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Review Article

Ginsenosides for the treatment of insulin resistance and diabetes: Therapeutic perspectives and mechanistic insights

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ABSTRACT

Diabetes mellitus (DM) is a systemic disorder of energy metabolism characterized by a sustained elevation of blood glucose in conjunction with impaired insulin action in multiple peripheral tissues (i.e., insulin resistance). Although extensive research has been conducted to identify therapeutic targets for the treatment of DM, its global prevalence and associated mortailty rates are still increasing, possibly because of challenges related to long-term adherence, limited efficacy, and undesirable side effects of currently available medications, implying an urgent need to develop effective and safe pharmacotherapies for DM. Phytochemicals have recently drawn attention as novel pharmacotherapies for DM based on their clinical relevance, therapeutic efficacy, and safety. Ginsenosides, pharmacologically active ingredients primarily found in ginseng, have long been used as adjuvants to traditional medications in Asian countries and have been reported to exert promising therapeutic efficacy in various metabolic diseases, including hyperglycemia and diabetes. This review summarizes the current pharmacological effects of ginsenosides and their mechanistic insights for the treatment of insulin resistance and DM, providing comprehensive perspectives for the development of novel strategies to treat DM and related metabolic complications.

1. Introduction

Diabetes mellitus (DM) is multifactorial endocrine disease characterized by sustained high blood glucose levels [1,2]. Since glucose serves as a primary energy source for most cell types in the body, aberrant regulation of circulating glucose levels can cause dysfunction of cellular metabolism in multiple tissues. DM has emerged as one of the most prevalent metabolic diseases worldwide, estimated to be 10.5% in 2021, with projections reaching up to 12.2% by 2045 [3,4]. DM has been well established to play a crucial role in increasing the risk of several other metabolic complications, causing two-to four-fold increase in mortality compared with that of the general population [5]. Although the pathogenesis of DM is complicated, it is generally classified into three subtypes, namely type 1, type 2 and gestational diabetes [6]. Type 2 diabetes (T2DM) accounts for over 90% of all DM cases and is frequently accompanied with obesity and other metabolic disorders related to nurtional overload, sedentary lifestyle, and increased life expectancy [6]. In general, the hallmarks of T2DM include chronic hyperglycemia, sustained hyperinsulinemia, and an impaired metabolic response to insulin in peripheral tissues (i.e., insulin resistance) [1,2]. As a variety of factors derived from dysregulated cellular metabolism in multiple tissues contribute to the complex pathogenesis of T2DM, therapeutic approaches targeting single molecules and/or a small subset of signaling pathways have limited success. For instance, metformin and sulfonylureas are the most frequently prescribed anti-diabetic drugs in clinical practice, but several undesirable side effects, such as lactic acidosis, hepatic failure, and hypothyroidism, may limit their extensive use in certain patients with T2DM who exhibit poor response to certain drugs [7]. T2DM substantially contributes to the morbidity and mortality of various associated complications, highlighting the urgent need to develop novel drugs with enhanced therapeutic efficacy and minimal safety concerns.

Phytochemicals are naturally occurring compounds derived from various agricultural plants, some of which are largely responsible for the health benefits associated with medicinal herbs [6,7]. Medicinal herbs are recognized as one of the most prominent sources of therapeutically active substances, serving as direct or indirect templates for the design of many synthetic drugs [7]. Currently, a broad range of phytochemicals derived from traditional herbal medicines are emerging as novel drug candidates for the prevention and treatment of chronic metabolic

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disorders, offering excellent therapeutic efficacy, sufficient safety, and relatively low cost [6]. In this regard, traditional herbal medicines and related functional foods, which are believed to have health benefits, have recently drawn ample attention for their potential to prevent and treat a number of metabolic diseases.

Ginseng is a perennial plant, belongings to the genus *Panax* (Antaliaceae family) that has been widely used for thousands of years in East Asian countries, including China and Korea, as a tranditional medicine to provide energy, tonify the spleen and lungs, and improve thirst and emaciation [8,9]. To date, a various biologically active ginseng compounds have been identified, including ginsenosides (ginseng-specific saponins), gintonin (non-saponins), polysaccharides, fatty acids, peptides, and flavonoids [10,11], which are the major ingredients primarily responsible for the pharmacological activities of ginseng [9,11]. Interestingly, ginsenosides exhibit promising therapeutic efficacy against a series of metabolic disturbances, including hyperglycemia, obesity, cardiovascular disease, stroke, and cancer [9,12]. This calls for a comprehensive review of therapeutic perspectives and mechanistic insights of ginsenosides for the treatment of metabolic diseases, such as insulin resistance and T2DM. Therefore, this review aims to summarize the current knowledge on pharmacological functions of ginsenoside and provide insights into the molecular mechanisms of ginsenosides to ameliorate insulin resistance at cellular level, and discuss future perspectives for developing ginsenosides as novel medications against T2DM and associated metabolic complications.

2. Chemical structures of ginsenosides and their classifications

Ginsenosides, also termed panaxosides, are classified as triterpene saponins and natural product steroid glycosides, which are mostly found in various parts of ginseng, mainly in the roots. Notably, the chemical profiles quite vary across *Panax* species; although ginsenosides from *P. ginseng* have been most extensively studied, a number of ginsenosides are uniquely found in *P. quinquefolius* (American ginseng) and *P. japonicus* (Japanese ginseng) [13]. Interestingly, the composition and content of ginsenosides are influenced by various factors, including species, sampling parts of the plant, age, methods of preservation after harvest, and other environmental effects [14]. For instance, steaming ginseng at 100 °C for several hours before drying transforms it into red ginseng by generating a unique saponin profile through heat and deglycosylation of natural ginsenosides [15].

