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REVIEW

Matrine in Liver Diseases: Mechanistic Insights and Therapeutic Potential

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Abstract: Matrine ($C_{15}H_{24}N_2O$), a quinolizidine alkaloid abundant in *Sophora flavescens* and other legumes, has attracted considerable attention in recent years due to its remarkable pharmacological effects against a range of liver diseases. Extensive research has demonstrated that matrine exhibits significant therapeutic potential in the prevention and treatment of various liver disorders, including liver injury of diverse etiologies, metabolic-associated fatty liver disease, liver fibrosis and hepatocellular carcinoma. This review integrates recent literature from CNKI, Web of Science, ScienceDirect and PubMed to summarize advances in the application of matrine for liver disease therapy. According to current data, the hepatoprotective effects of matrine involve multiple molecular mechanisms, such as inhibition of inflammatory responses, reduction of oxidative stress, alleviation of endoplasmic reticulum stress, improvement of insulin resistance, mitigation of lipid peroxidation, as well as suppression of hepatocellular carcinoma cell proliferation, invasion, and migration through induction of autophagy and apoptosis. Notably, several signaling pathways, including NF-κB, Nrf2, HSF1/PGC-1α, PI3K/AKT/mTOR, JAK2/STAT3, RhoA/ROCK and Mst1-JNK, have been identified as critical mediators of its hepatoprotective actions. Toxicological data indicate that excessive doses or prolonged exposure to matrine may induce multisystem toxicity, affecting the liver, kidneys, nervous system and gastrointestinal tract. Pharmacokinetic studies reveal that matrine undergoes rapid absorption, exhibits moderate oral bioavailability and is subject to relatively rapid metabolic clearance. Additionally, this review outlines the natural sources, physicochemical properties and current research challenges associated with matrine, aiming to provide a solid theoretical foundation and clinical translation in the treatment of liver diseases.

Keywords: liver diseases, matrine, hepatoprotection, mechanisms, toxicity, pharmacokinetics

Introduction

As the central metabolic organ of the body, the liver plays a pivotal role in essential physiological processes, including substance metabolism, detoxification, bile production and immune regulation.[1,2] It also serves as a crucial line of defense in maintaining the functional homeostasis of multiple organs. However, hepatic tissue is highly susceptible to progressive pathological changes under the persistent influence of endogenous and exogenous insults, such as alcohol, drugs, viral infections and lipotoxic metabolites.[3] These factors can trigger a cascade of pathological events ranging from steatosis and inflammatory necrosis to fibrosis and ultimately malignant transformation.[4] Currently, the global burden of liver diseases is increasing, driven by the rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), hepatocellular carcinoma (HCC) and various forms of end-stage liver dysfunction.[5,6] This escalating disease burden contrasts sharply with the limited efficacy of existing therapeutic options, which are often inadequate in halting disease progression or promoting hepatic regeneration and are frequently associated with significant adverse effects.[7,8] Therefore, there is an urgent need for the development of novel therapeutic strategies informed by a deeper understanding of liver disease pathogenesis. Ideally, such interventions should possess multi-target regulatory capabilities, high efficacy and low toxicity to better meet current clinical needs.

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In recent years, natural products have gained increasing attention as valuable resources in drug discovery, owing to their structural diversity, broad bioactivity and generally favorable safety profiles.[9–11] They offer unique advantages in the treatment of complex, multifactorial diseases and are regarded as promising candidates for novel therapeutic development.[12,13] Matrine, a tetracyclic quinolizidine alkaloid primarily derived from plants of the *Sophora* genus (Fabaceae), particularly *Sophora flavescens* Aiton, represents one such candidate.[14] This compound exhibits a broad range of biological activities, including anti-inflammatory, antioxidant, anti-fibrotic and anti-tumor effects, and has attracted considerable attention for its potential in liver diseases prevention and therapy.[15,16] Accumulating evidence indicates that matrine confers hepatoprotective effects through multiple mechanisms, including inhibition of inflammatory responses, reduction of oxidative and endoplasmic reticulum (ER) stress, improvement of insulin sensitivity, attenuation of lipid peroxidation, suppression of hepatic stellate cell (HSC) activation and extracellular matrix (ECM) remodeling, and induction of autophagy and apoptosis in HCC cells.[17–22] Notably, several signaling pathways, including nuclear factor erythroid 2-related factor 2 (Nrf2), heat shock factor 1 (HSF1)/peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), phosphatidylinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), Notch, mammalian sterile 20-like kinase 1 (Mst1)-c-Jun N-terminal kinase (JNK) and p53/AMP-activated protein kinase (AMPK), have been identified as key mediators of marine's hepatoprotective effects.[19,22–26]

Given the significant pharmacological activities of matrine in various liver diseases and its promising potential for clinical translation, this review provides a comprehensive summary of its mechanisms of action in various pathological contexts, including liver injury, MASLD, liver fibrosis and HCC. By systematically retrieving and integrating recent literature from major Chinese and international databases such as CNKI, Web of Science, ScienceDirect and PubMed, this review outlines the potential molecular mechanisms underlying the anti-inflammatory, antioxidant, antifibrotic and antitumor effects of matrine. Furthermore, the limitations of current research are critically analyzed, with emphasis placed on future directions, such as the in-depth elucidation of its mechanistic pathways, the development of novel drug delivery systems and comprehensive safety evaluations. This review aims to provide a robust theoretical foundation and research framework for the clinical application and precision therapy of matrine in liver-related diseases.

Biological Characteristics of Matrine

Matrine (Figure 1) is a quinoline alkaloid extracted from the dried roots of *Sophora flavescens* Aiton, a leguminous plant widely distributed in East Asia, including China, Japan and the Korean Peninsula.[27] It predominantly grows in mountainous regions, grasslands and forest edges.[27] According to the Shennong Bencao Jing, the medicinal use of *Sophora flavescens* Aiton in traditional Chinese medicine (TCM) dates back more than two millennia.[28] Its root bark, which is rich in matrine, is traditionally employed for its diuretic effects and in clearing heat and dampness, dispelling wind and expelling parasites.[28] In modern phytochemical practice, matrine is typically obtained by reflux extraction of powdered, dried roots in aqueous ethanol. This is followed by acid-base adjustment and purification via column chromatography to yield high-purity matrine. Studies have demonstrated that the plant's pharmacological activities are largely due to its alkaloid content.

Matrine typically appears as a white crystalline powder with well-defined physicochemical identifiers (CAS: 519–02-8; UNII: N390W430AC). It possesses unique solubility properties, being soluble in both water and lipophilic solvents such as ether, chloroform and benzene, making it advantageous for pharmaceutical formulation, chemical analysis, and biological research. It exhibits moderate lipophilicity, with a LogP of 2.144 ± 0.00 at 25°C, favoring its absorption and distribution in vivo.

Chemically, matrine has a melting point of 76°C and a boiling point of 396.738 ± 31.00°C, along with a low vapor pressure and a flash point of 172.748 ± 17.19°C, indicating excellent thermal stability and low volatility. Structurally, it features a rigid tetracyclic quinolizidine framework comprising two six-membered piperidine rings and two five-membered rings, connected via bridgehead carbons and an ether linkage, which confer high conformational stability and defined stereochemistry. A key structural element is its six-membered lactam ring, formed by intramolecular condensation of an amino group and a ketone. While stable under physiologically pH, this ring is prone to hydrolytic cleavage under strongly acidic or basic conditions, potentially affecting its chemical stability. Additionally, the presence

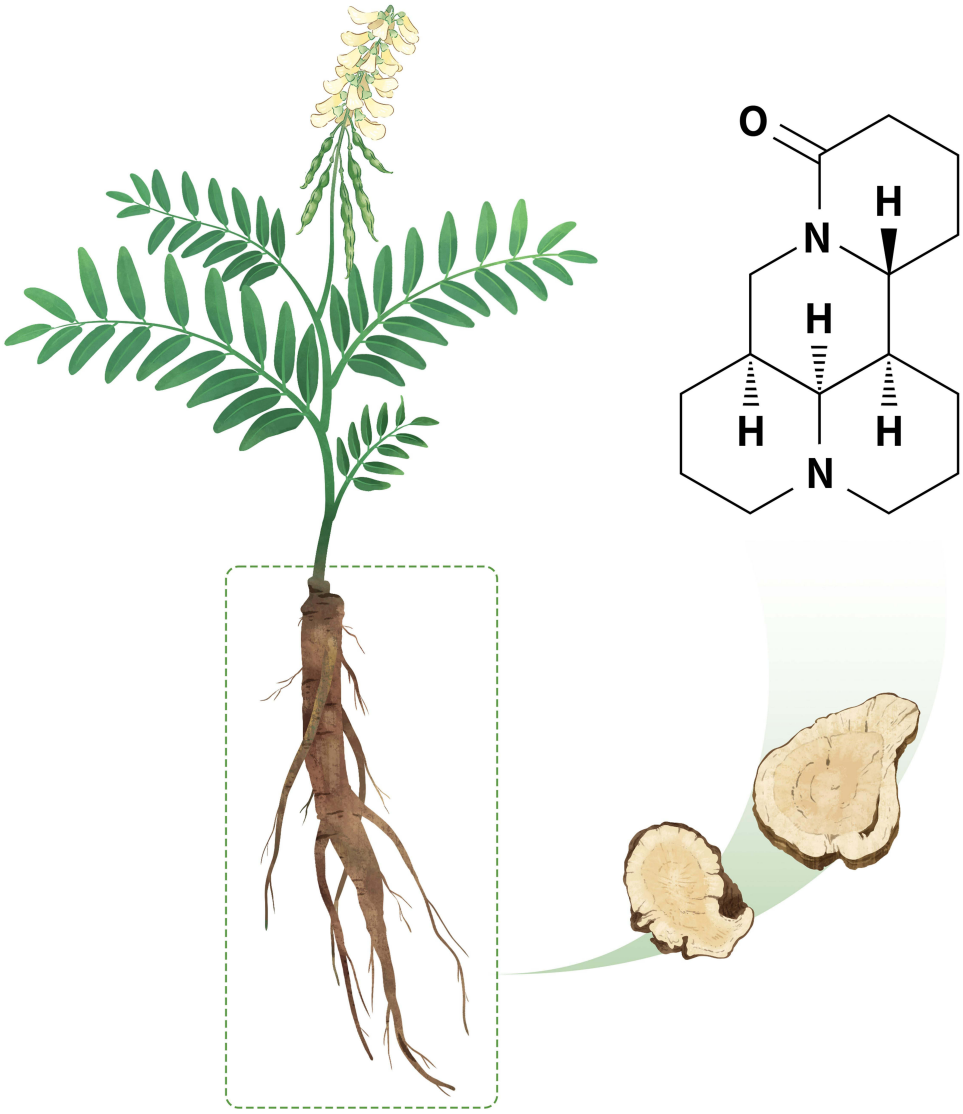

Figure 1 Chemical structure of matrine.

of at least one tertiary amine imparts weakly basicity, enabling salt formation via protonation, thereby improving water solubility and informing formulation strategies.

In summary, matrine's unique molecular architecture and favorable physicochemical properties support its promise in the modernization of TCM. Its broad pharmacological activity and chemical stability underscore its potential in drug development and pharmaceutical applications. For detailed physicochemical parameters, please refer to Table 1, with data sourced from SciFinder, PubChem, ChemSpider and the Chemical Book.

The Protective Mechanisms of Matrine Against Liver Injury

Chemical Liver Injury

Chemical liver injury refers to hepatic damage resulting from exposure to various exogenous chemicals, which exert hepatotoxic effects through multiple mechanisms, including oxidative stress, mitochondrial dysfunction, inflammatory responses, immune reactions and direct cytotoxicity.[29] The severity of liver injury is closely related to the type of chemical agent, dosage, duration of exposure and individual susceptibility. Common hepatotoxic agents include alcohol, acetaminophen (APAP), carbon tetrachloride (CCl_4), as well as various industrial chemicals and pharmaceuticals. Mechanistically, agents such as CCl_4 and APAP cause liver injury primarily via the formation of reactive metabolites

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Table 1 Physical and Chemical Properties of the Alkaloid Matrine

Name	Matrine
Source	*Sophora flavescens* Aiton (Kushen)
CAS number	519-02-8
CB number	CB8284723
UNII number	N390W430AC
Compound type	Alkaloid
Molecular formula	$C_{15}H_{24}N_2O$
Molecular weight	248.36
Form	Solid
Color	White
Solubility	Ethanol, chloroform, toluene, water and benzene
InChIKey	ZSBXGIUJOOQZMP-JLNYLFASSA-N
Density	1.164 ± 0.10 g/cm^3 (Temp: 25°C; Press: 760 Torr)
pKa	9.471 ± 0.20 (Most Basic Temp: 25°C)
Boiling point	396.738 ± 31.00°C (Press: 760.00 Torr)
Melting point	76°C
Flash point	172.748 ± 17.19°C
Vapor pressure	1.67 × 10^{-6} ± 0.92 Torr (Temp: 25.00°C)
Refractivity	1.5225 (λ: 589.3 nm; Temp: 86.4°C)
Polar surface area	23.6 Å ^{2}
LogP	2.144 ± 0.00 (Temp: 25°C)
Storage conditions	Sealed in dry, 2–8°C

that induce lipid peroxidation and mitochondrial damage.[30,31] In contrast, compounds like α-naphthyl isothiocyanate (ANIT) predominantly impair bile acid transport, leading to cholestatic liver injury.[32] A comprehensive understanding of these mechanisms is critical for developing effective preventive and therapeutic strategies for chemically induced liver diseases.

