Review Article

Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.apjtb.org

doi: 10.4103/2221−1691.340558

Impact Factor: 1.55

Cardiovascular protective properties of gastrodin

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ABSTRACT

Cardiovascular diseases cause significant morbidity and mortality worldwide, incurring a major public health burden. *Gastrodia elata* Blume is a traditional Chinese herbal medicine that has been widely used to treat central nervous system and cardiovascular diseases. Gastrodin, as the major active component in *Gastrodia elata* Blume, can confer protection against cardiovascular diseases. In this review, we summarize the anti-inflammatory actions, anti-cardiac hypertrophy, anti-hypertension, anti-atherosclerosis, and angiogenic effects of gastrodin, as well as its protective effects on vascular cells and against myocardial ischemia-reperfusion injury. The medical potential of gastrodin in diabetes-related cardiovascular diseases is also discussed.

KEYWORDS: Gastrodin; Cardiovascular diseases; Myocardial ischemia-reperfusion injury; *Gastrodia elata* Blume; Anti-atherosclerosis; Cardio-protection

1. Introduction

Cardiovascular diseases (CVDs) are a category of disorders caused by chronic inflammation, oxidative stress, and thrombosis. They are one of the main causes of death globally. They can also lead to more serious health problems such as stroke, myocardial infarction, and ischemia/reperfusion (I/R) injury[1,2]. Herbal monomer is gaining popularity due to its multitargeted benefits and low toxicity[3−5]. Tian ma, the dried rhizomes of *Gastrodia elata* Blume, is a well-known and valuable traditional Chinese herb with a long history of clinical application for central nervous system and cardiovascular issues[6]. Gastrodin (4-hydroxybenzyl alcohol-4-*O*-β-*D*-glucopyranoside, Figure 1) is a major active component of Tian ma in recent pharmacological investigations, as well as one of the phytochemical markers of Tian ma in the Chinese Pharmacopeia (2020 version)[7,8]. Gastrodin possesses a wide range of pharmacological benefits, including sedative, anticonvulsive, anti-vertigo, anti-epileptic, anxiolytic, enhancing learning, anti-aging, and anti-hypertensive effects, and can be used to treat neurasthenia[6,9,10]. Nonetheless, previous researches have mostly focused on the treatment of neurological illnesses, severely underestimating the effects on CVDs.

In this review, we summarized the pharmacological effects of gastrodin on CVDs to better understand its cardiovascular benefits and its mechanisms of action (Table 1). The relevant literature was retrieved from electronic databases, such as Web of Science, PubMed, and CNKI from April 1980 to December 2021, by using keywords of gastrodin and cardiovascular diseases.

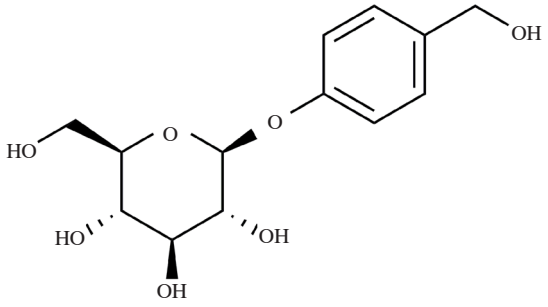

Figure 1. Chemical structure of gastrodin.

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How to cite this article: Yang ST, Liu SB. Cardiovascular protective properties of gastrodin. Asian Pac J Trop Biomed 2022; 12(4): 141-147.

Article history: Received 22 October 2021; Revision 6 December 2021; Accepted 16 March 2022; Available online 7 April 2022

2. Cardiovascular protective effects of gastrodin

2.1. Cardiac protective effects

2.1.1. Protection against hypoxic injury and myocardial ischemia-reperfusion injury (MI/RI)

Restoring blood flow is generally considered to be an effective therapeutic approach for ischemic heart diseases. While providing fresh blood to the ischemic myocardium, the myocardial ischemia-reperfusion also exacerbates cardiac dysfunction and myocardial cell damage. This pathophysiological feature is known as MI/RI, and treating ischemic heart diseases is still difficult. Therefore, new effective methods for preventing and treating myocardial ischemia are urgently needed[11,12].

The cardiac protective effects of gastrodin have been studied using animal models and cell cultures. By boosting autophagic flux, pretreatment with gastrodin (100 mg/kg, *i.p.*) reduced defective mitochondria and myocardial infarct size in a MI/RI rat model. Further *in vitro* tests revealed that the cardiac protective effects of gastrodin were mediated *via* phosphorylation of the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK)[13]. Gastrodin has also been shown to modulate autophagy, alleviate H/R injury, and improve proliferative activity in cardiomyocytes through the activation of mTOR signals in the PI3K-AKT-mTOR pathway[14].

