



Review Article

Motherwort: a mechanistic review on its health benefits of multiple-organ injury

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Abstract: *Leonurus japonicus* (motherwort) is included in China's List of Medicinal and Food Homologous Substances, thereby permitting its use as a health food and highlighting its significant potential for development in the application of herbal cuisine. At the same time, as an integral herb within the traditional Chinese medicine (TCM) repertoire, it has been extensively utilized for the amelioration of various clinical maladies since antiquity. Due to the great variety of active components and the wide range of pharmacological action, motherwort has garnered significant research attention. By summarizing and comparing the research on motherwort in recent years, this treatise has meticulously examined the chemical constituents and their safeguarding effects on the heart, kidneys, liver, and uterus, with the aspiration of offering valuable insights for subsequent clinical utilization and health functional food development of this herb.

Keywords: motherwort; chemical composition; multiple-organ protection

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1 Introduction

Leonurus japonicus Houtt. (motherwort) is the fresh or dry aboveground part of the Labiatae plant motherwort^[1]. According to the promulgation of the National Health Commission of the People's Republic of China, motherwort is incorporated into the catalogue of homology of medicine and food, thereby permitting its use as a health food and highlighting its significant potential for development in both nutritional and therapeutic applications. At the same time, as an integral herb within the traditional Chinese medicine (TCM) repertoire, it has been extensively utilized for the amelioration of various clinical maladies since antiquity. First published in *Divine Farmer's Classic of Materia Medica*, motherwort is widely used with the efficacy of activating blood circulation and regulating menstruation, diuretic and eliminating swelling, clearing heat, and detoxification^[2]. The *Supplement to Materia Medica* delineates its utility in the form of a poultice to mitigate mastitis-related inflammation and pain, as well as the ingestion of its juiced seedlings for the treatment of edema and noxious swellings^[3]. The *Compendium of Materia Medica* extols motherwort as the “sacred panacea for blood-related ailments,” attributing to it the abilities to “disperse fluid retention and invigorate blood circulation,” “stimulate blood production, dissipate blood stasis, regulate menstrual cycles, and counteract toxicity”^[4]. Its therapeutic spectrum encompasses the treatment of conditions such as fetal leakage, dystocia, syncope from blood loss,

blood wind, blood pain, collapse due to blood loss, hematuria, diarrhea, malnutrition, dysentery, hemorrhoids, internal hemorrhage, and constipation. The plethora of such historical annotations underscores the profound significance of motherwort in the realm of TCM.

With the progress of modern science and technology, a variety of chemical components have been gradually extracted and isolated from motherwort, such as alkaloids^[5,6], flavonoids^[7], diterpenoids^[8,9], ferulic acid, polysaccharides, volatile oils. Modern pharmacological studies have found motherwort to be effective in the treatment of cardiovascular diseases, acute kidney injuries, a variety of liver diseases, and especially in the treatment of uterine diseases. Further research into its mechanism of action has revealed that it is mostly responsible for protecting against a wide range of organ damage through anti-inflammatory, anti-oxidant and anti-apoptotic effects^[9]. Currently, the pharmacokinetic investigations of motherwort are predominantly centered on its alkaloidal constituents, indicative of its principal target organs being the heart, lung, and spleen, which exhibit a propensity for rapid absorption and metabolic processing. Furthermore, it is postulated that motherwort may engage in pharmacokinetic interactions with drugs that are metabolized by the CYP1A2, CYP2D6, and CYP3A4 enzyme systems^[10]. As a medicinal and edible Chinese medicinal herb, motherwort has good safety, but there are still some reports on the toxicity in clinical practice. Most

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of the existing literatures have reported that motherwort has liver and kidney toxicity^[11,12].

The diverse active substances and good pharmacokinetic characteristics of motherwort show great promise for clinical applications in the treatment of multiple-organ injury^[9]. In this paper, we review the active components of motherwort and its protective mechanism against multi-organ disease injury, with a view to providing new ideas for the diagnosis and treatment of clinically relevant organ diseases, as well as providing a theoretical basis for the development of clinical pharmaceutical products and associated food-drug combination products.

2 Chemical composition for motherwort

Motherwort has a wide variety of chemical components, including alkaloids, flavonoids, diterpenoids, phenylethanoid glycosides^[13,14], phenolic acids, cyclic polypeptides, and volatiles. It also contains trace elements such as zinc (Zn), copper (Cu), manganese (Mn), iron (Fe), nickel (Ni), lead (Pb), arsenic (As), selenium (Se), germanium (Ge), rubidium (Rb), etc. Among them,

the main effective components are alkaloids and diterpenoids^[15,16]. The primary constituents in motherwort are illustrated in Fig. 1.

2.1 Alkaloids

Alkaloids are the main active ingredients in motherwort. Motherwort contains various alkaloids, such as leonurine, leonuridine, stachydrine, and leonurinine^[17], with diuretic, antiplatelet aggregation, anti-inflammatory, antioxidant, and other biological activities^[18]. Leonurine, belonging to aromatic alkaloids, is a kind of alkaloid with the highest content and the strongest activity. It is almost insoluble in water, with a melting point of 238 °C, and mostly exists in the form of its salt in nature^[19]. Modern pharmacological studies have shown that it has significant biological activities, including antioxidant, anti-inflammatory, antiviral, antitumor, promoting blood circulation to remove blood stasis, brain antiaging, and other functional effects^[20-22]. It can be used to treat cardiovascular, neurological and uterine diseases, and its mechanism may be related to B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra large (Bcl-xl), hypoxia-inducible factor-1 alpha (HIF-1α) and vascular

