J Ginseng Res 45 (2021) 371–379

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: https://www.sciencedirect.com/journal/journal-of-ginseng-research/

Review Article

Review of ginsenosides targeting mitochondrial function to treat multiple disorders: Current status and perspectives

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ARTICLE INFO

Article history:
Received 22 April 2020
Received in revised form
8 November 2020
Accepted 9 December 2020
Available online 11 December 2020

Keywords:
ginsenosides
mitochondria
neurological disorder
cancer
heart disease

ABSTRACT

Mitochondrial dysfunction contributes to the pathogenesis and prognosis of many common disorders, including neurodegeneration, stroke, myocardial infarction, tumor, and metabolic diseases. Ginsenosides, the major bioactive constituents of *Panax ginseng (P. ginseng)*, have been reported to play beneficial roles in the molecular pathophysiology of these diseases by targeting mitochondrial dysfunction. In this review, we first introduce the types of ginsenosides and basic mitochondrial functions. Then, recent findings are summarized on different ginsenosides targeting mitochondria and their key signaling pathways for the treatment of multiple diseases, including neurological disorders, cancer, heart disease, hyperglycemia, and inflammation are summarized. This review may explain the common targets of ginsenosides against multiple diseases and provide new insights into the underlying mechanisms, facilitating research on the clinical application of *P. ginseng*.

1. Introduction

Panax ginseng (P. ginseng) has tonifying effects on important organs, maintaining their function and strengthens vitality and body resistance to inhibit physiological aging and withstand pathological stresses [1]. *P. ginseng* contains various pharmacological ingredients, such as ginsenosides, polysaccharides, polyphenols, and polyacetylenes [2]. Among them, ginsenosides are recognized as the major bioactive ingredients. The beneficial effects of ginsenosides have been extensively investigated, and various bioactivities have been identified, such as neuroprotection, cardioprotection, anti-tumor, anti-diabetes, and anti-inflammation and so on [3]. However, it remains unclear whether the beneficial effects of ginsenosides on various diseases are mediated by a common functional mechanism.

The mitochondria, a cytoplasmic double-membrane organelle, plays a crucial role in cell physiological processes, including energy homeostasis, autophagy, oxidative stress balance, and apoptotic signaling cascades [4]. Mitochondrial homeostasis dysfunction or disruption also contributes to the pathogenesis of many disorders, including neurodegeneration, stroke, myocardial infarction, cancer, and metabolic diseases [5]. Importantly, a large number of results from *in vitro* and *in vivo* studies have confirmed the beneficial effects of ginsenosides for preventing and treating various diseases are related to their interference with mitochondrial dysfunction [6–8].

To better understand how ginsenosides regulate mitochondrial function and its related signaling pathways to elicit their multiple pharmacological effects in mammalian cells, we summarize recent findings with respect to ginsenosides targeting mitochondrial

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https://doi.org/10.1016/j.jgr.2020.12.004

function in multiple disorders. First, we briefly introduce ginsenosides and the biological functions of mitochondria. Then, the roles of different ginsenosides in regulating mitochondrial biogenesis, bioenergetics, autophagy, motility, and apoptosis for the treatment of different diseases are summarized. For example, different ginsenosides have been reported to prevent acute and chronic diseases by influencing the opening of mitochondrial permeability transition pores (mPTPs), balancing reactive oxygen species (ROS), modulating mitochondrial fission and fusion, or mediating mitophagy [9]. A thorough understanding of the effects of ginsenosides on mitochondrial function and its key signaling pathways is necessary to explain how the main components of *P. ginseng* treat multiple diseases and to comprehensively explore the molecular mechanisms by which of *P. ginseng* treats multiple diseases.

2. Ginsenosides

Ginsenosides, a type of steroidal saponins, have a dammarane-type triterpenoid structure and a four-ring hydrophobic steroid-like structure conjugated with sugar moieties, which are divided into three different structural classes: protopanaxadiol (PPD-type), protopanaxatriol (PPT-type), and oleanolic acid (OA-type) groups [10]. PPD-type ginsenosides, including ginsenosides Rb1 (Rb1), ginsenosides Rb2 (Rb2), ginsenosides Rb3 (Rb3), ginsenosides Rc (Rc), ginsenosides Rd (Rd), ginsenosides Rg3 (Rg3), and ginsenosides Rh2 (Rh2), have conjugated sugar moieties attached to the 3-position of the triterpenoid dammarane structure, whereas PPT-type ginsenosides, including ginsenosides Re (Re), ginsenosides Rf (Rf), ginsenosides Rg1 (Rg1), and ginsenosides Rh1 (Rh1), have sugar moieties attached to the 6-position of the triterpenoid dammarane structure [11]. Quantitative and qualitative analysis for ginsenosides *in vivo* revealed that PPD-type ginsenosides exhibit higher plasma concentrations and longer half-lives than PPT-type ginsenosides [12]. Meanwhile, the absorption rate of intact ginsenosides in the intestines is as low as 1% to 3.7%, and most of them are metabolized and converted into other ginsenosides through acid hydrolysis in the stomach and bacterial hydrolysis in the intestine [12]. To date, more than 200 different natural and transformed ginsenosides and their metabolites have been identified and studied in a variety of pathological conditions [8,9].

