



# Pharmacological effects and mechanisms of *Gastrodia elata* and its active ingredients in the treatment of cardiovascular diseases

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## Author contributions

Chen XY searched databases, analyzed articles, reviewed them for eligibility, and evaluated their quality. Chen JY and He Y reviewed the draft critically. Chen JY and He Y was the guarantor of the study. All authors participated in the final approval of the manuscript.

## Competing interests

The authors declare no conflicts of interest.

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## Peer review information

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## Abbreviations

TCM, traditional Chinese medicine; AEG, aqueous extract of *Gastrodia elata*; EEG, ethanolic extract of *Gastrodia elata*; H/R, hypoxia/reoxygenation; I/R, ischemia/reperfusion; NF- $\kappa$ B, nuclear factor kappa-B; TC, total cholesterol; Akt, protein kinase B; AMPK, adenosine 5'-monophosphate-activated protein kinase; HUVECs, human umbilical vein endothelial cells; TNF- $\alpha$ , tumor necrosis factor-alpha; ROS, reactive oxygen species; NO, nitric oxide; ATP, adenosine triphosphate; PI3K, phosphatidylinositol 3-kinase; eNOS, endothelial nitric oxide synthase; mTOR, mammalian target of rapamycin; caspase-3, cysteine aspartate protease 3; Bcl-2, B-cell lymphoma-2; Bax, Bcl2 associated X protein; NLRP3, NOD-like receptor thermal protein domain associated protein 3; caspase-1, cysteine aspartate protease 1; IL-1 $\beta$ , interleukin-1 $\beta$ .

## Citation

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## Abstract

*Gastrodia elata*, a traditional Chinese medicine belonging to the Orchidaceae family, contains several major components such as gastrodin, polysaccharides of *Gastrodia elata*, and parishin. The pharmacological studies conducted on *Gastrodia elata* have revealed a variety of therapeutic properties, including antihypertensive, hypolipidemic, analgesic, and sedative-hypnotic properties. Thus, in this paper, we summarized the pharmacological effects of *Gastrodia elata*'s major components, namely gastrodin, polysaccharides of *Gastrodia elata*, parishin, and different types of *Gastrodia elata* extracts, on cardiovascular diseases such as atherosclerosis, hypertension, hyperglycemia, myocardial ischemia, myocardial hypoxia, myocarditis, and heart failure. Additionally, we conclude the mechanisms through which these active ingredients exert their therapeutic effects, including antioxidants, anti-inflammatory, and nitric oxide regulation. We provide insights into the therapeutic potential of *Gastrodia elata* with a detailed review of its pharmacological effects and molecular targets in cardiovascular disease protection and therapy, and can better understand the effect of traditional medicines in cardiovascular disease.

**Keywords:** *Gastrodia elata*; gastrodin; parishin; polysaccharides of *Gastrodia elata*; *Gastrodia elata* extracts; cardiovascular diseases

**Highlights**

This study comprehensively summarizes the pharmacological mechanisms of *Gastrodia elata* and its active ingredients for the treatment of cardiovascular diseases, including atherosclerosis, hypertension, hyperglycemia, myocardial ischemia-reperfusion injury, myocarditis and heart failure, providing new ideas for the treatment of cardiovascular diseases with the traditional Chinese medicine.

**Medical history of objective**

The *Gastrodia elata* has been used as a herb medicine named “Chijian”, and first recorded in *Shennong Ben Cao Jing* (100-200 B.C.). In tradition Chinese medicine for restoring wind and stopping spasm, calming liver-yang (clearing liver and soothing the spirit), dispelling wind (regulating body functions imbalance), and dredging collaterals from ancient times. In traditional, *Gastrodia elata* is used for the treatment of headaches, neuralgia, dizziness, hypertension and other related neuralgic disorders. Recently, *Gastrodia elata* and its active ingredients exhibits various pharmacological effects associated with the progression of cardiovascular diseases based on the preclinical findings and clinical findings.

**Background**

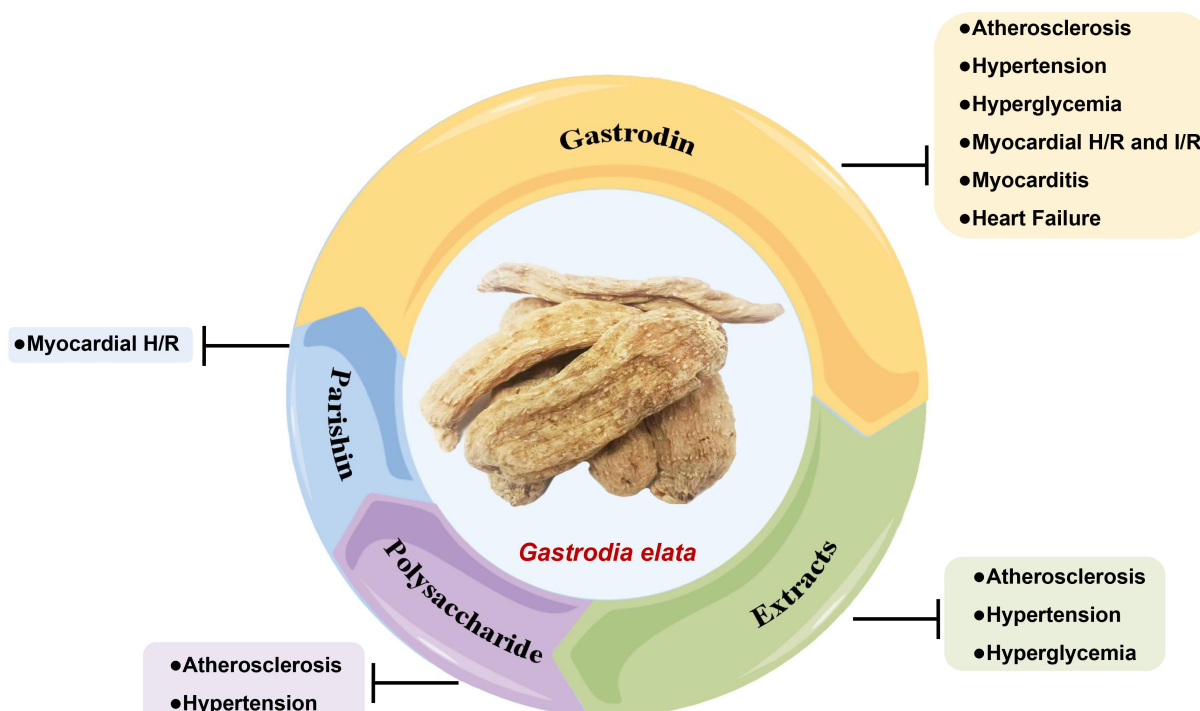
Around 31% of deaths worldwide are caused by cardiovascular disease. Although Western medicine has been instrumental in managing cardiovascular disease, it is imperative to acknowledge its significant adverse effects, such as rhabdomyolysis, polyneuropathy, and hepatotoxicity [1, 2]. In recent years, herbal medicine has garnered significant interest as a supplementary and alternative treatment for cardiovascular diseases, owing to its therapeutic properties that complement those of conventional Western medications, while exhibiting minimal adverse effects [3]. Traditional Chinese medicine (TCM) treatment for cardiovascular diseases is widely used in China, Korea, Japan, and other countries.

*Gastrodia elata* is a valuable TCM, derived from the dried tuber of *Gastrodia elata* Bl., a plant of the orchid family [4]. *Gastrodia elata* contains various chemical components, mainly phenols such as gastrodin, vanillyl alcohols, vanillins, 4-hydroxy benzyl alcohols, and p-hydroxybenzaldehyde, among others. Gastrodin is regarded as the primary bioactive constituent of *Gastrodia elata* among the various constituents present. Additionally, organic acids such as parishin are also key components of *Gastrodia elata*. Furthermore, *Gastrodia elata* also contains polysaccharides, steroids, amino acids, and peptides. *Gastrodia elata* extract is also a well-studied active ingredient [5]. The active ingredients of *Gastrodia elata* or its extracts exhibit a wide variety of biological actions, including anticancer, antiviral, anti-inflammatory, antioxidant, and anti-aging properties, according to a variety of recent pharmacological studies [6, 7].