On the basis of their chemical structure, ginsenosides can be largely categorized into dammarane and oleanane types. While over 100 types of ginsenosides have been identified from *P. ginseng*, most of them belong to the dammarane type, featuring a four-ring steroid-like structure with various sugar moieties attached to the C-3 and C-20 positions [16]. Dammaranes are further subdivided into two categories: protopanaxadiols (e.g., Rb1, Rb2, Rb3, Rc, Rd, Rg3) and protopanaxatriols (e.g., Rg1, Rg2, Re, Rf) based on the presence of carboxyl groups at the C-6 position, respectively [8]. Based on the chirality of carbon substitution sites at C-20, they are further classified into 20(S) and 20(R) types [8]. Oleanane-type ginsenosides are characterized by their five-ring structure substituted with an oleanolic acid group (Ro), and ocotillol saponin F11 (24-R-pseudoginsenoside) is recently identified, which serves as a signature compound of *P. quinquefolius* [8,17]. Fig. 1 illustrates the chemical structures and the classifications of these ginsenosides types.

3. Insulin signaling in health and disease

3.1. Insulin actions in metabolic tissues

Insulin is a representative endocrine hormone that is released from pancreatic β cells in response to increase in blood glucose level upon food intake. Insulin plays a crucial role in maintaining energy homeostasis by regulating blood glucose level and cellular nutrient metabolism. Interestingly, although the insulin receptor (IR) is broadly expressed in multiple tissues, the main metabolic outcomes of insulin action vary among the tissues [18]. Liver is responsible for maintaining blood glucose level under fasting state by promoting glucose production (i.e., gluconeogenesis). In the fed condition, hepatic glucose production and glycogenolysis are suppressed while the synthesis of fatty acids is increased by insulin for storage and secretion to other tissues. With

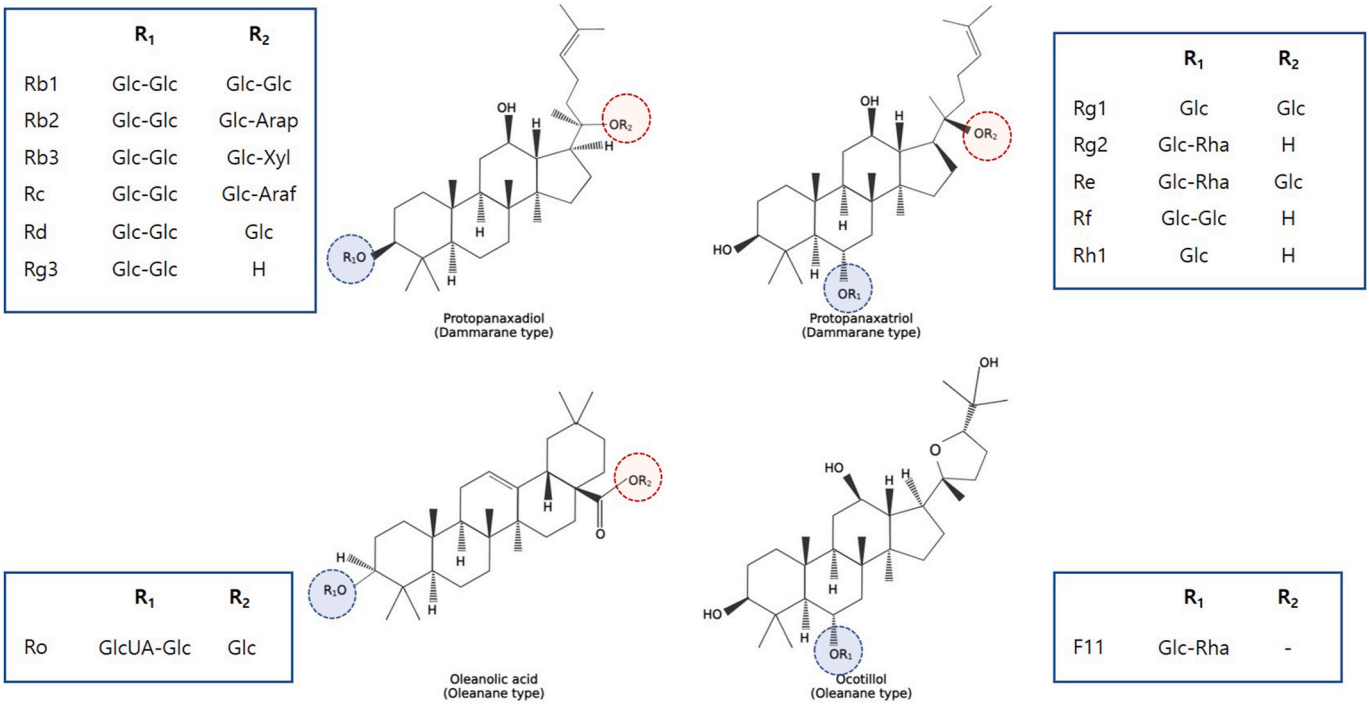

Fig. 1. Chemical structures with different substitute groups of four types of ginsenosides. Arap, D-arabinopyranose; Araf, D-arabinofuranose; Glc, glucose; GlcUA, D-glucuronic acid; Rha, Rhamnose; Xyl, Xylose.

regard to blood glucose clearance, skeletal muscle accounts for over 90% of insulin-stimulated glucose utilization, and thus plays a key role in regulating blood glucose levels and systemic energy homeostasis [19]. While adipose tissue utilizes less than 10% of glucose in response to insulin, insulin action in adipose tissue significantly contributes to maintaining systemic energy metabolism by promoting the conversion of glucose into lipids for energy storage and inhibiting lipolysis, leading to decreased plasma fatty acid levels, which affect lipid metabolism in extra-adipose tissues (e.g., skeletal muscle and liver) [18,20].