In rat models of ANIT-induced liver injury, matrine has demonstrated potent hepatoprotective effects, surpassing those of dexamethasone.[33] This protective effect may be partially attributed to matrine's ability to modulate ANIT metabolism and excretion, as with as its anti-inflammatory properties.[33] Yang et al[34] further confirmed that matrine significantly attenuated ANIT-induced liver injury in a dose-dependent manner, as evidenced by decreased serum levels of total bilirubin (TBIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP), along with the upregulation of CYP3A4 and pregnane X receptor (PXR) protein expression. These findings suggest that matrine's hepatoprotective effects in cholestasis are at least partially mediated through the induction of CYP3A4 via PXR activation.[34]

Acute or chronic liver injury is frequently associated with hyperammonemia, which can trigger neuroinflammation and oxidative stress, both of which are key contributors to the pathogenesis of anxiety and depression.[35,36] Interestingly, Khan et al[17] demonstrated that matrine significantly alleviated anxiety- and depression-like behaviors in a mouse model of CCl_4-induced acute liver injury, as assessed by the open field test, elevated plus maze, light-dark box, forced swim and tail suspension tests. Matrine also markedly suppressed CCl_4-induced neuroinflammation and oxidative stress by reducing pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in the hippocampus and prefrontal cortex and enhancing the activities of antioxidant enzyme such as GSH, CAT and GST.[17] Mechanistically, these neuroprotective effects are likely attributable to the attenuation of hyperammonemia-induced neuroinflammation and oxidative stress.[17] Furthermore, matrine has been shown to improve hepatic function in lithocholic acid-induced hepatocyte injury, possibly via modulation of the PXR-CYP3A4 axis.[37] Collectively, these findings suggest that matrine exerts protective effects against chemical liver injury and its neuropsychiatric manifestations through multiple hepatic and neurological mechanisms.

Drug-Induced Liver Injury

Drug-induced liver injury (DILI) refers to liver damage caused by the hepatotoxic effects of medications or their metabolites, typically through mechanisms such as direct cytotoxicity, immune-mediated responses and the accumulation of toxic intermediates.[38] Among the most well-known causes of DILI is APAP, whose overdose leads to the hepatic formation of the highly reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI).[39] NAPQI binds covalently to cellular macromolecules, triggering oxidative stress, mitochondrial damage, hepatocyte necrosis and inflammation.[39] Clinically, APAP-induced liver injury is characterized by jaundice and elevated serum levels of ALT/AST levels, and may progress to acute liver failure in severe cases.[40] These clinical consequences highlight the urgent need for effective therapeutic interventions.

Encouragingly, matrine has demonstrated significant hepatoprotective effects in a mouse model of APAP-induced DILI.[41,42] It significantly lowered serum AST and ALT levels, enhanced superoxide dismutase (SOD) activity, decreased malondialdehyde (MDA) content, and reduced hepatic histopathological damage and apoptosis.[41] Moreover, matrine suppressed APAP-induced production of inflammatory cytokines (TNF-α and IL-6) in a dose-dependent manner.[41] These protective effects are primarily mediated through the inhibition of inflammation, attenuation of oxidative stress and enhancement of antioxidant defenses.[41] Consistently, Bian et al[42] further confirmed the protective role of matrine in APAP-induced hepatotoxicity, underscoring the importance of its anti-inflammatory and antioxidant mechanisms. These findings support matrine's potential as a promising therapeutic agent for DILI.

Ischemic Liver Injury

Ischemic liver injury arises from a significant reduction or interruption of hepatic blood flow, which is commonly observed during liver transplantation, hepatic resection, severe trauma or hemorrhagic shock.[43] The ensuing hepatic ischemia leads to rapid depletion of intracellular ATP, triggering mitochondrial dysfunction, oxidative stress, ER stress, and excessive generation of reactive oxygen species (ROS), ultimately resulting in hepatocellular injury.[44] Paradoxically, restoration of blood supply during reperfusion further exacerbates ROS production, amplifies the inflammatory response, and promotes both apoptosis and necrotic cell death, culminating in ischemia-reperfusion injury (IRI).[45] Clinically, IRI is characterized by elevated serum liver enzymes, jaundice, coagulopathy, and in severe cases, progression to acute liver failure.[46] Therefore, developing effective therapeutic strategies to prevent and mitigate hepatic IRI is of paramount clinical importance.

Studies have shown that matrine exerts potent hepatoprotective effects in endotoxin-sensitized rat models of hepatic IRI.[20] Mechanistically, matrine inhibits the activation of nuclear factor kappa (NF-κB), reduces neutrophil infiltration, and suppresses the release of pro-inflammatory cytokines, while simultaneously upregulating anti-inflammatory mediators such as IL-6 and scavenging ROS to alleviate lipid peroxidation.[20] Moreover, matrine downregulates the expression of TNF-related apoptosis-inducing ligand (TRAIL), Bax and Caspase-3, thereby blocking mitochondrial apoptosis pathways and attenuating hepatocyte apoptosis.[47] These findings highlight the multi-targeted regulatory roles of matrine in hepatic IRI and its promising therapeutic potential.

Others

The Notch signaling pathway is a highly conserved intercellular communication cascade that plays a critical role in regulating cellular proliferation, differentiation and apoptosis.[48] Aberrant activation of Notch signaling has been implicated in the progression of liver fibrosis and HCC, potentially by promoting the malignant transformation of hepatic oval cells (HOCs) during chronic liver injury.[49] Interestingly, Shi et al[50] demonstrated that matrine significantly inhibited Notch signaling and promoted the differentiation of HOCs into functional hepatocytes, thereby restoring liver architecture and alleviating hepatic injury. This novel finding suggests that matrine may facilitate liver regeneration by modulating Notch-mediated cellular reprogramming, highlighting a new therapeutic avenue for chronic liver diseases. Additionally, matrine has shown therapeutic potential in COVID-19-associated liver injury, likely through its antiviral properties, immunomodulatory effects and suppression of pro-inflammatory cytokine release.[51] These emerging findings expand the scope of matrine's clinical applications to include viral and immune-mediated liver disorders.

The Protective Mechanisms of Matrine Against MASLD

Accumulating evidence indicates that matrine exerts protective effects against MASLD through the coordinated regulation of multiple intracellular signaling pathways and functional proteins. These mechanisms primarily involve attenuation of oxidative stress, improvement of mitochondrial function, restoration of ER homeostasis, and enhancement of hepatic lipid handling capacity. Key pathways and targets include activation of the Nrf2 antioxidant signaling pathway, modulation of the HSF1/PGC-1α axis, upregulation of HSP72, preservation of SERCA activity, and increased expression of L-FABP. Together, these pathways form an integrated network through which matrine mitigates hepatic steatosis, oxidative injury and metabolic dysregulation in MASLD.

Nrf2 Signaling Pathway

Nrf2 is a pivotal transcription factor that orchestrates the cellular defense against oxidative stress and plays a crucial protective role in the onset and progression of MASLD.[52] By activating various downstream antioxidant and detoxifying enzymes (HO-1, NQO1, GCLC), Nrf2 effectively alleviates oxidative stress, suppresses inflammatory responses, and improves hepatic lipid metabolism disorders and liver cell damage.[53] Furthermore, Nrf2 modulates the expression of genes related to fatty acid synthesis and β-oxidation, thereby attenuating hepatic lipid accumulation and preventing the progression of MASLD to steatohepatitis and liver fibrosis.[54] Activation of the Nrf2 pathway significantly ameliorates hepatic steatosis, reduces inflammation and inhibits fibrogenesis.

In a fructose-rich diet-induced rat model of steatohepatitis, matrine was found to reduce hepatic lipid droplet accumulation, inflammatory cell infiltration and hepatocellular necrosis in dose-dependent manner.[19] Mechanistically, matrine facilitates the nuclear translocation of Nrf2, leading to upregulation of antioxidant enzymes such as heme oxygenase 1(HO-1) and enhancement of endogenous antioxidant defenses.[19] In parallel, matrine suppresses the activation of the NF-κB signaling pathway and reduces circulating levels of TNF-α, thereby exerting potent anti-inflammatory effects.[19] Collectively, these actions attenuate the pathological progression of steatohepatitis. Notably, matrine also significantly improved fructose-induced hyperglycemia and insulin resistance, suggesting its potential to ameliorate metabolic disorders associated with MASLD through the dual modulation of oxidative stress and inflammatory pathways.[19] In summary, matrine activates the Nrf2 pathway while concurrently inhibiting inflammation and improving metabolic status, demonstrating promising therapeutic potential as a natural compound for MASLD intervention.

HSF1/PGC-1α Signaling Pathway

HSF1 and PGC-1α are critical regulators of cellular stress responses, mitochondrial function, and energy homeostasis, and play important roles in the pathogenesis of MASLD.[55] HSF1 alleviates ER stress and prevents protein misfolding by upregulating heat shock proteins, thereby mitigating hepatic inflammation and hepatocellular damage.[56] Additionally, HSF1 enhances the expression or activity of PGC-1α, promoting mitochondrial biogenesis and fatty acid oxidation, thereby improving hepatic metabolic status and reducing lipid accumulation and oxidative stress.[57] PGC-1α, as a master regulator of mitochondrial metabolism, further activates downstream targets such as peroxisome proliferator-activated receptor α (PPARα), which plays a key role in maintaining lipid homeostasis.[58] Therefore, activation of the HSF1/PGC-1α axis represents a promising therapeutic strategy for alleviating hepatic steatosis, suppressing inflammation and correcting metabolic dysfunctions associated with MASLD.

Notably, Li et al[23] developed a robust and specific screening system to identify activators of the HSF1/PGC-1α pathway and identified matrine as a potent natural alkaloid capable of activating this axis. Matrine was shown to induce mitogenesis and thermogenic gene expression in primary adipocytes derived from mouse adipose tissue.[23] In a murine model of diet-induced obesity using a high-fat, high-cholesterol diet, matrine significantly enhanced energy expenditure, restored impaired thermogenesis in brown adipose tissue, and promoted the browning of subcutaneous white adipose tissue, thereby alleviating obesity and associated metabolic abnormalities.[23] These effects are likely related to the activation of the HSF1/PGC-1α axis in adipocytes.[23] In summary, the HSF1/PGC-1α axis plays a synergistic role in regulating hepatic lipid metabolism, inflammation and energy homeostasis. Targeting this pathway may provide novel insights and therapeutic opportunities for the treatment of MASLD and related metabolic disorders.

Hsp72

Heat shock protein 72 (HSP72), an inducible member of the HSP70 family, plays a key role in maintaining proteostasis, mitigating oxidative and ER stress, and regulating inflammation and metabolic homeostasis.[59] Emerging evidence suggests that HSP72 exerts significant protective effects against the progression of MASLD. On the one hand, HSP72 inhibits pro-inflammatory signaling pathways, such as JNK, thereby attenuating hepatic cytokine production and alleviating chronic inflammation.[60] On the other hand, HSP72 improves insulin signaling and mitigates insulin resistance, leading to reduce de novo lipogenesis and lipid accumulation.[61] Moreover, it stabilizes mitochondrial function, enhances fatty acid β-oxidation and inhibits lipogenesis, ultimately reducing hepatic steatosis and oxidative stress.[62] Therefore, HSP72 is considered a central regulator of hepatic metabolic homeostasis, and its induction presents a potential therapeutic strategy to prevent or reverse MASLD pathogenesis.

Importantly, matrine has been shown to exert multiple HSP72-related metabolic protective effects across various experimental disease models. In mice fed a high-fat diet (HFD), matrine significantly improved glucose intolerance, reduced plasma insulin levels, decreased hepatic triglyceride content, and alleviated hepatic fat accumulation, comparable to the effects observed with metformin.[63] However, unlike metformin, which primarily acts through AMPK signaling, the metabolic benefits of matrine are closely associated with increased hepatic HSP72 expression.[63] Furthermore, in fructose-induced MASLD models, matrine ameliorated hepatic steatosis and corrected glucose metabolism abnormalities, indicating consistent efficacy under different metabolic stress conditions.[18] In a combined HFD and low-dose streptozotocin-induced type 2 diabetes model, matrine reduced hepatic lipid droplet accumulation and improved hyperglycemia, potentially by suppressing ER stress-mediated lipogenic signaling.[18] Notably, upregulation of HSP72 may play a key regulatory role in alleviating ER stress.[18]

Additional studies showed that in a methionine-choline-deficient (MCD) diet-induced nonalcoholic steatohepatitis (NASH) model, matrine significantly lowered serum ALT and AST levels, suppressed hepatic pro-inflammatory cytokine expression, and reduced collagen deposition, suggesting antifibrotic effects.[64] These therapeutic effects may be attributed to both HSP72 upregulation and inhibition of mTOR signaling, indicating that matrine exerts multi-target regulatory effects on hepatic inflammation, fibrosis and injury.[64] In summary, matrine mitigates hepatic steatosis, inflammation and metabolic disturbances largely through modulation of HSP72 and associated signaling pathways. Given its established clinical safety and tolerability, matrine holds considerable promise as a candidate for the treatment of MASLD and related metabolic disorders.