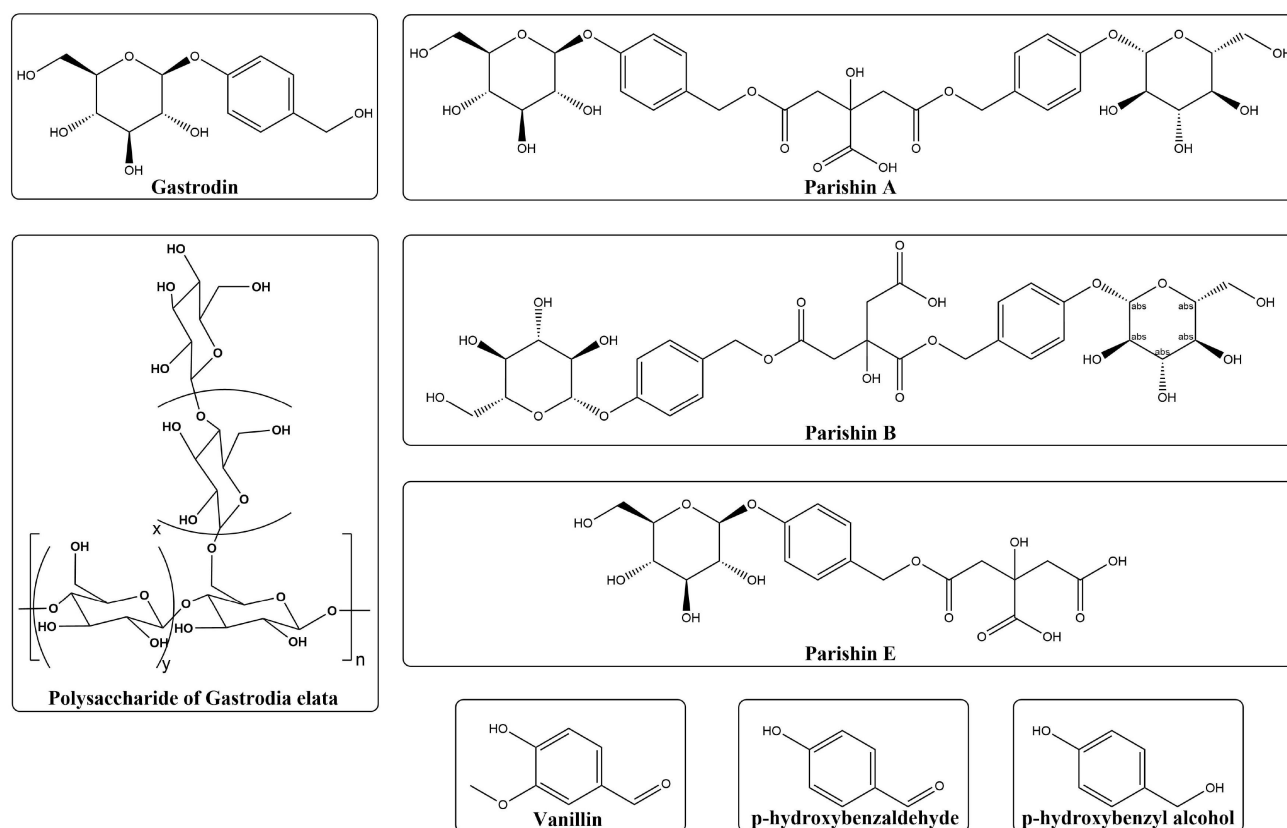
For centuries, *Gastrodia elata* has been utilized as a treatment for a variety of ailments, including headaches, dizziness, spasms, epilepsy, stroke, and amnesia [8]. Furthermore, recent research has shown that *Gastrodia elata* exhibits various pharmacological effects, including inhibition of foam cell formation, enhancement of vasodilation, immune-modulatory, anti-lipid peroxidation, and memory-enhancing effects. Several of these effects are intricately associated with the progression of cardiovascular disease [9]. Therefore, to facilitate a better understanding and utilization of *Gastrodia elata*, this review aims to summarize the pharmacological effects and underlying mechanisms of the main active ingredients such as gastrodin, polysaccharides of *Gastrodia elata*, parishin, and *Gastrodia elata* extract in the cardiovascular disease treatment (Figure 1).

**The pharmacological properties of *Gastrodia elata*****Medicinal ingredients in *Gastrodia elata***

In total, *Gastrodia elata* contains over 81 compounds, including gastrodin, polysaccharides, 4-hydroxy benzyl alcohol, vanillyl alcohols, vanillins, sterols, and organic acids (Figure 2). Gastrodin and polysaccharides are believed to be the main active ingredients of *Gastrodia elata* [10]. Polysaccharide is one of the highest contents of active substances of *Gastrodia elata*. A phenol-sulphuric acid method was used to determine the polysaccharide content of *Gastrodia elata*, with 21.6% being the highest [5, 11]. Meanwhile, the maximum



**Figure 1** Main components of *Gastrodia elata* and its treatment of cardiovascular disease. The Figure was drawn by Figdraw. H/R, hypoxia/reoxygenation; I/R, ischemia/reperfusion.

Figure 2 Main chemical constituents of *Gastrodia elata*

contents of gastrodin, amino acids, and total flavonoids were found to be 0.24%, 1.92%, and 0.24%, respectively [5, 12]. Additionally, the total phenolic content in *Gastrodia elata* was determined using the Folin-Ciocalteu colorimetric method, and the results showed that it reached 0.0485% [5, 13].

Gastrodin is a key compound found in *Gastrodia elata* and its chemical name is 4-hydroxymethyl phenyl-β-D-glucopyranoside, which is used as a standard for evaluating the quality of *Gastrodia elata* herbs [14]. Research suggests that gastrodin exhibits significant neuroprotective, antiinflammatory, and antioxidant properties [15, 16]. Moreover, polysaccharides are another essential component of *Gastrodia elata* that possesses certain pharmacological activities. The polysaccharides of *Gastrodia elata* contain xylopyranose, glucopyranose, and other monosaccharides, which are non-homogeneous components of the polysaccharide and the main structure of its sugar chain is α-glucopyranose D-glucose [17]. At the same time, the polysaccharides of *Gastrodia elata* have been identified as immunomodulators that not only have the effect of scavenging free radicals and delaying aging but also activate immune cells and improve the immune function of the body without toxic side effects on normal cells [18–20]. The parishin compounds are also an important active ingredient, synthesized from gastrodin, p-hydroxy benzyl alcohol, and its derivatives with citrate, which can metabolize to produce gastrodin [21]. In addition, various extracts of *Gastrodia elata*, such as aqueous extract, ethanol extract, ethyl acetate extract, etc., have shown good pharmacological activities, which have attracted widespread attention.

#### Pharmacokinetics of *Gastrodia elata*

**Absorption.** In terms of absorption, gastrodin is the most studied compound and is mainly absorbed in the digestive tract. However, the absorption time of gastrodin varies among different animal species. Tang et al. investigated the pharmacokinetic characteristics of gastrodin and found that gastrodin was detectable in rat plasma after gavage administration for 4.98 minutes, with a time to-peak concentration of  $0.42 \pm 0.14$  hours and a half-life of  $1.13 \pm 0.06$

hours, indicating that gastrodin is rapidly absorbed in vivo [22]. After oral administration of gastrodin to beagle dogs, the peak concentration reached within 1.5 hours [23]. In a different way, the time to-peak concentration of gastrodin in human plasma was  $0.81 \pm 0.16$  hours after oral administration of 200 mg gastrodin capsules [24]. Nevertheless, the bioavailability of gastrodin in *Gastrodia elata* was low, at only about 5–10% after oral administration, indicating that higher doses of *Gastrodia elata* were required to achieve therapeutic effects.