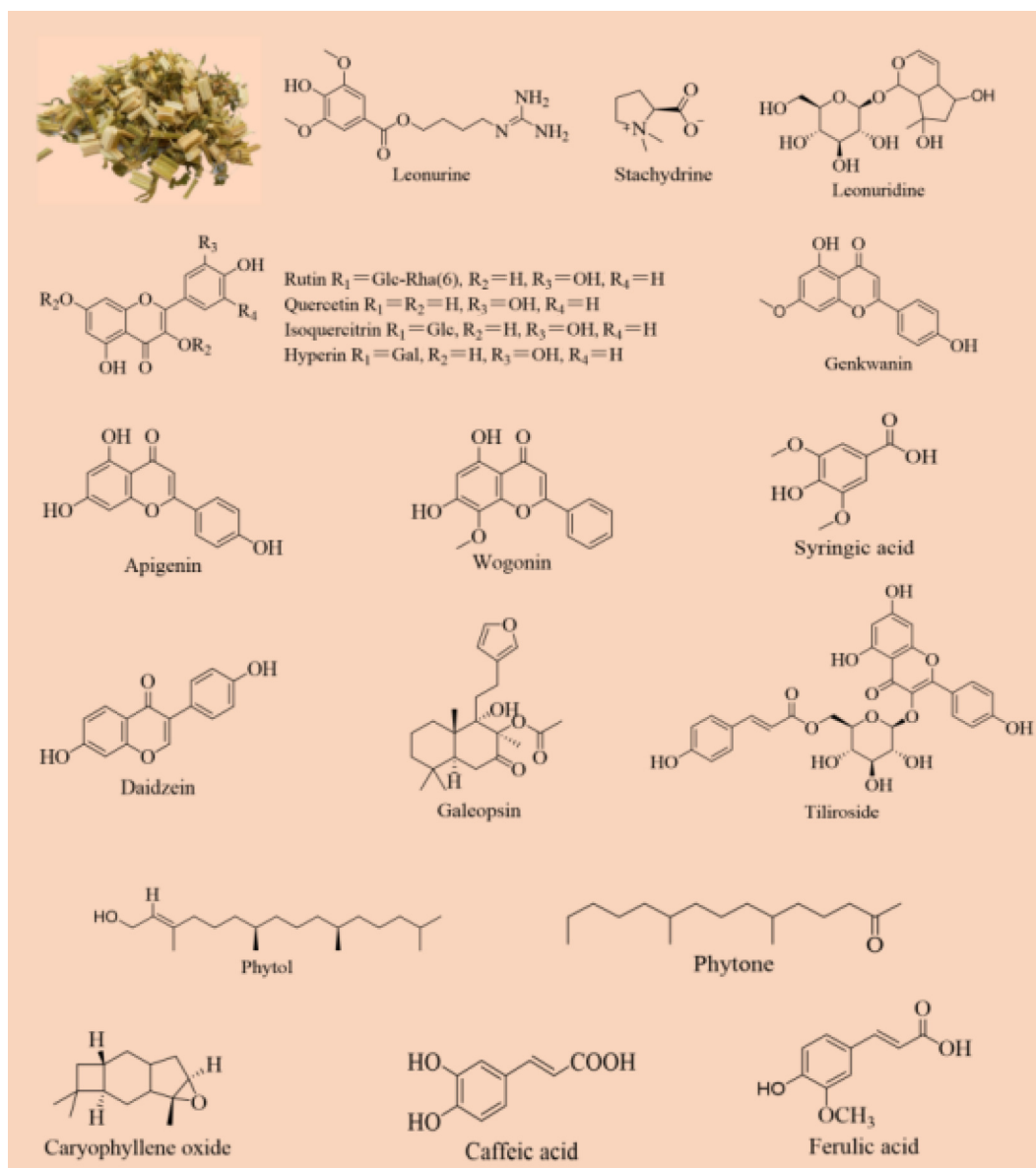


Figure 1 Primary constituents in motherwort.

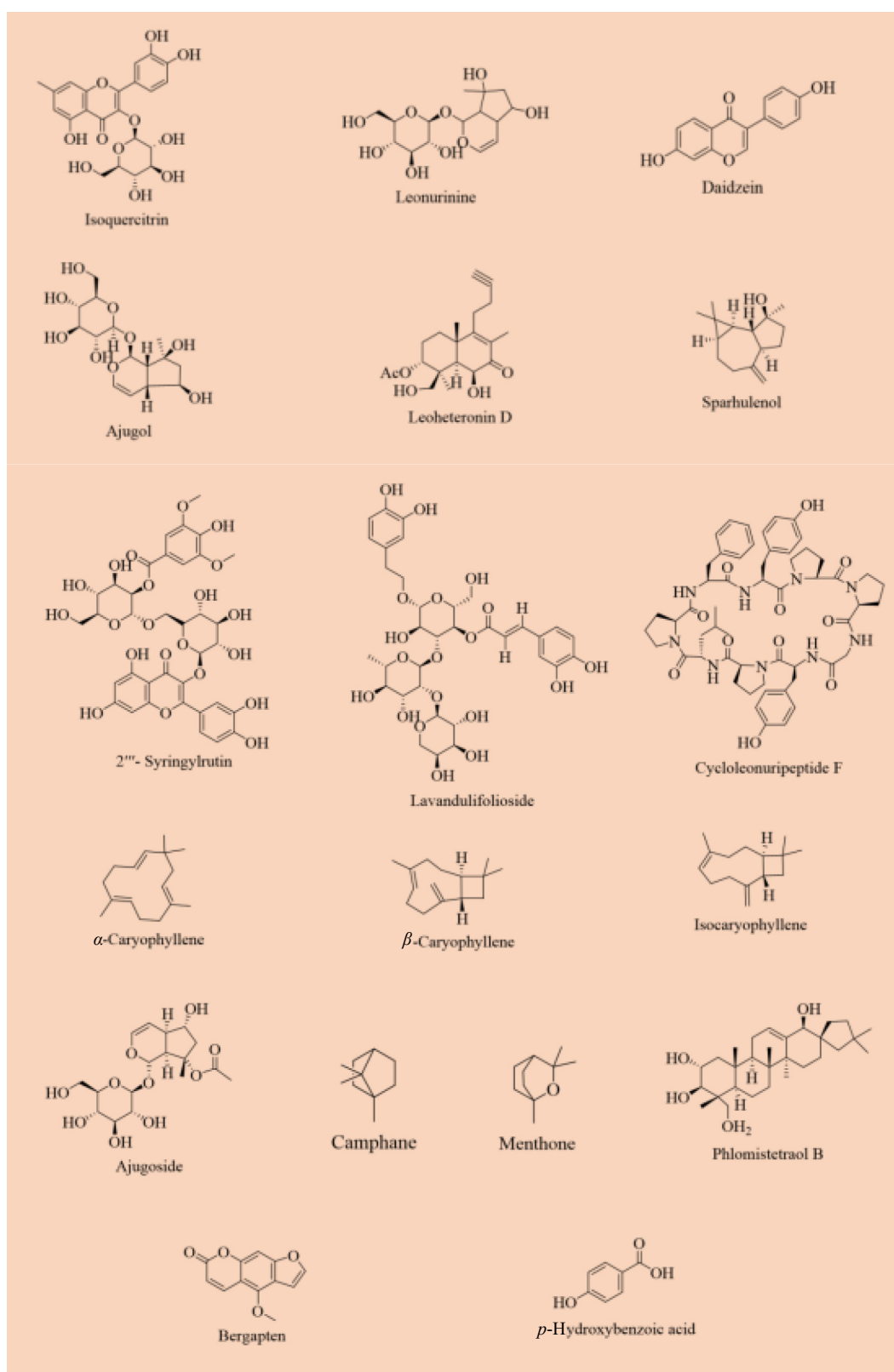


Figure 1 (Continued).

endothelial growth factor (VEGF). Some studies have shown that motherwort also has significant brain protection and has the potential to prevent stroke^[21]. In addition, motherwort is expected to become a prospective drug for the prevention of type II diabetes^[23]. Stachydrine is also the main component of motherwort, which is converted from ornithine. It belongs to

quaternary ammonium water-soluble alkaloids and has the effects of shrinking uterus, treating postpartum hemorrhage and improving umbilical vein endothelial injury. The mechanism is related to the regulation of Th1/Th2, Th17/Treg cells and the inhibition of tissue factor (TF) expression. At present, the research on motherwort alkaloids mainly focuses on leonurine and

stachydrine, and there are few studies on other alkaloids. Therefore, the exploration of new alkaloid components and the pharmacological effects and mechanism exploration of existing alkaloids still need to be strengthened.