SERCA

Sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) is a calcium pump located on the ER membrane, responsible for transporting cytosolic Ca^{2+} into the ER lumen to maintain calcium homeostasis, which is essential for protein folding, metabolism, and signal transduction.[65] SERCA dysfunction has been identified as a critical contributor to the pathogenesis of MASLD, primarily by inducing ER stress and hepatocellular injury. Reduced SERCA activity leads to ER calcium depletion, activation of the unfolded protein response, and persistent ER stress, which in turn trigger inflammatory pathways, promote hepatocyte apoptosis, and exacerbate insulin resistance and lipid metabolism disorders.[66,67] Restoring SERCA function or enhancing its expression has been shown to reduce hepatic lipid accumulation, alleviate oxidative stress and suppress inflammatory responses.[68] Therefore, SERCA is considered a promising therapeutic target for maintaining ER homeostasis and intervening in MASLD progression.

Gao et al[69] demonstrated that matrine effectively ameliorated hepatic steatosis in HFD-induced NAFLD mice, as evidenced by reductions in body weight, serum total cholesterol (TC), triglycerides (TG) levels, and the expression of lipogenic proteins. Similarly, in the MCD diet-induced NASH model, matrine attenuated hepatic steatosis and inflammation, lowered serum ALT, AST and pro-inflammatory cytokines, and markedly downregulated ER stress markers.[69] In palmitic acid (PA)-induced L02 hepatocyte models, matrine at low to moderate concentrations reduced intracellular lipid accumulation, suppressed ER stress and restored calcium homeostasis.[69] Collectively, these findings suggest that matrine may modulate SERCA activity, restore ER calcium stores, and suppress ER stress cascades, thereby improving lipid metabolism and attenuating hepatic inflammation and injury.[69] This study highlights a novel mechanism by which

matrine contributes to ER homeostasis and provides both theoretical and experimental evidence supporting its potential as a therapeutic candidate for MASLD.

l-Fabp

Liver-type fatty acid-binding protein (L-FABP) is abundantly expressed in hepatocytes and plays a pivotal role in the transport, storage, and oxidative metabolism of long-chain fatty acids and their derivatives.[70] In MASLD, L-FABP is critical for maintaining lipid homeostasis and enhancing antioxidant defense mechanisms. On the one hand, L-FABP promotes the trafficking of fatty acids to mitochondria and peroxisomes, enhancing β-oxidation and reducing hepatic lipid accumulation.[71] On the other hand, it regulates lipid metabolism and energy balance via nuclear receptors, particularly PPARα.[72] Thus, upregulation of L-FABP expression helps mitigate hepatic steatosis and inflammation, indicating its diagnostic and therapeutic potential in MASLD.

Interestingly, Ai et al[73] investigated the therapeutic effects of matrine in a HFD-induced NASH rat model and a H_2O_2-induced oxidative stress cell model. The results showed that matrine significantly decreased serum ALT and AST levels, while increased hepatic SOD and GSH levels.[73] Histological analysis revealed that matrine alleviated hepatocellular steatosis, inflammatory infiltration, focal necrosis and ballooning degeneration.[73] Mechanistically, the hepatoprotective effects of matrine may be attributed to the upregulation of L-FABP expression and enhancement of antioxidant enzyme activity, thereby slowing the progression of NASH.[73] These findings indicate that matrine improves hepatic lipid metabolism and oxidative stress by modulating L-FABP-related signaling pathways.

The Protective Mechanisms of Matrine Against Liver Fibrosis

Liver fibrosis is a pathological outcome of excessive accumulation and aberrant distribution of ECM components during the wound-healing response to chronic liver injury.[74] It is primarily triggered by persistent insults such as viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease, and autoimmune disorders.[74] The central mechanism involves activating and transdifferentiating HSCs into myofibroblasts, which leads to the overproduction of collagen and other ECM components.[75] Additionally, an imbalance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) impairs ECM degradation, further promoting fibrosis.[76] Without timely intervention, liver fibrosis may progress to cirrhosis and eventually HCC.[77] Current therapeutic strategies mainly focus on etiology-specific treatment and targeted antifibrotic therapies. The former aims to eliminate the causative factors and interrupt disease progression, potentially reversing early-stage fibrosis.[78] The latter includes approaches to inhibit HSC activation, induce HSC apoptosis, mitigate oxidative stress and modulate gut microbiota.[21] Moreover, emerging therapies such as mesenchymal stem cell transplantation, epigenetic modulation and combination drug regimens are under clinical investigation, though their efficacy and safety require further validation.[79,80]

Studies have shown that matrine possesses promising antifibrotic potential. In transforming growth factor β1 (TGF-β1)-activated HSC-T6 cells, matrine (50 μM) significantly downregulated the expression of α-smooth muscle actin (α-SMA) and collagen type I.[81] In a CCl_4-induced rat model of liver fibrosis, matrine (100 mg/kg) suppressed the expression of TGF-β1 and enhanced hepatocyte growth factor (HGF) activity, thereby alleviating hepatic fibrosis.[82] Additionally, in a thioacetamide (TAA)-induced liver fibrosis model, matrine (40, 80, 160 mg/kg) dose-dependently reduced serum levels of ALT, AST, hyaluronic acid, type IV collagen and procollagen type III.[83] The underlying mechanisms involve the inhibition of connective tissue growth factor (CTGF), α-SMA and TIMP-1 gene expression.[83] Collectively, these findings suggest that matrine exerts antifibrotic effects through multi-target inhibition of HSC activation and ECM remodeling, highlighting its therapeutic potential in the treatment of liver fibrosis. The therapeutic effects and mechanisms of matrine in treating liver disease are presented in Table 2.

The Protective Mechanisms of Matrine Against Liver Cancer

Monotherapy

Regulation of HCC Growth and Cell Cycle Progression

Uncontrolled proliferation and dysregulated cell cycle progression are fundamental drivers of HCC initiation and progression, contributing not only to tumor expansion but also to enhanced invasiveness and metastatic potential.[85]

Table 2 Therapeutic Effects and Mechanisms of Matrine in Treating Liver Disease

Models	Types	Routes	Dosages	Effects and Related Mechanisms	Years	Reference
ANIT-induced AVBDS in male SD rats	In vivo	i.p.	10 mg/kg matrine for 2 days (Once every 12 h)	Modification of the metabolism and excretion of ANIT and its anti-inflammatory effects	2007	[33]
ANIT-induced cholestasis in male SD rats	In vivo	i.p.	10 mg/kg matrine for 7 days	Upregulation of CYP3A4 expression through induction of PXR expression	2018	[34]
CCl_4-induced liver injury in male mice	In vivo	i.p.	50 mg/kg matrine for 7 days	Modulation of neuroinflammation, oxidative stress, reduced neurogenesis and apoptosis	2019	[17]
LCA-induced liver injury in Chang-liver cells	In vitro	N/A	0.5, 1, 2 μM matrine for 48 h	Regulation of the PXR-CYP3A4 pathway	2020	[37]
LCA-induced liver injury in Huh-7 cells	In vitro	N/A	0. 5, 1, 2 μM matrine for 48 h			
APAP-induced liver injury in male C57BL/6 mice	In vivo	i.v.	0.7, 1.4, 2.8 mg/kg matrine for 7 days	Reduction of inflammatory factor levels, oxidative stress and improvement of antioxidant capacity	2021	[41]
APAP-induced liver injury in male mice	In vivo	i.v.	0.7, 1.4, 2.8 mg/kg matrine for 7 days	Inhibition of inflammatory response and alleviation of oxidative stress	2024	[42]
LPS-induced acute liver injury in male Wistar rats	In vivo	i.p.	100 mg/kg matrine for 7 days	Through anti-inflammatory and antioxidant activities	2011	[20]
HIRI in SD rats	In vivo	i.p.	25, 50 mg/kg matrine at 30 min before surgery	Inhibition of TRAIL expression, leading to reduced Bax and Caspase-3 activation	2018	[47]
WB-F344 rat HOCs	In vitro	N/A	0.5, 1.47 mg/mL matrine for 72 h	Inhibition of the Notch signaling pathway	2020	[50]
Partial hepatectomy + DEN + AAF in SD rats	In vivo	i.g.	1.25, 12.5 mg/kg matrine for 2/4/7 weeks (Twice per day)			
LPS-sensitized liver injury in male C57BL/6 mice	In vivo	i.p.	9.17, 18.33, 36,67 mL/kg matrine for 7 days	Inhibition of cytokine storms, maintenance of liver function homeostasis, immunity regulation and viral resistance	2021	[51]
Wistar male rats fed abnormalities	In vivo	i.g.	40, 80, 160 mg/kg matrine for 4 weeks	Enhancement of antioxidant and anti-inflammatory defenses via Nrf2 translocation	2013	[19]
ADSCs-derived mature adipocyt	In vitro	N/A	1 mM matrine for 7 days	Induction of adipose thermogenesis through activation of the HSF1/PGC-1α axis	2022	[23]
C57BL/6 male mice fed HFC	In vivo	p.o.	100 mg/kg matrine for 6 weeks			
C57BL/6J male mice fed MCD	In vivo	p.o.	100 mg/kg matrine for 6 weeks	Enhancement of HSP72 expression and downregulation of mTOR	2019	[64]
C57BL/6 male mice fed HFD	In vivo	p.o.	100 mg/kg matrine for 4 weeks	Upregulation of hepatic HSP72 expression	2015	[63]
C57BL/6 mice fed HFru	In vivo	p.o.	100 mg/kg matrine for 4 weeks	Inhibition of ER stress-associated de novo lipogenesis and fatty acid influx	2018	[18]
C57BL/6 male mice fed HFD	In vivo	p.o.	0.5, 2.5, 10 mg/kg matrine for 8 weeks	Inhibition of SERCA	2018	[69]
C57BL/6J male mice fed MCD	In vivo	p.o.	0.5, 2.5, 10 mg/kg matrine for 4 weeks			
PA-induced in L02 cells	In vitro	N/A	200, 400, 800 μM matrine for 12 h			
Wistar rats fed HFD	In vivo	i.g.	36 mg/kg matrine for 3 weeks	Upregulation of L-FABP expression and enhancement of antioxidant enzyme system activity	2012	[73]
H_2O_2-induced in Chang liver cells	In vitro	N/A	16, 32, 64 μM matrine for 24/48 h			
CCl_4-induced liver fibrosis in BALB/C male mice	In vivo	p.o.	100 mg/kg matrine for 4 weeks	Preservation of HSP72 through modulation of the gut microbiota	2024	[84]
CCl_4-induced liver fibrosis in male SD rats	In vivo	i.g.	100 mg/kg matrine for 4/6 weeks	Reduction of TGF-β1 expression and enhancement of HGF activity	2014	[82]

(*Continued*)

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Table 2 (Continued).

Models	Types	Routes	Dosages	Effects and Related Mechanisms	Years	Reference
TGF-β1-treated HSC-T6 cells	In vitro	N/A	50 μM matrine for 24 h	Inhibition of HSC activation	2022	[81]
TAA-induced liver fibrosis in rats	In vivo	i.g.	40, 80, 160 mg/kg matrine for 6 weeks	Inhibition of CTGF, α-SMA and TIMP-1 expression	2020	[83]

Abbreviation: N/A, not applicable.

Suppression of tumor cell proliferation therefore represents a central therapeutic strategy, with the potential to reduce tumor burden, improve treatment outcomes and increase sensitivity to chemotherapy and radiotherapy.[86]

Multiple studies have demonstrated that matrine effectively inhibits the proliferation of various HCC cell lines, including HepG2, Huh-7, SNU-182 and BEL-7404.[87–89] Mechanistically, matrine downregulates key proliferation-associated markers such as AFP, PCNA, c-Myc and Bcl-2, while upregulating the pro-apoptotic protein Bax, thereby restraining tumor cell growth.[87] In addition to direct effects on proliferation-related proteins, matrine modulates several intracellular signaling pathways that govern cell cycle progression and metabolic activity. Activation of the p38 MAPK and JNK pathways has been shown to contribute to growth suppression in HCC cells.[90] Furthermore, matrine interferes with non-coding RNA regulatory networks, notably the circROBO1/miR-130a-5p/ROBO1 axis, leading to inhibition of the Warburg effect and reduced metabolic support for rapid cell proliferation.[88]

Collectively, these findings indicate that matrine suppresses HCC growth through coordinated regulation of cell cycle control, oncogenic signaling pathways and tumor metabolic reprogramming, rather than through a single antiproliferative mechanism.