**Distribution.** As far as distribution is concerned, *Gastrodia elata* is mostly found in various liver, kidney, lung, and spleen tissues. Despite its ability to penetrate the blood-brain barrier, gastrodin has a lower permeability than other substances [25, 26]. A recent study on rats revealed that after administering *Gastrodia elata* extract orally, gastrodin and parishin were present in the lungs and kidneys, with only parishin detected in the brain. However, in a higher oral dose of the extract, both gastrodin and parishin were found in the brain, as well as in the lungs and kidneys [27].

**Metabolism.** The metabolism of gastrodin in the liver involves glucuronic acid transferase, generating water-soluble metabolites [28, 29]. In this study, Jia et al. conducted preliminary identification of the metabolites of gastrodin in rats. Besides the metabolite p-hydroxy benzyl alcohol, other metabolites of gastrodin were detected in vivo, including p-hydroxy phenyl pyran glucose aldehyde acid, p-aldehyde phenyl-β-D-glucopyranoside, p-formyl phenyl β-D-glucopyranoside, and p-hydroxybenzaldehyde [30]. Furthermore, parishin can be transformed into gastrodin and other metabolites after being metabolized by intestinal microorganisms [31]. Tang et al. investigated the metabolism of parishin in rats and found that it was rapidly metabolized in vivo. Following administration, parishin metabolized into gastrodin, p-hydroxy benzyl alcohol, parishin B, and parishin C within five minutes. These four metabolites were rapidly eliminated in vivo, and 8 hours after administration of parishin, the concentrations of gastrodin, p-hydroxy benzyl alcohol, parishin B, and parishin C decreased to 343.2, 6.9, 40.7, and 25.0 ng/mL, respectively [22].

**Excretion.** Gastrodin and its metabolites are mainly eliminated through renal excretion, with a smaller proportion eliminated through fecal excretion [26, 28]. Liu et al. conducted a pharmacokinetic study of *Gastrodia elata* capsules orally administered in beagle dogs and found that gastrodin, parishin A, parishin B, parishin C, and parishin E had mean plasma clearances of 0.2, 3.14, 0.87, 0.96, and 1.61 L/h/kg, severally [32]. These findings imply that of all the compounds in *Gastrodia elata* capsules, gastrodin is eliminated the fastest [33, 34]. Based on an oral administration of gastrodin, Tang et al. determined that the elimination half-life of gastrodin was approximately  $1.13 \pm 0.06$  hours in rats [22]. In rabbits, the elimination half-life of gastrodin is 38 to 47 minutes, while in healthy males, it is higher, ranging from 226.8 to 330 minutes [9, 35]. This indicates that the clearance of gastrodin in humans is slower compared to rats and rabbits.

### The role of *Gastrodia elata* in the treatment of cardiovascular diseases

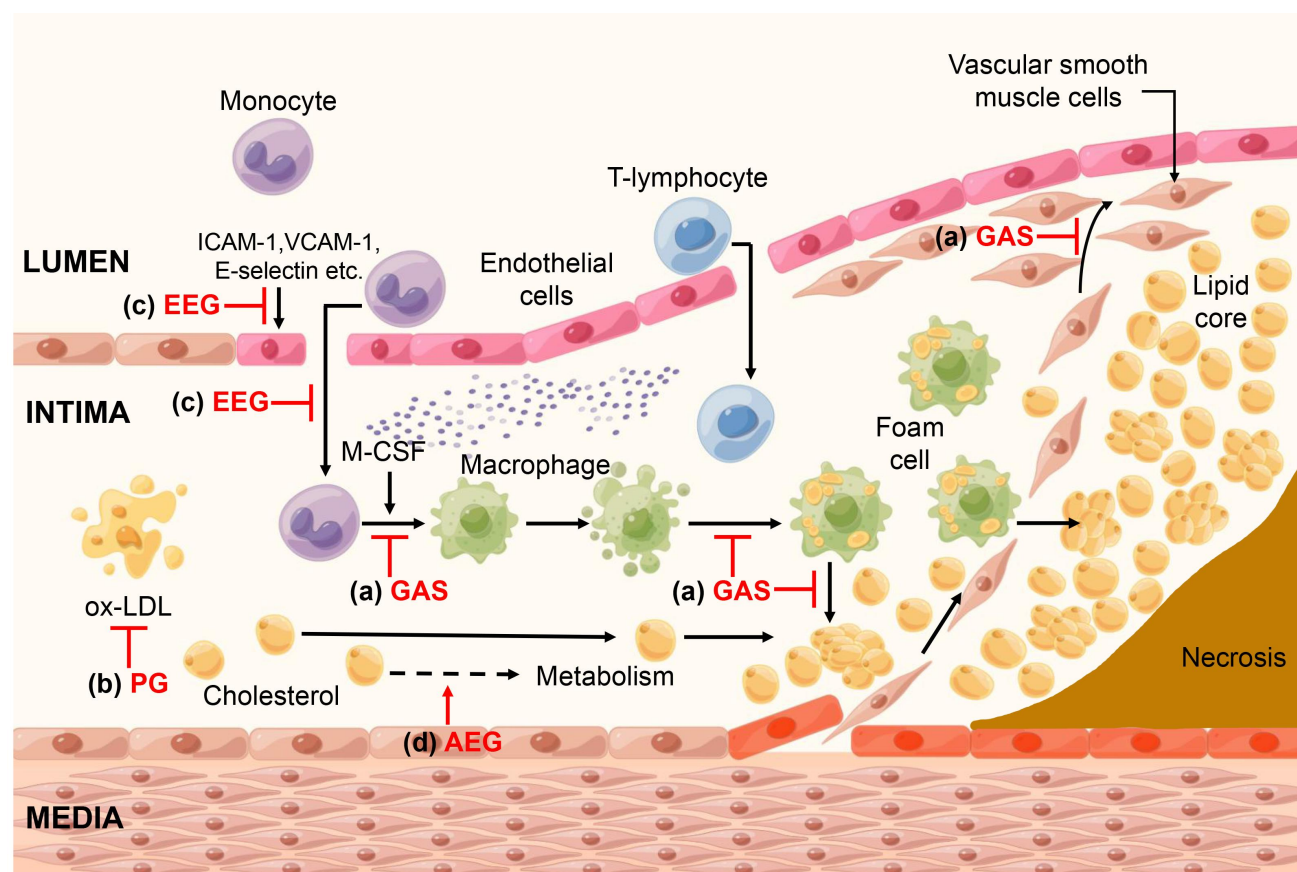
#### Atherosclerosis

Atherosclerosis is a chronic inflammatory disorder of the vascular wall and represents the most commonly observed pathological anomaly associated with coronary artery disease, peripheral artery disease, and cerebrovascular disease [36, 37]. Multiple mechanisms contribute to the formation of atherosclerotic plaques, including intimal lipid deposition, foam cell formation, endothelial dysfunction, vascular inflammation, and monocyte adhesion [38, 39]. The chronic accumulation of atherosclerotic plaque causes the lumen of medium

and large arteries to stenosis, resulting in reduced blood flow and tissue hypoxia [40]. Atherosclerosis is mostly associated with atherothrombotic events like myocardial infarctions and strokes, which are the major causes of death in the world [37, 41]. Several studies have demonstrated that *Gastrodia elata* could attenuate and regulate the progression of atherosclerosis (Figure 3).

