3 Green Extraction Approaches

In response to growing environmental concerns, green extraction methods have been developed for matrine isolation. Deep eutectic solvents (DESs) have been employed as eco-friendly extraction solvents for the selective extraction of oxymatrine and matrine from *Sophora flavescens* Aiton root (Kang et al., 2021). The highest matrine extraction yields (1.53 mg·g^{-1}) were obtained using DES -8 comprising choline chloride and ethylene glycol in a 1:2 molar ratio with 30% water as the extraction solvent (Kang et al., 2021). This DES-based extraction method followed by magnetic molecularly imprinted polymer (MMIP) secondary enrichment has proven to be an effective approach for the selective extraction of specific components from complex plant samples, with extraction efficiencies for matrine ranging from 85.33% to 95.28% (Kang et al., 2021).

4.4 Purification and Separation

Following extraction, matrine requires purification to remove co-extracted compounds and achieve the desired purity for pharmaceutical applications. Macroporous adsorption resin chromatography is widely used for the purification of matrine from crude extracts (Cao et al., 2018). Among various resins evaluated, SP825 demonstrated the highest adsorption capacity for matrine (Gao et al., 2019). The use of sulfonated cellulose nanocrystals/sodium alginate (SCNCs/SA) beads has been investigated as an adsorbent for the efficient separation and purification of matrine from plant materials (He et al., 2024). The equilibrium adsorption capacity of SCNCs/SA beads for matrine at 298 K was approximately 55.66 mg/g, with 95% of the adsorption equilibrium achieved within 60 minutes, and approximately 20 bed volumes of 80% ethanol aqueous solution were required for effective recovery (He et al., 2024). The adsorption process was determined to be spontaneous, exothermic, and primarily driven by physisorption (He et al., 2024).

Graphene oxide membranes have also been explored for the selective separation of structurally similar alkaloids, particularly for distinguishing between matrine and its N-oxide derivative oxymatrine, which coexist in *Sophora flavescens* and have similar structures but different clinical applications. This technology provides new insight into the membrane-based separation of isomeric alkaloids.

5 Pharmacokinetics

5.1 Absorption and Bioavailability

The pharmacokinetic profile of matrine has been characterized in preclinical studies, revealing important insights into its absorption, distribution, metabolism, and excretion characteristics. A sensitive and robust UPLC-MS/MS method was developed to analyze matrine and investigate its biopharmaceutical and pharmacokinetic behaviors in rats (Bui et al., 2021). The absolute oral bioavailability of matrine was determined to be 17.1% ± 5.4% at a dose of 2 mg/kg, indicating that a substantial portion of orally administered matrine does not reach the systemic circulation (Bui et al., 2021).

The intestinal absorption of matrine shows regional differences. Perfusion studies revealed significant differences in permeability across different intestinal regions, with the rank order of permeability being ileum (highest, Pw = 6.18), followed by colon (Pw = 2.07), duodenum (Pw = 0.61), and jejunum (Pw = 0.52) (Bui et al., 2021). These findings suggest that the ileum is the primary site of matrine absorption, which has implications for the design of oral formulations.

5.2 Metabolism

The metabolic fate of matrine has been investigated using rat liver microsome studies. Interestingly, cytochrome P450 (CYP) enzymes and UDP-glucuronosyltransferases (UGTs) were not found to be involved in

matrine metabolism (Bui et al., 2021). This finding suggests that matrine is relatively resistant to phase I and phase II metabolic transformations, which may contribute to its relatively long half-life despite its low oral bioavailability.

The physiologically based pharmacokinetics of matrine has been characterized in rats after oral administration of pure chemical and ACAPHA, a botanical drug formulation (Gao and Law, 2009). The results showed that pure matrine is absorbed and eliminated by rats at faster rates than crude matrine, and that the ACAPHA matrix may change the pharmacokinetics of matrine significantly (Gao and Law, 2009). This finding highlights the importance of considering formulation effects when interpreting pharmacokinetic data and when developing matrine-containing pharmaceutical products.

5.3 Distribution and Elimination

Matrine has been shown to cross the blood-brain barrier, a property that underlies its neuroprotective and central nervous system effects (Chhabra and Mehan, 2023). The ability of matrine to penetrate the blood-brain barrier allows it to exert direct effects on neuronal tissues, which has implications for its potential use in the treatment of neurodegenerative disorders such as Alzheimer‘s disease, Parkinson’s disease, and multiple sclerosis (Chhabra and Mehan, 2023).

6 Pharmacological Activities and Mechanisms

From the perspective of biological networks, matrine serves as a regulatory and controlling factor in the human biological network of self-organization (Zhang, 2016b, 2018, 2026, 2027a-c). Fig. 3 illustrates the metabolic and signaling pathway regulation of matrine.