3.2. Insulin signaling pathways

3.2.1. Akt/PKB pathway

At the cellular level, insulin signaling begins with the binding of insulin to its receptor on the surface membrane of target cells, leading to the phosphorylation of tyrosine residues of insulin receptor substrates (IRS) (Fig. 2) [2]. The activated IRS then functions as an anchoring site for p85/p110 phosphatidylinositol 3-kinase (class I PI3K) on the plasma membrane. Activated PI3K then phosphorylates the substrate phosphatidylinositol-4,5-phosphate (PtdIns(4,5)P2 or PIP2) to facilitate the conversion from PIP2 to PtdIns(3,4,5)P3 (PIP3) [1,2,21]. PIP3, which in turn, mediates subsequent signaling cues by coupling with phosphoinositide-dependent protein kinase-1 (PDK1) and Akt (protein kinase B, PKB). Among the several downstream signaling pathways of IR, Akt serves as a key mediator by regulating cellular processes responsible for insulin action, controlling not only glucose homeostasis but also other energy metabolic pathways such as glucose and lipid metabolism, protein synthesis, cell growth, and survival at both the cellular and systemic levels [1,2,18]. Among the three isoforms of Akt (Akt1, Akt2, and Akt3), Akt2 is mainly distributed in insulin-target tissues, including skeletal muscle, adipose tissue, and the liver, whereas Akt1 and Akt3 show ubiquitous and relatively restricted tissue distribution, respectively [18]. As representative upstream molecules, PDK1 facilitates Akt phosphorylation at the threonine 308 residue, whereas another protein kinase complex, known as mTOR Complex 2 (mTORC2), phosphorylates at the serine 473 residue. Both contribute to the full activation of Akt and subsequent downstream signaling cascades, including forkhead box O1 (FoxO1), glycogen synthase kinase 3 (GSK3) and mTOR Complex 1 (mTORC1) [1,2]. Akt directly phosphorylates FoxO1, which interferes with nuclear translocation of FoxO1 thus inhibiting its transcriptional activity for gluconeogenic genes induction (e.g., glucose-6-phosphatase catalytic subunit 1 (G6PC1), phosphoenolpyruvate carboxykinase 1 (PEPCK)) [22,23]. The role of Akt in regulating hepatic glucose production has been further confirmed in several studies, which demonstrate exacerbated glucose intolerance and insulin resistance in mice lacking hepatic Akt1 and Akt2 [18,19,24]. Similarly, insulin action mediates inhibitory phosphorylation of GSK3β by Akt, resulting in increased glycogen synthesis [18]. Moreover, Akt activation inhibits tuberous sclerosis 1/2 (TSC1/2), leading to mTORC1-mediated activation of a number of downstream signaling molecules such as ribosomal S6 kinase (S6K, for cell growth and proliferation), eukaryotic translational initiation factor 4E binding protein 1 (4EBP1, for protein synthesis), and sterol regulatory element binding protein (SREBP, for fatty acid synthesis) [1,2,18]. More importantly, Akt activation directly phosphorylates Akt Substrate of 160 kDa (AS160), which then stimulates glucose transporter type 4 (GLUT4) translocation to the plasma membrane, facilitating glucose uptake from the circulation into skeletal muscle and adipose tissue [2,24,25]. In line with this,