2.2 Flavonoids

Flavonoids are widely found in various natural medicinal plants. At present, dozens of flavonoids have been isolated from motherwort, mainly including flavonoid glycosides and their aglycones^[24,25], such as rutin^[26], quercetin^[24], hyperoside^[24], isoquercitrin^[24], apigenin^[24], genkwanin^[24], wogonin^[27], daidzein^[27], tiliroside^[28], Ajugol^[29], and 2'-syningylrutin^[7]. Those flavonoid glycosides and their aglycones are used for antioxidation, antibacterial, anti-inflammation, and protection of the uterus and cardiovascular system^[30].

2.3 Diterpenoids

The most abundant compounds in motherwort are diterpenoids. Currently, more than 50 diterpenoids have been isolated and identified from motherwort, all of which are hemijulipane-type diterpenes. These compounds can be categorized into five groups on the basis of the five-membered ring on C-12: furan ring, dihydrofuran ring, lactone ring, α,β -unsaturated lactone ring, and tetrahydrofuran ring. Many of these compounds exhibit significant biological activity *in vivo* or *in vitro*^[30]. Moreover, they can be divided into three types. The C-9 side chain type is the side chain at the C-9 position. The furan ring type includes diterpenes that form a five-membered lactone ring at the end of the C-9 side chain with a furan lactone ring structure and diterpenes with a furan ring or a tetrahydrofuran ring at the end of the side chain. The main feature of bis-spirocyclic diterpenes is the two spiro atoms at C-9 and C-13, which are bonded ring synthesized into ethers to form a five-membered epoxide. The two bonded ring synthesized into ether at the end of C-9 and C-13. C-15 and C-16 are linked by oxygen bridges to form a double spirocyclic structure with 9,13,15,16-diepoxy fragments. With further research, other structural types of diterpenes have been gradually discovered in motherwort^[31]. Related studies have shown that terpenoids have the effect of eliminating stasis and promoting blood circulation. Some terpenoids show significant anti-inflammatory activity by inhibiting the pro-inflammatory factor tumor necrosis factor- α (TNF- α).

2.4 Polysaccharides

In recent years, some polysaccharides extracted from natural plants with biological activities of disease prevention and treatment have attracted considerable attention in the field of biochemistry and pharmacology. For example, plant polysaccharide is a kind of natural biological macromolecule or its glycoconjugate with antitumor, anticancer, anticoagulant, immune stimulation, antioxidant, and other biological activities^[32-35]. The mechanism encompasses a diverse array of pathways, for instance, the scavenging ability of DPPH free radicals may be related to its antioxidant capacity, and its mechanism of action may be related to the supply of hydrogen^[36]. The crude polysaccharide contained in motherwort has significant antibacterial activity against a variety of microorganisms, which is related to the destruction of microbial cell wall and cell membrane^[37]. Box-Behnken experiment showed that motherwort polysaccharide was a natural antioxidant and preservative citation^[32]. Currently, the research on

polysaccharides from motherwort is still limited. Further study about the process of extracting polysaccharides and the antioxidant capacity and antibacterial activity of the extracted polysaccharides is still needed. Furthermore its clinical application potential needs to be further explored.

2.5 Volatile oils

The volatile oil of motherwort is mainly composed of diterpenes (32.77%) and sesquiterpenes (45.37%), of which phytoalexin (19.02%), phytol (13.75%), stigmaterol (11.49%), and β -caryophyllene (9.89%)^[38] are the main components. Other sesquiterpenes with high content are spatulate eucalyptus oleanol (5.31%), α -caryophyllene (3.38%)^[38], and isostigmaterol (3.00%). The main structural types are butyranes and juniperanes, which accounted for 41.73% of the total oil content. In addition, monoterpenes account for 7.82% of this oil, mainly menthane and camphene analogs (3.82%), with an absolute predominance of oxygenated monoterpenes^[39]. The volatile oil of motherwort has antibacterial, anti-inflammatory and zebrafish embryo toxicity. The study found that its main antibacterial component is β -caryophyllene^[39]. The embryo toxicity to zebrafish can lead to the increase of zebrafish embryo lethality rate and deformity rate, slow heart rate and different degrees of morphological changes^[40]. However, the related toxic components and mechanism of action are still unclear, and the pharmacological effects of other active components also need to be further investigated.

2.6 Other compounds

Motherwort contains phenylethanol glycosides, phenolic acids, triterpenoids, cyclic enol ether terpenoids, cyclic polypeptides, coumarins, lignans, trace elements, and other compounds^[41]. Modern pharmacological studies have found phenylethanol glycosides to possess pharmacological activities such as hepatoprotective^[42], neuroprotective^[43], anti-inflammatory^[44], antitumor^[45], and cardioprotective^[44]. The main phenolic acids are butyric acid, ferulic acid, *p*-hydroxybenzoic acid, and caffeic acid^[46], exhibited some hepatoprotective and antioxidant activities in relevant studies. Approximately a dozen kinds of phenylethanols are isolated from motherwort, such as leonurisode B, martynoside and cistanoside E. And pharmacological studies have shown that phenylethanol glycosides have antimicrobial, antioxidation, platelet inhibitory, and other activities^[30]. The chemical compounds from motherwort are shown in Table 1.

3 Protective effect of motherwort on various organs

3.1 Cardioprotective effects of motherwort

Heart disease is a common circulatory system disease. It belongs to the common internal medicine diseases, and it is mainly divided into congenital heart disease and acquired heart disease. The common heart diseases are coronary heart disease, myocarditis, myocardial infarction, and arrhythmia. Motherwort has a protective effect on various heart diseases^[47,48], for instance, leonurine can ameliorates lipopolysaccharide (LPS)-induced myocarditis. The mechanism is to inhibit the activation of nuclear factor- κ B (NF- κ B) signaling pathway in myocarditis, and inhibit LPS-induced apoptosis and LPS-induced nuclear translocation and nuclear protein expression of p65 in H9c2 cells. Motherwort