3. Mitochondrial dysfunction

Mitochondria are responsible for the physiological and pathological processes of aerobic respiration-based cells in mammalian, including oxidative phosphorylation (OXPHOS), the biosynthesis of intermediates for cell growth, and the metabolism of three major nutrients (glucose, amino acids, and fatty acids), and also mediate the essential processes that determine cell function and status [13]. Mitochondrial dysfunction is found in many diseases, including neurodegeneration, cancer, metabolic diseases, heart failure, and ischemia-reperfusion (I/R) injury, which have been reported in some reviews [14]. Numerous studies have shown that ginsenosides can regulate mitochondrial (mito)-ROS, mito-apoptosis, mito-bioenergetics, mito-biogenesis, mito-dynamics, and mitophagy to exert pharmacological effects, which have been summarized in Fig. 1.

4. Ginsenosides target mitochondria, treating different diseases

Some studies have demonstrated that ginsenosides act as protective agents of mitochondrial function, mainly by direct or indirect enhancement of mitochondrial biosynthesis, mitophagy, or

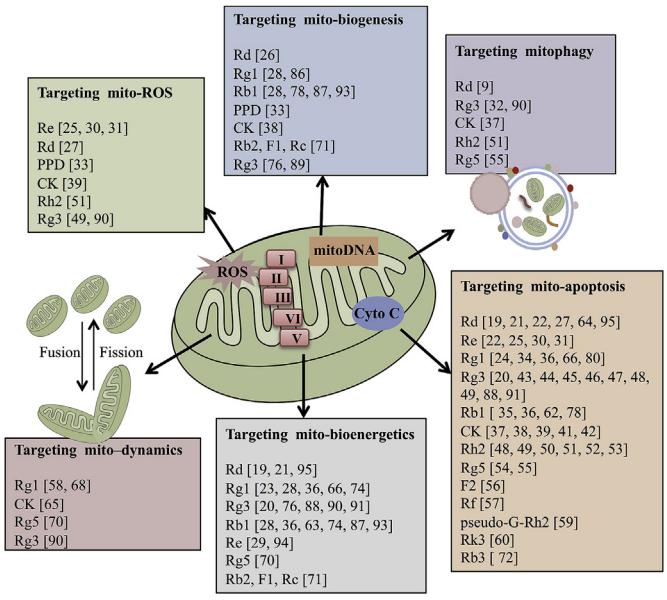

Fig. 1. Summary of different ginsenoside monomers targeting mito-ROS, mito-apoptosis, mito-bioenergetics, mito-biogenesis, mito-dynamics, and mitophagy.

electron transport chain (ETC) efficiency or inhibition of mito-ROS [8,15]. Conversely, ginsenosides also can treat cancer and other diseases by promoting mito-apoptosis and mitophagy [9,16]. In the models of different diseases, including nervous system disorders, cardiovascular system disorders, and tumors, different ginsenoside monomers cause mitochondrial function alterations by regulating transcription factors, the expression of mitochondria-related genes, and mitochondrial dysfunction pathway networks, which are discussed here (Fig. 2).

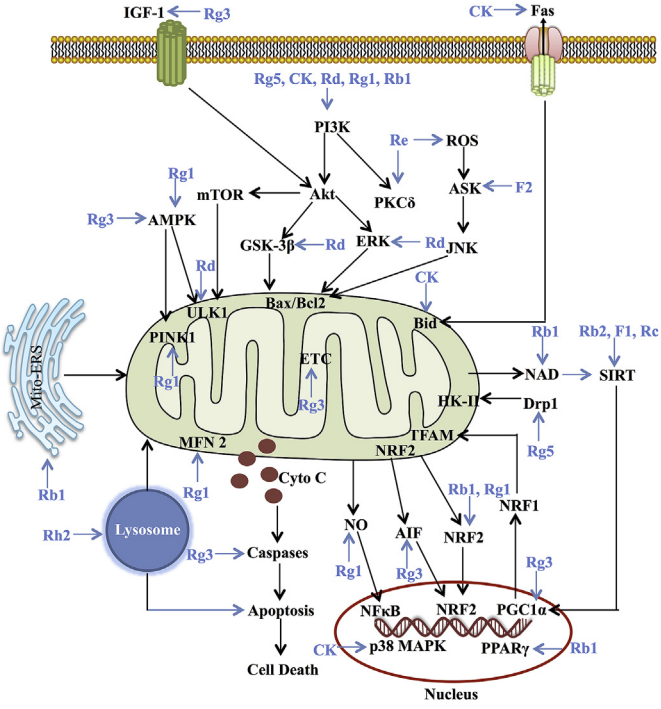

Fig. 2. Summary for the functional effects of ginsenoside monomers on mitochondria via multiple links across regulatory mechanisms and multi-target effects.

4.1. Neurological disorders

In the resting state of the human body, the brain consumes 20% of body energy, although it only has 2% of the total body mass [17]. Mitochondrial function can directly influence neuronal function, such as synaptic plasticity, axonal transport, and the release of neurotransmitters, and abnormal mitochondrial function in neurons precedes neurological changes and neuronal loss [18]. Multiple neurological diseases have been associated with mitochondrial dysfunction, such as Parkinson's disease (PD), Alzheimer's disease (AD), and ischemic stroke. Ginsenoside monomers can target different functions of mitochondria to preventing and treating neurological disorders [19–21].

