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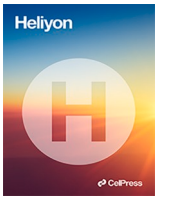

Review article

A review: Mechanism and prospect of gastrodin in prevention and treatment of T2DM and COVID-19

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A R T I C L E I N F O

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A B S T R A C T

Gastrodin is an extract from the dried tuber of the Chinese herb *Gastrodia elata* (*Tian ma*), with anti-inflammatory, antioxidant, and antiviral properties. Recent studies have shown that, compared to commonly used diabetes drugs, gastrodin has antidiabetic effects in multiple ways, with characteristics of low cost, high safety, less side effects, protection of β-cell function, relieving insulin resistance and alleviating multiple complications. In addition, it is confirmed that gastrodin can protect the function of lung and other organs, enhance antiviral activity via upregulating the type I interferon (IFN–I), and inhibit angiotensin II (AngII), a key factor in "cytokine storm" caused by COVID-19. Therefore, we reviewed the effect and mechanism of gastrodin on type 2 diabetes mellitus (T2DM), and speculated other potential mechanisms of gastrodin in alleviating insulin resistance from insulin signal pathway, inflammation, mitochondrial and endoplasmic reticulum and its potential in the prevention and treatment of COVID-19. We hope to provide new direction and treatment strategy for basic research and clinical work: gastrodin is considered as a drug for the prevention and treatment of diabetes and COVID-19.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia, β-cell dysfunction, insulin resistance, and dyslipidemia [1]. T2DM is the most common form of diabetes, accounting for 90–95 % of all cases, and is expected to increase to 439 million cases globally by 2030 [2]. T2DM is becoming a global epidemic and seriously threats to human health [3]. T2DM is characterized by the inability to use insulin efficiently (insulin resistance) and to produce enough insulin to overcome insulin resistance [4]. Insulin secretion disorder is closely related to β-cellular compensatory damage and mitochondrial dysfunction [5]. The direct cause of insulin resistance is impaired insulin signal transduction, including abnormal decrease in activation and content of insulin receptor (InsR) , insulin receptor substrate (IRS) and phosphatidylinositol 3-kinase and protein kinase B (PI3K/Akt) [6]. The common ultimate pathway leading to insulin signal damage is the accumulation of fatty acid and/or fatty acid-related products [7], which is mainly caused by inflammation, mitochondrial dysfunction and endoplasmic reticulum (ER) stress [8–10].

At present, the commonly used synthetic hypoglycemic drugs have some deficiencies, such as strict and multiple administration regimens, high cost, and adverse reactions such as gastrointestinal tract [11,12]. For example, although the classical drug metformin can improve insulin sensitivity, it has no significant effect on improving the function of β-cells [13]. Chinese herbal medicine has been used to treat diabetes for thousands of years. In recent years, many studies showed that the active components of some Chinese herbal

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medicines have the characteristics of stable therapeutic effect, high safety and few adverse reactions in the prevention and treatment of diabetes [14].

The herb *Gastrodia elata* belongs to *Orchidaceae*, which is mainly produced in Sichuan, Yunnan and other places in China. The dried tubers of *Gastrodia elata* are usually used as medicine. Gastrodin is an important medical component in the dried tuber of *Gastrodia elata*. Its main active ingredient is 4-hydroxybenzyl alcohol-4-*O*-*β*-*D*-glucopyranoside, with the molecular formula C13H18O7 and a molecular weight of 286 Da [15] (Fig. 1). In China, gastrodin has been used to treat headaches, dizziness, spasms, memory loss and other diseases for hundreds of years. Modern medical research has shown that it has antioxidant, anti-inflammatory, anti-apoptotic and antiviral properties and is widely used to treat vascular and neurological diseases [16]. Gastrodin has the advantages of multi-site action, multi-targeted action, high safety, large dosing space, less toxic side effects, systemic conditioning and low acquisition cost [15]. Recent studies have shown that gastrodin has good anti-diabetic effects [1,15,17–27]. And compared with metformin, gastrodin can repair β-cell damage [1]. Therefore, we reviewed the known studies on gastrodin improving β-cell function, enhancing insulin signal transduction (PI3K/Akt), reducing insulin resistance [1,27], and the studies on gastrodin relieving multiple diabetic complications through anti-inflammation [15,17,21,23,26], antioxidation [18,20,22,25], and inhibition of ER stress [19,24]. In addition, we also discussed the potential mechanisms of gastrodin in alleviating insulin resistance from four aspects: insulin signal pathway, multiple links of inflammatory response, mitochondrial function and ER stress.

In addition, studies have confirmed that gastrodin can protect lungs and other important organs [28]. What is more noteworthy is that gastrodin has antiviral effect via upregulating the IFN-I [29], anti-inflammatory effect via inhibiting the AngII in renin-angiotensin system (RAS) (AngII is a key factor in the pathogenesis and progression of COVID-19) [30] and antioxidative effect [31]. Therefore, on the basis of reviewing the pathogenesis of COVID-19, we also discussed the potential of gastrodin in the prevention and treatment of COVID-19.

With "gastrodin, T2DM (diabetes), insulin resistance, pattern recognition receptors, inflammatory kinase, macrophages, mitochondrial, endoplasmic reticulum stress, COVID-19 (SARS-CoV-2), ACE2, AngII, IFN-I, antivirus" as key words, we have searched Pubmed, MEDLINE and CNKI for a large number of related literatures from 1981 to the present, and finally selected 138 of them as references for this review. The purpose of writing this review is to provide new ideas and strategies for the prevention and treatment of T2DM and COVID-19.

2. Gastrodin and T2DM

2.1. Gastrodin protects β-cell function and relieves T2DM

2.1.1. The role of β-Cells in T2DM

Insulin resistance and β-cell failure represent core pathophysiological defects in type 2 diabetes. In the development of T2DM, insulin resistance places a major stress on pancreatic β-cells to augment their secretion of insulin to offset the defect in insulin action [32]. As β-cells undergo a compensatory expansion in response to insulin resistance, the β-cells begin to fail, cannot continue to produce these very large amounts of insulin, and plasma glucose levels begin to rise, leading to the onset of overt diabetes [33]. In fact, a significant loss of β-cell mass has been observed long before the onset of type 2 diabetes. Pre-diabetic individuals with impaired glucose tolerance have lost 80 % of their β-cell function [34]. In post-mortem specimens from patients with T2DM, β-cell mass is reduced by 30–40 % compared to specimens from non-diabetic subjects [35]. Therefore, interventions to prevent β-cell mass and functional decline are important.