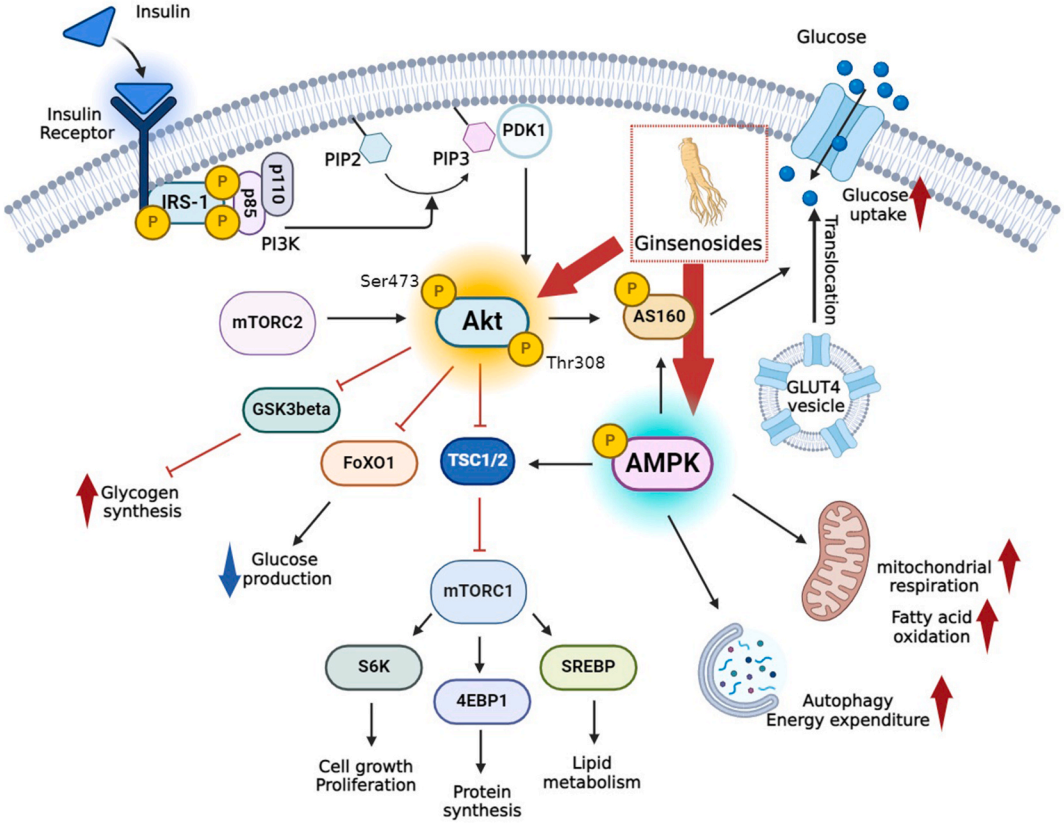

Fig. 2. Proposed model insulin signaling in cells regulated by ginsenosides via activating Akt and AMPK signaling. Akt, protein kinase B (PKB); AMPK, AMP-activated protein kinase; AS160, Akt substrate of 160 kDa; 4EBP, eukaryotic translation initiation factor 4E-binding protein; FoxO1, forkhead box O1; GLUT, glucose transporter type 4, insulin-responsive; GSK3β, glycogen synthase kinase 3 β; IRS-1, insulin receptor substrate-1; mTORC1/2, mammalian target of rapamycin, complex 1/2; PI3K, phosphoinositide 3-kinase; p110, PI3K subunit p110 delta; PI3K subunit p85 alpha; PIP2, Phosphatidylinositol 4,5-bisphosphate; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; S6K, ribosomal S6 kinase; SREBP, sterol regulatory element binding protein.

the activation of PI3K/Akt pathway has been reported to facilitate insulin secretion from pancreatic β cells [26]. Collectively, these insulin actions favor anabolic processes by promoting glucose uptake and storage in skeletal muscle and adipose tissue, as well as facilitating glucose retention and lipogenesis in the liver, suggesting that a defect in any of these signaling pathways may cause insulin resistance and associated metabolic complications [18,24].

3.2.2. AMP-activated protein kinase (AMPK)

Based on the complex nature of the intracellular signaling network affecting insulin sensitivity, no single medication has proven its therapeutic efficacy for T2DM. Instead life style modifications, such as exercise and caloric restriction, have long been recognized as the most reliable and safe interventions for preventing and treating insulin resistance and T2DM [27,28]. Emerging evidence has revealed that the beneficial effects of exercise and caloric restriction on health and disease are largely attributed to alterations in metabolic processes by activating numerous cellular signaling pathways, including AMP-activated protein kinase (AMPK) [27,29]. AMPK serves as a cellular energy sensor that is activated under energy-depleting conditions by detecting an increase in the intracellular AMP/ATP ratio, which controls the activities of various signaling molecules by phosphorylation at serine/threonine residues on its corresponding substrates [27–29]. Due to its involvement in multiple cellular processes such as mitochondrial respiration, fatty acid oxidation, and autophagy, AMPK has been considered the potential therapeutic target in variety of metabolic disorders related to energy metabolism [27–29]. Mechanistically, AMPK activation increases phosphorylation status of AS160, enhancing GLUT4 translocation to plasma membrane to facilitate glucose uptake in myocytes and adipocytes [27,29,30]. In addition, AMPK has been well established to enhance mitochondrial respiration capacity, contributing to increased fatty acid oxidation and ATP production. Interestingly, unlike Akt, activated AMPK is reported to inhibit TSC1/2, which subsequently attenuates mTORC1 and downstream effector molecules [27,29,30]. Instead, AMPK promotes autophagic flux by directly phosphorylating a number of downstream signaling molecules such as beclin1 and Unc-51 Like Autophagy Activating Kinase 1 (ULK1) [31].

Based on their highly druggable nature, several AMPK activators have been developed as pharmacological interventions for treating metabolic syndrome-associated disorders (e.g., MASLD, obesity, and T2DM) [27–29,32]. While numerous synthetic compounds have been developed as anti-diabetic drugs and their therapeutic efficacy has been extensively investigated in both preclinical and clinical studies, pharmacological agents derived from natural products have been recognized as novel candidate drugs based on their great therapeutic potential and safety concerns in clinical practice [6–8]. Among the various naturally occurring compounds derived from medicinal plants, ginsenosides are gaining increasing attention for their ability to activate AMPK, which is largely attributed to their broad range of pharmacological activities [33].