#### Mechanisms of gastrodin in the treatment of atherosclerosis.

Gastrodin could downregulate the nuclear factor kappa-B (NF- $\kappa$ B) pathway not only to inhibit foam cell formation but also to inhibit lipopolysaccharide-induced macrophage inflammatory response and pro-inflammatory cytokine secretion to reduce atherosclerosis [42]. In early-stage of atherosclerotic mice, both gastrodin and *Gastrodia elata* extract were found to attenuate lipid deposition and foam cell formation on the intima of the thoracic aorta. Lipid profiling indicated that total cholesterol (TC) and low-density lipoprotein cholesterol levels in a reduction in peripheral blood following treatment with gastrodin and *Gastrodia elata* extracts [43]. Furthermore, gastrodin inhibited platelet-derived growth factor-BB-induced phosphorylation of Extracellular signal-related kinases 1 and 2 (ERK1/2), p38 mitogen-activated protein kinase, protein kinase B (Akt), and glycogen synthase kinase-3 $\beta$  in the vascular smooth muscle cell, which reduced neointimal hyperplasia in response to vascular damage and decreased the proliferation of vascular smooth muscle cells [44]. Gastrodin was found to activate adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), promote phosphorylation and nuclear translocation of forkhead box O1, increase the expression of transcription factor EB, promote lysosomal biogenesis, enhance autophagy activity, and improve macrophage cholesterol efflux,



**Figure 3 Mechanisms of *Gastrodia elata* in the treatment of atherosclerosis.** The Figure was drawn by Figdraw. *Gastrodia elata* inhibits multiple processes in the pathogenesis of atherosclerosis. (a) Gastrodin inhibited the inflammatory response of macrophages. The lipid deposition and foam cell formation were reduced. It also reduced the proliferation of vascular smooth muscle cells. (b) Polysaccharides of *Gastrodia elata* decreased the synthesis of oxidized low-density lipoprotein. (c) EEG attenuated the expression of cell adhesion molecules. The adhesion of monocytes was reduced. (d) AEG improved cholesterol metabolism. AEG, aqueous extract of *Gastrodia elata*; EEG, ethanolic extract of *Gastrodia elata*; GAS, gastrodin; PG, polysaccharide of *Gastrodia elata*.



lowering lipid accumulation and preventing foam cell formation in the oxidized low-density lipoprotein induced foam cell model [45].

**Mechanisms of gastrodia polysaccharide in the treatment of atherosclerosis.** Polysaccharides extracted from *Gastrodia elata* rhizomes, including crude polysaccharide and acidic polysaccharide extracts, have been found to inhibit atherosclerosis in high-fat diet-fed rats. This is achieved by the de novo synthesis of TC and low-density lipoprotein is reduced, which is beneficial in lowering the incidence of cardiovascular disease and atherosclerosis [46].

**Mechanisms of *Gastrodia elata* extracts in the treatment of atherosclerosis.** An aqueous extract of *Gastrodia elata* (AEG) was reported to alleviate blood flow impairment and cholesterol and glucose metabolism in orchidectomized rats. An AEG treatment might be a good preventive therapy for cardiovascular disease caused by low testosterone levels [47]. In primary cultured human umbilical vein endothelial cells (HUVECs), the ethanolic extract of *Gastrodia elata* (EEG) attenuated the tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )-induced expression of cell adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin in mRNA and protein levels. Additionally, EEG significantly and dose-dependently reduced TNF-induced monocyte adhesion in HUVECs. Moreover, EEG effectively suppressed TNF- $\alpha$ -induced intracellular reactive oxygen species (ROS) production and NF- $\kappa$ B p65 activation by inhibiting the phosphorylation of I $\kappa$ B- $\alpha$ . Taken together, EEG may suppress oxidative stress and inhibit NF- $\kappa$ B activation in vascular endothelial cells, thus inhibiting vascular inflammatory processes induced by TNF- $\alpha$  [48, 49]. EEG reduced the activity and expression of matrix metalloproteinase-2/-9 (MMP-2/-9) in TNF- $\alpha$  induced HUVECs. These findings offer novel perspectives into the pathophysiological mechanisms underlying the cardiovascular illnesses that EEG prevents by reducing atherosclerotic implications [50].

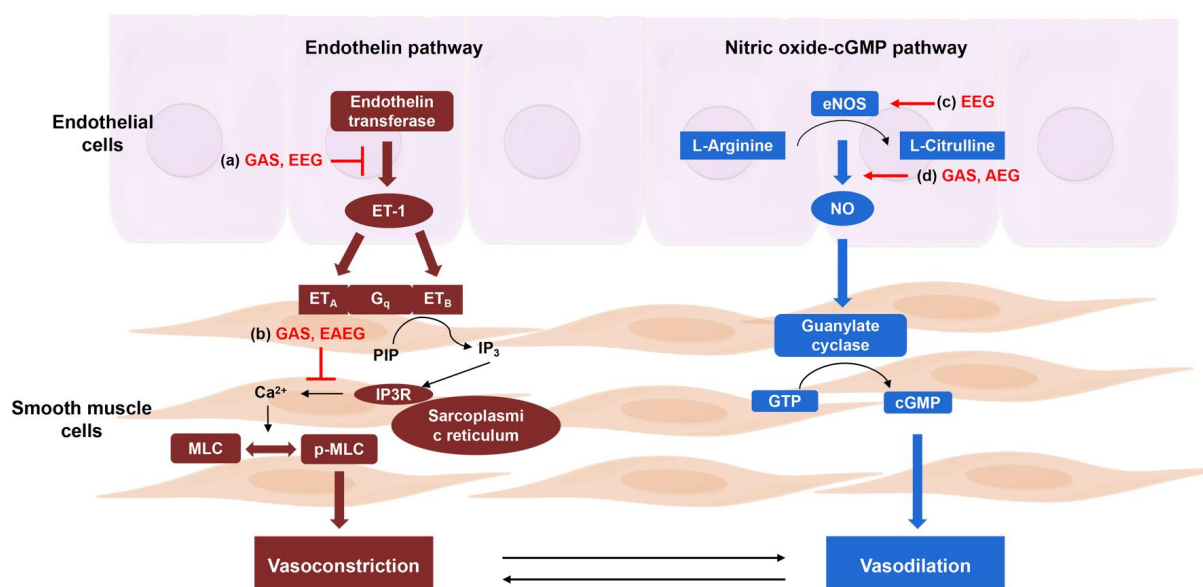
### Hypertension

Hypertension is a pathological state marked by chronically elevated blood pressure due to heightened cardiac output or peripheral resistance, and may be linked to organic or functional pathologies of the heart, kidneys, blood vessels, and other bodily tissues and organs. Various mechanisms affect the development of hypertension by influencing either cardiac output or peripheral resistance, including

endothelial dysfunction, chronic inflammation, reduced bioavailability of nitric oxide (NO), etc. [51]. Blood pressure and volume homeostasis are also influenced by hormonal factors, with the renin-angiotensin-aldosterone system playing a critical role [52, 53]. *Gastrodia elata* has been found to have a hypotensive effect and to provide protection against heart, kidney, and blood vessel damage caused by high blood pressure. The hypotensive effect of *Gastrodia elata* is widely used in clinical settings, with the active ingredients of *Gastrodia elata* such as gastrodin, polysaccharide of *Gastrodia elata*, and *Gastrodia elata* extract being the focus of research on the mechanism of its hypotensive effect (Figure 4).

**Mechanisms of gastrodin treatment of hypertension.** The improvement of gastrodin on the balance between endothelin and NO levels in the plasma are beneficial for elderly refractory hypertensive patients [54]. Meta-analyses have shown that gastrodin, when combined with conventional treatment, lowers blood pressure, improves systolic and diastolic blood pressure, enhances endothelial function, and improves clinical symptoms in hypertensive patients. Gastrodin can also improve the living quality of hypertensive patients and prolong their lives [55]. An isolated rat thoracic aorta ring treated with gastrodin has a vasodilatory effect. The primary mechanism by which gastrodin induces vasodilation appears to involve the inhibition of inositol 1,4,5-trisphosphate receptors situated on the sarcoplasmic reticulum of arterial smooth muscle cells, resulting in a decrease in the release of Ca<sup>2+</sup> from the sarcoplasmic reticulum [56]. Additionally, in response to phenylephrine induced mesenteric artery constriction, gastrodin also exerts a vasorelaxation effect through the activation of protein kinase A and subsequent opening of smooth muscle adenosine triphosphate (ATP)-sensitive potassium channels [57]. Gastrodin not only activates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B/endothelial nitric oxide synthase (eNOS) signaling pathway, which increases NO production and decreases ROS production but also initiates the nuclear factor erythroid 2-related factor 2/antioxidant response element pathway and enhances downstream enzyme expression to protect HUVECs from homocysteine damage and reduce vascular inflammation [58].