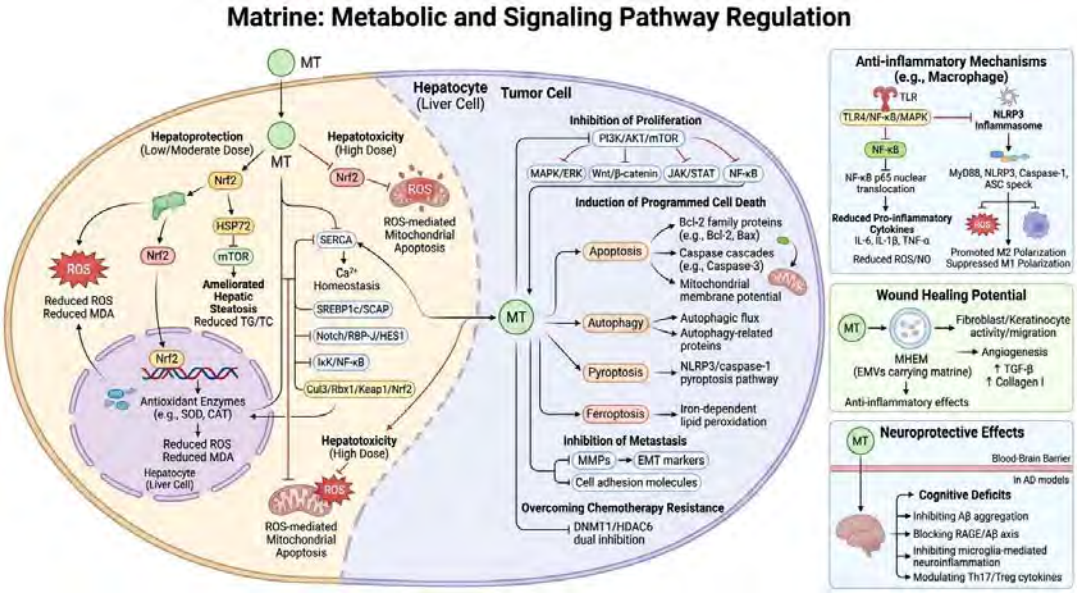

Fig. 3 Metabolic and signaling pathway regulation of matrine.

6.1 Antitumor Effects and Mechanisms

The antitumor activity of matrine has been extensively investigated across multiple cancer types, and a growing body of evidence supports its potential as a chemotherapeutic and chemopreventive agent (Meng et al., 2025; Xiong and Pu, 2025; Yang et al., 2025).

6.1.1 Regulation of Oncogenic Signaling Pathways

Matrine and its derivatives function as multi-target natural alkaloids that exhibit synergistic antitumor effects through the regulation of core oncogenic pathways (Xiong and Pu, 2025). These compounds inhibit tumor proliferation by suppressing epithelial-mesenchymal transition (EMT), inducing programmed cell death, and remodeling the tumor immune microenvironment (Xiong and Pu, 2025). The key signaling pathways targeted by matrine include Wnt/β-catenin, MAPK/ERK, and PI3K/AKT/mTOR (Xiong and Pu, 2025; Yang et al., 2025).

The PI3K/Akt signaling pathway is a central regulator of cell survival, proliferation, and metabolism that is frequently dysregulated in cancer (Huang and Zhang, 2012; Li and Zhang, 2013; Zhang, 2016a, 2017c). Matrine has been shown to inhibit this pathway, thereby suppressing tumor cell growth and promoting apoptosis (Yang et al., 2025). Similarly, the JAK/STAT pathway, which mediates signaling from cytokines and growth factors (Huang and Zhang, 2012; Li and Zhang, 2013; Zhang, 2016a, 2017c), is modulated by matrine treatment, contributing to its antiproliferative effects (Yang et al., 2025). The NF-κB pathway, a master regulator of inflammation and cell survival (Huang and Zhang, 2012; Li and Zhang, 2013; Zhang, 2016a, 2017c), is also inhibited by matrine in various cancer cell models (Yang et al., 2025).

6.1.2 Induction of Programmed Cell Death

Matrine induces multiple forms of programmed cell death in tumor cells, including apoptosis, autophagy, pyroptosis, and ferroptosis (Meng et al., 2025; Xiong and Pu, 2025). The induction of apoptosis by matrine involves the regulation of Bcl-2 family proteins, activation of caspase cascades, and modulation of mitochondrial membrane potential (Meng et al., 2025). In colorectal cancer cells, matrine inhibited tumor growth and induced apoptosis through effects on Bcl-2, Bax, and caspase-3 (Gu et al., 2018). The compound also arrested colorectal cancer cells in the G1 phase of the cell cycle (Gu et al., 2018).

Autophagy, another form of programmed cell death, is also induced by matrine in various cancer cell types. The induction of autophagy by matrine involves the activation of autophagic flux and the upregulation of autophagy-related proteins (Meng et al., 2025). Ferroptosis, a newly recognized form of regulated cell death characterized by iron-dependent lipid peroxidation, has recently been identified as a mechanism through which matrine exerts its antitumor effects (Meng et al., 2025; Xiong and Pu, 2025).