The pathogenic factors of cardiac I/R injury are complicated by cardiac microcirculation disruption and endothelial dysfunction. Furthermore, mitochondria have been implicated in the pathogenesis of most cardiovascular disorders, which entail signaling regulation in the heart microcirculation. Mitochondrial dynamics are disrupted during reperfusion of cardiac ischemia, with increased fission, reduced fusion, and impaired mitophagy. The vascular tone, inflammation, microvascular patency, viability, and mobility of endothelial cells are all affected by mitochondrial abnormalities, culminating in cardiac reperfusion injury[15,16]. Gastrodin (20, 50, and 100 μM) was found to significantly enhance cell viability in H9c2 cells with H_2O_2-induced oxidative damage. It has the potential to prevent apoptosis by activating Nrf2, modifying mitochondrial dynamics, and maintaining mitochondrial structure and function[17]. Gastrodin reduced caspase-3, creatine phosphokinase, and lactate dehydrogenase activity in another investigation by increasing 14-3-3η protein levels. Gastrodin (20 mg/L) can also restrict the opening of the mitochondrial permeability transition pore, reduce reactive oxygen species production, and change the maintenance of the mitochondrial membrane potential ($\Delta\Psi m$), thus providing significant protection against A/R injury[18].

Aside from the mechanisms of action outlined above, other processes contribute to the protective effects of gastrodin against MI/RI or hypoxic injury. Gastrodin at 5-10 μM was found to ameliorate hypoxia injury in H9c2 cells by up-regulating miR-21 and activating the PTEN/PI3K/AKT and NF-κB pathways *in vitro*[19]. In addition, gastrodin (500 mg/kg/twice a day, *i.g.*, for 7 d before model establishment and 3 d after model establishment) reduced myocardial apoptotic rate in a MI/RI rat model by downregulating Bax, activating caspase-3 expression and upregulating Bcl-2 expression[20]. Gastrodin (100, 200, and 400 mg/kg/twice a day, *i.g.*, for 7 d before modeling and 3 d after modeling) dose-dependently reduced the ratio of heart weight to left ventricular weight in rats, alleviating MI/RI and inflammation-induced injury. The cardioprotective effect was mediated by inhibition of calcium overload and regulation of sarcoplasmic reticulum calcium transport ATPase and calcium phosphate expression in the sarcoplasmic reticulum[21]. During myocardial I/R, gastrodin exhibited noticeable capillary formation, anti-inflammatory and anti-pyropthotic effects on microvascular injury *via* the NLRP3/caspase-1 pathway[22].

2.1.2. Inhibitory effect on the inflammatory responses

In severe sepsis/septic shock, septic cardiac dysfunction could be induced by the bacterial endotoxin lipopolysaccharide (LPS). Pro-inflammatory mediators and cytokines play significant roles in sepsis-associated myocardial dysfunction. Therefore, protecting myocardium cells from inflammatory responses appears to be a promising approach to reduce mortality in sepsis patients with cardiac dysfunction[23,24]. A previous study showed that gastrodin could lower the expression of inducible nitric oxide synthase, cyclooxygenase-2, tumor necrosis factor-α, and interleukin-6, and suppress the activation of nuclear factor-κB and mitogen-activated protein kinases family. The anti-inflammatory effect of gastrodin against septic cardiac dysfunction could be mediated *via* activation of PI3K/Akt pathway[25]. Another study also revealed that the lower expression of NLRP3 plays a major role in the treatment of septic shock-induced injury with gastrodin[26].

2.1.3. Anti-cardiac hypertrophy

Pathological cardiac hypertrophy is frequently associated with cardiac dysfunction, which increases the risk of heart failure. Furthermore, the evidence implies that reducing stress-induced cardiac hypertrophy is a beneficial treatment for heart failure[27]. In C57 mice with phenylephrine-induced myocardial hypertrophy, gastrodin (100 mg/kg/day, *i.p.*, for a week) dose-dependently inhibited myocardial hypertrophy by lowering the heart size and ratio of heart weight to body weight. Its action on Orai1 and STIM1 expression, as well as modulation of SOCE (store-operated Ca^{2+} entry) were related to cardio-protection[28]. Gastrodin (100 mg/kg/day, *p.o.*, for 8 weeks) suppressed the expression of cardiac hypertrophy markers including atrial natriuretic peptide, B-type natriuretic

Table 1. Cardiovascular protective effects of gastrodin.