2.1.2. Gastrodin protects β-Cells

At present, Metformin is a common drug for treating T2DM, which increases insulin sensitivity but has no significant effect on improving the function of islet β-cells [13]. However, a study showed that after 6 weeks of treatment, gastrodin repaired the degeneration and atrophy of islets in T2DM rats, increased islet β-cell expression, and reduced blood sugar levels [1]. This improvement in β-cells may result from gastrodin directly protecting β-cells through its powerful antioxidant and anti-inflammatory

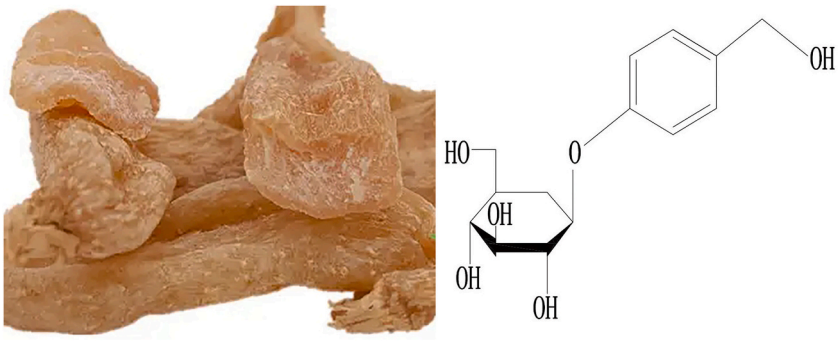

Fig. 1. The dried tuber of *Gastrodia elata*, and the chemical structures of gastrodin.

properties or from gastrodin indirectly reducing the compensatory damage of β-cells by alleviating insulin resistance. In short, the protective effect for β-cells is a prominent advantage of gastrodin in treating T2DM.

2.2. Gastrodin upregulates PI3K/AKT pathway and relieves insulin resistance

2.2.1. The role of PI3K/AKT pathway in insulin signal transduction

Phosphatidylinositol-3 kinase (PI3K) belongs to a family of kinases that catalyze the phosphorylation of inositol lipids [36]. Insulin binds to the insulin receptor (InsR) to initiate insulin receptor substrate (IRS) phosphorylation, consequently activating PI3K. PI3K then converts phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 recruits AKT (also known as protein kinase B or PKB) to the membrane [37]. Activated AKT participates in insulin-mediated glucose metabolism regulation via glucose transporter 4 (GLUT4), glycogen synthase kinase-3β (GSK3β) and forkhead box protein O1 (FOXO1) [36–38]. AKT directly phosphorylates AS160, inducing GLUT4 translocation, which translocates to the plasma membrane from storage vesicles and transports glucose in the skeletal muscle [39]. Activated AKT can also inhibit the activity of GSK3β and increase glycogen synthetase (GS) activity, thus promoting insulin-stimulated liver glycogen synthesis and lowering blood glucose levels *in vivo* [37]. In addition, AKT directly inhibits FOXO1, reducing gluconeogenesis and blood glucose levels *in vivo* [38]. In conclusion, upregulation of the PI3K/AKT pathway can reduce blood glucose levels by increasing glucose uptake in the skeletal muscle, stimulating liver glycogen synthesis, and inhibiting gluconeogenesis. Therefore, activation of the PI3K/AKT pathway is an important method for improving

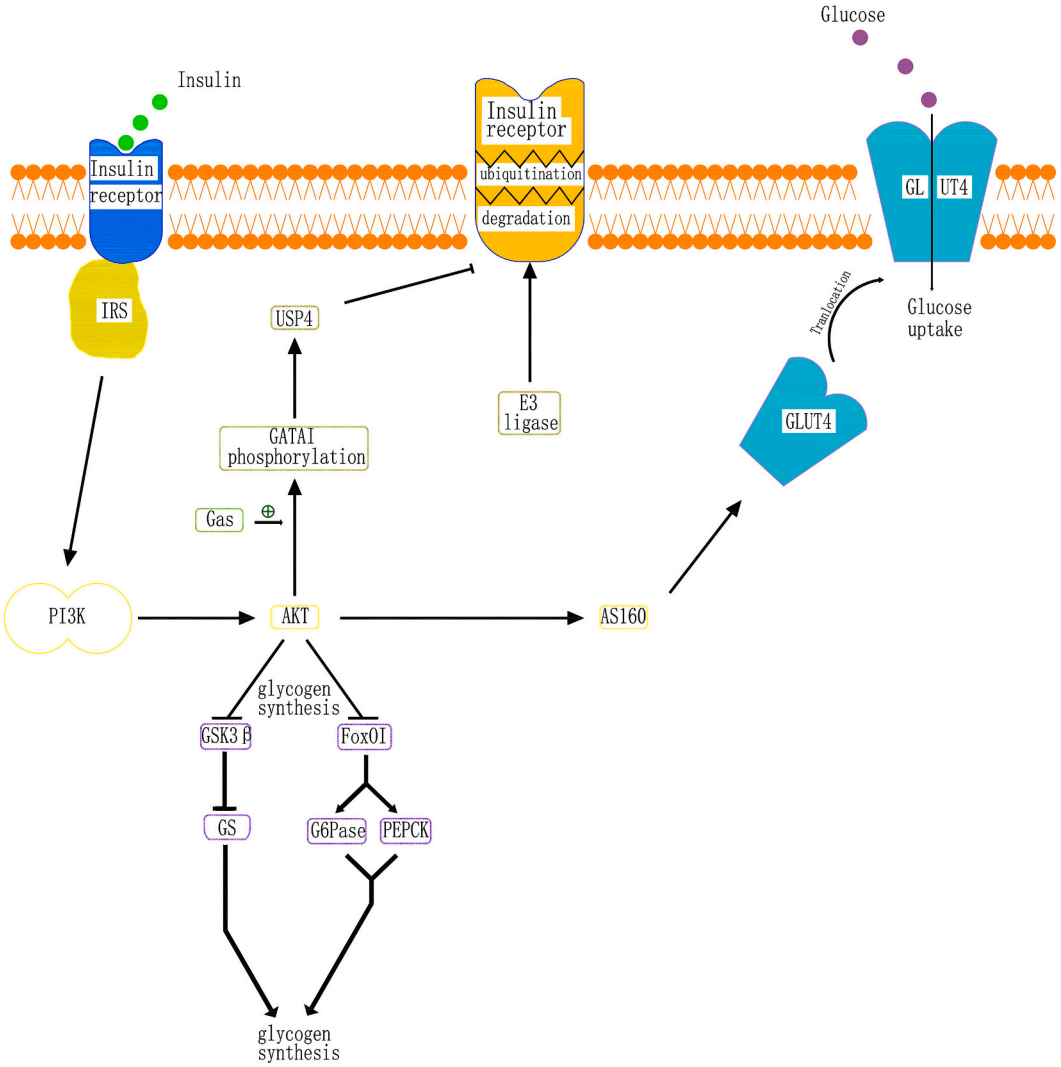

Fig. 2. Gastrodin relieves insulin resistance through upregulating PI3K/AKT pathways. Upon insulin stimulation, the InsR phosphorylates the IRS at tyrosine sites, which consequently activates PI3K/AKT. PI3K/AKT pathway reduces blood glucose levels by inducing GLUT4 translocation and inhibiting the activity of GSK3β and FOXO1. InsR can be ubiquitinated by E3 ubiquitin ligases and further degraded, resulting in insulin resistance. However, gastrodin promotes USP4 expression, which deubiquitinates InsR to inhibit its degradation, ultimately improving insulin resistance.

hyperglycemia in T2DM (Fig. 2).