Suppression of Invasion, Migration and Epithelial-Mesenchymal Transition (EMT)

The high invasive and metastatic capacity of HCC is a major determinant of poor prognosis.[91] Therapeutic strategies that limit tumor cell migration and invasion are therefore critical for reducing recurrence and improving long-term survival.[92,93] Matrine has been shown to inhibit HCC cell invasion and migration through a multi-layered regulatory network involving both classical signaling pathways and epigenetic mechanisms. At the signaling level, matrine suppresses extracellular regulated protein kinases 1/2 (ERK1/2) activity and blocks the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) axis, thereby inhibiting EMT and metastatic potential in multiple HCC cell models.[94,95] Beyond these canonical pathways, matrine regulates circRNA-miRNA-mRNA networks, including inhibition of the circ_0055976/miR-1179/LDHA axis and activation of miR-122, leading to suppression of Ras homolog family member A (RhoA)/Rho-associated coiled-coil containing protein kinase (ROCK) signaling and cytoskeletal remodeling.[89,96] These effects collectively impair both the metabolic and structural requirements for tumor cell motility.

Consistent with these mechanistic findings, in vitro and in vivo studies have demonstrated that matrine significantly reduces invasion, migration and lung metastasis in orthotopic HCC models.[97] Direct targeting of MMP-9 by matrine further limits extracellular matrix degradation and metastatic dissemination.[97,98] In parallel, matrine upregulates E-cadherin and downregulates mesenchymal markers such as vimentin, MMP-2, MMP-9 and snail family transcriptional repressor 1/2 (SNAI1/2) via a phosphatase and tensin homolog (PTEN)/AKT-dependent mechanism, reinforcing its inhibitory effects on EMT.[99]

Taken together, matrine suppresses HCC metastasis by synchronously targeting EMT signaling, cytoskeletal dynamics, extracellular matrix remodeling and tumor-associated metabolic adaptation.

Induction of Apoptosis and Cellular Stress Responses

Resistance to apoptosis is a hallmark of HCC progression and recurrence.[100] Restoration of programmed cell death pathways is therefore essential for effective tumor control and therapeutic sensitization.[101,102] Matrine induces apoptosis in HCC cells through multiple, partially overlapping mechanisms. At the mitochondrial level, matrine activates the Mst1-JNK signaling pathway, triggering intrinsic apoptotic cascades and promoting tumor cell death.[25] In addition, matrine

induces both caspase-dependent and caspase-independent apoptosis through Bid-mediated activation of apoptosis-inducing factor, highlighting its ability to engage diverse death programs under different cellular conditions.[103]

Beyond direct apoptotic signaling, matrine modulates key regulatory checkpoints controlling cell survival. Suppression of mouse double minute 2 homolog (MDM2) disrupts the MDM2-p53 negative feedback loop, thereby restoring p53-mediated apoptotic responses in HCC cells.[104,105] Furthermore, matrine regulates apoptosis-related non-coding RNA networks, including the microRNA-299-3p/PGAM1 axis and the circ_0013290/miR-139-5p/MMP-16 pathway, further reinforcing pro-apoptotic signaling at the post-transcriptional level.[106,107]

Overall, matrine induces robust apoptotic and cellular stress responses in HCC cells through integrated modulation of mitochondrial pathways, p53-dependent signaling, and non-coding RNA regulatory networks.

Regulation of Autophagy and Metabolic Homeostasis

Autophagy plays a context-dependent role in liver cancer, contributing to both tumor suppression and therapeutic resistance depending on its extent and timing.[108–110] Precise modulation of autophagic flux is therefore critical for effective HCC treatment. Recent studies have demonstrated that matrine induces autophagy in HCC cells via activation of the p53/AMPK signaling pathway, expanding its antitumor activity beyond classical apoptosis-dependent mechanisms.[26] This autophagic response may involve regulation of p53 splice variants and interferon-related gene expression, forming a distinctive autophagy-associated immune regulatory network.[26] Importantly, autophagy induction by matrine has been implicated in enhancing tumor cell susceptibility to treatment, particularly in settings where apoptotic responses are impaired.

Key autophagy regulators such as Beclin-1 and the PI3K/AKT/mTOR pathway have been identified as central mediators of matrine-induced autophagy.[22,111] Notably, Beclin-1 is also linked to Bax upregulation, suggesting crosstalk between autophagic and apoptotic pathways in matrine-treated HCC cells.[111]

These findings indicate that matrine modulates autophagy and metabolic homeostasis in a tightly regulated manner, contributing to its ability to overcome stress adaptation and therapy resistance in HCC.

Targeting Cancer Stemness and Therapeutic Resistance

Cancer stem cells (CSCs) are critical drivers of HCC initiation, metastasis, and resistance to conventional therapies.[112,113] Targeting CSC self-renewal and niche maintenance is therefore essential for achieving durable therapeutic responses. Matrine has been shown to significantly suppress stem-like properties in HCC cells by remodeling both intracellular signaling and the extracellular microenvironment. Specifically, matrine upregulates coxsackievirus and adenovirus receptor (CAR) and E-cadherin expression, strengthening cell-cell adhesion and disrupting EMT-associated stemness programs.[114] In parallel, matrine promotes the expression of extracellular matrix components such as laminin and fibronectin, thereby altering the CSC niche and inhibiting anchorage-independent growth.[114]

Through integrated regulation of cell adhesion, niche remodeling and EMT reversal, matrine effectively impairs CSC self-renewal and reduces mechanisms underlying metastasis and therapeutic resistance.

Others

The Notch signaling pathway plays a pivotal role in the development and progression of liver cancer by promoting HCC cell proliferation, inhibiting apoptosis, maintaining cancer stem cell self-renewal, and facilitating EMT, thereby exacerbating tumor invasion and metastasis.[115] Additionally, Notch signaling contributes to tumor immune evasion and fibrosis by modulating the tumor microenvironment.[116] Consequently, inhibition of the Notch pathway is considered a promising therapeutic strategy for HCC, particularly for overcoming drug resistance and reducing metastatic potential.

Shi et al[24] demonstrated that matrine can suppress early-stage features of hepatocarcinogenesis, including histological changes in hepatic lobular structure and alterations in AFP and ALB expression. Mechanistically, matrine is thought to exert these effects by modulating the activation of the Notch signaling pathway, thereby effectively impeding the early development of HCC-like lesions in a rat model.[24] These findings suggest that matrine may inhibit early hepatocarcinogenesis via regulation of Notch signaling, offering a novel therapeutic avenue for the clinical management of HCC. The therapeutic effects and mechanisms of matrine in liver cancer (monotherapy) are presented in Table 3.

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Table 3 Therapeutic Effects and Mechanisms of Matrine in Liver Cancer (Monotherapy)

Models	Types	Routes	Dosages	Effects and Related Mechanisms	Years	Reference
HepG2 cells	In vitro	N/A	0.2–3.5 mg/mL matrine for 24 h	Upregulation or downregulation of tumor-relevant protein expression	2010	[87]
Huh-7 cells	In vitro	N/A	0.4, 0.8, 1.6 mg/mL matrine for 24 h	Regulation of the circROBO1/miR-130a-5p/ROBO1 axis	2023	[88]
SNU-182 cells	In vitro	N/A	0.4, 0.8, 1.6 mg/mL matrine for 24 h			
BALB/c nude mice + Huh-7 cells	In vivo	i.p.	100 mg/kg matrine for 30 days			
HepG2 cells	In vitro	N/A	1-4 mg/mL matrine for 24 h	Regulation of the P38MAPK and JNK signaling pathway	2022	[90]
BEL-7404 cells	In vitro	N/A	1-4 mg/mL matrine for 24 h			
MHCC97L cells	In vitro	N/A	50, 100 μM matrine for 48 h	Direct targeting of MMP-9	2019	[97]
PLC/PRF/5 cells	In vitro	N/A	50, 100 μM matrine for 48 h			
BALB/c nude mice + MHCC97L cells	In vivo	i.p.	10, 20 mg/kg matrine for 8 weeks			
Huh-7 cells	In vitro	N/A	0.2, 0.4, 0.8, 1.6 mg/mL matrine for 24/48 h	PTEN/AKT-dependent inhibition of EMT	2018	[99]
HepG2 cells	In vitro	N/A	1, 2, 4 mg/mL matrine for 24/48/72 h	Downregulation of the ERK1/2 signaling pathways	2020	[94]
Huh-7 cells	In vitro	N/A	0.3, 0.6, 0.9 mg/mL matrine for 48 h	Modulation of the circ_0055976/miR-1179/LDHA axis	2023	[96]
MHCC97 cells	In vitro	N/A	0.3, 0.6, 0.9 mg/mL matrine for 48 h			
BALB/C nude mice + Huh-7 cells	In vivo	i.p.	45 mg/kg matrine for 15 days (Every 3 days)			
MHCC97-H cells	In vitro	N/A	0.125, 0.25, 0.5 mg/mL matrine for 24 h	Regulation of the JAK2/STAT3 pathway	2023	[95]
HepG2 cells	In vitro	N/A	0.5, 1, 2, 4, 8 mg/mL matrine for 48 h	Regulation of miR-122 expression to inhibit EMT process and RhoA/ROCK signaling pathway	2023	[89]
HepG2 cells	In vitro	N/A	1, 5 nM matrine for 48 h	Triggering mitochondrial fission and activation of Mst1-JNK signaling pathways	2019	[25]
Huh-7 cells	In vitro	N/A	1, 5 nM matrine for 48 h			
HepG2 cells	In vitro	N/A	0.25, 0.5, 1, 1.5, 2 mg/mL matrine for 24 h	Through bid-mediated nuclear translocation of apoptosis inducing factor	2014	[103]
Balb/c nude mice + HepG2 cells	In vivo	i.p.	50, 75, 100 mg/kg matrine for 3 weeks			
Hep3B cells	In vitro	N/A	0.25, 0.5, 1, 2, 4 mg/mL matrine for 24 h	Inhibition of the MDM2-IAP3 pathway	2016	[105]
L02 cells	In vitro	N/A	0.25, 0.5, 1, 2, 4 mg/mL matrine for 24 h			
MHCC-97H cells	In vitro	N/A	0.4, 0.8, 1.6 mg/mL matrine for 24 h	Modulation of the miR-299-3p/PGAM1 axis	2022	[106]
Hep3B cells	In vitro	N/A	0.5, 1, 1.5 mg/mL matrine for 48 h	Modulation of the circ_0013290/miR-139-5p/MMP-16 pathway	2023	[107]
Huh-7 cells	In vitro	N/A	0.5, 1, 1.5 mg/mL matrine for 48 h			
BALB/C nude mice + Huh-7 cells	In vivo	p.o.	45 mg/kg matrine for 15 days (Every 3 days)			
HepG2 cells	In vitro	N/A	0.4, 0.8, 1.6, 3.2 mg/mL matrine for 48 h	Induction of autophagy via the p53/AMPK signaling pathway	2015	[26]
SMMC-7721 cells	In vitro	N/A	0.4, 0.8, 1.6, 3.2 mg/mL matrine for 48 h			
HepG2 cells	In vitro	N/A	0.25, 0.5, 1, 2 mg/mL matrine for 24/48/72 h	Induction of apoptosis and autophagy	2010	[111]

(*Continued*)

Table 3 (Continued).

Models	Types	Routes	Dosages	Effects and Related Mechanisms	Years	Reference
HepG2 cells	In vitro	N/A	0.2, 0.4, 0.8, 1.2, 1.6, 3.2 mg/mL matrine for 24/48/72 h	Inhibition of the PI3K/AKT/mTOR pathway and upregulation of Beclin-1	2013	[22]
BEL-7404 cells	In vitro	N/A	0.2, 0.4, 0.8, 1.2, 1.6, 3.2 mg/mL matrine for 24/48/72 h			
SMMC-7721 cells	In vitro	N/A	5, 25, 50, 100, 200 μg/mL matrine for 72 h	Upregulation of CAR, E-cadherin, laminin and fibronectin expression	2018	[114]
DEN/2-AAF-induced liver cancer in Sprague-Dawley male rats	In vivo	i.g.	1.25, 12.5 mg/kg matrine for 2/4/7 weeks (Twice per day)	Activation of the Notch pathway	2019	[24]

Abbreviations:: N/A, not applicable.