4.1.1. Parkinson's disease

Mitochondrial dysfunction plays key roles in PD initiation and progression. In 1-methyl-4-phenylpyridinium-induced human neuroblastoma SH-SY5Y cells and Parkinsonian toxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse PD models, Rd shows a significant neuroprotective effect by enhancing antioxidant enzymatic activities, preserving the activity of ETC complex I, stabilizing the mitochondrial membrane permeabilization (MMP), and increasing intracellular ATP levels [19]. Additionally, the PI3K/Akt signaling pathway is involved in the protective effect of Rd against PD. In a rotenone-induced PD neuronal model with mitochondrial dysfunction, the combination of Rd with Re attenuates the extent of depolarization of MMP and restores calcium levels by modulating the Bcl_2/Bax ratio and inhibiting the release of Cyto C and caspase-3 activation [22]. These findings highlight the efficacies of Rd and Re in the prevention and treatment of PD through improving mitochondrial integrity and ETC efficiency, and inhibiting mito-apoptosis.

4.1.2. Alzheimer's disease

In Aβ peptide-treated neuroblastoma cells, proteomic analysis shows that Rg1 can alter the expression of 49 mitochondrial proteins, such as 3-hydroxyacyl-CoA dehydrogenase type-2, alanine-tRNA ligase, mitochondrial import receptor subunit TOM40 homolog, and Cyto C oxidase subunit 5A [23]. Moreover, the pretreatment of primary cultured cortical neurons with Rg1 (20 μM) for 24 h and exposure to 10 μM Aβ for 72 h can elevate the Bcl_2/Bax ratio, reduce Cyto C release from mitochondria into the cytoplasm, and then block mitochondrial apoptotic cascades after Aβ insult [24].

Metabolomic and apoptotic analysis for Rg3-administrated AD rats shows that Rg3 could prevent cognitive impairment by regulating the abnormality of energy metabolism, ETC efficiency, amino acid metabolism, and purine metabolism and regulating mito-apoptosis [20]. Re, another ginsenoside, inhibits the ROS/ASK-1-dependent mito-apoptotic pathway in Aβ-triggered SH-SY5Y cells through the inhibition of the apoptosis-related pathway (the elevation of the Bcl_2/Bax ratio and the reduction of Cyto release) and ROS production [25]. These results indicate that multiple ginsenoside monomers promote energy metabolism and inhibit the mitochondrial apoptosis by increasing ETC function in AD.

4.1.3. Ischemic stroke

In middle cerebral artery occlusion (MCAO) rat models, Rd administration reduces mtDNA damage and the cleavage of caspase-3, improving the survival rate and neurological function 7 days after MCAO [26]. Rd also protects against mitochondrial damage after reperfusion by preserving ETC activity and aconitase activity, which decreasing mitochondrial hydrogen peroxide production and depolarizing MMP in the aged MCAO mice [21]. In addition, the results from *in vitro* and *in vivo* models of cerebral ischemia demonstrate that Rd markedly decreases the secretion of lactate and attenuates mitochondrial swelling by preserving MMP and reducing the mitochondrial release of Cyto C and ROS production to minimize mitochondria-mediated apoptosis following ischemia [27].

In an oxygen–glucose deprivation/reoxygenation-induced primary mouse astrocyte injury model, Rb1 and Rg1 co-treatment decreases the mtDNA copy number and the MMP depolarization, and increases the activities of ETC complexes I, II, III, and V, promoting the production of ATP [28]. The results above show that ginsenoside monomers reduce ischemic stroke damage by enhancing ETC activity and inhibiting mitochondrial apoptosis.

4.1.4. Neuronal injury

The neuroprotective effect of ginsenosides is also closely related to mitochondrial function. Re treatment significantly attenuates phencyclidine-induced mitochondrial oxidative stress and ETC dysfunction by regulating NADPH oxidase activity in mouse dorsolateral cortex neurons [29]. Re also protects methamphetamine-induced mitochondrial burdens (i.e., decrease of MMP, Cyto C release from mitochondria, and activation of caspase-3) via the inhibition of protein kinase C δ (PKCδ) in SH-SY5Y cells and in *PKCδ knockout (+/−) mice* [30,31]. These Re-mediated protective effects are comparable to those observed in PKCδ knockout (−/−) or knockdown mice [30].

Mitochondrial quality control is regulated by successive rounds of fusion, fission, and mitophagy with the dynamic exchange of necessary components. Moon et al. reported that Rg3 can induce autophagy flux, attenuating human prion protein-mediated neurotoxicity and mitochondrial dysfunction in neuronal cells [32]. Furthermore, PPD inhibits mitochondrial morphological changes, scavenges the mito-ROS, improves MMP, and enhances mitochondrial counts compared with the cells exposed to glutamate only [33]. In the neurotoxicity model of PC12 cells induced by colistin, Rg1 also exerts neuroprotective effects via multiple mito-apoptosis-related pathways, including the decreases of Cyto C release and caspase-3/9 cleavages [34]. In primary cultured rat hippocampal neurons, Rb1 inhibits the burst of intracellular ROS and the depolarization of MMP induced by high glucose [35]. In addition, Rb1 and Rg1 protect neuronal cells against MMP loss, mito-apoptosis, and aconitase inhibition induced by mitochondrial complex I inhibitor, rotenone, in an *in vitro* neuronal model of neurotoxicity, which may be mediated by NRF-2 activation [36].