6.1.3 Inhibition of Tumor Metastasis

In addition to suppressing primary tumor growth, matrine inhibits tumor cell migration and invasion, thereby attenuating metastatic progression (Yang et al., 2025; Meng et al., 2025). This antimetastatic activity is mediated through the modulation of matrix metalloproteinases (MMPs), epithelial-mesenchymal transition (EMT) markers, and cell adhesion molecules (Yang et al., 2025). The inhibition of tumor cell migration and invasion by matrine has been demonstrated in multiple cancer cell lines, including breast cancer, lung cancer, and osteosarcoma models (Meng et al., 2025).

6.1.4 Breast Cancer Subtype-Specific Effects

Breast cancer is characterized by high heterogeneity across molecular subtypes, and the response to matrine treatment has been shown to vary depending on the specific subtype (Yang et al., 2025). Yang et al. (2025) systematically examined subtype-specific responses to matrine treatment, highlighting its potential utility in precision oncology for distinct breast cancer classifications. Matrine has also demonstrated the capacity to synergize with standard chemotherapeutic regimens, potentially overcoming drug resistance while reducing required dosages (Yang et al., 2025).

6.1.5 Overcoming Chemotherapy Resistance

One of the most significant challenges in cancer treatment is the development of resistance to chemotherapeutic agents. Matrine has been shown to overcome chemotherapy resistance in various cancer

models, including pancreatic and liver cancer patient-derived xenograft (PDX) models (Xiong and Pu, 2025). Third-generation derivatives such as MT-26 and YF-18 have demonstrated enhanced therapeutic efficacy by targeting DNMT1/HDAC6 dual inhibition and activating the NLRP3/caspase-1 pyroptosis pathway, achieving tumor suppression rates of 60–78% in these models (Xiong and Pu, 2025).

6.1.6 Preclinical to Clinical Translation Challenges

Despite the promising preclinical evidence for matrine‘s antitumor activity, translation to clinical application faces several challenges. These include low bioavailability, off-target toxicity (particularly hepatotoxicity via JNK/c-Jun activation), and tumor heterogeneity-driven resistance mechanisms such as SLC7A11-mediated ferroptosis evasion (Xiong and Pu, 2025). Notably, no Phase I/II clinical trials for matrine or its derivatives in cancer therapy have been registered to date, highlighting the significant gap between preclinical research and clinical development (Xiong and Pu, 2025).

6.2 Anti-inflammatory Effects and Mechanisms

Inflammation is a fundamental pathological process involved in numerous diseases, and the anti-inflammatory properties of matrine have been extensively characterized in both in vitro and in vivo models.

6.2.1 TLR4/NF-κB/MAPK Pathway Regulation

The primary mechanism through which matrine exerts its anti-inflammatory effects involves the suppression of the Toll-like receptor 4 (TLR4)/nuclear factor-κB (NF-κB)/mitogen-activated protein kinase (MAPK) signaling pathway (Mao et al., 2024). In LPS-induced RAW 264.7 macrophages, matrine inhibited the production of inflammatory cytokines, suppressed macrophage M1 polarization, and promoted M2 macrophage polarization (Mao et al., 2024). Matrine also reduced LPS-induced increases in reactive oxygen species (ROS) and nitric oxide (NO) levels, indicating its ability to regulate oxidative stress associated with inflammatory responses (Mao et al., 2024).

The anti-inflammatory mechanism of matrine involves the inhibition of NF-κB p65 subunit nuclear translocation (Mao et al., 2024). By preventing the translocation of NF-κB from the cytoplasm to the nucleus, matrine suppresses the transcription of pro-inflammatory genes, including those encoding interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) (Mao et al., 2024).

6.2.2 NLRP3 Inflammasome Inhibition

The NLRP3 inflammasome is a critical mediator of inflammatory responses, and its dysregulation is implicated in various inflammatory diseases. Matrine has been shown to inhibit IL-1β secretion in primary porcine alveolar macrophages through the MyD88/NF-κB pathway and NLRP3 inflammasome (Sun et al., 2019). Matrine treatment downregulates MyD88, NLRP3, and caspase-1 expression, inhibits ASC speck formation, suppresses IκBα phosphorylation, and interferes with the translocation of NF-κB from the cytoplasm to the nucleus (Sun et al., 2019).

6.2.3 Pulmonary Inflammation and Vascular Remodeling

Hypoxia-induced vasoconstriction and vascular remodeling are the main pathological features of hypoxic pulmonary arterial hypertension (HPAH), and inflammation participates in the occurrence of pulmonary vascular remodeling (Li et al., 2024). Matrine alleviates hypoxia-induced inflammation and pulmonary vascular remodeling via the RPS5/NF-κB signaling pathway (Li et al., 2024). Matrine treatment reversed hypoxia-induced changes, including the reduction of ribosomal protein S5 expression and activation of NF-κB signaling, and improved hypoxia-induced pulmonary vascular remodeling by reversing the imbalance of proliferation and apoptosis of pulmonary artery smooth muscle cells (PASMCs) (Li et al., 2024).