2.2.2. Gastrodin upregulates PI3K/AKT pathway

Insulin signaling defects are usually associated with a decrease in InsR tyrosine kinase activity and InsR content on the cell surface [40,41]. Under pathological conditions, the InsR can be ubiquitinated by E3 ubiquitin ligases and further degraded, thus reducing the level of InsRs on the cell membrane, resulting in insulin resistance [42]. Ubiquitin-specific protease 4 (USP4) is a deubiquitinating enzyme [43]. Bai et al. [1] indicated that gastrodin promotes the phosphorylation of GATA1, upregulates its transcriptional activity via the PI3K/AKT pathway, and promotes USP4 expression. USP4 upregulation reduces the ubiquitination and degradation of InsRs, upregulates the number of InsRs, and ultimately improves insulin resistance. The PI3K/AKT signaling pathway inhibitors MK-2206 and LY294002 abolish the beneficial effects of gastrodin (Fig. 2).

In addition to upregulating PI3K/AKT signal pathway in T2DM rat model [1], gastrodin also significantly upregulated PI3K/AKT pathway in a large number of other experimental models [31,44–51]. These results strongly support that gastrodin stimulates activation of the PI3K/AKT pathway and affects subsequent glucose uptake and glycogen synthesis *in vivo*, thus exhibiting the potential of alleviating insulin resistance and ameliorating T2DM. While the research of Bai et al [1]. mainly focused on the upregulation of USP4 expression and the increase of InsR content by gastrodin. However, in view of the fact that PI3K/AKT pathway can regulate insulin signal transduction and glucose metabolism in many ways, including GLUT4, GSK3β, and FOXO1 (38). Therefore the effects of gastrodin on the PI3K/AKT pathway and on downstream signal molecules related to glucose metabolism deserve more attention. Specifically, we urgently need to explore the effects of gastrodin on GLUT4/GSK3β/GS/FOXO1 through PI3K/AKT pathway, as well as the changes of glucose uptake, glycogen synthesis and blood glucose levels in the context of diabetes. At present, we only preliminarily realize that gastrodin can reduce blood glucose level and protect β-cells in T2DM, so elucidating its specific mechanism is of far-reaching significance to improve the efficacy of gastrodin hypoglycemic drugs and to develop a highly efficient and balanced drug combination in the future.

2.3. Gastrodin relieves insulin resistance by inhibiting inflammation

2.3.1. Pattern recognition receptors (PRRs) in diabetes

Inflammatory processes is initiated by PRRs, including toll-like receptors (TLRs) and NOD-like receptors (NLRs). Among the NLR family members, the NOD-like receptor protein 3 (Nlrp3) inflammasome is believed to contribute to insulin resistance [52]. Vandanmagsar et al. found that Nlrp3 ablation reduced inflammatory cytokines release and alleviated insulin resistance [52]. Another study showed that mice lacking the Nlrp3 reduced liver fatty acid content and were resistant to the development of obesity induced by a high-fat diet [53]. These findings suggest that inflammasome inhibition may be a potential therapeutic strategy for insulin resistance.

The role of Toll-like receptor 4 (TLR4) in insulin resistance has attracted increasing attention. In the tissues of animal models and human subjects with insulin resistance, TLR4 expression is enhanced. Whereas TLR4 inhibitors can ameliorate insulin signaling transduction [54,55]. Inhibition of TLR4 is a potential therapeutic strategy for insulin resistance [55].

2.3.2. Gastrodin inhibits PRRs in diabetes

The overactivation of Nlrp3 and TLR4 increases the inflammatory reaction and fatty acid accumulation, contributes to insulin resistance [52,55] and triggers a variety of diabetic complications, such as diabetic retinopathy [23,56], diabetic cognitive dysfunction [24], and depressive-like behaviors [19]. However, gastrodin ameliorated these diabetic complications by inhibiting the activation of Nlrp3 and TLR4, increasing GLUT3 expression, and reducing serum triglyceride levels [19,23,24,56]. In addition, gastrodin played a protective role by downregulating the expression of Nlrp3 and TLR4 in brain, nerve, myocardial, liver and kidney injury models [57–62]. Nlrp3 and TLR4 may be powerful targets of gastrodin in alleviating insulin resistance.

2.3.3. Kinases in diabetes

The activity of C-Jun N-terminal kinase 1 (JNK1) increases in liver, muscle, and adipose tissue in various obesity models, which increases serine phosphorylation of IRS-1 but inhibits tyrosine phosphorylation, leading to insulin resistance [63,64]. However, the inhibition of JNK1 can reduce endogenous liver glucose production, improve glucose tolerance, enhance insulin signal transduction, and reduce blood glucose levels [63–65].

Chronic inflammation in obese and T2DM patients is accompanied by activation of extracellular signal-regulated kinase 1/2 (ERK1/2) [66]. Which not only inhibits the tyrosine phosphorylation of IRS-1 [67], but also downregulates the expression of IRS-1 [68], thus inducing insulin resistance.

IκB kinase β (IKKβ) is the main regulator of nuclear factor-κB (NF-κB) signal activation, which stimulates nuclear translocation of NF-κB, triggers a series of inflammatory reactions and accumulation of free fatty acids and induces insulin resistance [69]. IKKβ signaling is upregulated in the tissues of insulin-resistant animal models and humans. IKKβ inhibitors (salicylates) can improve insulin resistance both *in vivo* and *in vitro* [69–71].

2.3.4. Gastrodin inhibits kinases in diabetes

The three kinases mentioned above can increase inflammatory reaction and free fatty acids release, inhibit IRS-1 tyrosine phosphorylation and downregulates the IRS-1 expression, thus contributing to insulin resistance. In a rat striatal neuron toxicity model induced by diabetes, gastrodin lessened the damage by reversing the high expression of ERK1/2 [22]. In addition, In addition, gastrodin inhibited the expression of JNK1 and ERK1/2 in experimental models of myocardial, liver and nerve injury [51,72,73].

Although there are no clear studies on the influence of gastrodin on IKKβ, the inhibitory effect of gastrodin on NF-κB is well known [74], which is vital for IKKβ regulation of NF-κB [75]. Therefore, gastrodin may alleviate insulin resistance by inhibiting the expression of kinases such as JNK1 and ERK1/2.

2.3.5. Cytokines in diabetes

TNF-α is considered as a pathogenic factor in the pathogenesis of T2DM. The expression level of TNF-α in the fat, muscle and circulation of human is positively correlated with the level of hyperinsulinemia [76]. Exogenous TNF-α can induce insulin resistance in human subjects and animal models. While the insulin sensitivity in diabetic rats/mice can also be improved by inhibiting TNF-α expression [77,78]. At present, it is believed that the mechanisms of insulin resistance induced by TNF- α mainly include increasing free fatty acid levels, inhibiting IRS-1 tyrosine phosphorylation [79], downregulating the expression of InsR and IRS protein [80] and decreasing the number of glucose transporter GLUT4 [78].