Based on these studies, we found that in AD, PD, ischemic stroke, and various chemically induced neuronal injury models, ginsenoside monomers not only inhibit mito-apoptosis and mito-ROS, but also enhance mtDNA replication, NADPH oxidase, and mitophagy. The beneficial effects of different ginsenoside monomers on neurological disorders are summarized in Table 1.

4.2. Cancer

Many studies have shown that ginsenoside monomers can promote tumor cell death by activating mitochondrial apoptosis and autophagy (Table 2).

4.2.1. Compound K on tumors

Compound K (CK), a main intestinal bacterial metabolite of protopanaxadiol saponin, can inhibit various cancers by inducing mito-apoptosis, mito-ROS, and autophagy [37]. A recent study has shown that CK promotes autophagosome accumulation by inducing early-stage autophagy, and inhibits late-stage autophagy inducing mitochondria damage in *in vitro* and *in vivo* neuroblastoma models [37]. In human hepatocellular carcinoma MHCC97-H cells, CK treatment induces the reductions in MMP, mtDNA copy

Table 1
Summary of Mitochondria-Related Neurological Protective Effects of Ginsenosides

Ref.	Ginsenoside	Model	Inducer	Experimental model	Effects
[19]	Rd	PD	1-Methyl-4-phenylpyridinium	SH-SY5Y cell	COXI, ATP, MMP
[20]	Rg3	AD	Senescence	Rat	ATP, ETC
[21]	Rd	Ischemic stroke	MCAO	Aged mice	ETC, MMP
[22]	Rd, Re	PD	Rotenone	SH-SY5Y cell	MMP, Cyto C, Bax/Bcl_2, Caspase-3
[24]	Rg1	AD	Aβ	Primary neuron	Bax/Bcl_2, Cyto C
[25]	Re	AD	Aβ	SH-SY5Y cell	Cyto C, Bax/Bcl_2
[26]	Rd	Ischemic stroke	MACO	Rat	mtDNA
[28]	Rb1, Rg1	Ischemic stroke	OGD/R	Primary astrocyte	mtDNA, MMP, COX I–V, ATP
[29]	Re	Neuronal injury	Phencyclidine	Mice	ETC, NADPH oxidase
[30]	Re	Neuronal injury	Methamphetamine	SH-SY5Y cell	Mito-ROS; Cyto C, PKCδ
[31]	Re	Neuronal injury	Methamphetamine	Mice	Mito-ROS, PKCδ
[32]	Rg3	Neuronal injury	Human prion protein	Primary neuron	Mitophagy
[33]	PPD	Neuronal injury	Glutamate	PC12 cell	MMP, mtDNA, mito-ROS
[34]	Rg1	Neuronal injury	Colistin sulfate	PC12 cell	Cyto C, Caspase-3, Caspase-9
[35]	Rb1	Neuronal injury	High glucose	Primary neuron	MMP, Bcl_2
[36]	Rb1, Rg1	PD	Rotenone	SH-SY5Y cell	MMP, Cyto C, Bax/Bcl_2, Caspase-3, NRF-2

Table 2
Summary of Mitochondria-Related Antitumor Effects of Ginsenosides

Reference	Ginsenoside	Experimental model	Effects targeting mitochondia
[37]	CK	Neuroblastoma cells	MMP, mito-ROS
[38]	CK	Hepatocellular carcinoma cells (MHCC97-H)	mtDNA, MMP, Bax/Bcl_2, Caspase-3/9, Cyto C
[39]	CK	Colon cancer cells (HT-29)	MMP, Bax/Bcl2, Caspase-3
[42]	CK	Bladder cancer cells (T24)	Cyto C, Caspase-3/9, Bax/Bcl_2
[43]	Rg3	HeLa cells	MMP
[44]	Rg3	Myeloma cells (U266, RPMI8226, SKO-007)	MMP, Cyto C, Bax/Bcl_2, Caspase-3
[45]	Rg3	Breast cancer cells (MDA-MB-231)	MMP, Cyto C, Bax/Bcl_2, Caspase-3
[46]	Rg3	Colon cancer cells (HT-29)	Cyto C, Bax/Bcl_2, Caspase-3/9
[47]	Rg3	Gallbladder cancer cells	Mitochondrial-mediated intrinsic caspase pathway
[48]	Rg3, Rh2	Hepatocellular carcinoma cells (Hep3B)	MMP, Cyto C, Bax/Bcl_2, Caspase-3
[49]	Rh2, Rg3	Leukemia cells (Jurkat)	Mito-ROS, mitophagy, MMP, mito-apoptosis
[50,52]	Rh2	Leukemia cells (lymphoblastic, Reh)	Mito-apoptosis, MMP, Cyto C, Caspase-3/9
[51]	Rh2	Hepatoma cells (HepG2)	mitochondrial apoptosis
[53]	Rh2	Breast cancer cells (MCF-7, MDA-MB-231)	Bcl_2, Bcl-xL, Bak, Bax, Bim
[54]	Rg5	Human esophageal cancer cells (Eca109)	MMP
[55]	Rg5	Breast cancer cells	PI3K-mediated mitochondria apoptosis
[56]	F2	Gastric carcinoma cells	MMP, Cyto C
[57]	Rf	Osteosarcoma cells (MG-63)	MMP, Cyto C, Bax/Bcl_2, Caspase-3/9
[58]	Rg1	Leukemia cells (K562)	Mitochondria morphology
[59]	pseudo-Rh2	Gastric cancer cells (SGC-7901)	MMP, Cyto C, Caspase-3/9, Bax/Bcl_2