**Mechanisms of *Gastrodia* polysaccharide in the treatment of hypertension.** Polysaccharides of *Gastrodia elata* have been shown to be one of the effective components in reducing blood pressure. In the spontaneously hypertensive rat, the acidic polysaccharide group had a



**Figure 4 Mechanisms of *Gastrodia elata* in the treatment of Hypertension.** The Figure was drawn by Figdraw. *Gastrodia elata* regulate the balance of vasoconstriction and vasodilation mainly by modulating Endothelin pathway and Nitric oxide-cGMP pathway. (a) GAS and EEG inhibited the expression of ET-1; (b) GAS and EAEG suppressed Ca<sup>2+</sup> release in smooth muscle cells; (c) EEG upregulated the expression of eNOS; (d) GAS and AEG promoted NO production in endothelial cells. AEG, aqueous extract of *Gastrodia elata*; EEG, ethanolic extract of *Gastrodia elata*; eNOS, endothelial nitric oxide synthase; AEG, aqueous extract of *Gastrodia elata*; GAS, gastrodin; PG, polysaccharide of *Gastrodia elata*; EAEG, ethyl acetate extract of *Gastrodia elata*.

significantly lower TC level ( $69.7 \pm 10.6$  mg/dL) compared to the crude polysaccharide group ( $75.0 \pm 6.0$  mg/dL) and the control group ( $89.2 \pm 7.4$  mg/dL) after 5 weeks of treatment. Furthermore, acidic polysaccharides considerably reduced triglyceride and low-density lipoprotein cholesterol levels compared to crude polysaccharide and control groups. The atherosclerosis index was reduced by 46.3% in the acid polysaccharide group than the control group. These results suggest that acidic polysaccharides of *Gastrodia elata* have hypotensive and lipid-improving effects in spontaneously hypertensive rats fed with high-fat chow [17].

**Mechanisms of *Gastrodia elata* extracts in the treatment of hypertension.** In hypertension, endothelial dysfunction leads to decreased vasodilation and increased vasoconstriction [59]. Four compounds were isolated from the ethyl acetate extract of *Gastrodia elata* and identified as 3,4-dihydroxy benzaldehyde, 4-hydroxybenzaldehyde, 4-methoxybenzyl alcohol, and 4,4'-dihydroxydiphenylmethane has been proved varying degrees of vasodilatory effects and are endothelium-dependent. Mechanically, 4,4'-dihydroxydiphenylmethane inhibits  $\text{Ca}^{2+}$  endocytosis-induced aortic ring contraction and intracellular  $\text{Ca}^{2+}$  release in rats; 3,4-dihydroxy benzaldehyde significantly increases NO production in aortic and endothelial cells, as well as NO synthase activity in endothelial cells. Hence, the regulation of vascular tone by the ethyl acetate extract of *Gastrodia elata* may potentially serve as a significant factor in the amelioration of hypertension [60]. In addition, EEG has also shown beneficial anti-hypertensive effects. In high-fructose diet rats, EEG treatment significantly reduces epididymal fat weight, blood pressure, plasma triglyceride, and TC levels, and effectively prevents the increase in adipocyte size and triglyceride accumulation in the liver. At the same time, by enhancing eNOS expression and reducing the expression of endothelin-1 in the aorta, EEG alleviates endothelial dysfunction. EEG also greatly upregulated AMPK-phosphorylation in liver, muscle, and fat tissues. The findings of this study indicate that the utilization of EEG is efficacious in ameliorating dyslipidemia, hypertension, and impaired vascular endothelial function in rats that have been subjected to a high-fructose diet [61]. AEG was discovered to significantly relax the rabbit aortic rings in the model of aortic rings that have been precontracted with norepinephrine. This suggests that an endothelium-dependent, nitric oxide as well as blocking receptor and potential-dependent calcium channels are involved in AEG's ability to relax an aorta [62].

### Hyperglycemia

Hyperglycemia is closely associated with cardiovascular diseases [63]. The pathological mechanism of hyperglycemia mainly involves insufficient insulin secretion and insulin resistance [64]. Insufficient insulin secretion is caused by damage or dysfunction of pancreatic  $\beta$  cells, which produce insulin, and results in elevated blood glucose levels [65]. Reduced sensitivity or responsiveness to the metabolic effects of insulin is a characteristic of insulin resistance, which results in reduced efficiency of insulin's effects on glucose utilization and ultimately causes hyperglycemia [66]. In addition, high glucose levels can cause endothelial cell damage, which can result in diabetic vascular complications [67]. *Gastrodia elata* has long been used for the care of diabetes as a TCM-based treatment. Several studies have shown that gastrodin and *Gastrodia elata* extract have pharmacological effects of lowering blood glucose levels, improving insulin resistance, and protecting cells from high glucose-induced damage [68–72].

**Mechanisms of gastrodin in the treatment of hyperglycemia.** Gastrodin protects HUVECs from high glucose injury, by up-regulated the mRNA and protein expressions of peroxisome proliferator-activated receptor- $\beta$  and eNOS, decreasing the expressions of inducible nitric oxide synthase, also reducing the protein expression of 3-nitrotyrosine, and increasing NO content [68]. At the same time, in the dexamethasone-induced insulin resistance cells model, gastrodin promotes the phosphorylation of GATA-binding factor 1 via the PI3K/Akt pathway, enhances the transcriptional activity of GATA-binding factor 1, and then increases the expression level of ubiquitin-specific peptidase 4, consequently, insulin receptor

ubiquitination and degradation are decreased and insulin resistance is improved [69]. Furthermore, in high glucose-induced H9c2 and HL-1 cell damage models, gastrodin promoted the nuclear translocation of Nrf2 via activating the glycogen synthase kinase-3 $\beta$  signaling pathway to protect cardiomyocytes against toxicity [73].

**Mechanisms of *Gastrodia elata* extracts in the treatment of hyperglycemia.** In partially-pancreatectomized rats, AEG has anti-diabetic effects by improving insulin secretion in response to glucose and raising the number of  $\beta$  cells [70]. The AEG significantly reduced hyperglycemia, insulin resistance, and inflammation in the high-fat diet-induced mouse model of type 2 diabetes by upregulating glucose transporter 4 and blocking the toll-like receptor 4 /NF- $\kappa$ B signaling pathway in white adipose tissue [74]. Meanwhile, in male Sprague-Dawley rats given a high-fat diet, the AEG lowers insulin resistance by inhibiting the formation of fat in adipocytes, promoting fat oxidation, and amplifying leptin signaling [75].

### Myocardial hypoxia/reoxygenation injury

Myocardial hypoxia/reoxygenation (H/R) injury leads to high mortality, and one of its pathogenesis's major contributors is oxidative stress [76, 77]. In hypoxic myocardial tissue, intracellular ROS production directly affects cell structure and function [78]. At the same time, mitochondria are the energy storehouse of cells, and the regulation of mitochondrial proteins is crucial in the pathological process of myocardial H/R [79]. Myocardial H/R damage causes the mitochondrial permeability transition pore to open, which lowers the membrane potential of the mitochondria, a reduction in ATP synthesis, and ultimately, apoptosis of the cells [80, 81]. Therefore, the prevention of oxidative stress and myocardial apoptosis is an effective strategy to treat myocardial hypoxic injury. Studies have shown that compounds in *Gastrodia elata* have antioxidant and anti-inflammatory effects. Thus, *Gastrodia elata* has the potential to serve as a natural agent for antioxidant and anti-inflammatory purposes, thereby mitigating cellular damage and inflammatory responses induced by oxidative stress [82, 83].