In addition, other cytokines such as interleukin-1β (IL-1β) and interleukin-6 (IL-6) are positively correlated with insulin resistance. IL-1β can downregulate the expression of IRS-1 and reduce GLUT-4 translocation in adipocytes [68,81]. However, neutralization of IL-1β reversed the insulin resistance of human adipocytes [81]. IL-6 promoted liver gluconeogenesis and insulin resistance by inhibiting tyrosine phosphorylation of IRS [82]. IL-6 also stimulated the expression of suppressor of cytokine signaling (SOCS) 3, a negative regulator of insulin signaling [83].

2.3.6. Gastrodin inhibits cytokines in diabetes

The anti-inflammatory properties of gastrodin are well known. Gastrodin can significantly reduce the expression of inflammatory factors such as TNF-α, IL-1β, and IL-6 in a variety of diabetic models [15,20,21,26] and other metabolic diseases [84,85]. Therefore, gastrodin has the potential to alleviate insulin resistance at the cytokine level.

2.3.7. Macrophages in diabetes

Macrophages, the key cells in inflammation, have been identified as key effector cells for initiating inflammation and insulin

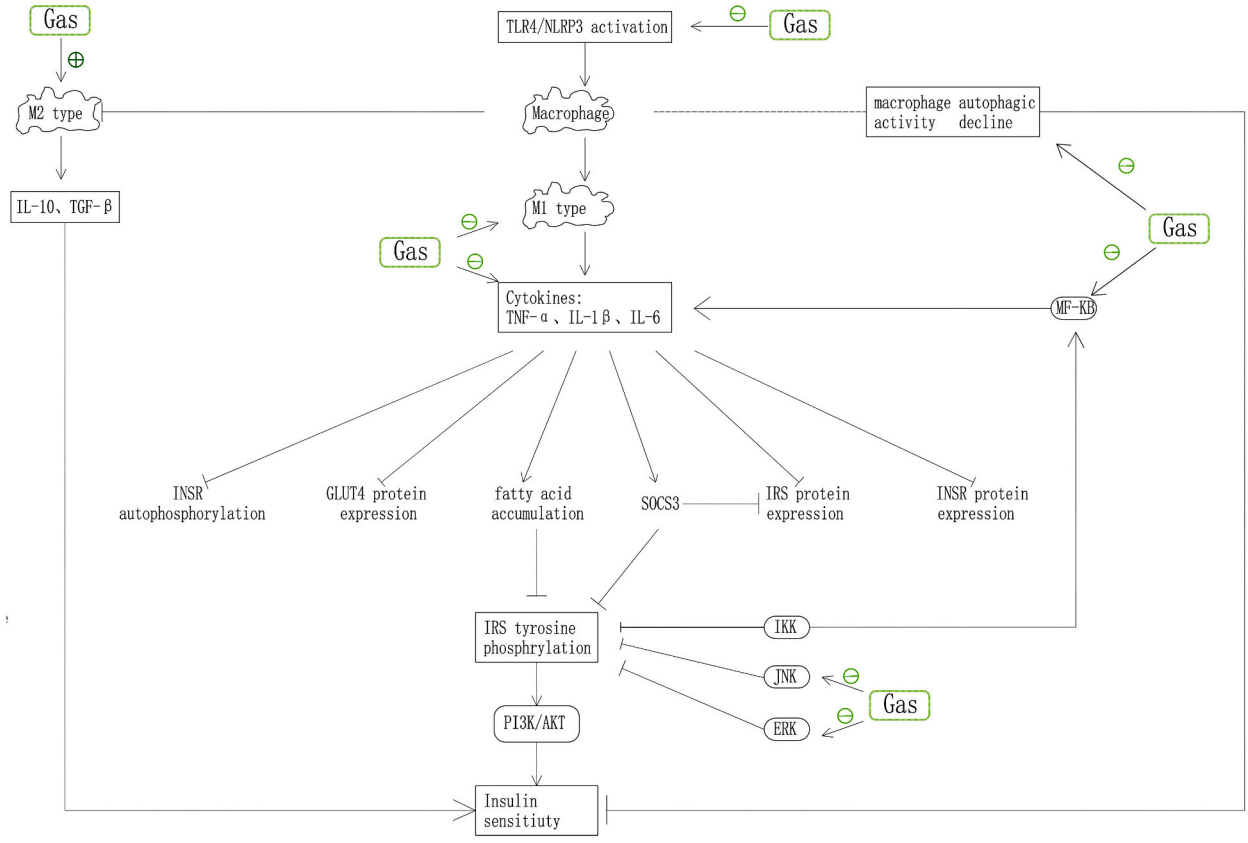

Fig. 3. Gastrodin may alleviate insulin resistance by inhibiting inflammation. Inflammatory cytokines and related kinases (JNK, ERK and IKKβ) cause insulin resistance through inhibiting the expression of InsR, IRS and GLUT4 proteins, decreased InsR autophosphorylation, and stimulating fatty acid accumulation and SOCS3 activation (which both inhibit IRS tyrosine phosphorylation). However, gastrodin inhibits the activation of PRRs (TLR4 and Nlrp3) and kinases, stimulates M2-type polarization of macrophages but inhibits M1-type polarization, recovers macrophage autophagic activity and reduces cytokines production.

resistance [86]. When mice are extremely obese, the number of adipose tissue macrophages increased by more than 50 % [87]. Macrophages can polarize into a pro-inflammatory (M1) type and anti-inflammatory (M2) type. High levels of glucose can promote macrophage M1 polarization, contributing to inflammation and insulin resistance. In adipose tissue of healthy mouse, macrophage mostly polarized to the M2 type, which produced anti-inflammatory cytokines, contributing to enhancing insulin sensitivity [88]. Macrophage autophagy is also associated with insulin resistance. When the specific autophagy of macrophages was impaired, the insulin sensitivity of adipose tissue in mice decreased [89].

2.3.8. Gastrodin regulates the polarization of macrophages in diabetes

It is well known that gastrodin induces M2 polarization but inhibits M1 polarization in macrophages. Gastrodin reprogrammed macrophages from M1 type to M2 type, resulting in higher expression of pro-regenerative cytokines and lower expression of pro-inflammatory cytokines [90]. Gastrodin can also protect macrophage from oxidative stress and apoptosis [91]. In addition, gastrodin can restore the autophagy activity of macrophages under pathological conditions [92]. In summary, gastrodin induces M2 polarization of macrophage, protectes the survival of macrophage and restores their autophagy activity, which may alleviate insulin resistance (Fig. 3).