number, Bcl_2/Bax ratio, and caspase-3/9 expression in an Akt phosphorylation-dependent manner [38]. Similarly, in human colon cancer HT-29 cells, CK induces a mito-apoptotic pathway by affecting Bax and Bcl_2 expression, resulting in the depolarization of the MMP [39]. During cytotoxic apoptosis, the translocation of full-length Bid from cell nuclei to mitochondria directly causes the release of Cyto C from mitochondria, indicating that full-length Bid is necessary to activate mito-apoptotic pathways [40]. In subcutaneous tumor and liver metastasis tissues, immunohistochemical staining revealed that Bid expression is obviously decreased by CK treatment, suggesting that a Bid-mediated mitochondrial apoptotic pathway is induced by CK [41]. In addition, in bladder cancer T24 cells, Western blot analysis demonstrated that CK treatment enhances the release of Cyto C, activates procaspases-3 and procaspases-9, and increases the Bax/Bcl_2 ratio by ROS generation and p38-MAPK activation [42].

4.2.2. *Rg3 on tumors*

Pretreatment with Rg3 decreases MMP and mito-apoptosis in HeLa cells by regulating autophagy [43]. In myeloma cells, Rg3 also induces apoptosis by altering the Bcl_2/Bax ratio, caspase activation, and the release of Cyto C from the mitochondria into the cytoplasm through the IGF-1/Akt/mTOR pathway [44]. In human breast cancer, MDA-MB-231 cells, treatment with Rg3 (30 μM) increases the Bax/Bcl_2 ratio, the depolarization of MMP, and the release of mitochondrial Cyto C and also induces the cleavage of caspase-3 and poly-(ADP-ribose) polymerase (PARP), which is attenuated by a caspase-3 inhibitor, Z-VAD-FMK, indicating that Rg3 induces breast cancer cell apoptosis via classical mitochondrial-dependent caspase activation [45]. Furthermore, in HT-29 colon cancer cells, Rg3 downregulates the expression of Bcl_2 and upregulates the expression of the pro-apoptotic protein, p53 or Bax, thereby inducing the release of mitochondrial Cyto C and the cleavages of PARP, caspase-9, and caspase-3 through the AMPK signaling pathway [46]. Similarly, Rg3 exposure suppresses the survival of gallbladder cancer via the activation of the mitochondrial-mediated intrinsic apoptosis pathway in NOZ cells, GBC-SD cells, and nude mice [47]. In addition, in human hepatocellular carcinoma Hep3B cells, the combination of Rg3 and 20(S)–Rh2 decreases MMP, enhances the release of Cyto C, and activates the cleavage of caspase-3, which suggests that they may induce apoptosis by direct activation of the mitochondrial pathway [48]. Another study reported that Rg3 combined with Rh2 and 20(S)–Rh2 can induce mito-ROS and mito-apoptosis in human leukemia Jurkat cells [49].

4.2.3. 20(S)−Rh2 on tumors

Mitophagy inhibition could aggravate mito-ROS generation and mitochondrial function and accelerate mito-apoptosis. Xia et al. have shown that mitophagy plays a protective role in 20(S)−Rh2-induced apoptosis in human acute lymphoblastic leukemia (ALL) cell lines and primary ALL cells via mito-apoptosis and autophagy without cytotoxic effects on normal blood cells [50]. In liver cancer -HepG2 cells, 20(S)−Rh2 incubation induces apoptosis by increasing the accumulation of ROS and the activation of the lysosomal-mitochondrial apoptotic pathway [51]. 20(S)−Rh2 can also induce MMP of human leukemia Reh cells in the shift in JC-1 fluorescence from red to green and cause the release of mitochondrial Cyto C and activation of cleaved caspase-9 and caspase-3 [52]. In human breast cancer cell lines and *in vivo* xenograft models, 20(S)−Rh2-induced apoptosis is accompanied by the downregulation of anti-apoptotic proteins, Bcl_2, Bcl-xL, and Mcl-1 and the induction of the pro-apoptotic members, Bak, Bax, and Bim, which leads to mito-apoptosis [53].

4.2.4. Rg5 on tumors

The exposure to various concentrations of ginsenosides Rg5 (Rg5) for 24 h in esophageal cancer Eca109 cells decreases MMP via the downregulation of the PI3K-Akt signaling pathway [54]. Moreover, Rg5 remarkably suppresses breast cancer cell proliferation through mito-apoptosis and autophagic cell death by targeting the PI3K signaling pathway [55].

