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THERAPEUTIC POTENTIAL OF GINSENOSIDES IN DIABETES - A BRIEF REVIEW

Ms.Snnehaa Bhosle, Mr.Shubham Gore, Dr. Meera Deshmukh, Dr. Pranati Tilak
Lokmanya Tilak Institute of Pharmaceutical Sciences, Pune-411037

ABSTRACT

Ginsenoside is a triterpenoid saponin extracted from Panax ginseng forms the active ingredient in ginseng, widely used in clinical practice as the main component of injections, granules, common tablets, dispersible tablets, capsules, and mixtures; thus, it has become a target of extensive research. They have been emerged to support antidiabetic efficacy for ginsenosides ascribe to their antioxidant, anti-inflammatory, and anti-hyperglycemic activities. A meta-analysis showed that ginseng reduced fasting blood glucose in patients. Ginseng also exerted antidiabetic effects as a supplemental treatment. Ginseng extracts significantly improved glucose tolerance, improved in plasma glucose and insulin levels.. Besides, studies on ginsenosides in pharmaceutical preparations have also been limited. Therefore, this review dominantly discusses the roles and mechanisms of ginsenosides in the intervention of blood glucose elevation, as well as the current clinical trials on ginsenosides pharmacology. The elucidation of molecular mechanisms and clinical trials at diabetic status could facilitate ginsenosides application in herbal medicines

KEYWORDS: ***ginsenosides, hyperglycaemic, antidiabetic***

INTRODUCTION

According to International Diabetes Federation (IDF) report published on 21 December 2018, there were approximately 425 million people lived with diabetes worldwide. By 2045-2048, the number is expected to rise to an estimated 650 million (Cho et al., 2018). Diabetes mellitus (DM) is a multifactorial and chronic endocrine disorder which is characterized by insulin resistance, β-cell impairment, and glucolipid metabolism disorder [1-3]. Conventional available drugs for diabetes and related complications, such as metformin and thiazolidinediones (TZDs), have been associated with a variety of side effects and discomforts, making herbal medicines become potential candidates in diabetes remedy. In ancient China, ginseng was used to treat Xiao Ke disease whose symptoms were described as polydipsia, polyuria, overeating but losing energy that is extremely consistent to diabetic symptoms in modern [4-7].

Although peptidoglycan and glycan (ginsenans) components have been demonstrated to express pharmacological activities, ginsenoside forms main component present in ginseng root [8, 9]. Ginseng root has long been used for health promotion, prevention of certain chronic diseases, and anti-aging intervention. The steroidal structure forms the main reason of its diverse pharmacological activities which enables ginsenoside to interact with cell membranes which controls bioactivity at the transcription level [10-12]. Recent studies have revealed that ginsenosides play roles in the treatment of diabetes and its complications dominantly through improving insulin resistance, regulating glucolipid homeostasis, preventing oxidative stress and inflammatory responses. In addition, antiangiogenesis, anti-apoptotic, and hepatoprotective properties have also been documented for their antidiabetic indication [13-16]. However, insufficient exploration of those unascertained ginsenoside monomers obstacle our understanding on the medicinal value of the majority ginsenosides [17]

Brief Introduction of Ginsenoside: types and components Panax Ginseng (P. ginseng), dry roots belong to family *Araliaceae*, have been employed as crude medicine for the treatment of lack of stamina, body fatigue, cardiovascular disease or certain chronic diseases for lonf period of time. Species of ginseng are classified into four types based on diverse origins: Panax ginseng (China, Korea), Panax quinquefolius (America, Canada), Panax notoginseng (China, Japan), and Panax japonicas (Japan) [18]. The main active ingredients in ginseng consist of ginsenosides, polysaccharides, polypeptides, flavonoids, amino acid, volatile oils, and vitamins, among which ginsenoside is the most important component. Ginseng roots have long been employed to extract active ingredients, just as they are used in traditional Chinese medicine (TCM) and dietary supplements. Recently, flowers, seeds, stem and leaves from P. ginseng, P. quinquefolius or P. notoginseng are investigated to exert potent pharmacological activities as well [19-21]. Comparison of pharmacological effects between various ginseng ingredients from different sources is shown in Table 1. Ginsenoside can be universally separated into three types: protopanaxadiol (PPD, such as Rb1, Rb2, Rb3, Rc, Rg3, Rh2, Rd, and compound K,) type, protopanaxatriol (PPT, such as Re, Rg1, Rg2, Rf, Rh1, etc.)