2.4. Gastrodin may relieve insulin resistance by protecting mitochondrial function

2.4.1. Mitochondrial dysfunction contributes to insulin resistance

Mitochondria play an important role in β-cells perceiving glucose to secrete insulin and removing fatty acids to alleviate insulin resistance [93]. Mitochondrial dysfunction has been observed in liver, muscle, adipose tissue, and brain of animal models and humans with T2DM [94]. In the insulin-resistant offspring of T2DM patients, the lipid content in skeletal muscle cells increased while the oxidative phosphorylation function of mitochondria decreased [8]. Another gene enrichment analysis showed that the expression of

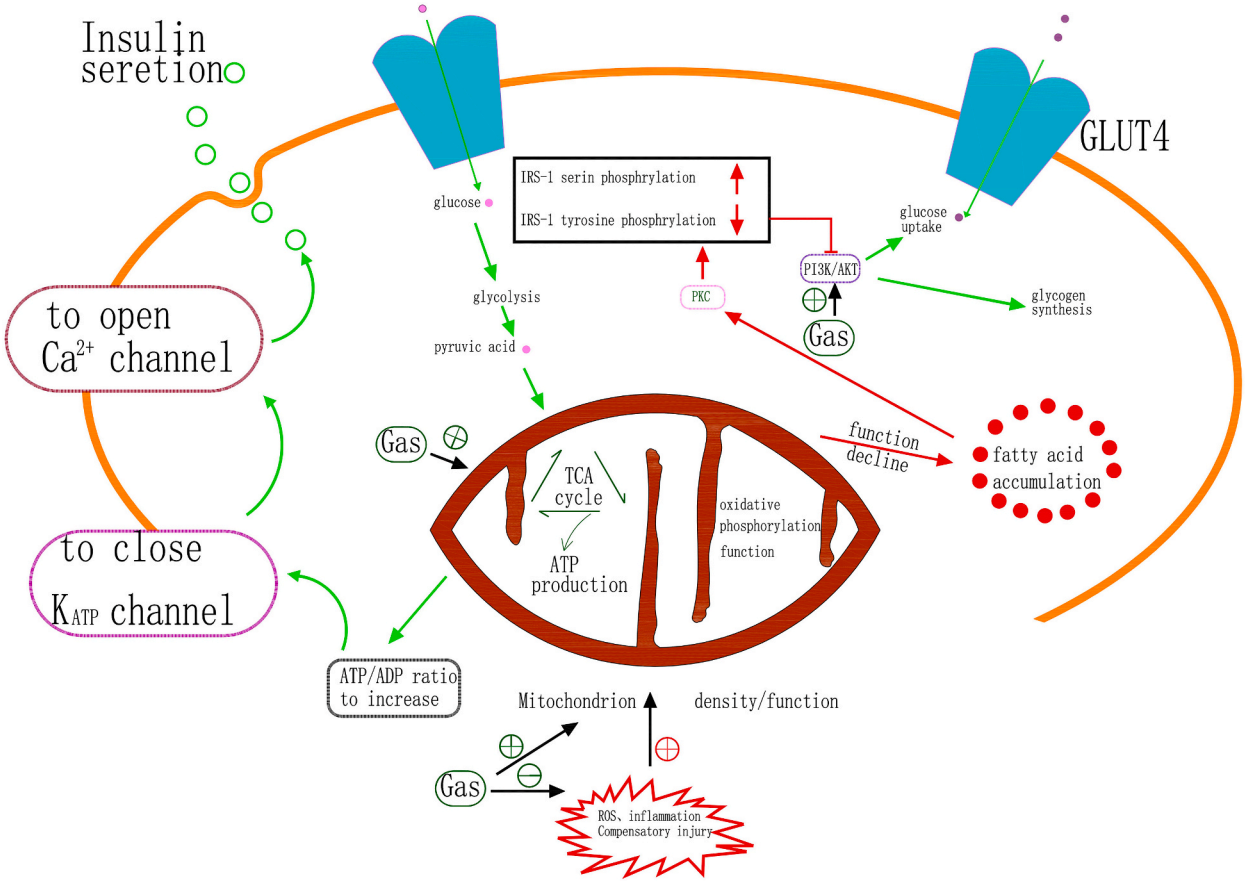

Fig. 4. Gastrodin may alleviate insulin resistance by improving mitochondrial function. Mitochondrial dysfunction induced by inflammation and ROS leads to decreased ATP production and ATP/ADP ratio decline, resulting in insufficient Ca2+ channel opening, ultimately contributing to decreased insulin secretion. In addition, the decreased oxidative phosphorylation activity of mitochondria leads to fatty acids accumulation, which reduces the IRS-1-mediated activation of the PI3K/AKT pathway, resulting in insulin resistance. However gastrodin can improve mitochondrial function and density, have the potential to ameliorant insulin resistance.

mitochondrial fatty acid oxidation-related genes in the offspring of insulin-resistant mice was significantly reduced [95]. In addition, mitochondria-targeted therapies for insulin secretion deficiency have been proposed in T2DM studies. For example, dimethyl succinate and coenzyme Q10, which are involved in mitochondrial activity, can improve insulin secretion in T2DM models and in patients [96, 97].

First, insulin secretion depends on the function that mitochondria metabolizes glucose to produce ATP [94]. The mitochondria produces ATP via the tricarboxylic acid cycle. At this time, the intracellular ATP/ADP ratio increases, inhibiting ATP-sensitive K^+ channels, but opening Ca^{2+} channels. Then the Ca^{2+} concentration in the cytoplasm increases. In the presence of ATP, Ca^{2+} stimulates the exocytosis of insulin granules to achieve insulin secretion [93,94]. Therefore, mitochondrial dysfunction in patients with T2DM can lead to an abnormal decrease in insulin secretion.

Secondly, many scholars believe that due to the decrease of mitochondrial content and its oxidative phosphorylation function, the ability of mitochondria to oxidize and remove fatty acids decreases, leading to the accumulation of fatty acids [8]. The increase of fatty acid activates a class of protein kinase C (PKC), such as PKC-θ. PKC-θ increases serine phosphorylation of IRS-1 but inhibits tyrosine phosphorylation, triggering insulin resistance [98] (Fig. 4).

2.4.2. Gastrodin improves mitochondrial function

In a variety of cell and animal experimental models, gastrodin protected the structure and function of mitochondria. For example, via anti-inflammatory and antioxidant properties, gastrodin attenuated mitochondrial damage, maintained the structure and function of mitochondrial, and ensured ATP production in the injury models of nerve cells, cardiomyocytes and osteoblasts [99–101]. In addition, gastrodin enhanced autophagic flux to eliminate dysfunctional mitochondria, thus protecting neighboring mitochondria [102]. Considering that mitochondrial damage can lead to insulin secretion dysfunction and insulin resistance, we believe that elucidating the role of gastrodin on mitochondria in diabetes is of great significance. Specifically, the effects of gastrodin on mitochondrial content, ATP production, and oxidative phosphorylation function under high glucose conditions should be explored. At the same time, changes in β-cell insulin secretion and insulin signaling transduction should be observed (Fig. 4).