3.3. Insulin resistance and T2DM

As mentioned above, the term “insulin resistance” refers to a defect in insulin’s ability to regulate circulating glucose concentrations at the systemic level [1,2]. Physiologically, skeletal muscle and adipose tissue play a crucial role in clearing circulating glucose, and insulin-mediated hepatic glucose production significantly contributes to the supply of blood glucose during hyperglycemia [1,2], suggesting that the dysregulated control of systemic glucose dynamics is mainly derived from insulin resistance in multiple tissues. In line with this, emerging evidence has demonstrated that insulin resistance is highly interconnected with a variety of metabolic dysregulations, such as obesity, dyslipidemia, cardiovascular disease, and T2DM [1,2]. In particular, chronic overnutrition has been widely recognized as a major contributor to insulin resistance in multiple metabolic tissues in the early onset of glucose intolerance, which in turn stimulates the secretion of insulin by pancreatic β cells (i.e., hyperinsulinemia) [1,2], however recent arguments exist regarding the temporal order of insulin resistance and hyperinsulinemia during disease progression in patients with T2DM [2,34,35]. Notably, a compensatory increase in blood insulin levels can occasionally be observed in obese individuals without diabetes in response to overnutrition through enhanced insulin secretion from pancreatic β cells [2,36] and/or suppressed insulin degradation [37], suggesting a possible causal role of primary hyperinsulinemia in insulin resistance [2]. Similarly, excessive consumption of dietary lipids causes metabolic stress, such as endoplasmic reticulum stress, oxidative stress, and mitochondrial damage, leading to an imbalance between mitochondrial fatty acid oxidation and subsequent lipid accumulation in cells. This leads to the elevation of intracellular levels of reactive lipid species, such as diacylglycerol and ceramide. This ectopic increase in reactive lipid species is a prerequisite for developing insulin resistance in non-adipose tissues. Protein kinase C isoform θ and ε in skeletal muscle and the liver, respectively, are activated by increased diacylglycerol and/or ceramide, inhibiting insulin-mediated IRS-1/2 phosphorylation on tyrosine residues and subsequent downstream signaling cascades [38]. Consistent with this, the amount of C16:0 ceramide in the adipose tissue of obese mice was significantly associated with the degree of hepatic insulin resistance [39,40]. Additionally, and increased inflammatory response upon high fat diet (HFD) feeding causes insulin resistance in adipose tissue, resulting in increased adipose lipolysis, which provides free fatty acids to the liver as a source of gluconeogenesis [2]. To summarize, the insulin responsiveness of each metabolic tissue is critical for the adequate maintenance of whole-body glucose homeostasis, and this notion strongly implies that insulin resistance in multiple tissues can aggravate other metabolic abnormalities.

4. Pharmacological effects of ginsenosides on insulin resistance and T2DM

Based on their long history of therapeutic application in improving glycemic control, numerous studies have explored the bioactive compounds and their pharmacological modes of action of ginsenosides. In particular, several ginsenosides have demonstrated substantial efficacy in preventing and/or treating insulin resistance and T2DM in both *in vitro* and *in vivo* models. In the following sections, this study presents a recent understanding of the therapeutic efficacy of various representative ginsenosides with anti-diabetic properties and their underlying molecular mechanisms.

4.1. Ginsenoside Rb1

Ginsenoside Rb1 is a major protopanaxadiol saponin primarily found in *P. ginseng*, *P. quinquefolius*, and *P. notoginseng* [41]. Although ginsenoside Rb1 is poorly absorbed across the intestine, it undergoes deglycosylation by intestinal microbes and is converted into the secondary ginsenoside compound K via a stepwise hydrolysis reaction [41]. Emerging evidence has proven the therapeutic potential of Rb1 against insulin resistance, hyperglycemia, and T2DM. Rb1 promotes GLUT4 translocation in 3T3-L1 and C2C12 cells by inducing PI3K activity and phosphorylation of IRS-1 and Akt [42]. Interestingly, the effects of Rb1 on glucose uptake in both cell lines seem to be partially mediated by the upregulation of the basal expression of adiponectin receptors (AdipoR1 and AdipoR2) and their downstream signaling pathways [42]. Similarly, Rb1 exerts beneficial effect on insulin sensitivity by activating AMPK [43], which is responsible, at least in part, for the suppression of hepatic fat accumulation and inflammatory response [41]. In line with this, Rb1 administration in HFD-fed rats significantly reduced body weight gain, body fat content, and fasting glucose, whereas it improved insulin sensitivity, as demonstrated by the inhibition of hepatic gluconeogenesis and enhancement of glucose uptake in skeletal muscle [41,43]. Similar results were also observed in *db/db* obese mice, showing enhanced

Rb1-induced insulin sensitivity mediated by decreased hepatic fat accumulation and adipocyte lipolysis [44]. Given the close association between insulin resistance and inflammation, Rb1 administration in mice significantly reduced inflammatory cytokine production in the liver and adipose tissue, thus improving insulin sensitivity by maintaining glucose and lipid metabolism in obese and/or T2DM conditions [41]. Similarly, Rb1 suppresses ER stress-mediated inflammasome activation in adipose tissue, leading to decreased secretion of inflammatory cytokines and subsequent insulin resistance [45]. Moreover, Rb1 has been shown to have a great potential to suppress oxidative stress and inflammation in skeletal muscle in various disease models related to T2DM [46–48]. It is well recognized that both type 1 and type 2 diabetes are characterized by progressive pancreatic β cell failure [49], suggestive of the potential of targeting pancreatic β cell death as a therapeutic strategy to improve T2D. Rb1 ameliorates high glucose-induced pancreatic β cell apoptosis by suppressing nitric oxide production and caspase-3 expression [50]. Overall, Rb1 shows promising efficacy in improving insulin resistance and T2D by enhancing insulin sensitivity and overall cellular metabolism, indicating its potential as an anti-hyperglycemic and anti-diabetic agent [41].