Combination Therapy

With Sorafenib

Sorafenib ($C_{21}H_{16}ClF_3N_4O_3$) is a multi-targeted tyrosine kinase inhibitor primarily used for treating advanced HCC and renal cell carcinoma.[117,118] It inhibits various tyrosine kinases, including vascular endothelial growth factor receptors (VEGFR), fibroblast growth factor receptors (FGFR) and the RAS/RAF/MEK/ERK signaling pathway, thereby suppressing tumor angiogenesis, tumor cell proliferation, and promoting apoptosis.[119] Despite its significant clinical efficacy in HCC patients, sorafenib faces challenges of drug resistance and adverse effects in clinical applications.

Interestingly, Lin et al[120] demonstrated that matrine could dose-dependently enhance the antiproliferative effect of sorafenib. Mechanistically, the combined use of matrine and sorafenib partly exerts its effect by inhibiting miR-21, leading to upregulation of PTEN and increased cytotoxicity against HCC cells.[120] This suggests that matrine is a promising natural compound to potentiate sorafenib's therapeutic efficacy against HCC. Similarly, Zhao et al[121] reported that compared to sorafenib alone, the combination of matrine and sorafenib more effectively inhibited proliferation, invasion and metastasis of HepG2-SR/Huh7-SR cells, while also promoting apoptosis. Further studies revealed that matrine combined with sorafenib reverses EMT phenotype of resistant cells via inhibition of the Notch1 signaling pathway, thereby effectively overcoming sorafenib resistance.[121]

Mechanistic Complementarity

While sorafenib primarily targets angiogenic and proliferative kinase signaling, matrine restores tumor suppressor pathways (PTEN) and suppresses EMT- and stemness-associated resistance programs, providing a rational mechanistic basis for combination therapy. Preclinical only (in vitro and xenograft models).

With Cisplatin

Cisplatin ($PtCl_2(NH_3)_2$) is a widely used platinum-based chemotherapeutic agent that exerts its antitumor effects primarily through forming DNA adducts, interfering with DNA replication and transcription, thereby inhibiting tumor cell proliferation and inducing apoptosis.[122] It is commonly applied in treating various malignancies, including ovarian, lung, head and neck, and bladder cancers.[123] However, its clinical use is limited by toxic side effects such as acute kidney injury, gastrointestinal disorders, bleeding and immunosuppression.[124] Currently, combination therapies and targeted treatments are being explored to mitigate these side effects and enhance cisplatin's efficacy.

In a BALB/c nude mouse xenograft model using subcutaneous HepG2 cells, the tumor inhibition rates with matrine or cisplatin monotherapy were 37.5% and 75%, respectively, while the combination treatment increased tumor inhibition to 83.3%.[125] Additionally, tumor tissues from the combination group showed significant downregulation of survivin and X-linked inhibitor of apoptosis protein (XIAP) expression, and notable upregulation of Caspase-3/7/9.[125] These findings suggest that matrine combined with cisplatin may promote HCC cell apoptosis and inhibit tumor progression by suppressing survivin and XIAP and activating the caspase signaling pathway.[125]

Mechanistic Complementarity

Cisplatin induces DNA damage-mediated apoptosis, whereas matrine attenuates intrinsic anti-apoptotic defenses by suppressing survivin/XIAP and amplifying caspase activation, thereby lowering the apoptotic threshold of HCC cells. Preclinical only (in vivo xenograft model).

With 5-Fluorouracil

5-Fluorouracil ($C_4H_3FN_2O_2$, 5-FU) is a clinically widely used anticancer drug for treating colorectal, gastric, breast, and other malignancies. It inhibits thymidylate synthase, disrupting DNA synthesis and repair, thereby suppressing tumor cell proliferation.[126] However, the therapeutic efficacy of 5-FU is often limited by its associated side effects, including myelosuppression, gastrointestinal reactions and oral ulcers.[127] Therefore, it is essential to carefully monitor the patient's clinical responses during treatment.

A study showed that matrine combined with 5-FU dose-dependently inhibited proliferation of HepG2 cells.[128] More importantly, the combination therapy demonstrated significant synergistic anti-HCC effects both in vitro and in vivo, mainly by inhibiting HepG2 cell proliferation and migration and inducing apoptosis.[128] This synergism is primarily mediated through regulation of the p38MAPK/AKT signaling pathway and induction of mitochondrial damage.[128] Collectively, the combined use of matrine and 5-FU may represent a novel strategy to overcome HCC drug resistance and provides a strong theoretical basis for clinical treatment.

Mechanistic Complementarity

5-FU disrupts nucleotide metabolism and DNA synthesis, whereas matrine enhances stress-activated signaling and mitochondrial apoptotic responses, collectively reinforcing cytotoxic stress and apoptotic signaling. Preclinical only (cellular and animal models).

With Lenvatinib

Lenvatinib ($C_{21}H_{19}ClN_4O_4$) is a multi-targeted tyrosine kinase inhibitor that suppresses tumor angiogenesis and proliferation by inhibiting VEGFR, FGFR and hepatocyte growth factor receptor, among other targets.[129] Approved in 2018 as a first-line treatment for advanced HCC in the US, EU, Japan, and China, lenvatinib has shown significant efficacy, especially for patients lacking surgical options.[130] However, its clinical use is limited by adverse events such as hypertension, fatigue and proteinuria, which can affect therapeutic outcomes.[131]

Interestingly, in vitro and in vivo studies by Wang[132] revealed that matrine combined with lenvatinib significantly overcomes lenvatinib resistance in HCC cells. Mechanistically, matrine reverses lenvatinib resistance by inhibiting PI3K/AKT/HIF-1α pathway-mediated glycolysis in HCC cells.[132] This research provides a new combined therapeutic approach to address lenvatinib resistance in liver cancer.

Mechanistic Complementarity

Lenvatinib targets angiogenic and proliferative signaling, whereas matrine suppresses adaptive metabolic rewiring and glycolysis-driven resistance, providing a metabolism-oriented rationale for combination therapy. Preclinical only (in vitro and in vivo studies).

With KU0063794

mTOR is a critical regulator of cell growth, proliferation, survival and metabolism, playing important roles in many cancers and metabolic diseases.[133] mTOR inhibitors block the activity of mTOR complexes 1 and 2, suppressing tumor cell proliferation and angiogenesis, inducing apoptosis, and modulating immune responses.[134] Common mTOR inhibitors include sirolimus and everolimus, widely used in renal cell carcinoma, breast cancer, neurofibromatosis and organ transplant immunosuppression.[135] However, mTOR inhibitors may cause immunosuppression, oral ulcers, and hyperglycemia, requiring close monitoring.[136]

Zhou et al[137] demonstrated that matrine combined with the mTOR inhibitor KU0063794 ($C_{25}H_{31}N_5O_4$) significantly enhanced dendritic cell maturation, T cell proliferation and cytokine secretion. Moreover, tumor weight and volume in

mice treated with the combination were significantly lower than those treated with either agent alone.[137] Dendritic cell vaccines prepared with mTOR inhibitor and matrine markedly enhanced antitumor immune responses both in vitro and in vivo.[137] These results suggest that the combination effectively promotes dendritic cell activation and differentiation, thereby enhancing immune system recognition and attack on tumors.

Mechanistic Complementarity

While mTOR inhibition modulates immune and metabolic checkpoints, matrine promotes dendritic cell activation and immune effector function, together enhancing antitumor immunity rather than direct tumor cytotoxicity. Preclinical only (immunological and animal models).

With Resveratrol

Resveratrol ($C_{14}H_{12}O_3$) is a natural polyphenol widely found in grape skins, red wine, peanuts, and certain berries, exhibiting antioxidant, anti-inflammatory, anticancer and cardiovascular protective activities.[138] It activates deacetylases such as sirtuin 1, regulating cellular metabolism, delaying aging, and enhancing stress tolerance.[139] Its potential has been widely studied in cancer, diabetes, cardiovascular, and neurodegenerative diseases.[140] However, clinical application is limited by low oral bioavailability and rapid metabolism, necessitating optimization via structural modification or combination therapy.

Notably, resveratrol effectively inhibits HepG2 cell proliferation and induces apoptosis by activating Caspase-3/9, upregulating the Bax/Bcl-2 ratio and inducing p53 expression.[141] Ou et al[141] investigated the combined effect of resveratrol and matrine, finding a significant synergistic inhibition of HepG2 cell proliferation. Matrine notably enhanced resveratrol-induced apoptosis, with this synergism linked to activation of Caspase-3/9, downregulation of survivin, accumulation of ROS and loss of mitochondrial membrane potential.[141] This study suggests that the combination of resveratrol and matrine holds promising synergistic antitumor effects against liver cancer cells, providing a strong basis for developing novel combined therapeutic strategies.

Mechanistic Complementarity

Resveratrol primarily induces oxidative stress and mitochondrial apoptosis, whereas matrine amplifies mitochondrial dysfunction and suppresses anti-apoptotic signaling, resulting in reinforced intrinsic apoptotic signaling. Preclinical only (in vitro studies).

The therapeutic effects and mechanisms of matrine in liver cancer (combination therapy) are presented in Table 4. The schematic diagram of matrine improvement of liver cancer is shown in Figure 2.

Toxicity of Matrine

Matrine is a naturally occurring alkaloid widely found in various traditional Chinese medicinal herbs such as *Sophora flavescens* Aiton (Kushen) and *Radix Sophorae Tonkinensis* (Shandougen).[142] Despite its multiple pharmacological activities, long-term or high-dose usage may induce adverse effects across multiple organ systems, including the liver, kidneys, nervous system, and gastrointestinal tract. For instance, clinical application of *Radix Sophorae Tonkinensis* has been reported to cause symptoms such as dizziness, vomiting, chest tightness, palpitations and dyspnea.[143] Studies indicate that the main active components of *Radix Sophorae Tonkinensis*, matrine and oxymatrine, are closely associated with these adverse reactions.[144] Notably, the acute toxicity of matrine is three times higher than that of oxymatrine, and oxymatrine can be partially metabolized into matrine in vivo, thereby amplifying the overall toxicity.[144] Consequently, matrine is considered the principal compound responsible for the toxic side effects induced by *Radix Sophorae Tonkinensis*.

Hepatotoxicity

Liu et al[145] demonstrated that intraperitoneal injection of matrine (50, 100 mg/kg) in mice for 7 days significantly elevated serum AST and ALT levels, accompanied by evident cytoplasmic vacuolar degeneration in liver tissues. In vitro studies further confirmed that treatment with matrine (0.5 mg/mL) induced a substantial accumulation of ROS, leading to

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Table 4 Therapeutic Effects and Mechanisms of Matrine in Liver Cancer (Combination Therapy)

Co-Administered Drugs	Combined Drug Dosage	Models	Types	Routes	Dosage of Administration	Molecular Mechanisms	Years	Reference
Sorafenib ($C_{21}H_{16}ClF_3N_4O_3$)	2.5 μM	HepG2 cells	In vitro	N/A	0.4–1.6 g/L matrine for 48 h	Suppression of miR-21 and subsequent upregulation of PTEN	2014	[120]
	2.5 μM	Hep3B cells	In vitro	N/A	0.4–1.6 g/L matrine for 48 h			
	8 μM	HepG2-SR	In vitro	N/A	0.5 mg/mL matrine for 12–48 h	Inhibition of the Notch1 signaling pathway	2023	[121]
	5 μM	Huh7-SR	In vitro	N/A	0.5 mg/mL matrine for 12–48 h			
	60 mg/kg	BALB/c nude mice + HepG2-SR	In vivo	i.g.	100 mg/kg matrine for 23 days			
Cisplatin ($PtCl_2(NH_3)_2$)	2 mg/kg	Nude mice + HepG2 cells	In vivo	i.p.	100 mg/kg matrine for 3 weeks (5 days per week)	Activation of the Caspase apoptosis pathway and suppression of survivin-associated inhibition of Caspase-9	2020	[125]
KU0063794 ($C_{25}H_{31}N_5O_4$)	100 nM	Dendritic cells	In vitro	N/A	1 mg/mL matrine for 48 h	Enhancement of DC maturation, T cells proliferation and cytokines secretion	2022	[137]
	100 nM	Nude mice + Huh-7 cells	In vivo	i.p.	1 mg/mL matrine for 3 weeks (Once a week)			
Resveratrol ($C_{14}H_{12}O_3$)	50, 100 μM	HepG2 cells	In vitro	N/A	0.5–12 mM matrine for 48 h	Activation of Caspase-3/9, downregulation of survivin, induction of ROS generation and disruption of $\Delta\psi m$	2014	[141]
5-Fluorouracil ($C_4H_3FN_2O_2$)	20 μM	HepG2 cells	In vitro	N/A	1.5 mg/mL matrine for 48 h	Regulation of p38MAPK/AKT signaling pathway expression and induction of mitochondrial damage within cells	2023	[128]
	10 mg/kg	BLAB/c nude mice + HepG2 cells	In vivo	i.g.	50 mg/kg matrine for 21 days			
Lenvatinib ($C_{21}H_{19}ClN_4O_4$)	1 μM	Huh7-LR cells	In vitro	N/A	0.5 mg/mL matrine for 24–72 h	Inhibition of the PI3K/AKT/HIF-1α signaling pathway	2024	[132]
	10 μM	HepG2-LR cells	In vitro	N/A	0.5 mg/mL matrine for 24–72 h			
	5 mg/kg	BALB/c nude mice + Huh7-LR cells	In vivo	i.g.	100 mg/kg matrine for 18 days			

Abbreviations:: N/A, not applicable; $\Delta\psi m$, mitochondrial membrane potential.