Table 1 Chemical compounds from motherwort

Name	Compound	Molecular formula	Reference
Alkaloids	Leonurine	C ₁₄ H ₂₁ N ₃ O ₅	[15]
	Leonuridine	C ₁₅ H ₂₄ O ₉	[15]
	Stachydrine	C ₇ H ₁₃ NO ₂	[15]
	Leonurinine	C ₁₅ H ₂₄ O ₉	[15]
	Rutin	C ₂₇ H ₃₀ O ₁₆	[30]
	Quercetin	C ₁₅ H ₁₀ O ₇	[28]
	Hyperin	C ₂₁ H ₂₀ O ₁₂	[28]
Flavones	Isoquercitrin	C ₂₁ H ₂₀ O ₁₂	[28]
	Apigenin	C ₁₅ H ₁₀ O ₅	[28]
	Genkwanin	C ₁₆ H ₁₂ O ₅	[28]
	Wogonin	C ₁₆ H ₁₂ O ₅	[31]
	Daidzein	C ₁₅ H ₁₀ O ₄	[31]
	Tiliroside	C ₃₀ H ₂₆ O ₁₃	[32]
	Ajugol	C ₃₆ H ₃₈ O ₂₀	[33]
Diterpenes	2'''-Syringylrutin	C ₃₆ H ₃₈ O ₂₀	[34]
	Leoheteronin D	C ₂₀ H ₃₆ O ₂	[36]
	Phytone	C ₁₈ H ₃₆ O	[41]
	Phytol	C ₂₀ H ₄₀ O	[41]
	Caryophyllene oxide	C ₁₅ H ₂₄ O	[41]
	Sparhulenol	C ₁₅ H ₂₄ O	[41]
	α-Caryophyllene	C ₁₅ H ₂₄	[41]
Volatile oil	β-Caryophyllene	C ₁₅ H ₂₄	[41]
	Isocaryophyllene	C ₁₅ H ₂₄	[41]
	Menthane	C ₁₀ H ₁₈	[42]
	Camphane	C ₁₀ H ₁₈	[42]
	Lavandulifolioside	C ₃₄ H ₄₄ O ₁₉	[43]
	Phlomisetraol B	C ₂₈ H ₄₆ O ₄	[43]
	Ajugoside	C ₁₇ H ₂₆ O ₁₀	[43]
Cycloleonoripeptide	Cycloleonoripeptide F	C ₅₅ H ₆₉ N ₉ O ₁₁	[43]
Coumarins	Bergapten	C ₁₂ H ₈ O ₄	[43]
	Syringic acid	C ₉ H ₁₀ O ₅	[48]
	Ferulic acid	C ₁₀ H ₁₀ O ₄	[48]
Phenolic acids	p-Hydroxybenzoic acid	C ₇ H ₆ O ₃	[48]
	Caffeic acid	C ₉ H ₈ O ₄	[48]

alkaloids exert effective cardioprotective effects against myocarditis through anti-inflammatory and antioxidant mechanisms^[49,50].

Motherwort also has a protective effect against cardiomyocyte hypertrophy^[51,52]. Hydrastine can significantly increase the ratios of cardiac index, left ventricular index, and cardiomyocyte cross-sectional area in isoproterenol-induced cardiomyocyte hypertrophy model rats, decreased the levels of cardiac natriuretic factor, B-type natriuretic peptide, and β-myosin heavy-chain mRNA; and lowered the levels of serum pro-inflammatory factors (interleukin-6 (IL-6), TNF-α, interferon-gamma (IFN-γ) and interferon-beta (IFN-1β)) levels, thus reducing oxidative stress^[53]. By observing the effects of hydrastine hydrochloride on cardiac hypertrophy and heart failure caused by transverse aortic narrowing showed that hydrastine hydrochloride improved cardiac function and calcium transient amplitude, inhibited sarcoplasmic reticulum (SR) leakage and the number of cardiomyocyte calcium sparks in the cardiomyocytes of cardiomyopathic hypertrophic mice; ameliorated phenylephrine-induced myonodal contraction, calcium transient, and

cardiomyocyte calcium sparks, downregulated the hyperphosphorylation of calmodulin-dependent kinase II (CaMKII), ryanodine receptor 2 (RyR2), and phospholamban (PLN), and prevented FK506-binding protein 12.6 (FKBP12.6) from dissociating from RyR2. These findings suggest that hydrastine hydrochloride has a favorable therapeutic effect on the heart^[54]. Meanwhile, the calmodulin neurophosphatase (CaN)/nuclear factor of activated T (NFAT) cell signaling pathway plays an important role in pathological cardiac hypertrophy. The potential effects of hydrastine hydrochloride, a bioactive ingredient extracted from motherwort capsules, and its effects on chronic α1-adrenoceptor activation during pathologic cardiac hypertrophy and the underlying mechanisms were investigated. First, transcriptome analysis was used to determine that a pathological hypertrophy model could be prepared after phenylephrine stimulation. In primary cultured lactating rat ventricular myocytes, hydrastine hydrochloride reduced the phenylephrine-induced mRNA expression of the cardiomyocyte surface area and cardiac hypertrophy markers cardiac natriuretic peptide, B-type

natriuretic peptide, and β -myosin heavy chain/ α -myosin heavy chain. In addition, phenylephrine stimulation strongly induced the activation of the CaN/NFAT signaling pathway. Hydrastine hydrochloride inhibited CaN activation and reduced nuclear translocation of nuclear factor of activated T-cells cytoplasmic 3 (NFATc3) in phenylephrine-stimulated lactating mouse ventricular myocytes. In phenylephrine-treated mice, hydrastine hydrochloride treatment attenuated cardiac hypertrophy and modulated cardiac function. In summary, hydrastine hydrochloride attenuated phenylephrine-stimulated cardiac hypertrophy by inhibiting the CaN/NFAT signaling pathway, the underlying mechanism may be related to the inhibition of CaN activation and NFATc3 nuclear translocation, suggesting that the modulation of the CaN/NFAT signaling pathway may be used as a strategy for the prevention or treatment of pathologic cardiac hypertrophy^[55].

Motherwort could inhibit myocardial fibrosis (MF), and it has a significant protective effect on cardiomyocytes. Previous studies have shown that inhibition of excessive activation of cardiac fibroblasts (CF) can effectively treat MF. By isolating neonatal rat CFs and stimulating them with angiotensin II (Ang II) to mimic the pathological process of MF *in vitro* revealed that leonurine significantly inhibited collagen synthesis and CF proliferation, differentiation, and migration and promoted apoptosis of CF cells, the mechanism is related to the up-regulation of p53 and miR-29a-3p expression by leonurine (LE)^[56]. Pyroptosis has been demonstrated to play an important role in MF. In a study of isoprenaline (ISO)-induced MF model in rats, leonurine was found to inhibit the expression levels of pyroptosis-related proteins and ameliorate cardiac fibrosis. *In vitro* experiments found that leonurine can inhibit the expression of pyroptosis and fibrosis-related proteins. In addition, Leonurine inhibits apoptosis by regulating the TGF- β /Smad2 signaling pathway to protect cardiomyocytes and improve MF^[57]. Therefore, in clinical practice, it is expected to treat MF through motherwort.

Hypertension is a common risk factor for heart failure, and excess Ang II leads to hypertensive cardiac changes such as hypertrophy, cardiac fibrosis, remodeling, and dysfunction. A study found that leonurine can significantly alleviate Ang II-induced cardiac hypertrophy, fibrosis, and inflammation in mice and cultured cardiomyocytes. Echocardiography showed that leonurine preserved cardiac function in mice. Leonurine attenuated Ang II-induced inflammatory response and injury in cardiomyocytes by inhibiting the activation of mitogen-activated protein kinase (MAPK) and NF- κ B pathways. Inhibition of MAPKs and NF- κ B in cardiomyocytes eliminated the anti-inflammatory effects of leonurine. That is, the inhibition of MAPK and NF- κ B pathways by leonurine exerted a protective effect on Ang II-induced cardiac remodeling and dysfunction in hypertension^[58]. Leonurine may be an effective drug in the clinical treatment of hypertensive heart failure, but at the same time, it may have effects on other target organs, so its safety needs to be further investigated.