4.2. Ginsenoside Rd

Ginsenoside Rd is mainly found in *P. ginseng*, and, to a lesser extent, in *P. quinquefoliu* and *P. notoginseng* [51,52]. Its chemical structure belongs to the protopanaxadiol group, in which various ginsenosides, such as Rb1, Rb2, and Rc, are capable of being transformed into Rd following absorption and metabolism *in vivo* [53]. Although the pharmacological function of Rd has been studied primarily as a neuroprotective agent based on its role in the potentiation of mitochondrial function and anti-inflammatory properties, recent evidence has demonstrated that Rd administration markedly improved hyperglycemia in diabetic rats fed a high-fat and high-sugar diet and administered streptozotocin by activating the Akt signaling pathway in the liver, resulting in increased glycogen synthesis and decreased hepatic gluconeogenesis [54]. Rd also demonstrates the potential to alleviate insulin resistance and obesity by promoting thermogenesis through the cyclic AMP (cAMP)/protein kinase A (PKA) signaling pathway in brown adipose tissue, thereby enhancing glucose tolerance and insulin sensitivity in adipose tissue, skeletal muscle, and the liver [55]. Similarly, Rd has been shown to ameliorate methylglyoxal-induced insulin desensitization and subsequent apoptosis in primary astrocytes isolated from rats [56]. This protective function of Rd against apoptosis may also alleviate T2D, as demonstrated by the suppressed progression of cell death and pro-apoptotic proteins in cultured human pancreatic islets [57]. A recent study demonstrated that Rd ameliorates retinal endothelial damage under high-glucose conditions by upregulating AMPK and Sirtuin 1 expression and their mutual interaction [58,59]. Collectively, these findings suggest the Rd is a promising pharmacological agent for diabetic intervention.

4.3. Ginsenoside Rg3

Ginsenoside Rg3 is primarily found in *P. ginseng*, and is enriched in Korean Red ginseng, although its concentration in naturally occurring ginseng plants is relatively low [60,61]. Rg3 can be further divided into two enantiomers, namely 20(R) and 20(S), based on the structural differences related to the hydroxyl group at the C20 position, which attributed to distinct pharmacological activities in a stereospecific manner [60]. It has been extensively studied for its anti-tumor efficacy in a number of cancer types [62], and emerging evidence has proven its other pharmacological benefits as an anti-inflammatory [63], anti-oxidant [64], anti-aging [65], and neuroprotective agent [66]. Recent studies have revealed the therapeutic potential of Rg3 in various diseases related to metabolic syndrome, such as MASLD, obesity, and diabetes [60,67]. Interestingly, Rg3 significantly promoted glucose uptake in mature 3T3-L1 cells by upregulating GLUT4 and IRS-1 transcription and PI3K-110α protein levels [68]. In line with this, Rg3 is found to directly bind to peroxisome proliferator-activated receptor γ (PPARγ) in adipocytes, thereby increasing adiponectin secretion and stimulating adiponectin signaling which partially contribute to attenuating hyperglycemia, hyperlipidemia, and aberrant lipid accumulation and dysfunction in adipose, liver and heart tissues [69]. Additionally, it stimulated insulin signaling in C2C12 myotubes by increasing the phosphorylation of IRS-1 under both basal and insulin-stimulated conditions, whereas AMPK activation was not observed [70]. Rg3 also promoted mitochondrial function in C2C12 myotubes by increasing the expression of genes involved in mitochondrial biogenesis, which may lead to an improvement in insulin resistance in skeletal muscle [70]. Similarly, Rg3 exerted an anti-hyperglycemic effect in INS-1 cells (a rat insulinoma cell line) by stimulating proliferation via the upregulation of extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (p38 MAPK) signaling, thereby alleviating cell death under intermittent hyperglycemic conditions [71]. Consistent with this, Rg3 increased insulin secretion in hamster pancreatic HIT-T15b cells and streptozotocin-induced diabetic mice [72]. A more recent study further confirmed that Rg3 markedly contributes to insulin secretion in pancreatic β cells by stimulating glucagon-like peptide-1 (GLP-1) secretion from enteroendocrine L cells (e.g., NCI–H716 cells) and T2D mouse model [73]. These findings indicate the potential of Rg3 as a pharmacological intervention against hyperglycemia, insulin resistance, and diabetes.

4.4. Ginsenoside Rg1

Ginsenoside Rg1 is a monomer of a tetracyclic triterpenoid derivative belonging to the protopanaxatriol family. Among the numerous ginsenosides, Rg1 is one of the most extensively investigated bioactive ingredients of ginseng because of its broad range of therapeutic targets with fewer side effects [74]. Although Rg1 plays a crucial role in the alleviation of Alzheimer's disease by enhancing memory disorders and synaptic loss in animal models [74], recent studies have highlighted Rg1's ability to restore glucose homeostasis and insulin sensitivity, thereby improving hyperglycemia, T2DM, and associated complications [75]. Rg1 markedly enhanced AMPK activity, resulting in elevated glucose uptake and GLUT4 expression in differentiated C2C12 cells [76]. Similarly, Rg1 activated the Akt pathway in the liver and primary hepatocytes isolated from HFD-fed mice, leading to the suppression of hepatic gluconeogenesis and fasting plasma glucose levels [77]. Moreover, Rg1 ameliorated palmitate-induced insulin resistance in HepG2 cells by activating Akt and inhibiting c-Jun N-terminal kinase (JNK)-mediated reactive oxygen species production [78]. Furthermore, Rg1 ameliorated hepatic insulin resistance in mice fed high-fat and high-sugar diet by suppressing inflammatory response and glucose output through activation of Akt signaling [79]. The antioxidant and anti-inflammatory properties of Rg1 contribute to its beneficial effects on pancreatic β cells, resulting in marked improvements in blood glucose and inflammatory cytokine levels in hyperglycemic rodent models [80]. Given the great pharmacological potential of Rg1 based on its antioxidant, anti-inflammatory, and anti-apoptosis activities, a growing body of research is expanding the therapeutic role of Rg1 in the treatment of various neurological disorders [81]. A recent study revealed that Rg1 treatment in T2DM mice fed an HFD plus streptozotocin injection significantly improved cognitive dysfunction and neuronal injury [82], suggesting the promising therapeutic efficacy of Rg1 in T2DM as well as various diabetic complications.