**Mechanisms of gastrodin in the treatment of myocardial H/R injury.** Gastrodin has been found to protect against H/R injury in neonatal rat cardiomyocytes by activating the mammalian target of rapamycin (mTOR) signaling in the PI3K-Akt pathway, promoting phosphorylation of Akt and mTOR, and reducing autophagy levels [84]. Furthermore, gastrodin can prevent cardiomyocytes from H/R damage through upregulating levels of 14-3-3  $\eta$ . This protective effect is evidenced by improvements in cell viability, reduction in phosphocreatine kinase and lactate dehydrogenase activity, decreased ROS production, inhibition of mitochondrial permeability transition pore opening, alteration of the balance of membrane potential of the mitochondria, reduced cysteine aspartate protease 3 (caspase-3) activation, and ultimately, reduced cardiomyocyte apoptosis [31].

**Mechanisms of parishin in the treatment of myocardial H/R injury.** Parishins J and B were found to have significant protective effects on rat embryonic cardiomyocyte line cardiomyocytes subjected to H/R injury. These parishins perform to protect the heart by upregulating the expression of cytochrome c and B-cell lymphoma-2 (Bcl-2) in the mitochondria and downregulating the expression of cleaved-caspase-3, cytochrome c, and Bcl2 associated X protein (Bax) in the cytoplasm. Additionally, parishin J is also thought to have a cardioprotective effect as it inhibits c-jun N-terminal kinase 1 phosphorylation levels, downregulates c-jun and activating transcription factor 2 phosphorylation levels, decreases 14-3-3 phosphorylation levels, and increases 14-3-3 binding to Bax. The aforementioned mechanisms propose that parishin J holds potential as a novel pharmaceutical agent for protecting the myocardium [85].

**Mechanisms of gastrodin in the treatment of the myocardial hypoxic injury.** Gastrodin may protect H9c2 cardiomyocytes from oxidative damage through enhancing Nrf2 nuclear translocation, modulating mitochondrial dynamics, and sustaining mitochondrial structure and function [86].

### Myocardial ischemia/reperfusion injury

Ischemic heart disease is defined as the existence of one or more obstructive plaques that result in decreased coronary blood flow, which in turn causes myocardial ischemia and makes a considerable burden on people and healthcare resources globally [87, 88]. Transient ischemia and reperfusion in the heart can induce myocardial ischemia/reperfusion (I/R) injury and severe inflammatory responses in vivo, which is a complex pathophysiological process resulting in myocardial injury [89, 90]. The mechanism involves various factors, such as decreased intracellular ATP levels, insufficient autophagic flux, calcium overload, increased production of ROS, and inflammatory cell infiltration [91, 92]. *Gastrodia elata* can intervene in several factors of ischemic heart disease and has a protective effect on myocardial ischemic injury. This makes it a promising drug for the treatment of myocardial I/R injury.

**Mechanisms of gastrodin in the treatment of myocardial I/R injury.** NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammatory vesicles are a critical intracellular sensor that detects cellular stress through the activation of cysteine aspartate protease 1 (caspase-1), leading to interleukin-1 $\beta$  (IL-1 $\beta$ ) maturation and focal cell death. In both in vitro experiments using cardiac microvascular endothelial cells and in vivo experiments using myocardial I/R animals, gastrodin was observed to inhibit the NLRP3/caspase-1 pathway, thus blocking cardiac microvascular endothelial cell scorching. Additionally, gastrodin reduces myocardial infarct size and inflammatory cell infiltration by decreasing IL-1 $\beta$  production in vitro and in vivo and increasing capillary formation [93]. Gastrodin also induced miR-30a-5p and down-regulated autophagy-related gene 5 expression, thereby attenuating autophagy in rat myocardial infarct tissue [94]. Based on a rat model of myocardial I/R injury, gastrodin exerts cardioprotective effects by upregulating the protein and mRNA expression levels of Bcl-2, while inhibiting the expression of active caspase-3 and bax protein and mRNA. Furthermore, gastrodin down-regulates inflammatory factors in Sprague-Dawley rat's serum and up-regulates the expression levels of anti-inflammatory factors such as interleukin-10 [95]. In a C57BL/6 mouse model of myocardial I/R injury, gastrodin promotes autophagic flux via phosphorylating AMPK and dephosphorylating mTOR, reducing myocardial I/R injury and protecting surrounding mitochondria and myocardial cells [96]. Lastly, gastrodin preconditioning reduces calcium load by regulating the expression of calcium-transporting ATPase (Ca<sup>2+</sup>-ATPase, SERCA) and calcium phosphate, thereby reducing rats' myocardial I/R and inflammatory injury [97].

### Myocarditis

The mechanism of myocardial cell inflammation involves multiple factors, including viral infection, immune response, and oxidative stress [98]. Viral infection can lead to the activation of the immune system, which releases inflammatory mediators, such as cytokines and chemokines [99]. These substances attract more immune cells into the myocardial tissue, causing an inflammatory reaction, resulting in damage and apoptosis of myocardial cells, ultimately leading to myocardial inflammation [100]. Prior research findings indicate that *Gastrodia elata* may potentially serve as a therapeutic agent for myocarditis by means of its antioxidant, anti-inflammatory, and immunomodulatory properties.

**Mechanisms of gastrodin in the treatment of myocarditis.** In lipopolysaccharide stimulated H9c2 cardiomyocytes, gastrodin suppressed NF- $\kappa$ B and MAPKs family activation, upregulated the expression of inducible nitric oxide synthase, cyclooxygenase-2, TNF- $\alpha$  and interleukin-6, thus alleviating the inflammatory response of cardiomyocytes [101]. In a mouse model of septic shock, as a result of gastrodin treatment, the expression of NLRP3, caspase-1, IL-1 $\beta$ , and Bax in mice's myocardium was decreased, while Bcl-2 was increased, thus promoting the recovery of cardiac function and protecting myocardial cells from inflammatory injury [102]. After mice with viral myocarditis were treated with *Gastrodia elata* injection, the mortality rate of mice and myocardial lesions were significantly reduced, and myocardial function indexes such as brain natriuretic

peptide, peak aortic flow velocity, and aortic flow velocity integral were significantly improved, which proved the myocardial cytoprotective effect of *Gastrodia elata* on mice with viral myocarditis [103]. At the same time, treatment of mice with viral myocarditis with *Gastrodia elata* injection down-regulated caspase-3 protein expression and attenuated apoptotic signal transduction, thereby inhibiting apoptosis of cardiomyocytes [104].

### Heart failure

Heart failure, a clinical syndrome attributed to the heart's dysfunction, is defined as insufficient blood flow to meet metabolic needs or systemic venous return [105]. The major risk factors for heart failure include myocardial hypertrophy and myocardial fibrosis. Hemodynamic overloads, such as pressure or volume overload, can increase tension in the ventricular wall, leading to myocardial hypertrophy [106]. On the other hand, myocardial fibrosis results from an imbalance in collagen synthesis and metabolism and is closely associated with heart failure [107]. Therefore, pharmacological interventions that regulate hemodynamics and myocardial fibrosis show promise for the prevention of heart failure [108]. The active ingredient extracted from *Gastrodia elata*, Gastrodin, exhibits a combination of pharmacological effects [109]. As a calcium channel blocker, gastrodin can inhibit excessive intracellular Ca<sup>2+</sup>, increase blood supply, enhance arterial compliance, reduce blood viscosity, and improve microcirculation, thus treating heart failure [110, 111].