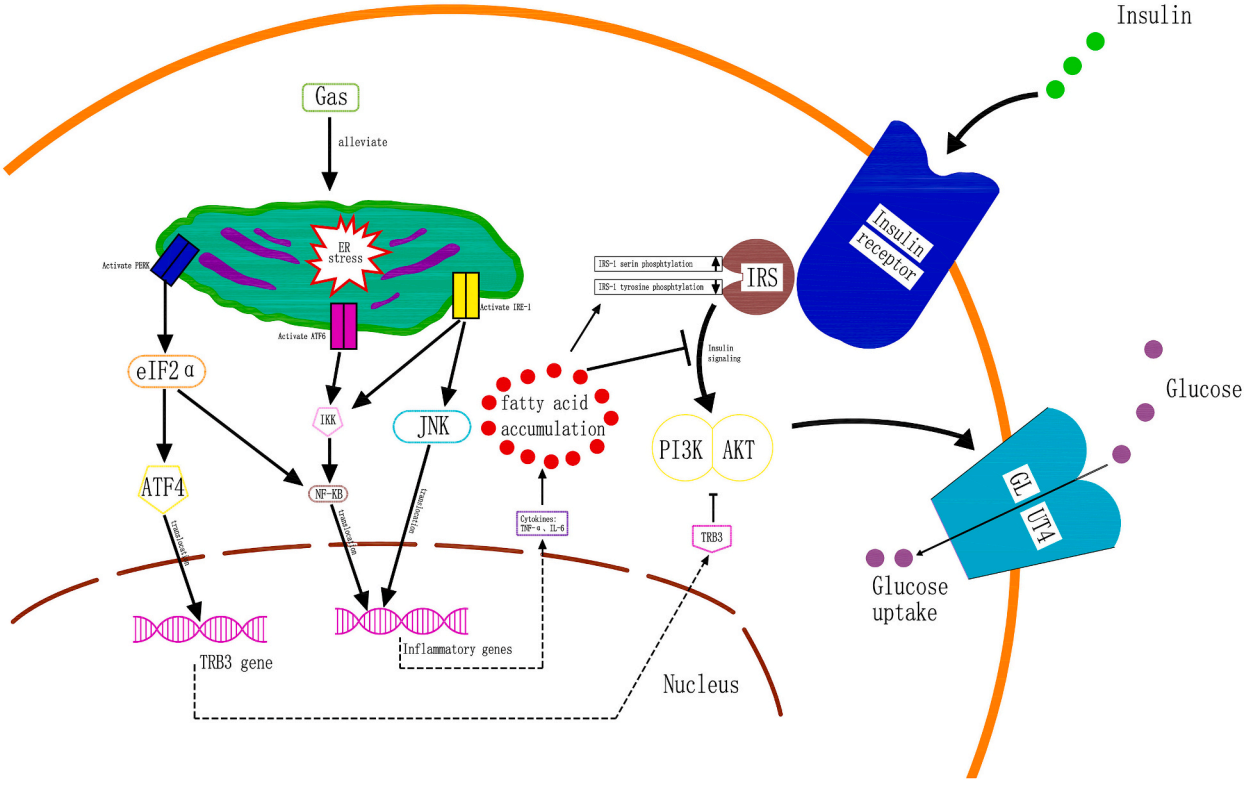

Fig. 5. Gastrodin may relieve insulin resistance by inhibiting ER stress. ER stress activates three characteristic sensors: PERK, ATF6 and IRE1α. PERK-ATF4-TRB3 pathway inhibits AKT activity and promotes insulin resistance. ATF6 and IRE1α upregulates the activity of JNK1 and IKK, which reduce IRS tyrosine phosphorylation, resulting in PI3K/AKT inhibition. However, gastrodin can reduce ER stress level in a dose-dependent manner *in vivo* or *in vitro*.

2.5. Gastrodin may relieve insulin resistance by inhibiting endoplasmic reticulum (ER) stress

2.5.1. ER stress contributes to insulin resistance

ER stress is believed to be involved in the development of insulin resistance and T2DM. Increased ER stress is found in adipose tissue, skeletal muscle, and liver of T2DM patients and insulin-resistant animal models [10]. ER stress activates the unfolded protein response (UPR). The UPR then activates three characteristic ER stress sensors: protein kinase RNA-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol requirement enzyme 1α (IRE1α) [103].

During ER stress, activated PERK enhances the expressions of eukaryotic initiation factor 2α (eIF2α) and activating transcription factor 4 (ATF4), leading to the increased expression of tripeptide-like protein 3 (TRB3) which inhibits PI3K/AKT activity and promotes insulin resistance [104]. In addition, IRE1α activated by ER stress increases the expression of inflammatory factors via upregulating the activity of C-Jun N-terminal kinase (JNK). Similarly, activated ATF6 also increases the expression of inflammatory factors through IκB kinase (IKK) —— NF- κB pathway [105,106]. Finally, these pro-inflammatory cytokines stimulate the accumulation of free fatty acid, which inhibits the tyrosine phosphorylation of IRS-1, leading to insulin resistance [107]. Currently, ER stress has been proposed as a targeted intervention strategy for insulin resistance [108]. For example, the use of phenylbutyrate or ursodeoxycholic acid can reduce chronic ER stress, improve insulin sensitivity, and facilitate the functional recovery of β-cells [109,110] (Fig. 5).

2.5.2. Gastrodin alleviates ER stress

ER stress is closely related to insulin resistance. While gastrodin showed an inhibitory effect on ER stress in multiple studies. Gastrodin alleviated diabetic encephalopathy by inhibiting ER stress in the hippocampus [19,24]. Gastrodin achieves a neuroprotective effect by inhibiting the expression of C/EBP homologous protein (a pro-apoptotic ER stress protein) [111]. Gastrodin reduces ER stress levels in osteoporotic mice in a dose-dependent manner [101]. Taking ER stress as a bridge, inhibition of ER stress by gastrodin may be an important breakthrough in exploring its mechanism of alleviating insulin resistance (Fig. 5).