Model	Treatment	Efficacy	Mechanism	Ref
MI/RI in SD rats; H/R injury in neonatal rat cardiomyocytes *in vitro*	Intraperitoneal injection of GAS (100 mg/kg) 30 min before establishing model; GAS (20 μmol/L) 1 h before H/R	Reduce myocardial injury, and improve cardiac function; increase cell viability, and enhance autophagic flux	Increase autophagic flux, and activate AMPK-mTOR pathway	[13]
H/R in neonatal rat cardiomyocytes *in vitro*	GAS (0.1 μmol/L, 1 μmol/L, 10 μmol/L) for 48 h before hypoxia treatment	Increase cell viability, reverse the cell autophagy	Activate PI3K-Akt pathway	[14]
H_2O_2-induced oxidative injury in H9c2 cells *in vitro*	GAS (20, 50, and 100 μM) for 4 h before treatment with H_2O_2	Decrease cell apoptosis, and ameliorate increased ROS	Induce the activation of Nrf2, modulate mitochondrial dynamics, and maintain the structure and functions of mitochondria	[17]
A/R injury in H9c2 cells *in vitro*	GAS (20 mg/L) for 24 h before the induction of A/R	Decrease cardiomyocyte apoptosis	Regulate the generation of ROS, the mitochondrial membrane potential and the activation of caspase-3 *via* increasing the 14-3-3η protein	[18]
Hypoxia-induced H9c2 cells *in vitro*	GAS (5 or 10 μM) for 2 h before hypoxia treatment	Attenuate hypoxia-induced H9c2 cell injury	Activate PTEN/PI3K/AKT and NF-κB pathways *via* upregulating miR-21	[19]
MI/RI in SD rats	Intragastric administration GAS (500 mg/kg), twice a day, for 7 d before model establishment and 3 d after model establishment	Alleviate MI/RI, reduce myocardial apoptosis rate	Downregulate the expression of Bax, IL-1β, TNF-α, and IL-6, activate caspase-3, upregulate Bcl-2 and IL-10 expression	[20]
MI/RI in SD rats	Intragastric administration of GAS (100, 200, and 400 mg/kg), twice a day, for 7 d before modeling and continued 3 d after modeling	Alleviate MI/RI, decrease IS/LV, IS/AAR, and AAR/LV	Regulate SERCA and PLB expression, and inhibit calcium overload	[21]
MI/RI in C57BL/6J mice	Intraperitoneal administration of GAS (100 mg/kg), once a day, for 3 d before ligation of the LAD; and treatment with GAS (100 mg/kg) 15 min before reperfusion	Ameliorate pyroptosis, reduce infarct size and inflammatory cell infiltration	Inhibit NLRP3/caspase-1 pathway	[22]
LPS-induced inflammatory responses in H9c2 cells *in vitro*	GAS (5, 10, 20 μM) before LPS (1 mg/mL) stimulation	Attenuate LPS-induced acute inflammatory responses	PI3-K/Akt pathway	[25]
LPS-induced septic shock model in C57BL/6 mice	Intraperitoneal injection of GAS (15, 30, 60 mg/kg) before LPS (1 mg/mL) stimulation	Promote cardiac function, alleviate septic shock-induced injury of myocardial cells	Inhibit NLRP3 expression	[26]
Phenylephrine- or angiotensin Ⅱ-induced cardiac hypertrophy in SD rats and neonatal rat cardiomyocytes *in vitro*	Intraperitoneal administration of GAS (100 mg/kg/day), for a week before the induction; treatment with GAS (100 μmol/L) 12 h before induction	Decrease the heart size and HW/BW	Attenuate the SOCE by reducing the expression of STIM1 and Orai1	[28]
Hypertrophy induced by pressure overload in C57/B6 mice	Dietary administration of GAS (100 mg/kg/day) for a week before aortic banding surgery and 7 weeks after aortic banding surgery	Inhibit cardiac hypertrophy and dysfunction, decrease HW/BW	Block ERK1/2 signaling	[29]
Hypertrophy induced by angiotensin Ⅱ in male C57BL/6 mice	Oral gavage of GAS (5 and 50 mg/kg/day) for 7 d before surgery	Decrease heart size and HW/BW	Inhibit IGF2/IGF2R expression	[30]
A perfusion model of isolated thoracic aorta rings of rats	GAS (5, 50, 100, 150, 200, and 250 μmol/L); incubation of GAS (200 mmol/L) in the Ca^{2+}-free (K-H) solution	Relax the PE-contracted aorta rings	Reduce the Ca^{2+} released from the sarcoplasmic reticulum, inhibit inositol 1, 4, 5-trisphosphate receptor	[33]
SHRs	Intraperitoneal administration of GAS (100 mg/kg/d), for 4 weeks	Decrease the SBP, angiotensin Ⅱ and ALD in serum	Direct or indirect intervention of RAAS *via* activation of PPARγ	[34]
Tension experiments on rat mesenteric artery ring without an endothelium	Rat MASMCs were incubated with 100 μM GAS for 24 h	Cause vasodilation	Activation of PKA and subsequent opening of smooth muscle K_{ATP} channels	[35]
PDGF-BB-induced VSMC proliferation *in vitro* and injury-induced neointimal formation *in vivo*	GAS (200 μg/mL) for 2 h prior to incubation with PDGF-BB; dietary administration of GAS (150 mg/kg/day) for 14 d	Influence the S-phase entry of VSMCs, reduce the intimal area and the number of PCNA-positive cells	ERK1/2, p38 MAPK, and Akt/GSK3β signaling pathways	[39]