6.2.4 Atopic Dermatitis and Skin Inflammation

Matrine has been shown to regulate Th1/Th2 inflammatory responses by inhibiting the Hsp90/NF-κB signaling axis to alleviate atopic dermatitis (Huang et al., 2023). Matrine inhibited the secretion of pro-inflammatory

cytokines including IL-4, IL-5, IL-13, and IL-6 by repressing the Hsp90/NF-κB signaling axis in inflamed HaCaT cells (Huang et al., 2023). By regulating the Th1/Th2 inflammatory response, matrine may represent a candidate for atopic dermatitis treatment (Huang et al., 2023).

6.2.5 Intestinal Inflammation

In an LPS-induced mouse model of intestinal inflammation, matrine significantly alleviated LPS-induced diarrhea, increased disease activity index, and shortened colon length (Mao et al., 2024). Matrine reduced the production of pro-inflammatory cytokines IL-6, IL-1β, and TNF-α and the pro-inflammatory mediator NO in mouse intestinal tissues while promoting the content of the anti-inflammatory cytokine IL-10 (Mao et al., 2024). Furthermore, matrine improved intestinal tissue structure, alleviated LPS-induced intestinal barrier damage, and increased short-chain fatty acid levels in the intestine (Mao et al., 2024).

6.3 Hepatoprotective Effects and Mechanisms

The liver is a major target organ for the pharmacological actions of matrine, which has been used clinically in China for the treatment of viral hepatitis and other liver diseases. However, the relationship between matrine and the liver is complex, as the compound exhibits bidirectional effects depending on dose and duration of treatment.

6.3.1 Protection Against Nonalcoholic Fatty Liver Disease

Matrine has demonstrated protective effects against nonalcoholic fatty liver disease (NAFLD; Zhang and Feng, 2017) and ameliorated hepatic steatosis by activating the Nrf2 signaling pathway (ScienceDirect, 2026). Matrine promotes Nrf2 translocation to the nucleus and upregulates the expression of antioxidant enzyme proteins. In high-fructose diet (HFD)-induced mice, matrine reduced glucose intolerance, plasma insulin levels, and liver triglyceride content, thereby inhibiting lipid synthesis, increasing fatty acid oxidation, and ameliorating hepatic steatosis. The protective effect was attributed to the activation of HSP72 in the liver (ScienceDirect, 2026).

The anti-nonalcoholic steatohepatitis (NASH) effect of matrine is associated with the upregulation of HSP72 and downregulation of mTOR (ScienceDirect, 2026). Matrine also improves endoplasmic reticulum stress state, mediates lipid metabolism disorder, mitochondrial dysfunction, and inflammatory reactions in mice, with the mechanism of action possibly related to the inhibition of SERCA (sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase) and its influence on Ca^{2+} homeostasis (Gao et al., 2018; ScienceDirect, 2026).

6.3.2 Anti-fibrotic Effects

Matrine has demonstrated significant effects on liver fibrosis. Matrine reduces TGF-β1 and enhances the activity of hepatocyte growth factor (HGF) at a dose of 100 mg/kg for liver fibrosis prevention (ScienceDirect, 2026). The mechanism involves preventing Gr1hi monocyte infiltration into the injured livers, as well as inhibiting monocyte chemoattractant protein-1 (MCP-1) production and activity (Tao et al., 2025; ScienceDirect, 2026). Matrine derivatives have also been investigated for their anti-fibrotic properties; for instance, WM130, a novel matrine derivative, significantly inhibits the activation of hepatic stellate cells (HSC-T6) and rat liver fibrosis by inhibiting the TGF-β/Smad and Ras/ERK signaling pathways (Yang et al., 2015; ScienceDirect, 2026).

6.3.3 Bidirectional Effects on the Liver

A systematic review and meta-analysis encompassing 24 studies involving 657 rodents comprehensively evaluated both the hepatoprotective and hepatotoxic effects of matrine (Feng et al., 2024). The results demonstrated that matrine has bidirectional effects on alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and it also regulates superoxide dismutase (SOD), malondialdehyde (MDA), serum triglycerides (TG), serum total cholesterol (TC), IL-6, TNF-α, and catalase (CAT) levels (Feng et al., 2024).

Based on comprehensive three-dimensional analysis, the optimal bidirectional effective dosage of matrine ranges from 10 to 69.1 mg/kg (Feng et al., 2024). At a dose of 20–30 mg/kg/day for 0.02–0.86 weeks, matrine demonstrated high liver protection and low toxicity (Feng et al., 2024). Molecular docking analysis revealed the interaction between matrine and SERCA as well as SREBP-SCAP complexes (Feng et al., 2024). Matrine can alter Ca^{2+} homeostasis in liver injury via multiple pathways, including the SREBP1c/SCAP, Notch/RBP-J/HES1, IκK/NF-κB, and Cul3/Rbx1/Keap1/Nrf2 pathways (Feng et al., 2024).

The conclusion of this meta-analysis is that matrine has bidirectional effects on the liver at doses ranging from 10 to 69.1 mg/kg by influencing Ca^{2+} homeostasis in the cytoplasm, endoplasmic reticulum, Golgi apparatus, and mitochondria (Feng et al., 2024). However, reports on the toxic effects of matrine have increased in recent years, with some studies showing that matrine can induce hepatotoxicity by inhibiting the Nrf2 pathway and activating ROS-mediated mitochondrial apoptosis pathway (ScienceDirect, 2026).