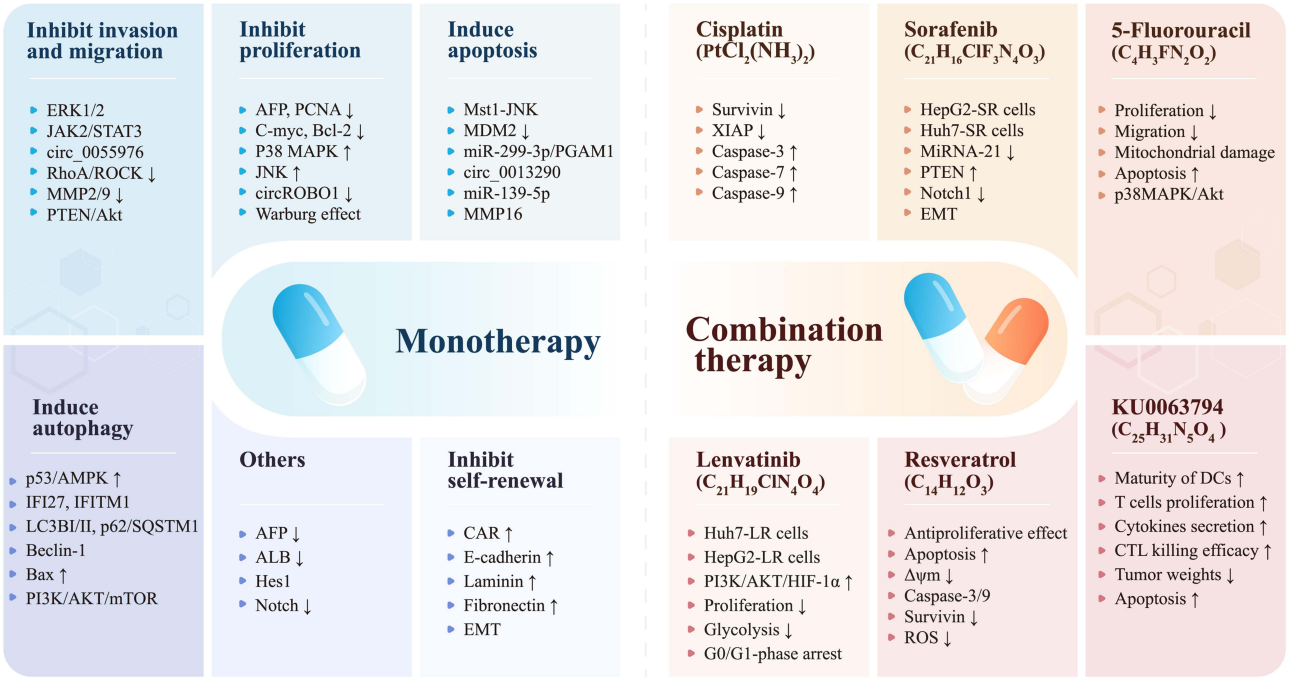

Figure 2 Schematic diagram of the anticancer effect of matrine. Upward arrows (↑) indicate upregulation or activation, whereas downward arrows (↓) indicate downregulation or inhibition of the indicated molecules, pathways or cellular processes.

mitochondrial membrane potential loss and ATP depletion, while activating mitochondrial apoptosis pathways including Bax/Bcl-2 and Caspase-3/9.[145] Interestingly, the antioxidant N-acetylcysteine (NAC) markedly reversed matrine-induced hepatotoxicity, suggesting that oxidative stress plays a pivotal role in its toxic mechanism.[145] Subsequently, You et al[146] validated in HL-7702 cells that matrine-induced hepatotoxicity involves suppression of the Nrf2 pathway, activation of ROS-mediated mitochondrial apoptosis, and cell cycle arrest at the S phase. Similarly, NAC pretreatment alleviated the cytotoxic effects induced by matrine, further supporting an oxidative stress-dependent mechanism.[146]

Nephrotoxicity

Metabolomic studies revealed that matrine significantly increased urinary levels of trimethylamine N-oxide (TMAO) in rats, indicating a close association with renal impairment.[147] Previous research suggests that TMAO plays a role in mitigating uremic toxin retention caused by renal failure, and elevated TMAO concentrations are commonly regarded as important biomarkers of kidney disease.[148] Furthermore, Wang et al[149] reported that continuous intraperitoneal administration of matrine (100 mg/kg) for 20 days induced marked pathological damage in mouse renal tissues, along with abnormal increases in serum creatinine and blood urea nitrogen levels. Mechanistically, matrine inhibits glutathione peroxidase 4 (GPX4) synthesis, resulting in the accumulation of lipid peroxides and triggering ferroptosis, which leads to acute kidney injury.[149] Notably, sodium selenite alleviated matrine-induced renal damage by promoting GSH synthesis, enhancing GPX4 activity and scavenging ROS, thereby inhibiting ferroptosis.[149] This finding highlights the critical role of ferroptosis in matrine-induced nephrotoxicity and provides a potential therapeutic target for toxicity intervention.

Neurotoxicity

Shen et al[150] demonstrated that increasing concentrations (2, 4, 8 mM) and exposure durations of matrine enhanced its cytotoxicity toward PC12 cells. Hoechst 33342 staining under fluorescence microscopy revealed typical apoptotic nuclear changes such as condensation and fragmentation.[150] Annexin V-FITC/PI double staining further confirmed that matrine induces apoptosis in PC12 cells, indicating neurotoxic potential.[150] The underlying mechanism likely involves excessive intracellular ROS accumulation, which activates mitochondrial apoptosis pathways.[150] In addition, zebrafish embryo assays showed that exposure to matrine (250 mg/L) for 96 hours induced cardiac edema, growth retardation and

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notochord malformations, suggesting potential neuro-muscular toxicity.[151] The toxic mechanism may involve activation of sphingosine receptors or inhibition of acetylcholinesterase activity, resulting in disrupted neural transmission.[151] Notably, even doses below lethal and teratogenic thresholds significantly impaired zebrafish larval locomotor activity, evidenced by decreased swimming frequency and speed.[151] Matrine also exhibited dose-dependent inhibition of embryonic heart rate, potentially related to suppression of hERG potassium channel expression.[151]

Gastrointestinal Toxicity

Metabolomic analyses indicated a significant decrease in hippurate levels in the urine of rats treated with matrine, suggesting interference with gut microbiota homeostasis and consequent gastrointestinal injury.[147] Hippurate is recognized as a key metabolite reflecting gut microbial metabolic activity, and its reduction may signal disruption of the intestinal microecological environment.[152] However, current research on matrine-induced gastrointestinal toxicity remains limited, and the precise mechanisms are not yet fully elucidated. Further investigation into the interactions among gut microbiota, metabolic products, and host mucosal barriers is needed to clarify its potential toxicological pathways.

In summary, although matrine exhibits potent pharmacological effects and promising clinical application prospects, its toxicity across multiple organ systems cannot be overlooked. Existing studies indicate that matrine's toxic mechanisms primarily involve oxidative stress, mitochondrial dysfunction, apoptosis, and ferroptosis, reflecting a complex interplay of multiple pathways. Therefore, comprehensive toxicological evaluation and safety monitoring are imperative in advancing matrine's drug development and clinical translation. Further mechanistic research is also essential to optimize risk management strategies and ensure the efficacy and safety of matrine in clinical use. A schematic diagram illustrating the toxicity of matrine is shown in Figure 3.

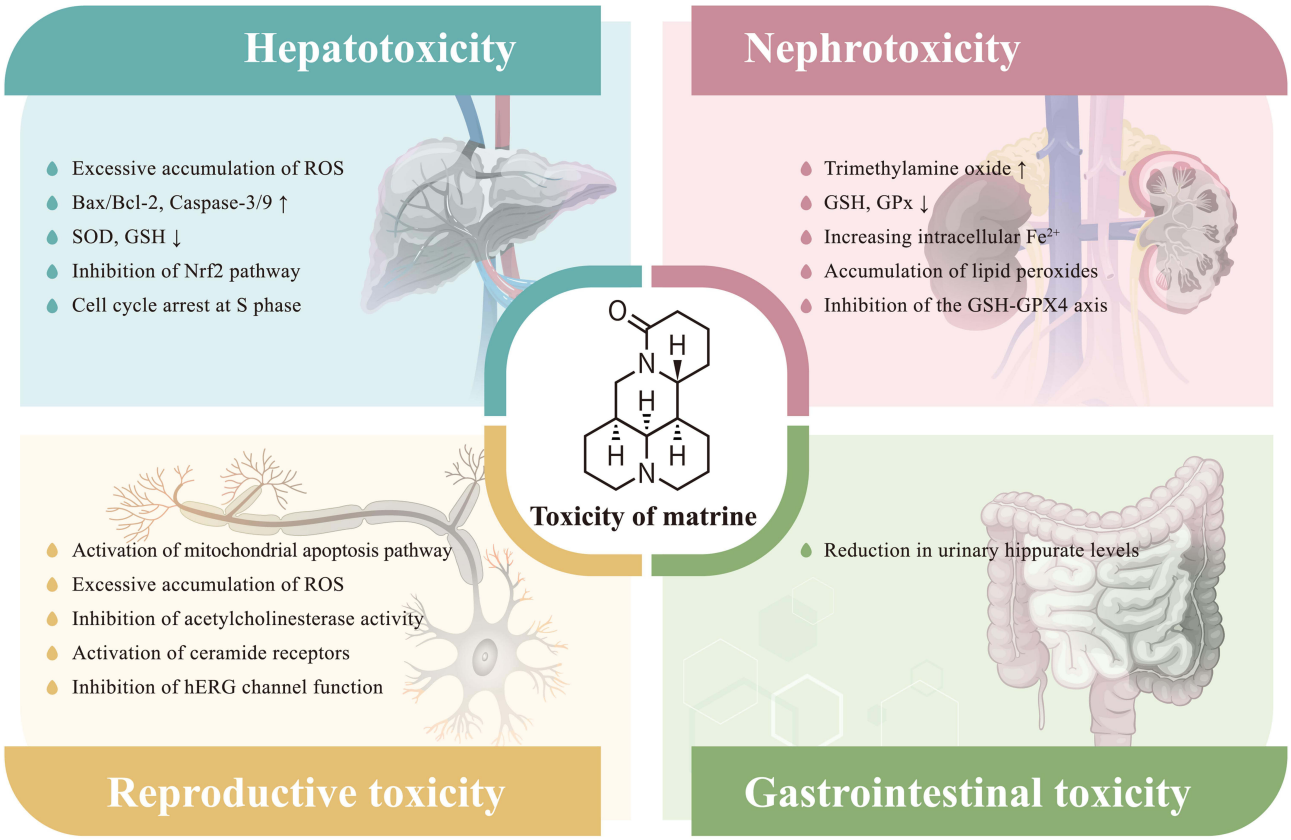

Figure 3 Schematic diagram of toxicity of matrine. Upward arrows (↑) indicate upregulation or activation, whereas downward arrows (↓) indicate downregulation or inhibition of the indicated molecules, pathways, or cellular processes.

Pharmacokinetics of Matrine

Existing pharmacokinetic studies have demonstrated that matrine can be absorbed at multiple intestinal sites, including the ileum, colon, duodenum and jejunum, with the ileum and colon being the primary absorption regions.[153] In vitro experiments using the Caco-2 cell model further confirmed that matrine possesses high absorption efficiency, rapidly crossing the intestinal epithelial barrier into systemic circulation.[153] Regarding metabolism, liver microsome incubation is a commonly employed in vitro method for metabolic investigation. The cytochrome P450 (CYP450) and UDP-glucuronosyltransferase (UGT) enzyme systems are major drug-metabolizing enzymes often used to evaluate the presence of first-pass metabolism.[154] Studies have shown that matrine undergoes no significant metabolism by either the CYP450 or UGT enzyme systems, suggesting that it likely avoids substantial first-pass metabolism, which favors increased systemic exposure.[153] In terms of distribution, matrine widely distributes via blood circulation to multiple organs and tissues, including the heart, liver, spleen, lungs, kidneys, adipose tissue and skeletal muscle.[155] Excretion studies reveal that matrine is eliminated primarily in its parent form through urine, feces, and bile, with urine serving as the main excretory route.[156] Taken together, these findings indicate that matrine undergoes limited metabolism in vivo and exerts its pharmacological effects mainly in the prototype form.