Table 1. Cardiovascular protective effects of gastrodin (continued).

Model	Treatment	Efficacy	Mechanism	Ref
Homocysteine-induced injury in HUVECs	GAS (50-800 μg/mL) for 24 h after modeling	Attenuate homocysteine-induced HUVEC apoptosis	PI3K/Akt/eNOS and Nrf2/ARE pathways	[40]
Early atherosclerosis induced by high-fat feed in C57BL/6J mice	Oral gavage of GAS (50, 100, and 200 mg/kg/day) for 20 weeks after modeling	Prevent aortic disease and decrease blood lipid levels	Rescue gut microbes and anti-inflammation	[42]
Ox-LDL-induced formation of foam cells in murine macrophage RAW264.7 cell line	GAS (20 μmol/L) for 24 h after modeling	Induce lysosomal biogenesis, enhance autophagic activity, and inhibit foam cell formation	AMPK-FoxO1-TFEB signal axis	[43]
HUVECs	10 ng/mL VEGF, GAS (10, 25 μM)	Increase the cell proliferation, migration and tube formation ability	PI3K/Akt signaling pathways	[45]
PTK787-treated Zebrafish	0.1, 1, and 100 μg/mL polysaccharide fraction and non-polysaccharide fraction + 0.2 μg/mL PTK787	Promote the vascular growth	-	[46]
"McFarlane flap" model in SD rats	Intraperitoneal injection of GAS (25 mg/kg, daily) for 7 d after model establishment	Improve the survival of the random-pattern flap	Increase autophagy flux, promote angiogenesis and attenuate apoptosis and oxidative stress	[47]

MI/RI: myocardial ischemia-reperfusion injury; H/R: hypoxia/reoxygenation; A/R: anoxia/reoxygenation; GAS: gastrodin; LAD: left anterior descending; LPS: lipopolysaccharide; SOCE: store-operated Ca^{2+} entry; HW/BW: heart weight/body weight; PE: phenylephrine hydrochloride; SHRs: spontaneously hypertensive rats; SBP: systolic blood pressure; ALD: aldosterone; RAAS: renin-angiotensin-aldosterone system; PPARγ: peroxisome proliferator-activated receptor γ; MASMCs: mesenteric artery smooth muscle cells; PDGF-BB: platelet-derived growth factor-BB; K_{ATP}: ATP-sensitive potassium channels; PCNA: proliferating cell nuclear antigen; VSMC: vascular smooth muscle cell; ox-LDL: oxygenized low-density lipoproteins; HUVECs: human umbilical vein endothelial cells; VEGF: vascular endothelial growth factor; SERCA: sarcoplasmic reticulum calcium transport ATPase; PLB: calcium phosphate; IS/LV: infarct size/left ventricular; IS/AAR: infarct size/area at risk, AAR/LV: area at risk/left ventricular; PKA: protein kinase A.

peptide (BNP), and myosin heavy chain 7 *via* the ERK1/2 signaling pathways, thus showing the protective effects on pressure-induced cardiac hypertrophy[29]. Furthermore, insulin-like growth factor type 2 and its receptor have been identified as a key potential target in the treatment of angiotensin Ⅱ-induced cardiac hypertrophy with gastrodin based on bioinformatics analysis[30].

