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Mini-Review article

Autophagy and its regulation by ginseng components

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ABSTRACT

Autophagy is the sequential process whereby cell components are degraded, which can occur due to nutrient deprivation. Its regulation has an essential role in many diseases, functioning in both cell survival and cell death. Autophagy starts when mTORC1 is inhibited, resulting in the activation of several complexes to form a cargo that fuses with a lysosome, where it undergoes degradation. In this review, we describe a plant extract that is well known in Korea, namely Korean ginseng extract; we studied how its derivatives and metabolites can regulate autophagy and thus mediate the pathogenesis of certain diseases.

1. Introduction

Autophagy is the sequential process of cytoplasm component degradation by lysosomes [1,2]. It plays an essential role in countering certain diseases and conditions, such as cancer, infection, aging, heart diseases, and neurodegradation [3,4]. There are different types of autophagy, classified by their mechanisms. Certain articles have classified autophagy into two types: nonselective (macroautophagy) and selective (classified by the cytosolic cargo sequestered) [3,5]. Other articles have classified autophagy into three main types: macroautophagy, microautophagy, and chaperone-mediated autophagy [4,6,7]. Autophagy generally occurs due to nutrient deprivation and/or starvation, functioning in both cell survival and cell death [8].

Macroautophagy, which is commonly referred as autophagy, is involved in several pathways to form double membrane vesicles (autophagosomes) and to sequester cytoplasmic components through the inhibition of the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway [9,10]. This inhibition activates the downstream complex Unc-51 like autophagy activating kinase 1/2 (ULK1/2), composed of ULK1/2, Atg13, and FIP200 [11]. This complex then triggers the Beclin-1/Phosphatidylinositol 3-kinase catalytic subunit type 3 (PI3KC3) complex to initiate phagopore formation. This in turn leads to autophagosome formation through the microtubule light-chain 3 protein or LC3 by activation through ubiquitin-like conjugation pathways [autophagy-related protein (ATG) conjugates] [12]. The autophagosome then fuses with a lysosome (autolysosome), and the materials inside are degraded. Furthermore, the proteins involved in autophagy would also be recycled at the end of the process.

While autophagy has a functional role in cell survival, it has several pathways in common with apoptosis, a pathway that causes cell death. Autophagy and apoptosis regulate each another: For example, autophagy mediates cell death by degrading the negative regulator of apoptosis signaling, particularly in the caspase signaling pathway [13], or by degrading catalase, increasing reactive oxygen species (ROS) accumulation, and leading to cell death [14]. On the other hand, apoptosis regulators such as Bcl-2 and Bcl-X_L prevent autophagy by interacting with Beclin-1 on their BH3 domain. This can be disrupted by BH3 mimetics, for example, Bcl-2-associated death promoter (BAD), to initiate autophagy [15]. The implication of autophagy involvement in some diseases is attracting attention. A number of cancer treatments involve autophagy inhibition or activation. In this review, we focus on how natural sources take part in autophagy regulation, in particular a very famous plant in Korea, Korean ginseng, and its components.

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Table 1
Target diseases and autophagy-mediated molecular targets responding to ginseng components

Component	Target diseases	Autophagy-mediated molecular target
Korean Red Ginseng extract	Testicular dysfunction [35]	Inhibits mTORC1 and mTOR phosphorylation.
	Diabetes mellitus [40]	Reduces LC3B puncta accumulation; increases LC3B-LAMP-2A colocalization.
	Hepatocellular carcinoma [36]	Increases LC3 puncta as indication of reducing the late stage of autophagy.
Ginsenoside Rb1	Melanoma [41]	Attenuates mTOR phosphorylation by induction of AMPK.
Compound K	Colon cancer [45]	Causes accumulation of LC3 after the upregulation of Atg5 and Atg7. Disrupts Atg6 (Beclin-1) and Bcl-2 interaction (also induces apoptosis).
Ginsenoside Rh2	Acute and chronic myeloid leukemia [58]	Increases LC3B activation after downregulation of p62.
Ginsenoside F2	Breast cancer [53]	Increases the accumulation of LC3, Beclin-1, and Atg-7.

mTORC1, mammalian target of rapamycin complex 1.