Ferroptosis is a novel form of programmed cell death caused by iron-dependent lipid peroxidation and excessive production of ROS. Its morphology is characterized by mitochondrial atrophy, increased mitochondrial membrane density, mitochondrial cristae degeneration and rupture, and unchanged nuclear morphology. A study of transverse aortic constriction (TAC)-induced heart failure model in mice demonstrated that the active ingredient stachydrine of motherwort could inhibit myocardial iron mutation and improve cardiac function. In the early stage of the experiment,

obvious morphological characteristics of iron allergy were found, and lipid peroxidation was increased in myocardial tissue, accompanied by abnormal cystine metabolism and iron metabolism. The contractile function of adult mouse cardiomyocytes was severely impaired after the occurrence of TAC-induced ferroptosis. In heart failure mice and elastase-induced cardiomyocyte iron poisoning models, stachydrine significantly improved mitochondrial morphological characteristics and related signaling pathways of ferroptosis, and its mechanism was mainly related to lipid peroxidation level, cystine metabolism and iron metabolism^[59]. Ferroptosis pathway plays an important role in the progression of heart failure. The studies have shown that multi-target Chinese medicine monomers represented by stachydrine provide new ideas for the prevention and treatment of cardiac ferroptosis.

In summary, motherwort has a therapeutic effect on myocarditis, myocardial hypertrophy, myocardial fiber and other diseases, and can have a certain protective effect on the heart. However, there are fewer reports on the treatment of related diseases by motherwort in clinical practice, and the effect and mechanism of motherwort components on related diseases need to be further investigated.

3.2 Protective effect of motherwort on kidney

Kidney belongs to the urinary system organs of the human body. It filters impurities in the blood and maintains the balance of body fluids and electrolytes. It also has the role of regulating blood pressure in important organs. Kidney injuries are extremely common, accounting for about 65% of all genitourinary tract injuries, such as blunt injuries (80%), penetrating injuries, and injuries of medical origin (as a result of surgery, extracorporeal shockwave lithotripsy, or renal biopsy). Open kidney injuries are often associated with injuries to other intra-abdominal organs, and complications include hemorrhage, urinary extravasation, abscess formation, and hypertension. Previous studies have found that stachydrine may inhibit the expression of apoptosis by down-regulating the expression of endoplasmic reticulum stress-related apoptosis pathway C/EBP homologous protein (CHOP) and caspase-3, interfering with the conduction pathway of endoplasmic reticulum stress-specific transcription factors, thereby slowing down the occurrence and development of renal interstitial fibrosis. Further research found that motherwort extract could significantly reduce the levels of serum uric acid and creatinine in hyperuricemia model rats, increase the level of uric acid, and significantly downregulate the mRNA levels of urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9) in kidney. The mRNA levels of organic cation transporter (OCT) and carnitine transporter (OCTN) could be upregulated, and renal uric acid excretion could be promoted, its mechanism of action may be related to kidney-related transporters, suggesting that motherwort has a certain protective effect on the kidney^[60]. The animal model of renal interstitial fibrosis induced by unilateral ureteral obstruction in rats was found that stachydrine could upregulate the expression levels of endoplasmic reticulum stress proteins glucose-regulated protein 78 (GRP78) and GRP94, hinders the apoptosis of renal tubular epithelial cells, and reduces the progression of renal interstitial fibrosis^[61]. Its mechanism may be related to the inhibition of the secretion of apoptotic effector molecules, which provides an effective treatment for delaying or reversing renal tubulointerstitial fibrosis. Later studies have found that stachydrine can inhibit the increase of activating transcription factor 4 (ATF4) protein expression mediated by protein kinase

r-like endoplasmic reticulum kinase (PERK) signaling pathway and the activation of CHOP protein expression by ATF4, prevent apoptosis, and thus slow down the occurrence and development of renal interstitial fibrosis^[62].

Acute kidney injury (AKI) is a common and severe syndrome characterized by renal tubular injury and sudden loss of renal function within a few hours. Its high morbidity and mortality is a global health problem^[63]. Cisplatin, as an antitumor drug, is widely used in the treatment of solid tumors and is also one of the main causes of AKI in patients with cancer^[64]. Ferroptosis plays a key role in cisplatin-induced AKI^[65]. Nuclear factor erythroid 2-related factor 2 (Nrf2) deficiency induces ferroptosis-related protein expression and iron accumulation *in vivo* and aggravates cisplatin-induced AKI^[66]. Previous studies have found that Nrf2/NRF2 pathway regulates oxidative stress and lipid peroxidation and positively regulates cisplatin-induced AKI. *In vitro*, leonurine activated Nrf2 to prevent iron accumulation, lipid peroxidation, and ferroptosis, which was abolished in siNrf2-treated cells. In addition, leonurine effectively inhibited cisplatin-induced renal injury, as evidenced by evaluation of serum creatinine, blood urea nitrogen, kidney injury molecule-1, and neutrophil gelatinase-associated lipocalin (NGAL). The protective effect of leonurine on cisplatin-induced AKI is achieved by activating the antioxidant signaling molecule Nrf2 and inhibiting ferroptosis-related morphological and biochemical changes. Hence, in the evaluation of the antiferroptotic effect of Nrf2 and leonurine in a cisplatin-induced AKI mouse model, detecting the effect of leonurine on erastin and (1S,3R)-2-(2-Chloroacetyl)-2,3,4,9-tetrahydro-1-(4-(methoxycarbonyl)phenyl)-1H-pyrido[3,4-b]indole-3-carboxylic acid methyl ester (RSL3)-induced ferroptosis in HK-2 human proximal tubular epithelial cell (PTEC) found that Nrf2 knock out (KO) mice were more prone to ferroptosis after cisplatin-induced AKI than control mice. The renal protective effect of Nrf2 activation on cisplatin-induced AKI was achieved at least in part by inhibiting lipid peroxide-mediated ferroptosis, highlighting the potential of leonurine in the treatment of AKI^[47]. In recent years, relevant research groups have established a classical AKI model induced by cisplatin and conducted leonurine intervention experiments. Leonurine can inhibit endoplasmic reticulum stress-related ferroptosis by regulating the ATF4/CHOP/ASCL4 signaling pathway to reduce AKI and protect renal tubular epithelial cells, thus providing a new mechanism for the treatment of AKI^[67]. Leonurine pretreatment significantly reduced serum creatinine and urea nitrogen in ischemia/reperfusion (I/R) rats and alleviated acute renal tubular injury^[68]. In addition, leonurine can significantly increase the expression levels of antioxidant proteins and reduce the level of inflammatory factors. Further studies have found that LE promotes Nrf2 into the nucleus, promotes the expression levels of heme oxygenase-1 (HO-1) and quinone oxidoreductase-1 (NQO-1), and inhibits the TLR4/NF- κ B signaling pathway in the renal tissue of ischemic AKI rats; these findings revealed that LE resists oxidative stress injury by activating Nrf2 nuclear translocation, inhibits the expression levels of inflammatory genes mediated by the TLR4/NF- κ B pathway, and possesses a protective effect on ischemic AKI^[69]. In summary, motherwort is expected to be a natural product for the treatment of AKI.