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type and oleanolic acid type (such as Ro, Ri, Rh3). Both PPD type and PPT type ginsenosides belong to tetracyclic triterpene saponins due to the similarity of their parent nuclei, while oleanolic acid type ginsenosides belong to pentacyclic triterpenoid saponins for their particular structure. Interestingly, most ginsenosides with antidiabetic effects are PPD or PPT type saponins, which remind us of the significance of tetracyclic triterpene parent nuclei. It is noteworthy that compound K (CK), the main intestinal metabolite of PPD saponin, is of great significance for clinical monitoring [22-25]

Antidiabetic mechanisms of ginsenoside DM can be generally divided into type I (T1DM), type II (T2DM), gestational diabetes mellitus (GDM) and other specific types due to different causes ("(2) Classification and diagnosis of diabetes," 2015). T1DM is known for a primary insulin deficiency caused by β-cell dysfunction, which is to some extent related to genetic factors and always appears in children and youth. Here, T2DM is being featured by insulin resistance and obesity forms leading external cause of T2DM. Since diabetes is characterized by insulin resistance, β-cell dysfunction, and glucolipid metabolism disorder, therapeutic approaches should be involved in improving insulin resistance, accelerating glucose and lipid metabolism normalization, and protecting β-cell from oxidative stress and inflammatory responses injury. Nowadays, insulin injection is the most common method for T1DM patient treatment because innate insulin deficiency could not be cured completely, while oral hypoglycemic agents such as metformin, TZDs, and acarbose along with an appropriate diet and weight control are monitored under T2DM therapy. Nevertheless, adverse drug reactions including hypoglycemia, gastrointestinal stimulation, and edema, etc. have been reported [26-30]. Herbal medicines emerge as potential candidates against diabetes are known to bring about fewer adverse effects than chemical or biochemical drugs, and ginseng is a well-known elector. Various antihyperglycemic mechanisms have been detected for ginsenosides from cell and animal models