**Mechanisms of gastrodin in the treatment of heart failure.** Gastrodin dramatically reduced heart size, heart weight, and body weight in a mouse model of angiotensin II-induced cardiac hypertrophy. Mechanically, gastrodin prevented cardiac hypertrophy by suppressing the expression of insulin-like growth factor type 2/insulin-like growth factor type 2 receptor [112]. Gastrodin effectively reduced pathological cardiac hypertrophy in mice via upregulating myosin heavy chain  $\alpha$ , downregulating myosin heavy chain  $\beta$ , and upregulating atrial natriuretic peptide [113]. In another study of myocardial hypertrophy, authors found gastrodin inhibits calcium inward flow by downregulating the expression of two key store-operated calcium entry proteins, stromal interaction molecule 1 and calcium release-activated calcium channel modulator 1. Consequently, gastrodin attenuates myocardial hypertrophy in mice and significantly inhibits phenylephrine-induced cardiomyocyte hypertrophy by blocking store-operated calcium entry [114]. Furthermore, gastrodin prevents mice's myocardial hypertrophy provoked by aortic constriction by blocking the ERK1/2 signaling pathway and GATA-4 activation to attenuate fibrosis and collagen synthesis [115].

### Conclusion

In recent years, due to the unmet need for Western medicine to control cardiovascular diseases, hence, there has been an increase in studies on the use of TCM in the prevention and treatment of cardiovascular illnesses. A large amount of related basic and clinical research has also been focused on by the cardiovascular community [116, 117]. *Gastrodia elata*, as a TCM, has significant therapeutic effects on neurological diseases [118]. At the same time, many studies suggest that *Gastrodia elata* also has good pharmacological effects on cardiovascular diseases [119]. This article comprehensively reviews the in vitro and in vivo experimental studies of *Gastrodia elata* in the cardiovascular disease treatment, revealing its therapeutic effects on various cardiovascular diseases such as atherosclerosis, hypertension, hyperglycemia, myocardial ischemia, myocardial hypoxia, myocarditis, and heart failure. The literature review indicates that *Gastrodia elata* may benefit cardiovascular diseases by inhibiting inflammation, oxidative stress, cell apoptosis, endothelial damage, foam cell formation, vascular smooth muscle cell proliferation, myocardial hypertrophy, and fibrosis; enhancing lipid-lowering activity, vascular generation, and vasodilation; and regulating calcium channels and autophagy. These effects involve complex mechanisms, involving multiple targets and signaling pathways, including

AMPK-mTOR, PI3K-Akt, NF- $\kappa$ B signaling pathways, among others (Table 1). Gastrodin, being one of the primary active components of *Gastrodia elata*, has demonstrated significant potential for clinical application and has proven efficacy in the management of

atherosclerosis and other cardiovascular ailments (Figure 5). Therefore, *Gastrodia elata* has significant potential for use in the prevention and therapy of cardiovascular disorders.

**Table 1 Summary of targets or pathways of *Gastrodia elata* in cardiovascular diseases**

Type	Drug	Test Model	Effect	Target or Pathways	References
Atherosclerosis					
In vitro	Gastrodin	Macrophage	↓foam cell formation, ↓IL-1 $\beta$	NF- $\kappa$ B pathway	[42]
In vivo	Gastrodin and <i>Gastrodia elata</i> extract	Early-stage atherosclerotic mice	↓lipid deposition and foam cell formation	/	[43]
In vitro	Gastrodin	Vascular smooth muscle cell	↓vascular smooth muscle cell proliferation, ↓neointimal hyperplasia	ERK1/2, p38 MAPK, Akt	[44]
In vitro	Gastrodin	In vitro foam cell model with macrophage	↑AMPK, ↑FoxO1, ↑TFEB, ↑lysosomal biogenesis, ↑lysosomal function and autophagic activity, ↑cholesterol efflux, ↓lipid accumulation, ↓foam cell formation	AMPK, FoxO1, TFEB, lysosomal biogenesis, autophagy	[45]
In vivo	Polysaccharides of <i>Gastrodia elata</i>	SD rats	↓total cholesterol and LDL levels, ↓the incidence of cardiovascular disease and atherosclerosis	/	[46]
In vivo	AEG	Orchidectomized rats	↑cholesterol and glucose metabolism, improves impaired blood flow	/	[47]
In vitro	EEG	Primary cultured HUVEC	↓ICAM-1, VCAM-1, E-selectin, ↓monocyte adhesion, ↓ROS production, ↓NF- $\kappa$ B p65 activation, ↓phosphorylation of I $\kappa$ B- $\alpha$	ICAM-1, VCAM-1, E-selectin, ROS, NF- $\kappa$ B p65, I $\kappa$ B- $\alpha$	[48, 49]
In vivo	EEG	HUVEC	↓activity of MMP-2/-9	MMP-2/-9	[50]
In vivo	Gastrodin	Elderly patients with refractory hypertension	↑balance between ET and NO levels	ET, NO	[54]
Meta-analyses	Gastrodin	Hypertensive patients	↓blood pressure, ↑endothelial function	/	[55]
In vitro	Gastrodin	Isolated thoracic aorta rings of rats	↓Ca <sup>2+</sup> release	inositol 1,4,5-trisphosphate receptors	[56]
In vivo	Gastrodin	Rat mesenteric artery ring	↑vasorelaxation	protein kinase A, ATP-sensitive potassium channels	[57]
In vitro	Gastrodin	HUVEC	↑NO production, ↓ROS production, ↑Nrf2 nuclear translocation	PI3K/Akt/eNOS signaling pathway, Nrf2/ARE pathway	[58]
In vivo	Polysaccharides of <i>Gastrodia elata</i>	Spontaneously hypertensive rats	↓TC, triglyceride, LDL-C levels, ↓atherosclerotic index	/	[17]
In vivo	Ethyl acetate extract of <i>Gastrodia elata</i>	Rats	↓aortic ring contraction and intracellular Ca <sup>2+</sup> releases, ↑NO production and NO synthase activity	Ca <sup>2+</sup> endocytosis	[60]
In vivo	EEG	Rats	↓expression of ET-1 and adhesion molecules, ↑vasorelaxation, ↑eNOS expression, ↑phosphorylation of AMPK- $\alpha$	AMPK- $\alpha$ , eNOS	[61]
In vitro	AEG	Rabbit aortic ring	relax the rabbit's aortic rings	endothelium-dependent, NO, potential-dependent calcium channels	[62]



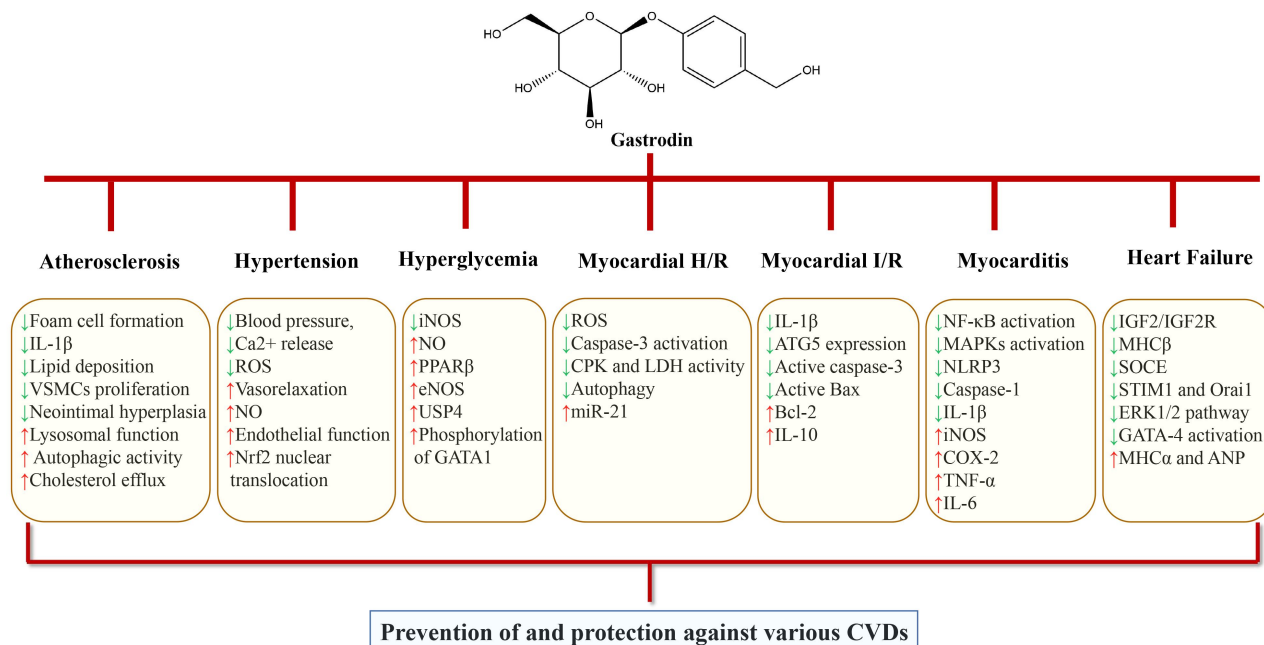
**Table 1 Summary of targets or pathways of *Gastrodia elata* in cardiovascular diseases (continued)**