4.2.5. Other ginsenosides on tumors

In addition to the abovementioned ginsenosides, other ginsenosides can also target mitochondria to inhibit tumorigenesis and development. In humor gastric carcinoma *in vivo* and *in vitro* models, ginsenoside F2 (F2) decreases MMP, and accelerates the release of Cyto C, which induces mitochondria-dependent apoptosis [56]. In human osteosarcoma MG-63 cells, Rf induces G_2/M phase cell cycle arrest and apoptosis through the mito-apoptotic pathway [57]. In human leukemia K562 cells, Rg1 treatment at a concentration of 20 μM for 48 h inhibits dramatic morphological alterations, such as larger mitochondria and increased numbers of lysosomes [58]. In human gastric cancer SGC-7901 cells, pseudo-Rh2-induced apoptosis is associated with a decrease in MMP, downregulation of the Bcl_2/Bax ratio, and cleavages of caspase-9 and caspase-3 [59]. Furthermore, in a non-small cell lung cancer mouse xenograft model, ginsenosides Rk3 (Rk3) induces the activation of caspase-8, -9, and -3, promotes the change in MMP, decreases the Bcl_2/Bax ratio and causes the release of Cyto C, which indicates that the apoptosis-inducing effect of Rk3 is triggered via mitochondria-mediated pathways [60].

In terms of tumor inhibition, CK and Rg3 are the most widely studied among ginsenoside monomers. Ginsenoside basically exerts its tumor-inhibitory effects by reducing MMP, increasing the release of Cyto C, and reducing the proportion of mitochondrial apoptotic pathways.

4.3. Heart disease

Heart diseases are characterized by persistent mitochondrial dysfunction. For example, during myocardial infarction, the supply of oxygen and energy is significantly compromised, and the mitochondrial structure in cardiomyocytes undergoes rapid changes, which cause heart functional damage: the suppression of OXPHOS, mainly due to the inhibition of complex I and/or ATP synthase, the loss of mitochondrial membrane integrity, due to the opening of mPTPs, and the release of Cyto C from mitochondria [61]. Numerous studies have shown that ginsenosides can target mitochondrial function, suppressing heart diseases (Table 3).

Mito-apoptosis plays a key role during myocardial I/R injury. In I/R-induced H9c2 cardiomyocytes, Rb1 can reduce mPTP by stabilizing MMP, leading to mito-apoptosis by reducing the release of Cyto C and the expression of cleaved caspase-3 in the cytoplasm, ultimately reducing programmed cell death [62]. In isolated rat hearts perfused with palmitate, high-fat diet-induced mice, and cardiomyocyte models, Rb1 prevents hypoxic succinate accumulation and improves pyruvate dehydrogenase (PDH) activity by blocking succinate-associated HIF-1α activation and GPR91 signaling, which ameliorates mitochondrial dysfunction and thereby reduces apoptosis during I/R [63]. *In vivo* and *in vitro* rat cardiomyocyte I/R injury models show that Rd pretreatment significantly stabilizes MMP, and attenuates cytosolic translocation of mitochondrial Cyto C and the activation of caspase-3/9, and increases the p-Akt or GSK-3β levels and the Bcl_2/Bax ratio [64]. CK significantly inhibits mitochondrial swelling by partly mediating the activation of the PI3K pathway and phosphorylation of Akt in *in vivo* I/R injured mouse models [65]. Under conditions with insufficient nutrients, Rg1 rescues ATP levels and MMP in nutrient-starved cells induced by glucose deprivation and in mice with nutritional stress via aldolase/AMPK/PINK1 signaling [66].

The dysfunction of mitochondrial dynamics (fusion/fission) is a prominent feature of ischemia heart disease [67]. Rg1 moderates glutamate dehydrogenase dysregulation, increases mitochondrial length, and Mfn2 expression to reduce the number of cells with fragmented mitochondria, and prevents the imbalance of mitochondrial dynamics following I/R [68]. Hexokinase-II (HK-II) and Drp1 differently regulate mitochondrial glucose metabolism and fission [69]. In cardiomyocyte I/R injury models and isoproterenol-induced ischemic mouse hearts, Rg5 improves PDH activity and ATP production, preventing the opening of mPTPs and mitochondrial fission via Drp1 recruitment and HK-II activation [70].

Sirtuin-1 (SIRT1), an NAD^+-dependent histone deacetylase, plays a critical role in cellular metabolism, ETC function, and the response to oxidative stress in mitochondria [71]. Rb2, F1, and Rc can enhance the deacetylated activity of SIRT1 and increase ATP content, the oxygen consumption rate (OCR), and mtDNA copy number in tert-butyl hydroperoxide-induced H9c2 cardiomyocytes, suggesting that these ginsenosides attenuate oxidative stress-induced mitochondrial damage through the activation of SIRT1 [71]. In a myocardial infarction-induced heart failure mouse model and an I/R-induced H9c2 injury model, Rb3 treatment upregulates the levels of the mitochondrial deacetylase SIRT3 and peroxisome proliferator-activated receptor α, protecting mitochondrial membrane integrity [72].

4.4. Hyperglycemia

When the concentration of glucose in the blood exceeds normal levels, the mitochondria in muscle cells and neurons can undergo excessive fragmentation, leading to mito-ROS burst and damaging the integrity of mtDNA [73]. Furthermore, mitochondrial fission transmits mito-apoptotic signaling that increases the sensitivity of cells to undergo apoptosis, whereas the fusion of mitochondria can enhance cell survival [73]. In oral glucose (0.5 g/kg body weight)-treated rats, Rb1 (0.01 and 0.1 mg/kg body weight) increases postprandial glucose levels, citrate synthase activity, and glycogen content, whereas Rg1 (0.01 mg/kg body weight) decreased these indices in the red gastrocnemius muscle [74]. Meanwhile, both ginsenosides can influence mitochondria turnover dynamics and alter muscle metabolism [74]. Type II diabetes mellitus and metabolic syndrome are characterized by mitochondrial dysfunction accompanied by insulin resistance in skeletal muscle [75]. Kim et al. have shown that Rg3 treatment increases ATP production and the OCR and upregulates the levels of mitochondrial biosynthesis-