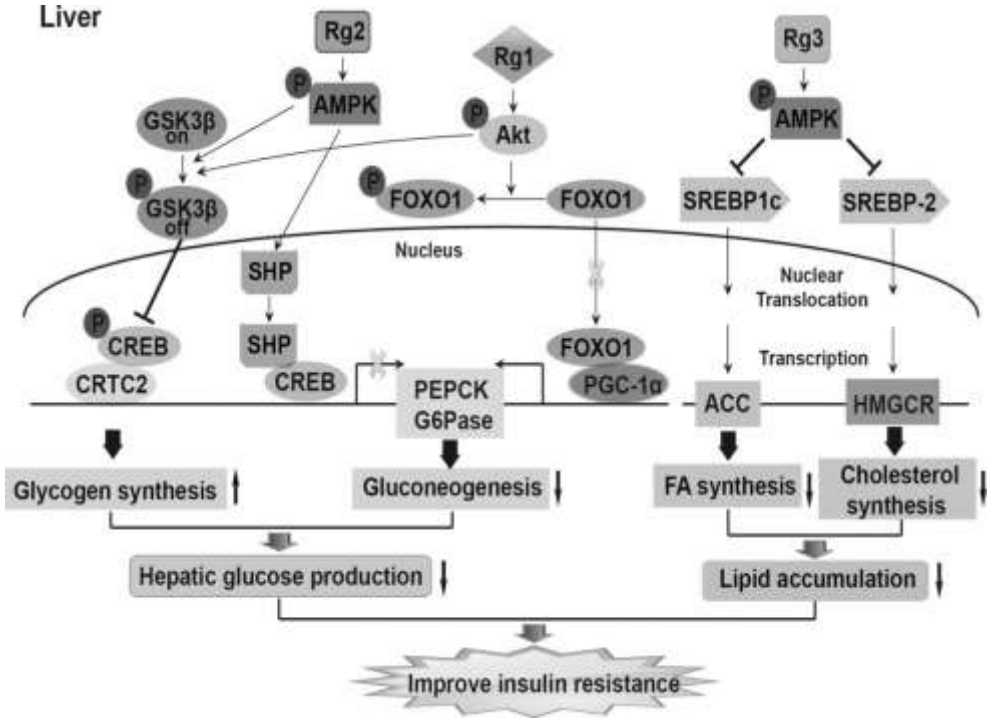

Fig. 1. Proposed model for Ginsenosides to improve insulin resistance through reduc- tion of hepatic glucose production and lipid accumulation via AMPK or Akt signaling pathways. AMPK, 5′-AMP-activated protein kinase; ACC, acetyl-CoA carboxylase; CREB, cAMP response element-binding protein;

Effect on insulin resistance Insulin resistance is a leading cause of T2DM that makes the body lack of sensitivity to insulin. Mitochondria play a pivotal role in liver, skeletal muscle and adipose tissue since these tissues are targets of insulin in glucose metabolism [31-37]. Insulin is known to decrease blood glucose via binding to insulin receptor, which in turn leads to IRS-1 activation, and subsequently caused phosphorylation of downstream pathway involving PI3K and Akt substrates. Here,the activation of IRS-1 is possibly triggered by phosphorylation of tyrosine residues or dephosphorylation of serine residues of IRS-1 [38-40]. Consequently, "phosphorylation of IRS-1" is an inapposite word to describe IRS-1 activation. Liver

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is a key target organ for insulin and is of remarkable significance in the regulation of insulin resistance. Ginsenosides improve insulin resistance in liver mainly through two aspects including modulation of hepatic glucose production and lipid accumulation in transcriptional level. The Ser/Thr kinase Akt, also known as protein kinase B (PKB), acts as a crucial signal in insulin dysfunction [41-43]. GSK3β, FOXO1, and PGC-1α are three main substrates of Akt that involved in liver glucose production. Akt activation dependent on its upstream signal PI3K activation and activated Akt is well-known for participating in insulin metabolism primarily by means of two methods: (i) Translocating GLUTs (notably GLUT4) to the cell membrane, which causes glucose uptake improvement. (ii) Promoting phosphorylation on glycogen synthase kinase 3 (GSK3β) so as to enhance glycogen synthesis leading to hepatic glucose production attenuated ultimately (Fig. 1). In addition, FOXO, a key family of transcription factors that regulate glucose homeostasis and insulin responsiveness, is negatively regulated by Akt/PKB. Effects of ginsenosides on Akt-induced attenuation of glucose production and their activities in lipid accumulation would be discussed later. It is well-established that insulin resistance of skeletal muscle plays a crucial role in T2DM. The antidiabetic effect of ginsenosides in skeletal muscle is produced by promoting glucose uptake. G-Rg5 prevented insulin resistance in muscle through inhibition of protein kinase C (PKC) which was ascribed to the reduction of diacylglycerols (DAGs) and ceramides [43-47]. G-Re reversed insulin resistance of muscle glucose transport in an insulin-dependent manner and that was mainly associated with GLUT4 translocation. Rather than mediate insulin-dependent signaling (such as IRS-1 or Akt), G-Rc was known for its ability to activate AMPK/p38 MAPK (an insulin-independent signaling pathway), which contributes to glucose uptake promotion in the C2C12 myoblasts [48] in recent years, adipocyte has turned out to be a hotspot in investigating the mechanism of insulin resistance. Ginsenosides ameliorate insulin resistance in adipose tissues primary through adjustment of glucose transport and adipogenesis. G-Rg3 and G-Re increased glucose uptake and glucose transport via IRS-1/PI3K pathway in 3T3-L1 adipocytes. G-Rb2 was documented to improve insulin resistance via downregulating phosphorylation of IRS-1 serine residues and upregulating phosphorylation of Akt. Moreover, G-CK and G-Rg1 enhanced glucose uptake and GLUT4 translocated to cell membrane through activation of AMPK and PI3K pathways [49]. Ginsenosides have been confirmed to ameliorate insulin resistance in liver, skeletal muscle, and adipocytes via multiple signaling pathways. However, it has been observed that oral GRe therapy could not prominently improve insulin resistance or β-cell function in humans with impaired glucose tolerance (IGT) or newly diagnosed T2DM. Taking together, ginsenosides only express effects on glucose transport or insulin resistance under insulin-stimulated, and low oral bioavailability may be the main reason for its poor efficacy. Therefore, most data from studies conducted in animals elucidated that ginsenosides show antidiabetic effects were given an injection