Yang et al[153] investigated the pharmacokinetics of matrine in rats by analyzing plasma concentration-time profiles. After oral administration of 2 mg/kg, matrine reached peak plasma concentration (T_{max}) at approximately 105 minutes, with an area under the curve (AUC) of 18,453 ± 5,885 ng·min/mL.[153] Combined with intravenous data, the oral bioavailability was calculated to be 17.1%.[153] Compared with oral dosing, intravenous administration of the same dose prolonged the elimination half-life ($t_{1/2}$) to 142 minutes and decreased clearance rate, indicating a slower clearance of matrine when administered intravenously.[153] Wang et al[157] compared the pharmacokinetic characteristics of matrine in Beagle dogs following intravenous injection and oral gavage. Using a two-compartment model, after oral gavage of 30 mg/kg, peak plasma concentration occurred around 0.4 hours, with a distribution half-life of approximately 1 hour, elimination half-life of 11.2 hours, and mean residence time (MRT) of 4.5 hours.[157] The oral bioavailability was estimated at about 60%.[157] Moreover, the $t_{1/2}$ and MRT values were similar between the two administration routes, indicating that the route of administration had little effect on the metabolism and elimination of matrine, which displayed consistent pharmacokinetic behavior.

Significant interspecies differences exist in the clearance of matrine. Zhang et al[158] conducted clinical trials in healthy volunteers to evaluate matrine's pharmacokinetic profile. After oral administration of soft capsules at doses of 100, 200 and 400 mg, plasma matrine concentrations peaked within 1–2 hours, showing a similar absorption rate to that observed in rats.[158] However, the elimination half-life in humans (8 hours) was significantly longer than that in rats (1.5 hours), suggesting slower clearance and prolonged duration of action in humans.[158] This provides a theoretical basis for sustained therapeutic effects of matrine in clinical use and highlights the need to consider interspecies differences when designing dosing regimens for humans.

Dose also influences the pharmacokinetic behavior of matrine. Jiang et al[159] studied the oral administration of 10 mg/kg in rats and found a T_{max} of approximately 1.49 hours. This is consistent with the 2 mg/kg data of Yang et al,[153] but the $t_{1/2}$ was markedly prolonged to 7.8 hours and the apparent clearance decreased. This suggests dose-dependent slower clearance, potentially reflecting nonlinear pharmacokinetics. At higher doses, metabolic enzymes or transporters may become saturated, resulting in reduced clearance and extended half-life. Additionally, Jiang et al[159] modified matrine at the 14th position with a thienyl methylene group, which prolonged both T_{max} and $t_{1/2}$, indicating increased retention time in vivo. This modification may help enhance drug efficacy duration and offers a theoretical foundation for structural optimization.

Synergistic effects from other components in compound formulations may also extend matrine's duration of action. For example, Kushen Gancao Tang, a classical TCM formula containing matrine and other active components, is widely used to treat conditions such as dysentery. Wang et al[160] extracted Kushen and licorice in a 1:1 ratio and administered the extract orally to rats, then evaluated the pharmacokinetics of matrine. The peak plasma concentration occurred around 3.1 hours, significantly later than most single-compound studies, with a $t_{1/2}$ of about 6 hours.[160] This suggests that the compound formulation can prolong matrine's systemic exposure, potentially due to effects of licorice components on its

solubility, absorption rate, or metabolism. However, nonlinear kinetics due to saturation of transporters or metabolic enzymes under high-dose conditions cannot be ruled out. Thus, compound preparations may improve matrine's pharmacokinetic properties via synergistic mechanisms, providing new insights for its clinical use and the optimization of TCM formulas.

In summary, matrine exhibits rapid absorption, minimal first-pass metabolism, and moderate bioavailability, providing a theoretical basis for its quick onset of action. However, its relatively fast elimination and short half-life may limit sustained efficacy and clinical application. Therefore, extending matrine's in vivo retention time to achieve longer-lasting and more stable pharmacological effects remains an important focus of current and future pharmacokinetic research. The pharmacokinetic comparison parameters of matrine are summarized in Table 5.

Discussion and Perspectives

Matrine is a natural quinolizidine alkaloid primarily derived from the traditional Chinese medicinal herb Kushen. In recent years, it has garnered significant attention as a promising candidate for the prevention and treatment of liver diseases due to its notable hepatoprotective properties. Accumulating evidence suggests that matrine exerts broad therapeutic potential across a range of liver disorders, including liver injury of various etiologies, MASLD, liver fibrosis, and HCC. The hepatoprotective effects of matrine are mediated through multiple molecular mechanisms, including inhibition of inflammatory responses, reduction of oxidative stress, attenuation of ER stress, mitigation of lipid peroxidation, improvement of insulin resistance, enhancement of antioxidant defenses, regulation of glucose metabolism disorders, interference with HSC activation and ECM remodeling, as well as suppression of HCC cell proliferation, invasion, and migration via the induction of autophagy and apoptosis. Importantly, several signaling pathways, such as NF-κB, Nrf2, HSF1/PGC-1α, PI3K/AKT/mTOR, Notch, ERK1/2, JAK2/STAT3, RhoA/ROCK, Mst1-JNK and p53/AMPK, have been identified as mediators of these effects. These findings deepen the understanding of matrine's pharmacological mechanisms and provide a solid theoretical foundation for its further development and clinical application in liver disease therapy. The molecular pathways involved in matrine's hepatoprotective effects are shown in Figure 4.

A critical paradox highlighted by this review is that while matrine demonstrates hepatoprotective effects in liver injury, fibrosis and MASLD models, hepatotoxicity has also been reported under certain conditions. This apparent duality is likely driven by a strong context dependence involving factors such as dose, exposure duration, disease state, and cell-type specificity. At appropriate doses and in diseased livers, matrine preferentially targets inflammatory cells, activated HSCs, or malignant hepatocytes, suppressing inflammation and fibrogenesis, while inducing apoptosis in HCC cells. In contrast, excessive doses or prolonged exposure, particularly in healthy or non-inflamed liver tissue, may disrupt hepatocyte homeostasis, leading to mitochondrial dysfunction, oxidative stress and toxicity. Similarly, the seemingly contradictory pro-apoptotic effects in HCC cells and anti-apoptotic effects in liver injury models can be reconciled by differential cellular targeting, wherein matrine promotes survival in stressed but non-malignant hepatocytes while facilitating apoptosis in transformed cells through context-dependent modulation of key signaling pathways, such as NF-κB, PI3K/AKT/mTOR, and p53/AMPK. Together, these findings suggest that matrine acts as a context-sensitive regulator of hepatic cell fate, rather than a uniformly protective or toxic agent. A schematic illustration of the hepatoprotective-hepatotoxic duality of matrine is shown in Figure 5.

From a toxicological perspective, current preclinical evidence indicates that matrine may induce multi-organ toxicities, including effects on the liver, kidneys, nervous system, and gastrointestinal tract, particularly under high doses or prolonged administration. These adverse effects are closely associated with excessive oxidative stress, mitochondrial dysfunction, apoptosis, and ferroptosis. These findings underscore the importance of dose and exposure duration in determining whether matrine exerts hepatoprotective or hepatotoxic effects, highlighting its context-dependent biological profile.

Pharmacokinetic studies show that matrine is rapidly absorbed, undergoes minimal first-pass metabolism, and exhibits moderate bioavailability, with primary absorption occurring in the ileum and colon. However, animal studies consistently demonstrate rapid systemic clearance and a short elimination half-life, suggesting a high metabolic rate that may limit sustained therapeutic efficacy. Although the elimination half-life in humans is relatively longer, it may still fall short of

Table 5 Pharmacokinetic Studies of Matrine

Route of Administration	Species	Dose	Pharmacokinetic Parameters								References
			T_{max} (a: min; b:h)	C_{max} (a: ng/mL; b: μg/L)	$AUC_{(0-t)}$ (a: ng ħ/mL; b: μg ħ/mL; c: ng min/mL)	$AUC_{(0-\infty)}$ (a: ng ħ/mL; b: μg ħ/mL; c: ng min/mL)	$T_{1/2}$ (a:min; b:h)	CL (a: mL/min/kg; b: L/h/kg)	$MRT_{(0-t)}$ (h)	Vz (a: mL/kg; b: L/kg)	
i.v.	Rats (SD, male)	2 mg/kg	N/A	N/A	108637 ± 11801 (c)	108794 ± 11712 (c)	142 ± 79 (a)	18.6 ± 2.0 (a)	N/A	3704 ± 1874 (a)	[153]
Oral	Rats (SD, male)	2 mg/kg	94.6 ± 38.6 (a)	105 ± 30 (a)	18453 ± 5885 (c)	18593 ± 5931 (c)	92 ± 32 (a)	19.7 ± 5.5 (a)	N/A	2433 ± 1668 (a)	[153]
Oral	Human	100 mg	1.3 ± 0.6 (b)	603.3 ± 131.8 (a)	6203 ± 2206 (b)	6375 ± 2253 (b)	8.7 ± 1.3 (b)	N/A	N/A	N/A	[158]
Oral	Human	200 mg	1.6 ± 0.8 (b)	1207.3 ± 332.0 (a)	12816 ± 4666 (b)	13047 ± 4781(b)	8.3 ± 1.0 (b)	N/A	N/A	N/A	[158]
Oral	Human	400 mg	1.7 ± 0.7 (b)	2384.4 ± 720.7 (a)	20078 ± 6842 (b)	20316 ± 6939 (b)	7.8 ± 0.8 (b)	N/A	N/A	N/A	[158]
Oral	Rats (SD, male)	16.05 mg/kg	3.1 ± 0.2 (b)	2115.4 ± 120.0 (b)	18969.1 ± 427.8 (a)	19057.5 ± 447.1 (a)	6.0 ± 1.7 (b)	N/A	7.1 ± 0.3	N/A	[160]
Oral	Rats (SD, male)	10 mg/kg	1.49 ± 0.20 (b)	1437 ± 137.5 (b)	7341 ± 1195 (a)	7635 ± 1224 (a)	7.80 ± 2.25 (b)	0.315 ± 0.147 (b)	5.86 ± 0.78	3.219 ± 0.885 (a)	[160]
i.v.	Beagle dogs	6 mg/kg	N/A	N/A	N/A	2757 ± 876 (b)	0.7 ± 0.1 (b)	N/A	4.3 ± 1.0	N/A	[157]
Oral	Beagle dogs	30 mg/kg	0.4 ± 0.1 (b)	3821 ± 705 (b)	N/A	7446 ± 1456 (b)	1.0 ± 0.3 (b)	N/A	4.5 ± 1.0	N/A	[157]

Abbreviations: T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; $AUC_{(0-t)}$, area under the concentration-time curve from 0 to t h; $AUC_{(0-\infty)}$, area under the concentration-time curve from 0 h to infinity; $T_{1/2}$, elimination half-life; CL, clearance; $MRT_{(0-t)}$, mean residence time from 0 to t h; Vz, clearance, vertical distribution phase; i.v., intravenous administration; N/A, not applicable.

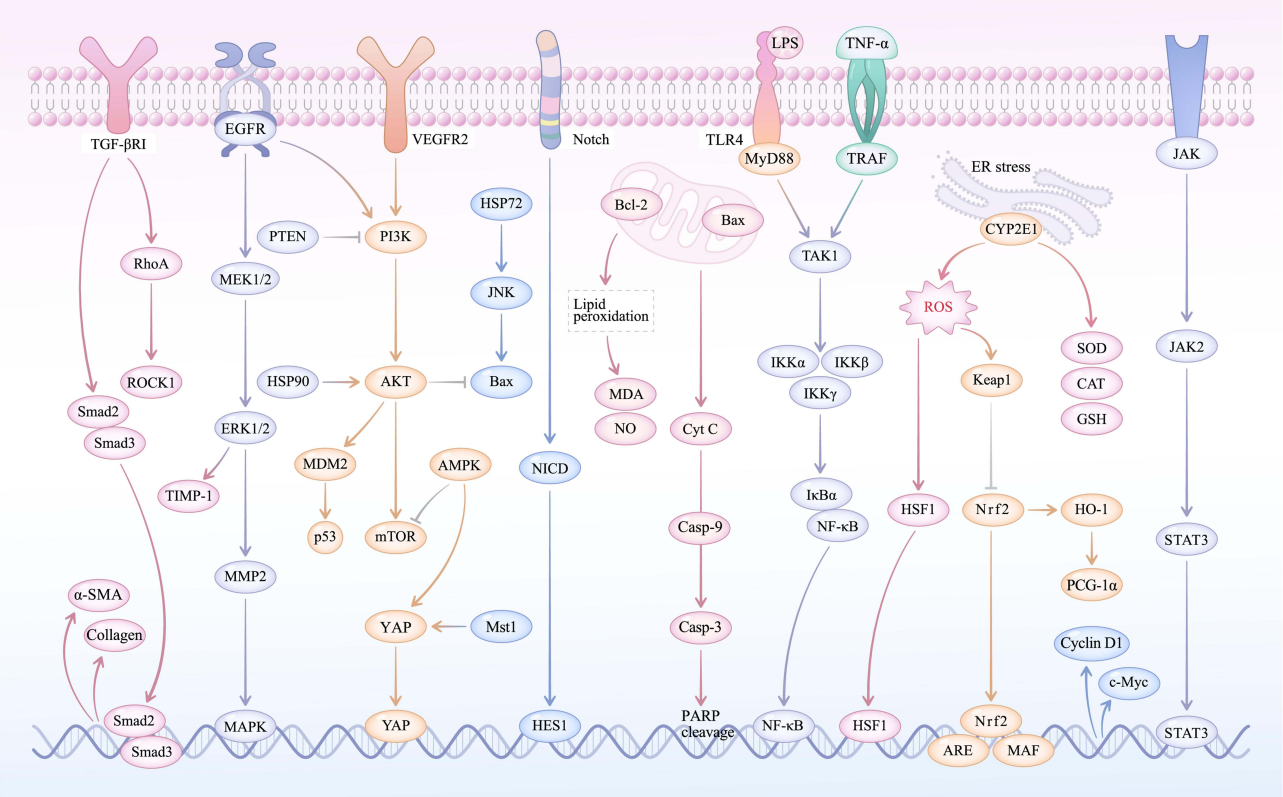

Figure 4 Mechanisms of matrine in the treatment of various liver diseases. The figure summarizes the major signaling pathways reported to be regulated by matrine, including TGF-β/Smad, PI3K/Akt, MAPK, JNK, NF-κB, JAK/STAT, Nrf2-mediated antioxidant signaling, Notch signaling and mitochondrial apoptosis pathways.