4.5. Csompound K

Notably, most orally administered substances inevitably cross the gastrointestinal tract, inhabited by trillions of gut microbes [83]. The gut microbiota considerably influences the bioavailability and

Table 1
Pharmacological activities and molecular mechanisms of ginsenosides against insulin resistance and T2DM in preclinical studies.

Ginsenosides	Experimental models and Treatment	Pharmacological activities and molecular targets	References
Rb2	**[in vivo]** C57BL/6J mice fed HFD Rb2 40 mg/kg/day, i.p. injection daily for total 10 consecutive days **[in vitro]** 3T3-L1 cells Rb2 25 μM, 2 h	Activates Akt pathway Inhibits MAPK and NF-κB pathway Inhibits fat accumulation Improves insulin resistance	[90]
	[in vitro] H4IIE cells Rb2 0.001–1 μM, 3 h	Induction of SHP by AMPK activation Alleviates ER stress Inhibits hepatic gluconeogenesis	[91]
	[in vivo] *db/db* mice Rb2 10 mg/kg/day, i.p. injection daily for total 4 weeks **[in vitro]** HepG2 cells, Rb2 50 μM, 12 h	Activates AMPK and SIRT1 Inhibits hepatic fat accumulation via upregulating autophagic flux Improves glucose tolerance	[92]
Rb3	**[in vitro]** HepG2 cells, Rb3 25 μM, 24 h	Activates AMPK Inhibits hepatic gluconeogenesis	[93]
Rc	**[in vitro]** HUVEC cells Rb3 25–50 μM, 24 h	Activates Akt/PI3K pathway Improves insulin sensitivity Inhibits NOX2 and proinflammatory cytokines expression	[94]
	[in vitro] C2C12 cells Rc 50–200 μM, 1 h	Activates AMPK and p38MAPK Increases glucose uptake Inhibits NOX2 and proinflammatory cytokines expression	[95]
Rg2	**[in vitro]** HepG2 cells, Rg2 5–20 μM, 3 h	Induction of SHP by AMPK activation Inhibits hepatic gluconeogenesis Inactivates GSK3β	[96]
Rg5	**[in vivo]** *db/db* mice Rg5 30–60 mg/kg/day, gastric irrigation daily for total 8 weeks **[in vitro]** HepG2 cells, Rg5 40 μM, 24 h	Activates SIRT1/PGC-1α pathway Increases glucose uptake and insulin sensitivity in cells Lowers blood glucose level in mice	[97]
Re	**[in vitro]** 3T3-L1 cells Re 1–100 μM, 8 days (following differentiation)	Activates PPARγ pathway Improves insulin resistance Inhibits TNFα production	[98]
	[in vivo] Wistar rats fed HFD plus streptozotocin Re 25 mg/kg/day, gastric irrigation daily for total 9 weeks	Activates AMPK Alleviates blood glucose level Improves insulin resistance Increases insulin secretion	[99]
	[in vivo] Wistar rats fed high-fat-high-sucrose diet Re 20 mg/kg/day, gastric irrigation daily for total 8 weeks	Activates p38 MAPK, ERK1/2, JNK Decreases blood glucose level Improves glucose tolerance Increases blood insulin level	[100]
	[in vivo] HFD-fed C57BL/6J mice Re 5–20 mg/kg/day, p.o. administration daily for 3 weeks **[in vitro]** HepG2 cells, Re 20 μM, 3 h	Activates LKB1-AMPK pathway Inhibits hepatic glucose production Decreases blood glucose level	[101]
Rk3	**[in vivo]** C57BL/6J mice fed HFD plus streptozotocin Rk3 10–60 mg/kg/day, p.o. administration daily for total 4 consecutive weeks	Activates AMPK and Akt pathways Inhibits hepatic glucose production Increases glucose uptake in the liver Ameliorates glucose tolerance and insulin resistance	[102]

AMPK, AMP-activated protein kinase; ERK1/2, extracellular signal-regulated kinases 1/2; ER stress, endoplasmic reticulum stress; GSK3β, glycogen synthase kinase-3 beta; HFD, high-fat diet; HUVEC cells, human umbilical vein endothelial cells; i.p., intraperitoneal; JNK, c-Jun N-terminal kinase; LKB1, liver kinase B1; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOX2, NADPH oxidase 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PI3K, phosphoinositide 3-kinase; p.o., per os; PPARγ, peroxisome proliferator-activated receptor gamma; SHP, small heterodimer partner; SIRT1, Sirtuin 1; TNFα, tumor necrosis factor alpha.