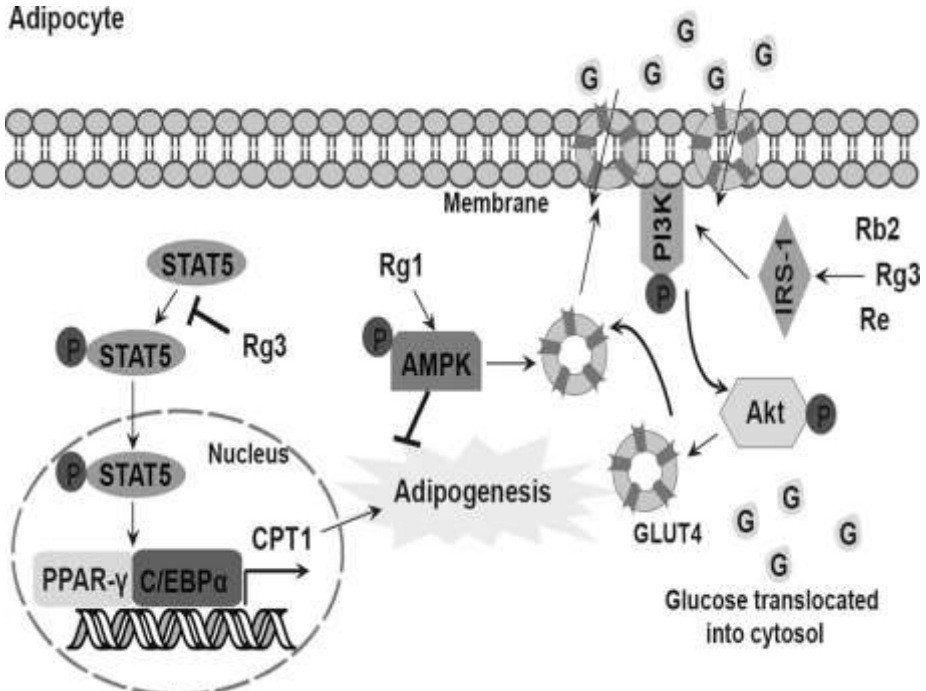

Fig. 2. The mechanism of ginsenosides in- volved in adipogenesis and glucose uptake on adipocytes. C/EBPα, CCAAT/enhancer- binding protein α; IRS-1, insulin receptor substrate 1; PI3K, phosphatidylinositol 3- kinase; GLUT, glucose transporter; PPAR-γ, peroxisome proliferator-activated receptor γ; STAT, Janus kinase (JAK)-signal trans- ducer and activator of transcription.