Table 3
Summary of Mitochondria-Related Heart Protective Effects of Ginsenosides

Ref.	Ginsenoside	Model	Inducer	Experimental model	Effects
[62]	Rb1	I/R	Hypoxia-reoxygenation	H9c2 cells	MMP, Cyto C, Caspase-3
[63]	Rb1	I/R	Palmitate and high-fat diet	Isolated rat hearts, mice	Succinate, PDH
[64]	Rd	I/R	Ligature of left anterior descending heart	Rat model	Caspase-3/9, MMP, Cyto C
[65]	CK	I/R	Ligature of left anterior descending heart	Mice	Mitochondrial swelling
[66]	Rg1	Nutritional stress	Glucose deprivation	Mice	ATP, MMP
[68]	Rg1	I/R	Hypoxia-reoxygenation	Cardiomyocyte	Mitochondrial dynamics
[70]	Rg5	Myocardial damage	PA, Ligature of left anterior descending heart	H9c2 cells, mice	HK-II, Drp1, ATP, MMP
[71]	Rb2, F1, Rc	Oxidative damage	Tert-butyl hydroperoxide	H9c2 cells	ATP, mtDNA, OCR
[72]	Rb3	Heart failure	Myocardial infarction and I/R	Mice and H9c2 cells	MMP

related proteins, including PGC1α, NRF-1, and complex IV/V, leading to an improvement of insulin resistance in skeletal muscle C2C12 cells [76]. Diabetic encephalopathy is a severe diabetic complication with characteristic symptoms of cognitive dysfunction and neuropsychiatric disability, which can be aggravated by mitochondrial dysfunction [77]. Rb1 could enhance the ratio of Bcl_2/Bax, inhibit the expression of cleaved caspase-3/9, and alleviate mitochondrial damage and ROS production in the methylglyoxal-induced damage of SH-SY5Y cells through the activation of PI3K/Akt signaling pathway [78].

4.5. Inflammation

Oxidized mtDNA and other damage-associated factors are released from impaired mitochondria and act as pro-inflammatory molecules [79]. In an IL-1β-induced chondrocyte cell model of osteoarthritis, treatment with Rg1 for 2 h decreased IL-1β activity, reducing Bcl_2 levels and Akt phosphorylation, and increased Bax activity, Cyto C release, and caspase-3 activation through PI3K/Akt signaling [80]. In contrast, Rb1 showed an inhibition of MMP permeability and caspase-3 activity and increased Bcl-xL/Bax ratio in H_2O_2-induced rat articular chondrocytes [81]. Moreover, Rd remarkably inhibits the activation of the NLRP3 inflammasome, which is dependent on the mitochondrial translocation of p62 and mitophagy via regulation of the AMPK/ULK1 signaling pathway in a dextran sulfate sodium-induced murine colitis model [9].

4.6. Other disorders

Other diseases, such as obesity, myotube atrophy, and sepsis, have also been associated with the disruption of mitochondrial functions and homeostasis [82–84]. Mitochondria play a key role in energy homeostasis in adipose tissues. White adipose tissue primarily stores excess energy, whereas brown adipose tissue predominantly dissipates energy by non-shivering thermogenesis [85]. In an animal model of subcutaneous white adipose cells isolated from C57BL/6 mice and 3T3-L1 adipocytes, UCP1 expression and mitochondrial biogenesis are upregulated by Rg1 via AMPK signaling pathway, which suggests that Rg1 exerts its anti-obesity effect by promoting adipocyte browning [86]. In addition, Rb1 promotes the browning of 3T3-L1 adipocytes by increasing basal glucose uptake and energy production, and upregulating the expression of brown fat-related transcriptional factors, including UCP-1, PGC-1α, and zinc finger protein 16 [87].

For myotube atrophy, the decreases of MMP and ATP synthesis, and the increase of ROS levels are reversed by Rg3 pretreatment in TNF-α-treated C2C12 myoblasts [88]. Furthermore, Rg3 upregulates the activity and expression of PGC1α, NRF-1, and mitochondrial transcription factor A [88].

Mitochondrial function also influences virus propagation and adaptation through morphology changes mediated by mitochondrial fusion and fission [89]. Kim et al. demonstrated that Rg3 inhibits hepatitis C virus (HCV) propagation by restoring the Drp1-mediated aberrant mitochondrial fission and mitophagy, thereby suppressing HCV infection [89]. In addition, in *in vitro* and *in vivo* sepsis models, Rg3 shows beneficial functions, such as OCR promotion, ROS attenuation, and the maintenance of GSH pools, by regulating AMPK-mediated mitophagy [90].