2. Korean ginseng extract and its components

Korean ginseng (*Panax ginseng* Meyer) belongs to the Araliaceae family [16]. Korean ginseng has been found to have antidiabetic, antiinflammatory, antimicrobial, antifungal, neuroprotective, antioxidant, anticancer, and antitumor activity [17–22]. The plant is especially rich in ginsenosides, a group of triterpene saponins, which comprise the active components [23]. Ginsenosides are classified into two categories based on their chemical structures, 20-S-protopanaxadiol and 20-S-protopanaxatriol [24]. Some ginsenoside components have been reported to play a role in certain diseases. Some ginsenoside derivatives such as Rb1, Rb2, Rg3, Rg1, and Rb1's metabolite compound K (Fig. 1) have been reported to have antidiabetic activity, involving the sites of activation or inhibition of proteins responsible for diabetes [25–29]. Some ginsenoside derivatives also have antiinflammatory activity; for example, ginsenoside Rg1 decreases nitric oxide (NO) and tumor necrosis factor (TNF)-α levels in macrophage cells [30], as well as interleukin (IL)-1β and IL-6 *in vivo* [31]. There is also a report that the nuclear factor (NF)-κB signaling pathway is downregulated in the presence of ginsenoside Rg3 in lung tissue of humans with asthma [32]. Ginsenoside Rp1 downregulates the insulin-like growth factor 1 receptor (IGF-1R)/protein kinase B (Akt) pathway in breast cancer cells, reducing their proliferation and colony formation [33]. In addition, ginsenoside Rk3 has been found to downregulate the expression of cyclin D1 and CDK4, followed by the upregulation of p21, in lung cancer *in vitro* and *in vivo* [34].

3. Regulation of autophagy by Korean ginseng extract

The components and derivatives of Korean ginseng extract (KGE) play important roles in treating certain serious diseases, and the effects of Korean ginseng on autophagy may be one of the mechanisms (Table 1 and Fig. 2). Several studies have investigated KGE-mediated autophagy. Cha et al [35] reported that the extract had the potential to attenuate testicular dysfunction as treatment decreased molecules responsible for spermatogenesis and downregulated the mRNA levels of sex hormone receptors including the