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Improving glucose tolerance and glucose homeostasis

Glucose tolerance is regarded as another evaluation index of diabetes: it demonstrated the ability of the organism to regulating blood glucose level. IGT and/or impaired fasting glucose (IFG) is commonly referred to as prediabetes. Since IGT is one of the chief risk factors for T2DM, improving glucose tolerance tends to be a key measure for the prevention and treatment of diabetes. Glucose homeostasis depends on the balance between levels of insulin and glucagon, and glucagon elevates glucose output mainly attributes to gluconeogenesis. Ginsenosides improve glucose homeostasis generally through inhibiting hepatic glucose production and accelerating glucose uptake in skeletal muscle and adipose tissues. Both increased glycogen synthesis and decreased gluconeogenesis can reduce hepatic glucose production. Gluconeogenesis is a way of increasing blood glucose which leads to hyperglycemia. In addition to being regulated by insulin, glucagon and glucocorticoid, hepatic gluconeogenesis is also controlled by a series of transcription factors, through which the signal is eventually fed back to two key enzymes of gluconeogenesis: PEPCK and G6Pase. AMPK, a well-known serine/threonine kinase, was confirmed to be a pivotal target during the gluconeogenic program. Current hypoglycemic agents in the clinic such as metformin and TZDs are both AMPK activators. As a key transcription factor of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), CREB can hardly activate its target gene expression unless combine with CRTC2 (also known as TORC2) to form CREB·CRTC2 complex. G-Rg2 suppressed hepatic glucose production via promoting AMPK activation, which thereby induced SHP gene expression and GSK3β phosphorylation. The inner mechanism is that SHP directly interacts with CREB, leading to disruption of CREB·CRTC2 complex, which consequently suppresses the activation of PEPCK and G6Pase (Fig. 1). Besides, G-CK has been detected to repress gluconeogenesis by inhibiting the expression of PPAR-γ coactivator-1α (PGC-1α). Moreover, G-Rg1 promotes Akt phosphorylation and facilitating Akt binding to FOXO1 to decrease transcription of PEPCK and G6Pase so as to decrease hepatic gluconeogenesis.[51-53]

Modulating lipid metabolism The sterol regulatory element binding protein (SREBP) is a key regulator of lipid homeostasis. There are three isoforms of SREBPs, SREBP-1c involves in fatty acid (FA) oxidation, whereas SREBP-2 is in charge of cholesterol synthesis [54]. G-Rg3 was found to activate AMPK and suppress SREBP-2, subsequently downregulated HMGCR expression to inhibit hepatic lipid accumulation. G-Rb2 regulated lipid accumulation via restoring autophagy through the induction of SIRT1 and activation of AMPK. G-CK also regulates lipid metabolism by AMPK/ PPAR-α pathway. AMPK also controls lipid metabolism through inhibiting adipogenesis, promoting both FA oxidation and lipolysis. Acetyl-CoA carboxylase (ACC) and 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMGCR) were two earliest discovered AMPK targets that were ratelimiting enzymes in the synthesis of FA and cholesterol, respectively. In summary, AMPK activation is closely associated with lipid metabolism, activated AMPK will not only inhibit SREBPs cleavage and nuclear translocation but also promote the expression of CPT1 (a key enzyme in FA β-oxidation), thereby suppress ACC and HMGCR expression, resulting in FA synthesis restraint and FA oxidation stimulation. Additionally, G-Rg3 ameliorated hepatic steatosis via downregulation of STAT5/PPARγ pathway, while G-Rg1 suppressed lipogenesis through increasing C/EBP homologous protein-10 (CHOP10) and subsequently reducing C/EBP transcription, indicating the significance of PPAR-γ and C/EBP in lipid accumulation [55] (Fig. 2). In fact, G-Rc was found to directly induced lipolysis in adipocytes and downregulated PPAR-γ and C/EBP (Yang & Kim, 2015), and G-Rg2 decreased the expression of PPAR-γ, C/EBPα, and SREBP1-c by inducing phosphorylation of AMPK as well In lipolysis, AMPK performs a controversial role with groups reported either inhibition, activation, or no effect. AMPK was considered to inhibit lipolysis via direct phosphorylating hormone-sensitive lipase (HSL) or blocking HSL activation. In contrast, suggested that red ginseng extracts effectively activated HSL so that induces lipolysis in (white adipose tissue) WAT and FA oxidation in (brown adipose tissue) BAT. Overall, the data above indicate that AMPK plays a fundamental part in the modulation of glucolipid metabolism. [56, 57]