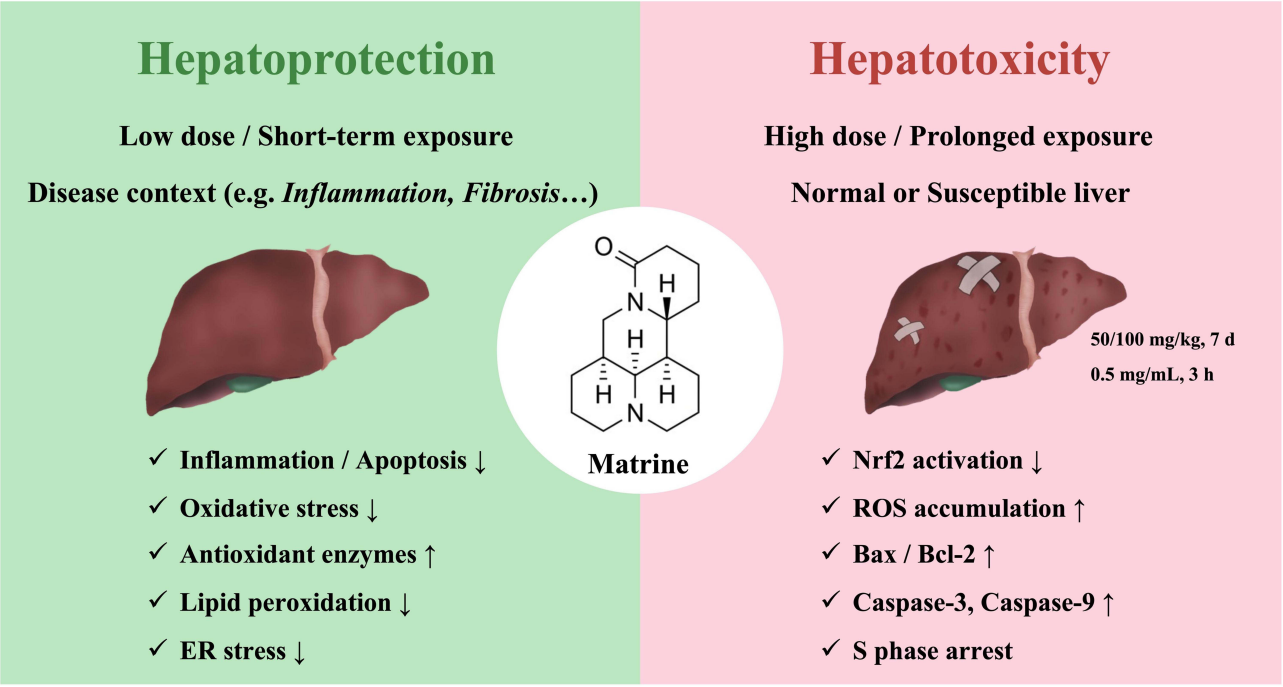

Figure 5 Schematic illustration of the hepatoprotective-hepatotoxic duality of matrine.

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the requirements for long-acting therapeutic agents, especially in the context of chronic liver diseases. Consequently, prolonging the in vivo retention time of matrine has emerged as a critical direction for future research.

Although clinical research on matrine is relatively limited, some existing reports indicate its therapeutic potential in liver and gallbladder diseases. In patients with hepatitis B, matrine has been found to significantly reduce HBV-DNA and HBsAg levels, contributing to the seroconversion of the hepatitis B virus.[161] In patients with primary liver cancer, matrine injection has shown liver-protective effects following trans-artery chemo-embolization, reducing hepatocyte damage and improving treatment tolerance.[162] However, the clinical evidence supporting the use of matrine in liver and gallbladder diseases remains limited, with most studies involving small sample sizes and requiring further validation of their methodologies and reproducibility. Therefore, while current data provide preliminary support for the potential of matrine in the treatment of liver and gallbladder diseases, larger-scale and rigorously designed clinical trials are needed to assess its efficacy and safety, providing a more solid scientific foundation for its broader application.

Despite extensive studies confirming matrine's pharmacological effects, such as anti-inflammatory, antioxidant, anti-fibrotic and anti-HCC properties, its clinical translation still faces several obstacles, including unclear mechanisms, limited dosage forms and low bioavailability. Therefore, to promote the translational application of matrine in liver disease treatment, this article proposes the following research directions and optimization strategies, aiming to provide a reference for its drug development and clinical use.

Comprehensive Elucidation of Matrine's Targets and Mechanisms of Action

Existing research has demonstrated that matrine modulates multiple key signaling pathways involved in the prevention and treatment of liver diseases, including NF-κB, PI3K/AKT/mTOR and Mst1-JNK. However, the critical regulatory nodes and cell type-pecific mechanisms underlying matrine's effects across different forms of liver pathology remain insufficiently defined. Future studies should employ cutting-edge technologies such as single-cell RNA sequencing and spatial transcriptomics to systematically map matrine's action networks in hepatocytes, Kupffer cells, HSCs and other relevant cell populations, thereby clarifying its modulatory effects on the hepatic microenvironment. Meanwhile, gene-specific tools such as RNA interference and CRISPR/Cas9 should be applied to dissect matrine's modulation of key targets in depth. By integrating multi-omics profiling with functional validation, it will be possible to construct a comprehensive "drug-target-pathological process" mechanistic atlas, providing a solid theoretical and technical foundation for target verification, new indication expansion, and individualized therapy.

Accelerating Pharmacokinetic and Toxicological Studies

Systematic characterization of matrine's in vivo pharmacokinetic remains limited. Critical parameters, including absorption kinetics, bioavailability, primary metabolic pathways, enzyme interactions and excretion routes, are yet to be fully delineated. Advanced analytical techniques such as LC-MS/MS and stable isotope tracing should be leveraged to profile matrine's pharmacokinetic behavior following different administration routes, with particular emphasis on its hepatic distribution, tissue retention time, and potential for accumulation. These data will be instrumental in guiding the design of controlled-release or targeted delivery formulations, optimizing dosing regimens, and rationalizing dosage and administration frequency. In parallel, toxicological data remain inadequate for a comprehensive preclinical safety assessment. Future work should establish multi-dimensional toxicity models encompassing acute, sub-chronic, chronic, reproductive and carcinogenic evaluations to thoroughly define safety margins and identify potential risks.

Development of Novel Matrine Delivery Systems

Given matrine's poor water solubility and low oral bioavailability, constructing efficient delivery systems is a key strategy to enhance its therapeutic efficacy. Recently, nanotechnology-based carriers, such as nanoparticles, solid dispersions, liposomes and polymeric micelles, have shown considerable promise in improving the solubility, stability and bioavailability of natural products.[163] Incorporating liver-targeting modifications into such systems may further increase matrine's preferential accumulation in diseased hepatic tissues, thereby enhancing therapeutic outcomes while

minimizing off-target effects. For example, liposomes or exosome carriers functionalized with N-acetylgalactosamine ligands could exploit asialoglycoprotein receptor (ASGPR)-mediated uptake in hepatocyte, increasing hepatic enrichment of matrine. Alternatively, smart nanoparticles engineered with dual ROS/pH sensitivity could enable stimulus-responsive release within fibrotic or tumor microenvironments, thereby achieving high local drug concentrations and greater treatment specificity.

Development of Combination Therapy Strategies

To maximize matrine's therapeutic potential and expand its clinical utility in liver diseases, rational design of combination regimens with existing agents is warranted. For instance, matrine could be combined with antifibrotic agents (eg, ursodeoxycholic acid), targeted antitumor drugs (eg, sorafenib), or other bioactive constituents from TCM (eg, flavonoids) to achieve synergistic effects, potentially improving efficacy, delaying resistance and reducing adverse effects. To ensure safety and scientific validity, systematic in vitro and in vivo studies should evaluate the pharmacokinetic compatibility, pharmacodynamic synergy and additive toxicities of such combinations, while elucidating underlying mechanisms. Moreover, optimization of dose ratios, administration sequences and scheduling will be necessary to define the optimal therapeutic window, thereby providing guidance for clinical application.

In summary, matrine is a bioactive natural compound with substantial potential for treating liver disease. However, its successful clinical application requires overcoming key challenges, such as context-dependent efficacy, dose-related toxicity, limited bioavailability and insufficient clinical validation. Through a mechanism-driven, cell-type-resolved investigation, an integrated pharmacokinetic-toxicological assessment, rational delivery system design, and well-founded combination strategies, matrine may progress from experimental promise to precise and safe clinical application in the management of liver diseases.

Abbreviations

5-FU, 5-Fluorouracil; AFP, alpha-fetoprotein; AKT, protein kinase B; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; ANIT, α-naphthyl isothiocyanate; APAP, acetaminophen; ASGPR, asialoglycoprotein receptor; AST, aspartate aminotransferase; CAR, coxsackievirus and adenovirus receptor; CAT, catalase; CCl_4, carbon tetrachloride; CSCs, cancer stem cells; CTGF, connective tissue growth factor; CYP450, cytochrome P450; DILI, Drug-induced liver injury; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; ERK1/2, extracellular regulated protein kinases 1/2; ECM, extracellular matrix; FGFR, fibroblast growth factor receptors; GSH, glutathione; GPX4, glutathione peroxidase 4; GST, glutathione S-transferase; HCC, hepatocellular carcinoma; HFD, high-fat diet; HGF, hepatocyte growth factor; HOCs, hepatic oval cells; HO-1, heme oxygenase 1; HSC, hepatic stellate cell; HSF1, heat shock factor 1; HSP72, heat shock protein 72; IL-1β/6, interleukin-1β/6; IRI, ischemia-reperfusion injury; JAK2, Janus kinase 2; JNK, c-Jun N-terminal kinase; L-FABP, liver-type fatty acid-binding protein; MASLD, metabolic dysfunction-associated steatotic liver disease; MCD, methionine-choline-deficient; MDA, malondialdehyde; MDM2, mouse double minute 2 homolog; MMPs, matrix metalloproteinases; mTOR, mammalian target of rapamycin; Mst1, mammalian sterile 20-like kinase 1; NAC, N-acetylcysteine; NAPQI, N-acetyl-p-benzoquinone imine; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor kappa; Nrf2, nuclear factor erythroid 2-related factor 2; PA, palmitic acid; PCNA, proliferating cell nuclear antigen; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1α; PI3K, phosphatidylinositide 3-kinase; PPARα, peroxisome proliferator-activated receptor alpha; PTEN, phosphatase and tensin homolog; PXR, pregnane X receptor; RhoA, Ras homolog family member A; ROCK, Rho-associated coiled-coil containing protein kinase; ROS, reactive oxygen species; SERCA, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase; SNAI1, snail family transcriptional repressor 1; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TAA, thioacetamide; TBIL, total bilirubin; TC, total cholesterol; TGF-β1, transforming growth factor β1; TG, triglycerides; TIMP, tissue inhibitors of metalloproteinase; TMAO, trimethylamine N-oxide; TNF-α, tumor necrosis factor α; TRAIL, TNF-related apoptosis-inducing ligand; TCM, traditional Chinese medicine; UGT, UDP-glucuronosyltransferase; VEGFR, vascular endothelial growth factor receptors; XIAP, X-linked inhibitor of apoptosis protein; α-SMA, α-smooth muscle actin.

Author Contributions

All authors have read and agreed to the published version of the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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