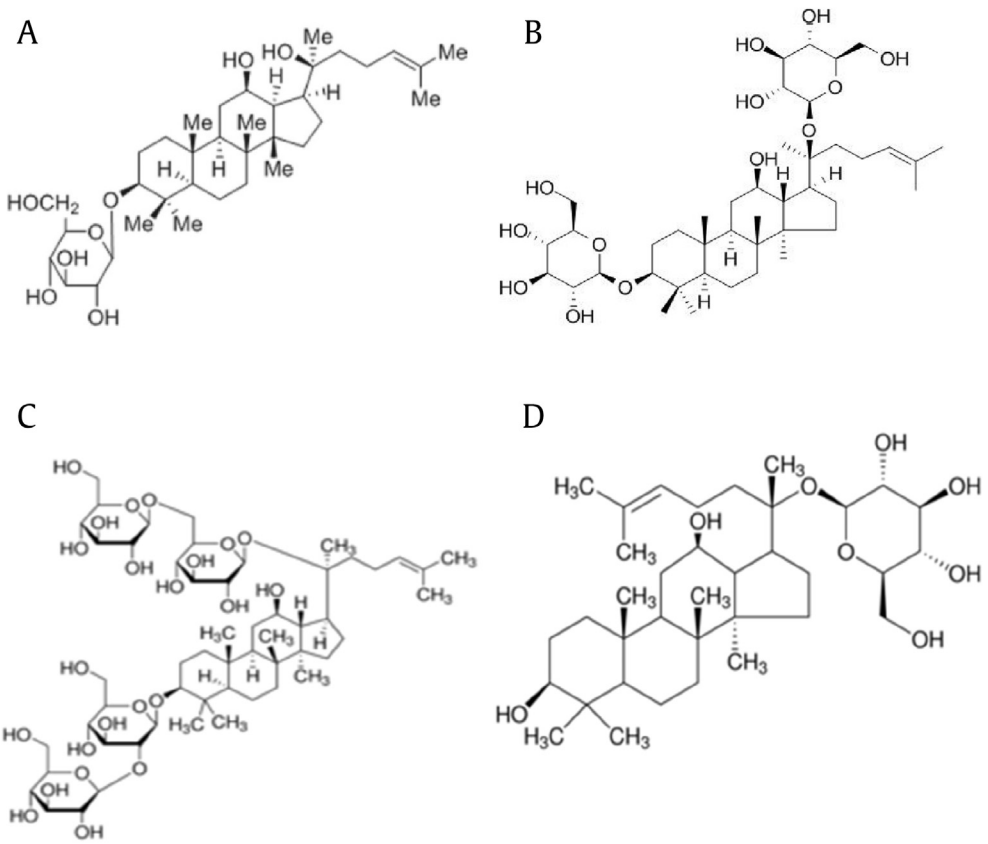

Fig. 1. Chemical structure of ginseng components. (A) Ginsenoside Rh2. (B) Ginsenoside F2. (C) Ginsenoside Rb1. (D) Compound K.

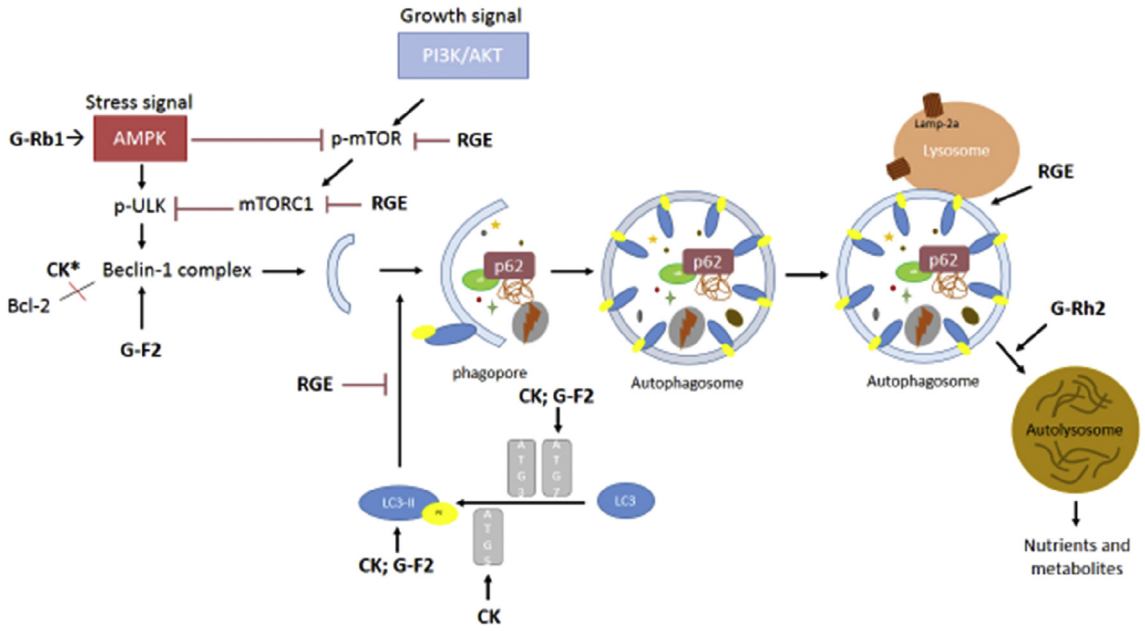

Fig. 2. Schematic flow chart of autophagy-mediated molecular targets regarding ginseng components.
AMPK, AMP-activated protein kinase; CK, compound K; mTORC1, mammalian target of rapamycin complex 1; PI3KC3, Phosphatidylinositol 3-kinase catalytic subunit type 3; RGE, Red Ginseng extract; ULK1/2, Unc-51 like autophagy activating kinase 1/2.

androgen, luteinizing hormone, and follicle-stimulating hormone receptors. Concomitantly, Korean Red Ginseng extract (RGE) also modulated autophagy responses by decreasing the mTORC1 mRNA and protein levels after they had been elevated by doxycycline (DOX)-induced testicular damage [35]. Nonetheless, further study is needed to determine the stage at which autophagy regulates testicular dysfunction and vice versa.