Multiple stimulations, such as UV, elevated glucose, particulate matter of 2.5 μm and smaller (PM2.5), and H_2O_2 can increase mito-ROS production and oxidative stress damage, which are associated with the depressed activity of the mitochondrial respiratory chain. In UV-irradiated normal human dermal fibroblast cells, Rg3 restores mitochondrial ATP levels and MMP, which leads to an increase in proteins linked with extracellular matrix, cell proliferation, and antioxidant activity [91]. In high glucose-induced rat retinal capillary endothelial cells, treatment with Rb1 significantly increases cell viability and mtDNA copy number, and inhibits ROS burst through the up-regulation of SIRT1 and SIRT3 expression [92]. In PM2.5-induced human HaCaT keratinocytes and normal dermal fibroblasts, Rb1 restores the production of ATP and blocks ER stress via the mitochondrial pathway [93]. Proteomic analysis has shown that 23 proteins spots are upregulated by Re pretreatment, which are mainly involved in the restoration of mitochondrial functions in H_2O_2-induced human umbilical vein endothelial cells [94]. In particular, in isolated spinal cord mitochondria, Rd regulates mPTP formation, Cyto C release, mitochondrial swelling, and NAD(P)H matrix content through Akt and ERK pathways [95].

Overall, emerging evidences has shown that several ginsenosides can target mitochondria to treat different diseases through multiple mitochondria-related signaling pathways (Fig. 3).

5. Conclusion and perspective

Ginsenosides have attracted much attention based on a wide range of pharmacological effects and medical applications. In the present review, we summarized recent findings about major ginsenosides from *P.* ginseng targeting mitochondrial function, hoping to partially explain the common targets of ginsenosides against multiple diseases. Currently, a huge body of pre-clinical evidences focuses on therapeutic role of ginsenosides in the cell and animal models. There are only a few clinical studies aim to evaluate the protective/therapeutic effects of several ginsenosides, such as Rd, and Rb1, which cannot explore the molecular mechanism of these ginsenosides [96,97]. In the future, our missions mainly contain two directions as below: one is to explore the potential targets or molecular networks of ginsenosides, and the other is to investigate the synergistically function of various ginsenosides as a mixture from ginseng extracts against a variety of diseases. Extensive and

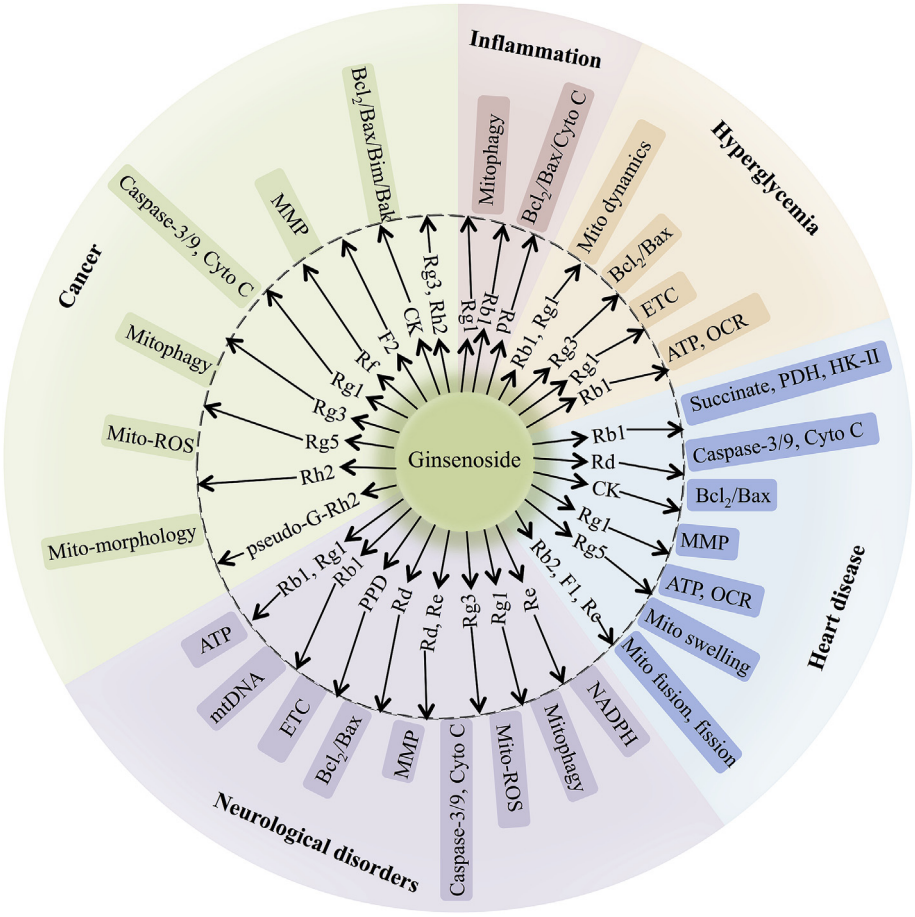

Fig. 3. Summary of the effects of different ginsenoside monomers on mitochondria function during neurological disorders, cancer, heart disease, hyperglycemia, and inflammation.

deep studies for ginsenosides targeting mitochondrial function could provide new insights into the clinical therapeutic application of *P. Ginseng* against multiple disorders.

Conflicts of interest

The authors have declared no conflict of interest.

Acknowledgments

This work was supported by the National Key Research and Development Program of China (No. 2017YFC1702103, 2019 YFC1709901), Regional Innovation and Development Joint Fund (U19A2013), National Natural Science Foundation of China (81602257), the Science and Technology Development Plan Project of Jilin Province (No. 20190101010JH, 202002053JC)), Jilin Provincial Administration of Traditional Chinese Medicine (2020168) and the Project for Science and Technology Bureau of Changchun (No. 18YJ013).

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