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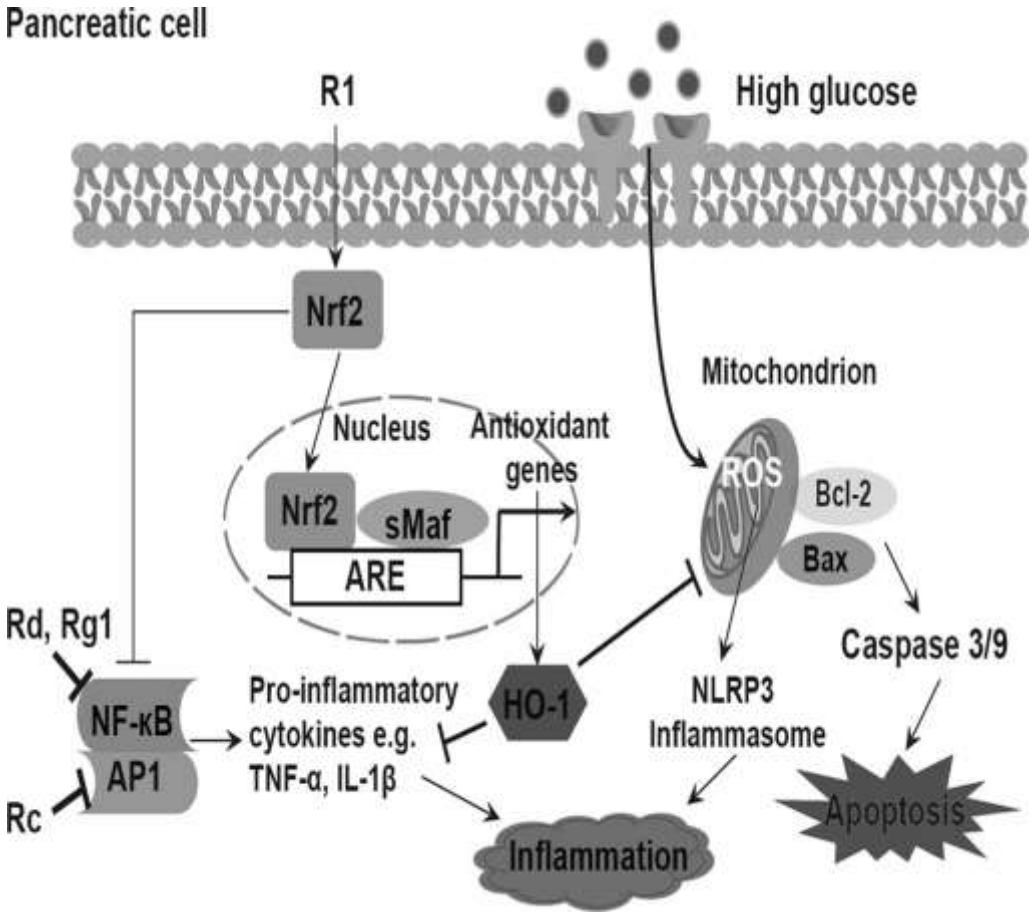

Fig 3. Ginsenosides generate antioxidant and anti-inflammatory activities through reduction of ROS production or activation of Nrf2, resulting in either inhibition of β-cell apoptosis or suppression of NF-κB and AP1 pathways. AP1, activator protein 1; Bax, Bcl- 2-associated X protein; Bcl-2, B-cell lym- phoma 2; HO-1, heme oxygenase-1; IL-1β, interleukin-1β; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TNF- α, tumor nuclear factor-α