Diabetic nephropathy (DN) is a microvascular complication of diabetes and the main cause of end-stage renal disease. The incidence of DN accounts for more than 40% of diabetes^[70]. High glucose and lipid metabolism disorder is the main reason for the occurrence and development of DN^[71,72]. Early studies have shown

that the expression or activity of sterol regulatory element-binding proteins (SREBPs) was increased in DN models, increasing the degradation of mature SREBPs is a powerful method to reduce lipid and improve lipid metabolism disorders. Leonuride, as the main active ingredient of motherwort, has many biological activities such as antioxidation and anti-inflammation. Studies have shown that LE can effectively improve glucose and lipid metabolism disorders. In streptozotocin-induced type 2 diabetic mice, kidney function was also improved by inhibiting the activity of SREBPs. This study was the first to describe the detailed mechanism by which LE inhibits the precursor SREBPs, providing a new direction for the treatment of diabetes^[73].

3.3 Protective effect of motherwort on liver

Liver is the largest solid organ in the human body, and it is responsible for performing several key biological functions such as metabolism, detoxification, and protein production^[74]. It also has a high degree of immune activity^[75]. In addition to maintaining a local immune regulatory environment and promoting tolerance to frequently encountered antigens, liver has a systemic barrier function against pathogens and toxins discharged from the intestine^[76]. Common clinical liver diseases include hepatitis, cirrhosis, liver fibrosis, and liver cancer. Relevant studies have found that the extract of motherwort has certain pharmacological effects on liver diseases. For example, stachydrine has a protective effect on CCl₄-induced acute liver cell injury in mice through antioxidation^[77]. Through the experiment of hyperlipidemia model rats, it was found that motherwort helps the liver to decompose and metabolize total cholesterol and triglycerides, removes excess cholesterol, and has a preventive and therapeutic effect on hyperlipidemia^[78], however, its research and specific mechanism of action on lipid metabolism-related diseases need further in-depth study. In a study of the effect of ethanol extract of motherwort on NAFLD, by established a nonalcoholic fatty liver model it was found that motherwort could reduce serum glucose and insulin levels, improve insulin sensitivity, increase the expression levels of phosphorylated AMP-activated protein kinase (p-AMPK) and peroxisome proliferator-activated receptor α (PPAR α) to improve hepatic steatosis, suggesting that *L. japonicus* extract (LJE) may be a potential drug for the treatment of NAFLD^[79].

Stachydrine is an alkaloid with anti-inflammatory and antioxidant properties extracted from motherwort. Through acetaminophen (APAP)-induced liver injury mouse model experiments, it was found that excessive APAP can significantly increase serum alanine aminotransferase levels, liver pro-inflammatory cytokines, malondialdehyde activity, ERK, phosphoprotein kinase B (AKT) and macrophage-stimulating protein expression levels. In APAP-induced liver injury mice, stachydrine treatment significantly reduced these parameters. The results showed that stachydrine could prevent APAP-induced liver injury by reducing inflammatory response, inhibiting ERK and AKT pathways and macrophage-stimulating protein expression^[80]. In addition, there are also studies have found that leonurine can reduce APAP-induced mouse primary hepatocyte injury, promote proliferation, and inhibit oxidative stress injury. Leonurine also significantly regulated APAP-induced mouse alanine aminotransferase levels. In *in-vivo* and *in-vitro* experiments, leonurine can protect APAP-induced acute liver injury (ALI) by reducing serum aspartate aminotransferase and alanine aminotransferase levels, liver histopathological damage, hepatocyte necrosis, inflammation, and oxidative stress-induced damage. In

addition, leonurine reduced APAP-induced hepatocyte necrosis by reducing the expression levels of Bax and cleaved calpain I and increasing the expression of Bcl-2. Leonurine promotes Nrf2 nuclear translocation by activating the Nrf2 pathway, upregulates the expression levels of oxidative stress-related proteins in liver tissue, and alleviates APAP-induced oxidative stress-induced damage. Leonurine inhibited APAP-induced liver inflammation by inhibiting Toll-like receptor 4 (TLR4) and NLR family pyrin domain protein 3 (NLRP3) pathways. In addition, leonurine promoted the activation of phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway in liver tissue of ALI mice. Network pharmacology, molecular docking, and immunoblotting experiments showed that PI3K was a potential target for LEO in the treatment of ALI. Molecular docking and cell thermomigration assay showed that leonurine could bind to PI3K protein stably. In summary, leonurine alleviates ALI by regulating the PI3K/Akt/mTOR signaling pathway and reverses liver cell necrosis, inflammatory response, and oxidative stress-induced injury^[81]. Therefore, it is suggested that leonurine is a potential target for the treatment of APAP-induced liver injury, and more studies are needed to confirm its clinical application prospects.

Cytochrome P450 (CYPs) enzymes can catalyze the metabolism of various exogenous and endogenous substances and participate in most phase I biotransformation. To study the effect of leonurine hydrochloride (LH) on CYPs' enzyme activity, phenacetin (1A2), coumarin (2A6), diclofenac (2C9), S-mephenytoin (2C19), paclitaxel (2C8), dextromethorphan (2D6), chlorzoxazone (2E1), and testosterone (3A4) were used as enzyme selective substrates. The half maximum inhibitory concentration (IC₅₀) value was calculated to represent the inhibition intensity, the inhibition of CYPs was fitted by a competitive or non-competitive inhibition model, and the corresponding parameters were obtained. The results showed that LH inhibited the activity of CYP1A2 and CYP2D6 in a competitive manner ($K_i = 8.667$ and $7.805 \mu\text{mol/L}$) and that of CYP3A4 in a non-competitive manner ($K_i = 9.507 \mu\text{mol/L}$). The inhibitory effect of LH on CYP3A4 was time-dependent, and its K_i/Kinact value was $4.31/0.044 \text{ L}/(\mu\text{mol}\cdot\text{min})$. The inhibitory effect of LH on CYP1A2, CYP2D6, and CYP3A4 was confirmed by *in-vitro* experiments, suggesting potential drug interactions. Therefore, the pharmacokinetic interaction between LH and CYP1A2 or CYP2D6 or CYP3A4 substrates is likely to occur, indicating that LH has a certain effect on the activity of CYPs enzymes in human liver microsomes^[82].

3.4 Protective effect of motherwort on uterus

The uterus is an important reproductive organ of women. It has the function of conceiving embryos and fetuses. The lesions that may occur in the uterus include cervical inflammation, cervical tumors, endometriosis, adenomyosis, and abnormal uterine development. Motherwort, as a famous multi-product medicine, has the effect of "regulating menstruation". Since ancient times, it has been a good medicine for the treatment of women's "multi-product belt"^[18,30]. The uterus is the key target organ of the "regulating menstruation" effect of motherwort^[83].