6.4 Wound Healing Effects and Mechanisms

Chronic skin wounds represent a significant clinical challenge, particularly among the elderly and individuals with diabetes. The wound healing potential of matrine has recently gained attention, with several studies demonstrating its ability to promote tissue repair and regeneration.

6.4.1 Exosome-Mimetic Vesicle Delivery System

A novel approach for delivering matrine to wounds involves the use of fibroblast-derived exosome-mimetic vesicles as carriers (EMVs carrying matrine, designated MHEM) (Zhang et al., 2024). Both matrine and MHEM enhanced cellular activity and migration of fibroblasts and keratinocytes, two cell types essential for wound healing (Zhang et al., 2024). The potent anti-inflammatory effect of matrine diluted the inflammatory response in the vicinity of wounds, while MHEM worked synergistically to promote angiogenesis and the expression of transforming growth factor β (TGF-β) and collagen I (Zhang et al., 2024).

MHEM contained growth factors from fibroblasts that regulated the functions of fibroblasts, keratinocytes, and monocytes, which synergistically promoted wound healing with the anti-inflammatory effect of matrine (Zhang et al., 2024). MHEM showed enhanced therapeutic efficacy in the inflammatory microenvironment, promoting new tissue formation and angiogenesis during wound healing (Zhang et al., 2024).

6.4.2 Self-Assembled Nanoparticles

Carrier-free self-assembly has emerged as a promising strategy for improving the bioavailability and drug-loading rate of natural products (Wu et al., 2024). A nano-delivery system fabricated through the direct self-assembly of Rhein and matrine (RM NPs) was characterized and evaluated for wound healing applications (Wu et al., 2024). The morphology of RM NPs was spherical with an average size of approximately 75 nm (Wu et al., 2024). Molecular dynamics simulation analysis predicted the self-assembly behavior, and an in vivo skin wound-healing model demonstrated that RM NPs present better protective effects against skin damage compared to free drugs (Wu et al., 2024).

6.4.3 Mechanism of Skin Protection

Matrine has been shown to protect against skin damage induced by ultraviolet exposure in rats, with the mechanism related to the inhibition of CYR61, NF-κB, and AP-1 mRNA and protein expression in the skin after UVB exposure, thereby inhibiting the activation of the CYR61/NF-κB/AP-1 pathway (Li et al., 2024). This pathway inhibition reduces inflammation and oxidative stress in UV-exposed skin, contributing to the protective effects of matrine.

6.5 Neuroprotective Effects

Matrine has demonstrated neuroprotective effects in various models of neurological disorders, including Alzheimer‘s disease, Parkinson’s disease, multiple sclerosis, and cerebral ischemia-reperfusion injury (Chhabra and Mehan, 2023). Numerous studies have demonstrated that matrine protects neurons by altering

multiple signaling pathways and crossing the blood-brain barrier (Chhabra and Mehan, 2023).

In Alzheimer‘s disease models, matrine has been identified as a novel multi-target natural drug candidate that improves cognitive deficits in transgenic mice by inhibiting Aβ aggregation and blocking the RAGE/Aβ axis (Cui et al., 2017). Matrine could inhibit Aβ42-induced cytotoxicity and suppress the Aβ/RAGE signaling pathway in vitro, and these findings were consistent with in vivo evaluations (Cui et al., 2017). Furthermore, matrine reduced proinflammatory cytokines and Aβ deposition and attenuated the memory deficits of AD transgenic mice (Cui et al., 2017). Matrine also ameliorates cognitive deficits via inhibition of microglia-mediated neuroinflammation in AD mouse models (Li et al., 2020).

In a rat model of Aβ -induced Alzheimer‘s disease, matrine improved cognitive impairment and modulated the balance of Th17/Treg cytokines (Zhang et al., 2015). Matrine also alleviates neurobehavioral alterations via modulation of JNK-mediated caspase-3 and BDNF/VEGF signaling in a mouse model of burn injury (Khan et al., 2020).

7 Structural Modification and Derivatives

The chemical modification of matrine represents a promising strategy for improving its pharmacological properties, enhancing its therapeutic efficacy, and reducing its toxicity. Several research groups have synthesized novel matrine derivatives and evaluated their biological activities.

7.1 Anticancer Derivatives

A study designed and synthesized a novel chiral matrine derivative and assessed its cytotoxicity against three types of tumor cells (Qiu et al., 2024). Comparing the newly synthesized derivatives to the parent matrine, most compounds exhibited significantly enhanced inhibitory effects on cancer cells (Qiu et al., 2024). Among them, compound Q12 exhibited the highest activity, with IC_{50} values of 8.31 μM against rat glioma cells C6, 6.3 μM against human liver cancer cells HepG2, and 7.14 μM against human gastric cancer cells HGC-27, while showing low toxicity (Qiu et al., 2024). Compound Q12 significantly suppressed the cloning and migration of HepG2 cells, and further mechanistic studies indicated that Q12 inhibited Topo I in HepG2 cells, leading to DNA damage, induction of G0/G1 cell cycle arrest, and ultimately causing apoptosis (Qiu et al., 2024). Molecular docking experiments provided a rational binding mode of Q12 with the Topo I-DNA complex, and in vivo experiments demonstrated that Q12 exhibited a higher tumor growth inhibition rate compared to the positive control drug Lenvatinib while maintaining good safety (Qiu et al., 2024).