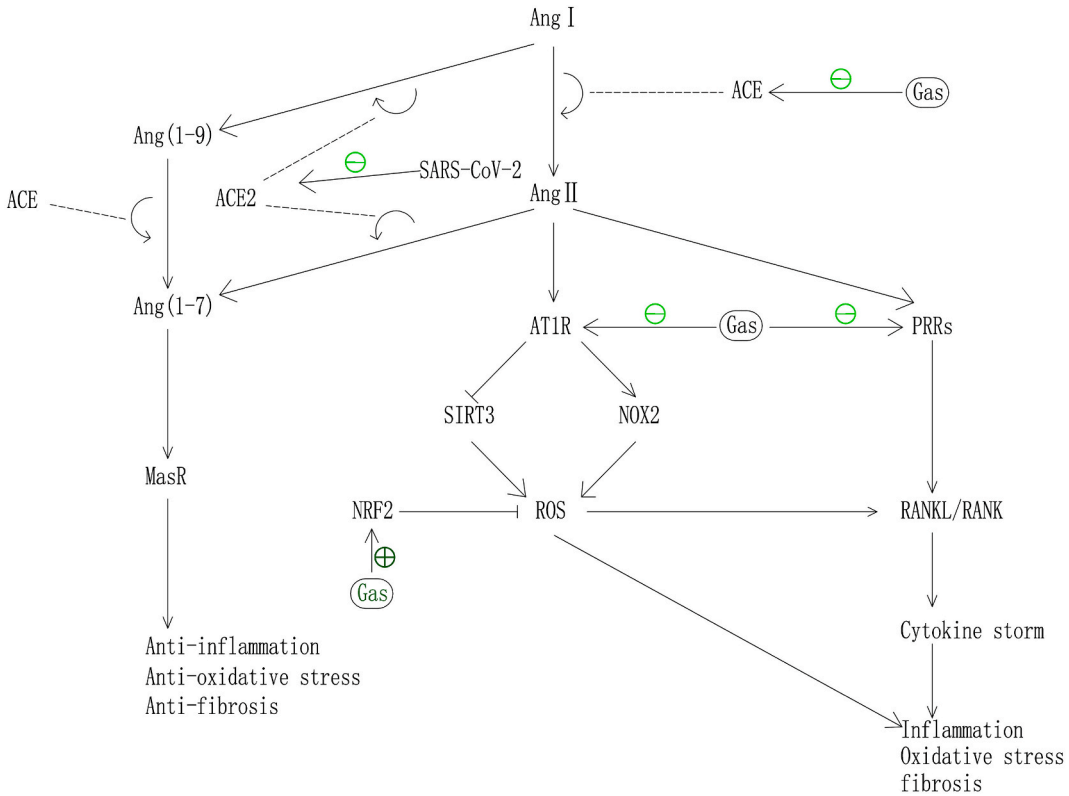

Fig. 6. Gastrodin may alleviate the damage caused by SARS-CoV-2 by inhibiting Ang II. After SARS-CoV-2 infection, ACE2 expression is downregulated, but Ang II levels are increased. Ang II, combining with AT1R, induces oxidative stress by affecting NOX2 and SIRT3 and results in "cytokine storm" by initiating inflammatory reaction, eventually causing multiple organs damage. However, gastrodin can reduce the production of AngII by inhibiting the activation of ACE; gastrodin can also inhibit AT1R and PRRs activation but upregulate NRF2 expression. Ultimately, gastrodin reduces AngII-mediated inflammation, oxidative stress.

3. Gastrodin and COVID-19

3.1. Infection and damaging effects of SARS-CoV-2

Angiotensin-converting enzyme 2 (ACE2) provides a pathway for SARS-CoV-2 to enter human cells. The spike protein of SARS-CoV-2 helps the virus to enter the host cell [112] by interacting with the ACE2 receptor on the target cell. Because ACE2 is occupied by SARS-CoV-2, RAS abnormalitie is induced, which leads to a series of reactions. Renin cleaves angiotensinogen to produce angiotensin I, which is further cleaved by ACE to produce AngII. AngII mainly combines with the angiotensin type 1 receptor (AT1R) and triggers a range of biological effects such as inflammation, oxidative stress, and fibrosis [15]. ACE2 cleaves AngII into angiotensin (1–7) and exerts anti-inflammatory and antioxidant effects by binding to the Mas receptor. After SARS-CoV-2 infection, ACE2 expression is downregulated, but Ang II levels are increased [113]. On the one hand, it induces oxidative stress by affecting nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2) and Sirtuin 3 (SIRT3). On the other hand, it initiates inflammatory reactions to limit viral infection [15]. When the inflammatory response cannot solve the problem, a disorder of excessive inflammation occurs, namely "cytokine storm", which ultimately leads to functional impairment of multiple organs [114] (Fig. 6).

Current treatment strategies include antiviral drugs, biological response regulators, and RAS inhibitors [115]. However, some current antiviral or glucocorticoid drugs increase the risk of serious adverse reactions [116]. Some Chinese herbal medicines has attracted attention because of its extensive biological activity and few side effects [117,118].

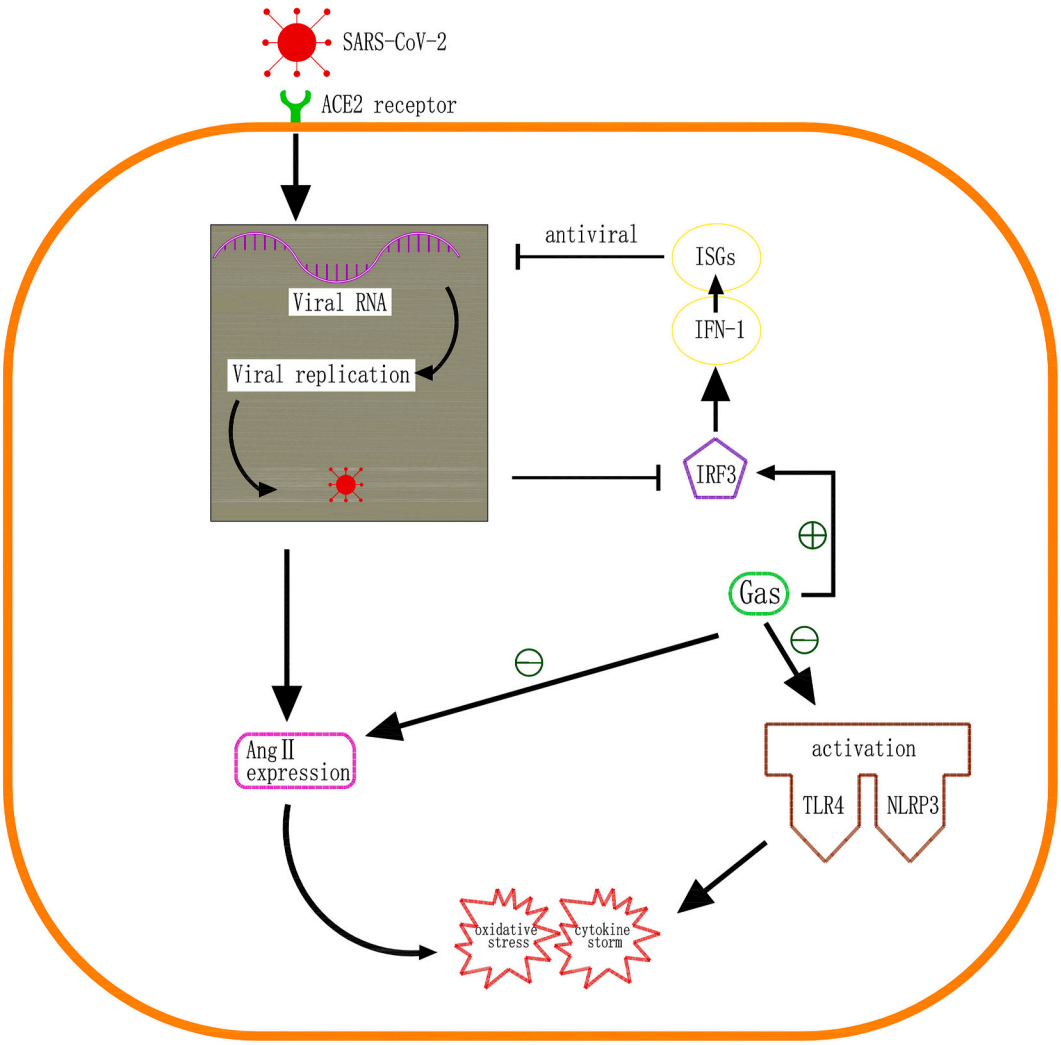

Fig. 7. Gastrodin enhances antiviral defense by promoting the production of IFN-I. IFN-I activated by IRF3 can induce the expression of interferon-stimulated genes (ISGs), which show direct antiviral activity, such as inhibiting viral replication, translation and assembly. But SARS-CoV-2 inhibits IFN-I production by acting on IRF3, to evade antiviral defenses. However, gastrodin can enhance IRF3 activation and promote IFN-I production, thus resisting RNA and DNA virus infection. Meanwhile, gastrodin can also inhibit "cytokine storms".