Early studies have found that motherwort has bidirectional modulatory effects on the uterus. It stimulates uterine contractions in normal guinea pigs^[84] and inhibits oxytocin-induced uterine convulsions^[85]. It also inhibited LPS-induced abnormal proliferation of uterine smooth muscle cells (MSMCs) by downregulating calponin expression^[86]. The water-soluble alkaloids and total flavonoids of *L. japonicus* have an excitatory

effect on the isolated uterus, which is related to the increase in Ca^{2+} content in the cytoplasm of MSMCs, whereas fat-soluble alkaloids have a certain inhibitory effect on the isolated uterus^[87]. The aqueous extract of motherwort has an excitatory effect on normal rat uterus and a diastolic effect on spastic uterus^[88]. Motherwort injection enhances the sensitivity of isolated uterine smooth muscle, promotes energy metabolism, and protects the ischemia-reperfusion uterus by opening Ca^{2+} channels^[89,90]. Therefore, stachydrine can enhance uterine contraction and promote angiogenesis, and it plays an important role in the treatment of postpartum hemorrhage and uterine invagination^[91-93].

The pathological mechanism of incomplete postpartum uterine involution is complex, which is closely related to apoptosis, inflammatory response and endometrial fibrosis^[94]. Motherwort can promote postpartum (Cesarean section) uterine involution^[95,96]. According to a study, motherwort injection can promote uterine regeneration after Cesarean section, and the mechanism may be related to the improvement of inflammatory indexes (decrease in C-reactive protein and IL-6), endometrial and sub-endometrial blood flow (increase in flow index, vascularized flow index, and vascularization index), and coagulation function (increase in thrombin time and decrease in fibrinogen), with obvious efficacy and good safety^[97]. In a study of the restorative effect of motherwort granules on postnatal uterine insufficiency in rats, motherwort granules could effectively improve postnatal uterine insufficiency, and the mechanism may be related to the inhibition of uterine tissue cyclooxygenase-2 (COX-2), TGF- β 1 expression, and the lowering of the serum TNF- α level^[94].

Endometritis is an inflammatory response of the endometrium^[98], it has been reported that postpartum endometritis is the most important and common cause of postpartum uterine involution^[99]. Related experiments showed that motherwort could reduce the inflammatory response of the endometrium and has a protective effect on the endometrium. In related experiments, analysis of pathological section results revealed that Epsom saline attenuated LPS-induced uterine damage. Quantitative real-time polymerase chain reaction (qRT-PCR) and ELISA experiments showed that Epsom saline inhibited the expression levels of TNF- α and IL-1 β in uterine tissues and bovine endometrial epithelial cells (bEECs). Motherwort alkaloids inhibited TLR4 expression and NF- κ B activation. The above results suggest that leonurine has a therapeutic effect on LPS-induced endometritis in mice and bEECs, and its mechanism is to inhibit the expression of TLR4 and its downstream-mediated NF- κ B pathway. Therefore, leonurine can be used as an effective drug to prevent and treat LPS-induced endometritis^[100]. In a later study investigating the anti-inflammatory effect of epsomine on LPS-induced endometritis in mice, epsomine reduced the uterine index, the TNF- α , IL-1 β , and IL-6 inflammatory factor levels; and the myeloperoxidase activity in mice with LPS-induced endometritis, attenuating inflammatory responses and showing good anti-inflammatory effects^[101]. By observing the effect of motherwort on postpartum endometritis model rats and exploring its mechanism of action, motherwort was found to inhibit the expression levels of inflammatory factors and reduce oxygen free radical damage, endometrial cell apoptosis, and the expression of 6-keto-prostaglandin F1 α . It also increased the expression of thromboxane B2, thereby protecting and ameliorating postpartum endometritis, promoting endometrial hyperplasia and repair to restore postpartum uterus^[102]. In summary, the above studies have shown that motherwort can be

used for the treatment of clinical endometritis, thereby promoting postpartum uterine recovery and protecting the uterus.

3.5 Protective effect of motherwort on other organ injuries

The blood-brain barrier (BBB) exists in the vascular system of the brain, which is mainly composed of brain capillary endothelial cells, tight junction proteins between endothelial cells, basement membrane, astrocyte end-feet and pericytes^[103,104], protecting the brain from blood-borne substances. It is an important arm of the body's defense. Under physiological conditions, it is a highly specialized selective barrier that controls the entry of unnecessary blood toxic components into the brain parenchyma and transmits 'dangerous signals' to regulate homeostasis and play an important role in maintaining the appropriate homeostasis of the brain^[105]. Leonurine can prevent BBB decomposition, reduce the volume of cerebral infarction and improve neurological deficits. Studies have shown that leonurine can increase the expression of histone deacetylases-4 (HDAC-4), inhibit the expression of NADPH oxidase-4 (NOX-4) and matrix metalloproteinase-9 (MMP-9), and increase the expression of tight junction proteins, including claudin-5, occludin and ZO-1, suggesting that leonurine protects BBB integrity by regulating the HDAC4/NOX4/MMP-9 pathway tight junction pathway^[106]. The leonurine nanoliposomes prepared by Tang *et al.*^[107] can realize the reconstruction of BBB *in vitro* and *in vivo*. In the rat ischemic stroke model, the above pathway can be observed by tail vein injection to reduce the inflammatory response and brain tissue damage. Compared with intragastric administration of leonurine solution, it has better bioavailability, safety and biocompatibility, which is an expected new drug research and development direction.

Stomach is the main digestive organ of the human body^[108], and the gastrointestinal tract is mainly subject to the dual innervation of the central nervous system and the enteric nervous system. Common gastrointestinal disorders include gastritis, gastric ulcer, and gastric cancer. Relevant studies have shown that motherwort has certain pharmacological effects on gastric injury. In an experiment of detecting the effect of *Leonurus* extracts (EELs) (50, 100, and 300 mg/kg p.o. (per os) 1 h before induction) on acidified ethanol (ACET)-induced gastric ulcer, by detecting the role of EELs (administered *via* duodenum) in a pyloric ligation (PL) model, the relative area and lipid peroxidation of ACET-induced gastric ulcer decreased, and the content of sulfhydryl in the stomach increased compared with the control group. EELs (300 mg/kg) reduced mucus production and gastric juice secretion after PL, but it did not affect gastric acid nor pH. EELs play a gastric protective role in mice, and its mechanism is related to oxidative stress, non-protein sulfhydryls (NP-SH), ATP-sensitive potassium channels (KATP channels), and mucus production^[109].