Another study synthesized 27 matrine derivatives by incorporating indole structures with known antitumor activity (Wang et al., 2025). The antiproliferative effects of these derivatives were evaluated against human cancer cell lines, and several derivatives showed enhanced activity compared to the parent compound (Wang et al., 2025). These derivatives demonstrated the characteristics of endoplasmic reticulum stress induction and apoptosis activation (Wang et al., 2025).

7.2 Hsp90 Inhibitor Derivatives

A new modification strategy for matrine as Hsp90 inhibitors based on its specific L-conformation has been proposed for cancer treatment (Xu et al., 2020). This targeted design approach may represent an effective strategy for discovering anticancer candidates among matrine derivatives (Xu et al., 2020).

7.3 Structure-Activity Relationships

Based on IC_{50} values of various derivatives, a preliminary structure -activity relationship (SAR) has been constructed (Qiu et al., 2024). Understanding the SAR of matrine derivatives is essential for guiding further optimization efforts and for identifying the most promising candidates for clinical development.

8 Nano-Delivery Systems

The low oral bioavailability and short half-life of matrine in vivo present significant challenges for its clinical application (You et al., 2020). In response, various nano-delivery systems have been developed to improve the biopharmaceutical properties of matrine.

8.1 Antitumor Nano-Delivery Strategies

A comprehensive review has discussed and analyzed the antitumor mechanisms of matrine and its application in nano-delivery systems, highlighting their progress and potential in major disease intervention strategies (Meng et al., 2025). The integration of natural products into cancer therapy has gained renewed significance in the context of innovative delivery systems (Meng et al., 2025).

8.2 Types of Nano-Delivery Systems

Recent advances in matrine-loaded nanocarriers have been summarized, highlighting their design, functionality, and applications in biomedicine (Wang et al., 2026). These systems offer several advantages over conventional formulations, such as improved solubility, controlled release, enhanced stability, and targeted delivery to specific tissues or cells (Wang et al., 2026).

Self-assembled matrine-PROTAC encapsulating zinc(II) phthalocyanine with GSH-depletion-enhanced ROS generation has been developed for cancer therapy (Lai et al., 2024). This system degrades p-Erk and p-Akt proteins, and the nanoparticles formed via self-assembly exhibit stronger anti-tumor activity and glutathione depletion ability, enabling enrichment in lysosomes through the enhanced permeability and retention (EPR) effect (Lai et al., 2024).

8.3 Future Directions for Delivery Systems

Future research priorities for matrine delivery systems should include the development of intelligent delivery systems such as DNA origami nanorobots and magnetically guided micro/nano-swimmers (Xiong and Pu, 2025). Multi-omics-driven precision strategies, including spatial metabolomics and single-cell epi-drugomics, as well as synthetic biology platforms such as PROTAC bifunctional molecules and AI-assisted crystal screening, represent exciting directions for future research (Xiong and Pu, 2025). Integrating organ-on-chip technologies and real-world data analytics will accelerate the transformation of matrine-based compounds into next-generation intelligent anticancer agents (Xiong and Pu, 2025).

9 Clinical Trials and Applications

9.1 Chronic Hepatitis B

The most extensively studied clinical application of matrine is in the treatment of chronic hepatitis B (CHB). A systematic review of 22 randomized trials involving 2,409 patients evaluated the effects of Sophorae flavescentis extract (matrine) for CHB (Liu et al., 2003). The combined results showed that matrine had antiviral activity, positive liver biochemical effects, and improved symptoms and signs compared with non-specific treatment and other herbal medicines (Liu et al., 2003). The combination of matrine and interferon-alpha, thymosin, or basic treatment showed better effects on viral and liver biochemical responses, and the antiviral and biochemical responses were not significantly different between matrine and interferon-alpha alone (Liu et al., 2003). No serious adverse events were reported (Liu et al., 2003). However, the methodological quality of the trials was generally low, and the evidence was not sufficient to recommend matrine for routine clinical use, indicating the need for further rigorous trials (Liu et al., 2003).

A randomized clinical trial involving 120 patients with chronic hepatitis B demonstrated that intramuscular matrine (100 mg daily for 90 days) significantly improved clinical symptoms and signs, liver functions, and serum conversion from hepatitis Be antigen to HBe antibody and from positive to negative serum HBV DNA compared to control (Long et al., 2004). Serious side-effects were not observed except mild pain at the

injection site in a few patients, leading the authors to conclude that intramuscular matrine may be an economical, efficacious, and safe drug for the treatment of chronic hepatitis B (Long et al., 2004).