2.2. Vascular protective effects

2.2.1. Hypotensive effect

Hypertension is a chronic disease that has a significant negative impact on people's health. It can lead to serious health consequences such as myocardial infarction, stroke, renal failure, coma, and even death if unproperly treated[31,32]. Gastrodin has been exhibited to have significant vascular relaxing effects on thoracic aorta rings of rats, mainly inhibiting the sigaling of inositol 1, 4, 5-trisphosphate receptor in the sarcoplasmic reticulum[33]. Meanwhile, gastrodin (100 mg/kg/d, *i.p.*, for 4 weeks) reduced systolic blood pressure levels in spontaneously hypertensive rats (190.2 ± 8.9 versus 169.8 ± 6.4). The antihypertensive properties of gastrodin were achieved directly or indirectly through intervening with the renin-angiotensin-aldosterone system[34]. Moreover, gastrodin produced vasodilation in rat mesenteric artery rings through opening smooth muscle K_{ATP} channels and activating protein kinase A[35].

2.2.2. Protection of vascular cells

Multiple growth factors and cytokines stimulate the proliferation of vascular smooth muscle cells, which is the frequent pathological process in many cardiovascular diseases, such as arteriosclerosis and restenosis following vein grafting or coronary intervention[36-38]. Gastrodin has been shown to reduce the proliferation of vascular smooth muscle cells *in vitro* and suppress neointimal hyperplasia *in vivo*. Inhibition of ERK1/2, p38, and Akt/GSK3β signaling was partially responsible for the protective effect of gastrodin[39]. Gastrodin also significantly reduced homocysteine-induced injury in human umbilical vein endothelial cells, which could be associated with the regulation of PI3K/Akt/eNOS and Nrf2/ARE pathways[40].

2.2.3. Anti-atherosclerosis effects

Myocardial infarction and stroke are both caused by atherosclerosis, which is a major risk factor of acute cardiovascular events. It has been linked to chronic inflammation and lipid dysbolism[41]. Gastrodin (50, 100, and 200 mg/kg, *p.o.*, for 20 weeks) reduced the levels of blood lipid and inflammatory factors in C57BL/6J mice through remodeling intestinal flora[42]. Another study found that gastrodin inhibited the development of foam cells in murine macrophage cells, indicating that it has significant anti-atherosclerosis properties[43].

2.2.4. Angiogenic effects

Angiogenesis is an effective treatment for various CVDs that aims to improve the function of ischemic tissues by increasing blood supply[44]. In both *in vivo* and *in vitro* studies, gastrodin exhibited prominent angiogenic effects. Gastrodin (10 and 25 μM) could improve cell proliferation, migration, and tube formation in human umbilical vein endothelial cells by activating the PI3K/Akt signaling pathway[45]. The network pharmacologic analysis revealed that gastrodin has a significant correlation coefficient with proangiogenic

activity in an animal model[46]. Furthermore, gastrodin has been shown to increase the survival rate of flaps (random pattern), which is linked to the promotion of angiogenesis[47].

3. Conclusion

Some Chinese herbal medicines containing Tian ma have been widely used to treat CVDs in clinical practice. Gastrodin has long been regarded as an intriguing and promising active molecule because it is a major ingredient of Tian ma. With the advancement of synthesis technology[48–50], it is expected that gastrodin will continue to have a high value in medical applications.

Cardiovascular problems are the leading cause of mortality in diabetes patients. Diabetes mellitus promotes the risk of peripheral vascular disease, heart failure, and ischemic stroke. In the overall management of diabetes mellitus, there is substantial unmet demand for cardiovascular prevention[51–53]. Gastrodin had a protective effect on myocardial cells in a high glucose-induced cell damage model[54]. Gastrodin has also been shown to reduce cognitive dysfunction and retinopathy, two typical consequences of diabetes, by maintaining vascular function[55,56] and have significant effects in the treatment of type 2 diabetes mellitus[57]. Therefore, these results could imply that gastrodin with cardiovascular protective properties could be useful in the prevention and management of diabetes and its associated diseases.

Gastrodin has long been known for its ability to treat illnesses of central nervous system diseases[9,58,59]. Nonetheless, we highlight gastrodin as a promising therapeutic candidate for the prevention and treatment of CVDs in this review. As previously stated, gastrodin protects against CVDs primarily through ERK1/2, AMPK-mTOR, PI3K-AKT, NF-κB, and Akt/GSK3β pathways, *etc*. Furthermore, we also discussed the medical potential of gastrodin in diabetes-induced CVDs. Thus, gaining a better knowledge of these mechanisms may provide new directions for the development of therapeutic approaches in the treatment of CVDs. More detailed mechanisms, on the other hand, will necessitate further investigation.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Authors' contributions

STY conceived and composed the article. SBL critically reviewed and revised the final draft of the article.

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