3.2. Gastrodin may relieve symptoms of COVID-19 through anti-inflammation (inhibiting AngII) and antioxidation

In the cell or animal models of neuroinflammation and cardiovascular inflammation, gastrodin can reduce the production of AngII by inhibiting ACE. And gastrodin can also inhibit the activation of AT1R. Ultimately, gastrodin reduces AngII-mediated inflammation and oxidative stress [30,119–121]. SARS-CoV-2 causes the downregulation of ACE2, resulting in the increase of AngII. However, we cannot casually increase the expression of ACE2, because ACE2 may increase the susceptibility to SARS-CoV-2 [115]. However, gastrodin reduces the source of AngII and inhibits the AT1R by which the AngII works. Therefore, gastrodin may inhibits the "cytokine storm" in COVID-19.

In addition, in various experimental models, gastrodin has shown excellent antioxidative capacity whether through the RAS-SIRT3/NOX2 pathway [30] or the NRF2 pathway [31]. The increased oxidative stress level in COVID-19 patients is related to the severity of disease [122]. Therefore, the antioxidative effect of gastrodin may alleviate the serious symptoms of COVID-19 (Fig. 6).

3.3. The antiviral activity of gastrodin

Gastrodin has natural antiviral activity. A series of substituted aryl glycoside analogs of gastrodin has been identified as potential anti-influenza agents. Among them, methyl4-fluoro-3-((2*S*,3*R*,4*S*,5*R*,6*R*)3,4,5-triacetoxy-6-(acetoxymethyl)-tetrahydro-2*H*-pyran-2-yloxy) benzoate (1a) is the most potent inhibitor, which increases the survival rate and time of test animals [123]. The antiviral mechanism of gastrodin may be the up-ragulation of interferon regulatory transcription factor 3 (IRF3) and the increased expression of IFN-I [29]. IFN-I can suppress viral infection in multiple stages from invasion to release, such as the infection of SARS-CoV-2 and vesicular stomatitis virus [124,125]. Because viruses, including SARS-CoV-2, inhibit IFN-I production through evolution, increasing the production of IFN-I is an effective strategy to combat viral infections [126]. Therefore, gastrodin is a potential drug to prevent COVID-19 (Fig. 7).

In addition, a new view is that inhibition of excessive inflammation is a better treatment option while taking advantage of the antiviral activity of IFN-I [127]. It is worth noting that gastrodin did not enhance the inflammatory response when it inhibited viral infection through IFN-I [29] (Fig. 7).

3.4. Potential protective effect of gastrodin on organs in COVID-19

Lungs. SARS-CoV-2 caused progressive severe diffuse alveolar injury through "cytokine storm" and oxidative stress [128]. Enhancing the antioxidant and anti-inflammatory functions of lung tissue is of great significance. In a mouse model of acute lung injury, gastrodin upregulated the expression of antioxidant protein (Nrf2 and HO-1), downregulated the expression of pro-inflammatory cytokine, and alleviated pulmonary edema and dysfunction [28]. In an inflammatory lung injury model, gastrodin reduced the expression of NF-κB in the lung tissue and alleviated inflammatory pathological changes in the lung [129]. Therefore, gastrodin may alleviate lung injury caused by SARS-CoV-2.

Vascular microcirculation. SARS-CoV-2 invades endothelial cells, causing inflammation around the blood vessels, leading to microcirculation disorders, ultimately increasing the risk of coagulopathy [130]. Many studies have shown that gastrodin can alleviate the injury of human umbilical vein endothelial cells and protects blood vessels [31,131]. In addition, gastrodin has anticoagulant effect [132]. In a mouse model of early atherosclerosis, gastrodin reduced serum cholesterol and low-density lipoprotein in blood [133]. Therefore, gastrodin may improve the microcirculation disorder caused by SARS-CoV-2.

Heart. SARS-CoV-2 leaded to myocardial injury by inflammatory reaction, oxidative stress and microcirculation disorder [134,135]. However, in the models of myocardial injury induced by ischemia/reperfusion, hypoxia, high glucose, inflammation, and oxidative stress, gastrodin protected the function of myocardial cells and reduced myocardial injury [18,48,59,72,100]. Therefore, gastrodin is expected to alleviate myocardial damage caused by SARS-CoV-2.

Bone. SARS-CoV-2 directly or indirectly harmed the bone health by "cytokine storm" and oxidative stress [136,137]. Secondly, the use of corticosteroids in severe COVID-19 patients often leaded to iatrogenic osteoporosis [138]. It is well known that gastrodin can treat osteoporosis through its anti-inflammatory, antioxidant and anti-apoptotic effects [15]. Gastrodin has great potential to protect the bone health of SARS-CoV-2 patients.

4. Conclusion

We reviewed the current studies on gastrodin protecting β-cells, alleviating insulin resistance and improving a variety of diabetic complications. We also speculated the potential mechanisms of gastrodin in alleviating insulin resistance from four aspects: insulin signal pathway, multiple links of inflammatory response, mitochondrial function and ER stress. It points out the potential and characteristics of gastrodin, such as low cost, high safety, less toxicity and side effects, protection of β-cell function, anti-diabetes in multiple ways and alleviating multiple complications. The aim is to discuss the potential and advantages of gastrodin as a new therapeutic or adjuvant drug for diabetes. So as to provide new and beneficial treatment strategies for patients with diabetes.

In addition, gastrodin has anti-inflammatory, antioxidant and antiviral activities, and can protect lung and other organs. In particular, gastrodin inhibits AngII, a key factor in COVID-19. Therefore, we speculateed the therapeutic potential of gastrodin in treating COVID-19 and its complications. In a word, gastrodin is a component of traditional Chinese medicine with extensive biological activities, high safety and low acquisition cost, which plays specific role in some pathogenesis of diabetes and COVID-19. This review hopes to provide a new perspective for basic research and clinical work: gastrodin is considered as a drug for the prevention and

treatment of diabetes and COVID-19.

Author Contributions

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5. Data availability statement

Data sharing not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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