A systematic review and meta-analysis of nine studies involving 1,089 participants evaluated the clinical efficacy and adverse effects of interferon combined with matrine for chronic hepatitis B (Wang et al., 2017). Compared with interferon monotherapy, the combination of interferon 5 MU with matrine 150 mg augmented hepatitis B e-antigen negative conversion rate after 3-month treatment (RR = 1.41; 95% CI: 1.18, 1.69) and after 12-month treatment (RR = 1.96; 95% CI: 1.21, 3.19), as well as HBV DNA negative conversion rates (Wang et al., 2017). Combination therapy also reduced the risk of leucopenia and thrombocytopenia (RR = 0.55; 95% CI: 0.36, 0.85) (Wang et al., 2017). The authors concluded that combination therapy with interferon plus matrine exhibited better clinical efficacy and fewer adverse effects than interferon monotherapy, except in the improvement of HBsAg negative conversion rate and influenza-like symptoms (Wang et al., 2017). However, given the poor methodological quality of the evidence currently available, future high-quality, three-blinded randomized control trials are necessary to confirm these results (Wang et al., 2017).

A pediatric clinical trial involving 95 children with chronic hepatitis B examined the effects of intravenous matrine (50–150 mg depending on age) followed by oral capsules (Xi, 2010). While the study design had several limitations, including lack of blinding and incomplete outcome reporting, it provided preliminary evidence of matrine‘s effects in the pediatric population (Xi, 2010).

9.2 Liver Cirrhosis

Matrine has also been investigated for the treatment of liver cirrhosis. A study on the effect of matrine on sex hormone levels, metal ion content, and soluble tumor necrosis factor receptor in male patients with liver cirrhosis concluded that matrine adjuvant therapy could regulate sex hormone and metal ion levels, reduce soluble tumor necrosis factor receptor levels, and improve liver function in patients with cirrhosis. Another study demonstrated that matrine could reduce TGF-β1 in decompensated patients with hepatitis B virus cirrhosis, reduce the load of HBV-DNA, play an important role in antiviral and anti-hepatic fibrosis effects, and benefit the recovery of liver function (Zhang and Ke, 2017). Compound Matrine Injection has also shown clinical efficacy in patients with hepatitis C cirrhosis, with the mechanism possibly related to the influence of peripheral mononuclear cell IL-10 and regulation of the body‘s inflammatory response.

9.3 Primary Liver Cancer

A randomized and multicenter clinical trial evaluated compound matrine injection combined with hepatic artery interventional therapy in the treatment of primary liver cancer (Yan et al., 2013). The combination therapy could relieve pain, improve liver function and traditional Chinese medicine symptoms, and enhance patients’ quality of life effectively and safely (Yan et al., 2013). Matrine injection has also been used to protect liver function for patients with primary hepatic carcinoma after trans-arterial chemoembolization (TAE), to relieve liver cell damage, and to improve tolerance of TAE, enabling timely performance of subsequent TAE procedures (Lao, 2005).

9.4 Trichomonal Vaginitis

A systematic review and meta-analysis evaluated the efficacy and safety of matrine alkaloid preparation in combination with nitroimidazoles in the treatment of trichomonal vaginitis (Bao et al., 2022). The results indicated that the combination regimen improved the overall rate of clinical effectiveness for both drug-resistant and non-resistant trichomonal vaginitis (Bao et al., 2022).

10 Quality Control and Standards

Ensuring the quality and consistency of matrine-containing products is essential for both research and clinical applications. High-performance liquid chromatography (HPLC) is the “gold standard” for matrine detection,

particularly for quantitative analysis in complex matrices (Beijing Research Institute of Chemical Industry, 2025). Using a C18 column with acetonitrile-phosphate buffer as the mobile phase, UV detection at 220 nm provides good sensitivity with a detection limit of 0.1 μg/mL (Beijing Research Institute of Chemical Industry, 2025).

HPLC methods have been established for the determination of matrine in various formulations, including Xuanlijing Liniment, Fufang Shen'an granules, Fuyanling soaking tablets, and Mongolian medicine Ganlekang capsules (Liu et al., 2010; Bao et al., 2014). The linear range for matrine detection by HPLC is typically 5–100 μg/mL with $R^2 = 0.9999$ (Tian et al., 2006).

Ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) has been developed for the determination of matrine residues in various matrices, including Liupao tea, with isotope internal standard methods providing enhanced accuracy and precision (Shi et al., 2024). The dosage of matrine is essential in the formulation of products based on plant extracts, the standardization of food supplements, as well as in the quality control of biopesticides of natural origin.

11 Safety Evaluation and Toxicity

While matrine is generally considered to have a favorable safety profile, an increasing number of published studies indicate that matrine has serious adverse effects, with the most obvious being liver toxicity and neurotoxicity, which are major factors limiting its clinical use (You et al., 2020).

11.1 Hepatotoxicity

The bidirectional effects of matrine on the liver have been systematically characterized (Feng et al., 2024). While low to moderate doses of matrine exert hepatoprotective effects, higher doses can induce hepatotoxicity. The mechanism of matrine-induced hepatotoxicity involves the inhibition of the Nrf2 pathway and activation of ROS-mediated mitochondrial apoptosis pathway (ScienceDirect, 2026). The interaction between matrine and SERCA as well as SREBP-SCAP complexes plays a role in both the protective and toxic effects of matrine on the liver (Feng et al., 2024).