3.4. Effect on beta-cell injury

Glucose-stimulated insulin secretion is the main task assigned to pancreatic beta-cell, and overproduction of ROS in mitochondrial refers to the critical cause which leads to beta cells dysfunction. G-Rb1 was documented to protect β-cell against diabetic injury through modulation of oxidative stress, inflammation, autophagy, and apoptosis. Oxidative stress (OS) derives from an imbalance between the generation of ROS and its scavengers, and was deemed to be a driver in the pathogenesis of insulin resistance). OS can activate sorts of transcription factors, among which nuclear factor-kappa B (NF-κB), activator protein 1 (AP1), and nuclear factor erythroid 2-related factor 2 (Nrf2) are probably the most important three pathways in diabetic inflammatory responses (Choudhury, Ghosh, Gupta, Mukherjee, & Chattopadhyay, 2015). Accumulating lines of evidence have unraveled that activation of Keap1-Nrf2 system conduces to the inhibition of DM through protecting pancreatic β-cells against oxidants and inflammation, as well as suppressing the progression of insulin resistance [58] Notoginsenoside R1 exerted an inhibitory effect of oxidative stress via Nrf2–HO-1 signaling in advanced glycation end products (AGEs)-induced db/db mice and HK-2 cells. The up-regulation of Nrf2 system also suppressed NLRP3 inflammasome activation. By the way, aside from OS alone, researchers in recent years believe in OS closely interconnected with ER stress to induce βcell apoptosis as well as inhibit insulin biosynthesis and secretion more likely. Recently it has become clear that inflammation can be initiated by FA, inflammatory cytokines, OS and ER stress, which were associated with two key intracellular inflammatory pathways, JNK-AP1 and IKKβNF-κB. Low-grade inflammation emerges as a driver of both insulin resistance and glucose dysfunction. G-Rd inhibits iNOS and COX-2 expression via repressing NF-κB[59]. G-Rg1 suppresses pro-inflammatory cytokines IL-1β and TNF-α release, which highlight the anti-inflammatory potential of ginsenosides. G-Rc can not only repress TNF-α, IL-6, and IFN but also attenuate IRF-3 and AP-1 pathways. Additionally, G-Rb1 and G-CK ameliorate insulin resistance by inhibition of NLRP3 inflammasome activation. The relationship between NF-κB and Nrf2 pathways

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on stress and inflammation responses has been investigated in previous studies). Nrf2 has been shown to negatively regulate NFκB pathway (Fig. 3). Moreover, activated NF-κB in return stimulated Nrf2 activation as a protective anti-inflammatory mechanism via GTPbinding protein RAC1. Briefly, transcription factors and signaling pathways involved in stress and inflammatory responses coordinately to maintain homeostasis of intracellular free radicals. Autophagy also plays a crucial role in maintaining β-cell physiology, especially in the maintenance of mitochondria and ER. In addition, abnormal β-cell autophagy contributes to the progression of diabetes; hence, induction of autophagy may be a benefit for diabetes inhibition. For instance, G-Rg2 activated autophagy thereby prevented high-fat diet-induced insulin resistance through AMPK/ULK1 or AMPK/mTOR pathway. GRb1 suppressed cell apoptosis via enhancing autophagy.[60-61]

CONCLUSION

Apoptosis is a typical form of β-cell death in DM. Under its pathological state, the up regulation of Bax/Bcl-2 and/or caspase 3/9 will lead to β-cell apoptosis. Numerous literatures demonstrated that JNK pathway is of remarkable significance in the process of β-cell apoptosis. This is not unexpected for JNK which is activated by a variety of stimulating factors, including free fatty acid (FFA), cytokines (especially TNF-α) and extra- or intracellular ROS. G-CK treatment attenuated caspase-3 activity and protected β-cell from apoptosis via suppression of JNK activation, and ROS bridges the linkage between AMPK and JNK pathways. Moreover, in contrast to apoptosis, pyroptosis is another form of cell programmed death that requires the function of caspase-1, associated with anti-inflammatory responses. Ginsenosides have been proved to suppress inflammatory responses by inhibition of NLPR3. It was also confirmed that ginsenosides inhibit caspase-1 leading to decrease secretion of proinflammatory cytokines, such as IL-1β and IL-18. Besides, further studies are needed to verify the effects of ginsenoside on pyroptosis of β cell

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