therapeutic efficacy of drugs or phytomedicines by metabolizing orally administered compounds to generate various metabolite subtypes. Similar to other natural products and medicinal herbs, ginsenosides undergo biotransformation by intestinal microbes, thereby acquiring hydrophobic properties that are more suitable for absorption [83]. Interestingly, these metabolites exhibit potent pharmacological actions compared to their parent ginsenosides, indicating the necessity for considering the influence of the gut microbiota when evaluating the therapeutic efficacy of ginsenosides. Among numerous secondary ginsenosides, compound K represents a major deglycosylated metabolite of protopanaxadiol-type ginsenosides (e.g., Rb1, Rb2, Rc and Rd) [83,84]. This bio-transformed ginsenoside metabolite has shown advantages in terms of safety and tolerability when orally administered to healthy participants [85]. Previous studies have revealed the anti-diabetic actions of compound K *in vitro* and *in vivo* models. Compound K markedly enhanced insulin sensitivity in adipose tissue by increasing GLUT4 expression and suppressing gluconeogenesis in the liver of diabetic *db/db* mice, contributing to a reduction in fasting blood glucose levels and improvement of glucose tolerance [86]. Similarly, compound K markedly upregulated insulin secretion accompanied with increased cellular ATP production and GLUT2 expression in MIN6 pancreatic β cell lines [87]. The pharmacological activity of compound K is mediated by AMPK activation, as demonstrated by increased fatty acid oxidation coupled with decreased *de novo* lipogenesis in the liver, leading to improved glucose intolerance and hepatic steatosis in T2DM rats [88]. Similar results were obtained in another *in vitro* study showing the AMPK-dependent anti-steatotic effects of compound K [89]. Furthermore, a recent study demonstrated that compound K is capable of remodeling the gut microbiota and secondary bile acid pool, resulting in the amelioration of impaired glucose tolerance and obesity in *db/db* mice [84]. In addition, compound K induced GLP-1 secretion in intestinal L-cells via Takeda G protein-coupled receptor 5 (TGR5) activation, thereby contributing to improved glucose homeostasis in diabetic mice [84]. To summarize, pharmacological intervention with compound K

presents a promising therapeutic option for patients with T2DM.

The detailed pharmacological effects of the other ginsenosides on insulin resistance, hyperglycemia and diabetes are summarized in Table 1.

5. Clinical trials of ginsenosides

The broad range of established biological activities of ginseng/ginsenosides in numerous diseases has led to a growing number of clinical trials being conducted to monitor their therapeutic efficacy in diabetes [8]. Thus far, the various effects of ginseng have been mostly studied in clinical trials in its extract formula possibly due to their stable efficacy derived from the complex and diverse bioactive constituents. In line with this, they often exhibit not only anti-diabetic but also other beneficial efficacy such as anti-hyperlipidemic effect, implying that the various effects of ginseng extract may result, at least in part, from simultaneous and/or synergistic actions between numerous constituents of ginseng [15]. For example, diabetic patients who were administered with Korean red ginseng (KRG) extract have shown marked amelioration in glucose tolerance or chronic neuropathy [103,104]. Similarly, patients with T2DM and hypertension who administered with KRG and American ginseng showed significant improvements in central systolic blood pressure and components of pulse waveform with subtle changes in reactive hyperemia index [105]. While a relatively small numbers of clinical studies are using individual ginsenoside(s) in evaluating the therapeutic efficacy of ginseng, there have been a few clinical trials monitoring the effect of ginsenosides in patients with DM. In one study, T2DM patients were intravenously administered Shen-mai injection, containing 41 mg/day of Rb1 and Rg1, for 2 weeks, resulting in moderate decrease in blood glucose levels and significant reductions in total cholesterol and triglyceride levels compared to those of healthy individuals [106]. However, conflicting results were observed in other clinical studies, where the administration of Re had no effect on circulating glucose and insulin levels in patients with impaired glucose tolerance and overt diabetes [107]. Similarly, Rb1 supplementation after an acute bout of resistance exercise resulted in no significant changes in circulating glucose and insulin levels [108]. The discrepancy between preclinical studies and clinical trials regarding the pharmacological actions of ginsenosides may be partly attributed to the relatively small number of participants recruited in those studies, inappropriate study designs, or low efficacy and/or poor bioavailability resulting from the complex chemical structure of ginsenosides in humans. Thus, future clinical studies should consider novel strategies to preserve the therapeutic effects observed in preclinical studies by modulating several conditions such as solubility, gut microbiota-driven biotransformation, or dosage regimens [8].

6. Conclusion and future perspective

Considering the complicated mechanisms of glucose homeostasis, the identification and validation of novel pharmacological agents are urgently needed to develop therapeutic strategies against insulin resistance and T2DM. A growing amount of evidences has shown that ginsenosides are promising targets for the treatment of not only T2DM but also numerous diabetic complications with minimal adverse effects. Moreover, ginsenosides (or ginseng extracts) exhibit advantageous features in terms of safety, enabling their development as adjuvant therapies for the treatment of T2DM and its associated metabolic diseases. However, the therapeutic efficacy and underlying modes of action of ginsenoside and ginseng-derived bioactive components have not yet been entirely investigated. Further research is warranted to enhance the therapeutic potential of ginsenosides owing to their complex chemical structures and biotransformation by the gut microbiota. In line with this, the comprehensive understanding for the relationship between the chemical structural features of ginsenosides and their anti-diabetic efficacy is limited. For instance, most ginsenosides having anti-diabetic effects have been found to largely fall into dammarane group (e.g., PPD or PPT type) [8,12,15]. Recently, one study has examined to compare the therapeutic efficacy of PPD and PPT mixtures against T2DM in mice subjected to HFD plus streptozotocin injection [109]. The results showed the trend that PPD seems to work slightly better than PPT in a few parameters such as blood glucose and lipid metabolite levels, although these differences were not statistically significant and the study did not provide the mechanistic perspectives [109]. Finally, well-designed clinical trials involving patients with diabetes need to be conducted to demonstrate the therapeutic potential of ginsenosides and/or ginseng.

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Declaration of competing interest

The author declares no conflicts of interests.

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