11.2 Neurotoxicity

Neurotoxicity is another major concern associated with matrine use, particularly at higher doses or with prolonged administration (You et al., 2020). The neurotoxic effects of matrine limit its clinical application and necessitate careful dose optimization (You et al., 2020).

11.3 Dose Optimization for Safety

In future applications, controlling the dosage of matrine is an effective way to reduce its toxic and side effects, thereby ensuring its safety and efficacy (Gao et al., 2019). The optimal bidirectional effective dosage of matrine ranges from 10 to 69.1 mg/kg, with the highest safety profile observed at 20–30 mg/kg/day for short durations (Feng et al., 2024).

12 Research Perspectives and Future Directions

Despite the substantial progress made in understanding the pharmacology of matrine, several challenges and opportunities remain for future research.

12.1 Clinical Translation

The translation of matrine from preclinical research to clinical application faces significant hurdles. The low oral bioavailability of matrine (17.1% ± 5.4%) limits its efficacy when administered orally, necessitating the development of improved formulations (Bui et al., 2021). The lack of registered Phase I/II clinical trials for matrine or its derivatives in cancer therapy represents a major gap that must be addressed through well-designed clinical studies (Xiong and Pu, 2025).

12.2 Advanced Delivery Systems

The development of intelligent delivery systems represents a promising direction for overcoming the pharmacokinetic limitations of matrine. DNA origami nanorobots, magnetically guided micro/nano-swimmers, and other advanced delivery platforms could enhance the targeted delivery of matrine to disease sites while minimizing off-target effects (Xiong and Pu, 2025).

12.3 Multi-Omics and Precision Medicine

The application of multi-omics approaches, including spatial metabolomics and single-cell epi-drugomics, could provide deeper insights into the mechanisms of action of matrine and facilitate the identification of patient populations most likely to benefit from matrine-based therapies (Xiong and Pu, 2025). Precision medicine strategies based on molecular biomarkers could optimize patient selection and treatment regimens.

12.4 Synthetic Biology Approaches

Synthetic biology platforms, including PROTAC (proteolysis-targeting chimera) bifunctional molecules and AI-assisted crystal screening, offer new opportunities for the development of matrine-based therapeutics with enhanced potency and selectivity (Xiong and Pu, 2025). These approaches could enable the rational design of matrine derivatives with improved pharmacological profiles.

12.5 Combination Therapies

The potential for matrine to be used in combination with conventional chemotherapeutic agents, immunotherapies, or other natural products warrants further investigation (Yang et al., 2025; Wang et al., 2017). Combination strategies could overcome drug resistance, reduce required dosages of toxic agents, and improve overall treatment outcomes.

12.6 Organ-on-Chip Technologies

The integration of organ-on-chip technologies and real-world data analytics could accelerate the transformation of matrine-based compounds into next-generation intelligent therapeutic agents (Xiong and Pu, 2025). These advanced models can better predict human responses and reduce the reliance on animal testing.

12.7 Neurodegenerative Disease Applications

The ability of matrine to cross the blood-brain barrier and exert neuroprotective effects suggests potential applications in the treatment of neurodegenerative diseases beyond Alzheimer‘s disease, including Parkinson’s disease and multiple sclerosis (Chhabra and Mehan, 2023). Further research is needed to explore these applications and to optimize dosing regimens for central nervous system indications.

12.8 Cardiovascular Applications

Matrine and oxymatrine have demonstrated cardioprotective effects through multiple mechanisms, including antioxidative stress, anti-inflammatory actions, anti-atherosclerosis, restoration of vascular function, and inhibition of cardiac remodeling and failure (Chen et al., 2024). The investigation of matrine in cardiovascular disease models represents a promising area for future research.

13 Conclusion

Matrine is a remarkable natural alkaloid with a rich history in traditional medicine and a growing body of evidence supporting its diverse pharmacological activities. The compound exhibits potent antitumor effects through the regulation of multiple oncogenic signaling pathways and the induction of various forms of programmed cell death. Its anti-inflammatory properties, mediated primarily through the suppression of TLR4/NF-κB/MAPK signaling and NLRP3 inflammasome activation, have been demonstrated in multiple disease models. The hepatoprotective effects of matrine are complex and dose-dependent, with the compound exhibiting bidirectional actions on the liver through Ca^{2} homeostasis regulation. Matrine also shows promise in promoting wound healing, protecting against neurodegenerative diseases, and treating cardiovascular

conditions.

Despite these promising findings, the clinical translation of matrine faces significant challenges, including low oral bioavailability, potential toxicity at higher doses, and a lack of high-quality clinical trials. Future research should focus on the development of advanced delivery systems, the synthesis of optimized derivatives, the conduct of rigorous clinical trials, and the application of multi-omics and precision medicine approaches. With continued research and development, matrine and its derivatives have the potential to emerge as valuable therapeutic agents for a wide range of diseases, offering new hope for patients in need of safe, effective, and affordable treatment options.

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