Type	Drug	Test Model	Effect	Target or Pathways	References
Hyperglycemia					
In vitro	Gastrodin	HUVEC with high glucose injury	↑mRNA and protein expressions of PPAR $\beta$ and eNOS, ↓expressions of iNOS, ↓protein expression of 3-nitrotyrosine, ↑NO content	protecting vascular endothelial cells from high glucose injury	[68]
In vitro	Gastrodin	Dexamethasone-induced insulin resistance cells	↑phosphorylation of GATA1, ↑transcriptional activity of GATA1, ↑expression level of USP4, ↓ubiquitination and degradation of insulin receptors	GATA1, USP4	[69]
In vitro	Gastrodin	H9c2 and HL-1 cell	↑nuclear translocation of Nrf2	GSK-3 $\beta$ , Nrf2	[73]
In vivo	AEG	Partially-pancreatectomized rats	↑insulin secretion, ↑number of $\beta$ -cells	insulin, $\beta$ -cells	[70]
In vivo	AEG	Mice model of type 2 diabetes	↑GLUT4, ↓TLR4/NF- $\kappa$ B signaling pathway	GLUT4, TLR4/NF- $\kappa$ B signaling pathway	[74]
In vivo	AEG	Male SD rat	↑fat oxidation, ↑leptin signaling, ↓fat accumulation, ↓insulin resistance	fat oxidation, leptin signaling	[75]
Myocardial H/R					
In vitro	Gastrodin	Cardiomyocytes	↑cell viability, ↓CPK and LDH activity, ↓ROS production, ↓mPTP opening, alteration of the balance of $\Delta\Psi_m$ , ↓caspase-3 activation	14-3-3 $\eta$	[31]
In vitro	Gastrodin	Neonatal cardiomyocytes	rat ↑phosphorylation of Akt and mTOR, ↓autophagy levels	mTOR signaling in the PI3K-Akt pathway	[84]
In vitro	Gastrodin	H9c2 cardiomyocytes	↑nuclear translocation of Nrf2, maintaining the structure and function of mitochondria	Nrf2, mitochondrial dynamics	[86]
In vitro	Parishin	H9c2 cardiomyocytes	↓cleaved-caspase-3, cytochrome c, and Bax in the cytoplasm, ↑cytochrome c and Bcl-2 in the mitochondria	cleaved-caspase-3, cytochrome c, Bax, and Bcl-2	[85]
In vitro	Parishin J	H9c2 cardiomyocytes	↓JNK1 phosphorylation levels, ↓c-jun and ATF-2 phosphorylation levels, ↓14-3-3 phosphorylation levels, ↑binding of 14-3-3 to Bax	phosphorylation levels of JNK1, c-jun, ATF-2 and 14-3-3	[85]
Myocardial I/R					
In vitro and In vivo	Gastrodin	Cardiac microvascular endothelial cells and myocardial I/R animals	↓NLRP3/caspase-1 pathway, ↓IL-1 $\beta$ , ↓myocardial infarct size, ↓inflammatory cell infiltration, ↑capillary formation	NLRP3/caspase-1 pathway, IL-1 $\beta$	[93]
In vivo	Gastrodin	SD rats	↓ATG5 expression, ↓autophagy	miR-30a-5p	[94]
In vivo	Gastrodin	SD rats	↓active caspase-3 and Bax, ↑Bcl-2, ↑IL-10	active caspase-3, Bax, Bcl-2, IL-10	[95]
In vivo	Gastrodin	C57BL/6 mouse	↑autophagic flux	AMPK phosphorylation, mTOR dephosphorylation	[96]
In vivo	Gastrodin	Rats	↓calcium load	calcium-transporting ATPase, calcium phosphate	[97]

**Table 1 Summary of targets or pathways of *Gastrodia elata* in cardiovascular diseases (continued)**

Type	Drug	Test Model	Effect	Target or Pathways	References
<b>Myocarditis</b>					
In vitro	Gastrodin	H9c2 cardiomyocytes	↓NF-κB and MAPKs activation, ↑expression of iNOS, COX-2, TNF-α and IL-6	NF-κB, MAPKs, iNOS, COX-2, TNF-α, IL-6	[101]
In vivo	Gastrodin	Mice with septic shock	↓expression of NLRP3, caspase-1, IL-1β and Bax, ↑expression of Bcl-2	NLRP3, caspase-1, IL-1β, Bax, Bcl-2	[102]
In vivo	<i>Gastrodia elata</i>	Mice with viral myocarditis	↑brain natriuretic peptide, peak aortic flow velocity, aortic flow velocity integral	brain natriuretic peptide, peak aortic flow velocity, aortic flow velocity integral	[103]
In vivo	<i>Gastrodia elata</i>	Mice with viral myocarditis	↓caspase-3 protein expression, ↓apoptotic signal transduction	caspase-3, apoptotic signal	[104]
<b>Heart Failure</b>					
In vivo	Gastrodin	Mice of cardiac hypertrophy	↓heart size, heart weight, body weight, ↓IGF2/IGF2R expression, ↓cardiac hypertrophy	IGF2/IGF2R	[112]
In vivo	Gastrodin	Mice of cardiac hypertrophy	↑MHCα and ANP, ↓MHCβ	MHCα, MHCβ, ANP	[113]
In vitro and In vivo	Gastrodin	Mice and cells of myocardial hypertrophy	↓SOCE, ↓STIM1 and Orai1	SOCE, STIM1, Orai1	[114]
In vivo	Gastrodin	Mice of myocardial hypertrophy	↓ERK1/2 signaling pathway, ↓GATA-4 activation	ERK1/2 signaling pathway, GATA-4	[115]

SD, Sprague-Dawley; AEG, aqueous extract of *Gastrodia elata*; Akt, protein kinase B; EEG, ethanolic extract of *Gastrodia elata*; HUVEC, human umbilical vein endothelial cell; mPTP, mitochondrial permeability transition pore; NO, nitric oxide; ROS, reactive oxygen species; TC, total cholesterol; ΔΨ<sub>m</sub>, membrane potential of the mitochondria.



**Figure 5 Mechanisms of gastrodin in the treatment of various cardiovascular diseases.** VSMCs, vascular smooth muscle cell; ROS, reactive oxygen species; NO, nitric oxide.

In conclusion, *Gastrodia elata* also has certain research and development value in the management of cardiovascular diseases. This article hopes to expand the clinical application value of *Gastrodia elata* and its effective components by reviewing its pharmacological mechanisms in cardiovascular diseases, and also provides new ideas and evidence for the clinical application of cardiovascular diseases.

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