The lungs are the respiratory organs of the body, and they are located in the thoracic cavity, one on each side, overlying the heart. Common lung injuries include localized lung contusions, parenchymal lacerations, pulmonary hematomas, and traumatic emphysema. In recent years, related studies have shown that motherwort has a certain therapeutic effect on some lung injuries. In the *in vivo* experiment of exploring the effect of leonurine on sepsis-induced acute lung injury, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and Cell Counting Kit-8 assay were used to detect cell viability. The levels of reactive oxygen species, lactate dehydrogenase, and malondialdehyde and the activity of superoxide dismutase were quantified using

commercial detection kits. The expression levels of specific inflammatory cytokines were detected by ELISA. The expression levels of cytokines TNF- α , IL-6, Nrf2, and HO-1 were detected by Western blotting. The results showed that leonurine increased the viability of LPS-stimulated BEAS-2B human lung epithelial cells in a dose-dependent manner. In addition, leonurine inhibited LPS-induced oxidative stress and inflammatory factor release in BEAS-2B cells. Nrf2 inhibitor treatment reversed the effects of leonurine treatment on LPS-induced oxidative stress and inflammatory response in BEAS-2B cells. In summary, leonurine alleviated LPS-induced ALI by inhibiting oxidative stress and inflammation regulated by the Nrf2 signaling pathway. Therefore, leonurine has a certain preventive and protective effect on acute lung injury caused by sepsis^[110].

Lung ischemia-reperfusion injury (LRI) is a common pathological process in lung transplantation, cardiac surgery or pulmonary thromboendarterectomy, cardiopulmonary bypass, pneumonectomy, cardiac arrest, and pulmonary embolism^[111,112]. It is mainly manifested as non-specific alveolar injury, hypoxia, and pulmonary edema after reperfusion. Severe cases can develop to acute respiratory distress syndrome (ARDS)^[113], which seriously affects the prognosis of patients. Establishment of a rat LRI model preliminarily confirmed that stachydrine can reduce the levels of inflammatory factors IL-6 and IL-1 β after LRI, promote HIF-1 α ubiquitination modification, inhibit HIF-1 α accumulation during LRI, and reduce NLRP3 inflammasome-mediated pyroptosis, thereby inhibiting LRI inflammatory response. That is, *in vivo* studies have shown that stachydrine has a protective effect on LRI in rats, and its mechanism is related to the inhibition of the HIF-1 α /NLRP3 pyroptosis pathway^[114]. The mechanism of action for motherwort is outlined in Fig. 2.

4 Conclusion

Motherwort, as one of the commonly used TCM, has played an extremely important role since ancient times. *The Compendium of Materia Medica* records that it can be used for women's menstrual disorders, women's various diseases in pregnancy and childbirth, elimination of edema and run the blood. This indicate that people were already in the habit of eating motherwort at that time. There are, of course, many other records which suffice to prove that it played a decisive role.

Early research on motherwort focused on its treatment of gynecological diseases, mainly on its protective effect on the uterus. In recent years, with the deepening of research, more active components of motherwort with medicinal value have been isolated. The mechanism of action of active substances, such as epsilon alkaloids and silymarin on diseases, has been clarified. Motherwort has shown positive effects on the uterus, the blood system, the immune system, analgesia and anti-inflammation, the heart, tumors, antioxidation, and antibacterial. It has been used in a wider and more definite manner in the clinic. However, at present, the research on the effective components of motherwort mainly focuses on alkaloids such as leonurine and stachydrine. The research on flavonoids, phenolic acids and other components is still limited, and their extraction and separation technology and potential pharmacological effects need to be further explored. With the deepening of pharmacological research and the progress of science and technology, the safety and effectiveness of motherwort as a traditional clinical Chinese medicine have been widely confirmed. However, some mechanisms of motherwort in the treatment of related diseases are not clear, which need to be further explored from multiple levels such as cells, molecules and

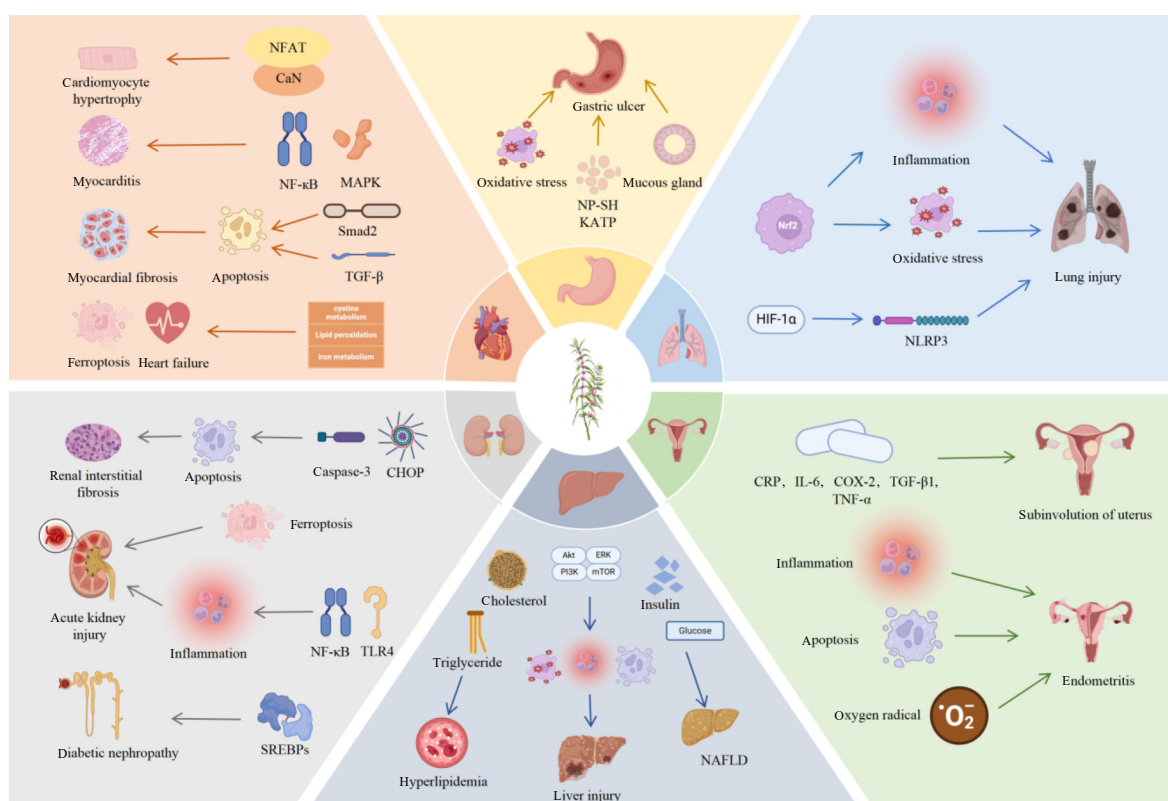


Figure 2 Mechanism of action for motherwort.

genes. In terms of pharmacokinetics, it is necessary to solve the problems of first pass elimination and hepatoenteral circulation. At the same time, the research on the toxicity of motherwort is not systematic and in-depth, and the existing research results are not consistent. In conclusion, motherwort has a good potential in the treatment of multiple-organ diseases. It is necessary to vigorously develop the resources of motherwort for both food and medicine.

Conflicts of interest

The authors declared no conflicts of interest in the publication of this paper.

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