On the other hand, RGE inhibited autophagic flux synergistically with doxorubicin, leading to cell death in hepatocarcinoma cell lines [36]. RGE-mediated prevention of autophagic flux increased the sensitivity of the cancer cells to the doxorubicin. Autophagic flux inhibition increases cell starvation by preventing autophagosome—lysosome fusion, which is marked by a decrease in the protein level of p62 due to autophagy cargo degradation [37,38]. When chloroquine treatment was used to block lysosome function, in turn inhibiting autophagy, RGE did not upregulate the expression levels of both LC3 and p62, which indicates that RGE upregulates LC3 in the last stage of autophagy [38].

Through regulation of autophagy, KGE may reduce immunosuppressant-associated adverse effects, such as diabetes mellitus associated with tacrolimus [39,40]. Tacrolimus-induced diabetes mellitus is characterized by the accumulation of autophagic vacuoles, whose conversion to autophagosomes results from the activation of LC3 [39]. These autophagosomes mediate beta cell injury, leading to diabetes mellitus. RGE can modulate this activity to prevent the sustainable formation of autophagosomes, markedly by the inhibition of LC3B as an autophagosome marker after enhancement of the colocalization of LC3B and lysosome-associated membrane protein-2A during autophagosome—lysosome fusion, to enhance the autophagy clearance [40].

4. Regulation of autophagy by ginsenoside derivatives

KGE contains many derivatives and metabolites, which have divergent roles in regulating autophagy (Table 1 and Fig. 2). One ginsenoside Rb1 metabolite, 20-O-β-D-glucopyranosil-20(S)-protopanaxadiol (compound K), has been shown to play a role in malignancy by inducing autophagy and apoptosis via activation of AMP-activated protein kinase (AMPK)/c-Jun N-terminal kinase (JNK) [41]. The parallel activity in the mitogen activated protein kinase (MAPK) and AMPK signaling pathways initiates autophagy as follows: JNK phosphorylates Bcl-2 to dissociate with Beclin-1, inhibiting mTOR [42], whereas mTOR generally is inhibited by AMPK activation to initiate autophagy processes and negatively regulate the transformation and proliferation of melanoma cells [43,44]. Compound K also has been reported to induce autophagy in human colon cancer by regulating JNK and ROS generation [45] because in cancer cells, intracellular ROS concentration is found to be increased, which could mediate autophagy [46]. Activation of autophagy is also part of atherosclerosis: Macrophages form cholesterol-laden foam cells after engulfing oxygenized low-density lipoproteins, resulting in the formation of atherosclerotic plaques [47]. In brief, autophagy regulates lipid metabolism in macrophages through the hydrolysis of intracellular lipids and cholesterol efflux promotion. Moreover, autophagy dysfunction may lead to the abnormalities of atherosclerotic plaque formation and progression of atherosclerosis [48—50].

In breast cancer, metastasis can lead to drug resistance [51,52]. Mai et al [53] found an association between apoptosis and autophagy with ginsenoside F2 in breast cancer stem cells. They concluded that ginsenoside F2 blocks proliferative activity via activation of the intrinsic apoptotic pathway and triggers mitochondrial dysfunction. Moreover, it also induced the recruitment of LC3, Beclin-1, and Atg-7 in the context of autophagy, controlled by the apoptosis—autophagy conjunction controller protein p53. The upregulation of p53 phosphorylation resulted in the activation of AMPK, which inhibits mTOR as an initiator of autophagy via AMPK-TSC/1/TSC2-mTOR [54,55]. In short, ginsenoside F2 in this case has a dual role including activation of apoptosis after protective autophagy against breast cancer stem cells.

Another ginsenoside derivative, Rh2 (G-Rh2), was shown to induce apoptosis in leukemia cells by upregulating transforming growth factor (TGF)-β expression and regulating the mitochondria signaling pathway [56,57]. Furthermore, autophagy may play another role in leukemia by upregulating the activation of LC3-II

from LC3-I, together with downregulating p62, which indicates the autophagy flux in a dose-dependent manner [58]. This regulation protects the cells against apoptosis. Conclusively, to increase the efficiency of the therapeutic effect of G-Rh2 in both acute and chronic myeloid leukemia, it is necessary to inhibit autophagy to increase cancer cell death.

5. Conclusion

Studies of KGE and its components are helping to provide an understanding of the role of autophagy in the pathogenesis of certain diseases (Fig. 2). More studies are needed to determine the role of each stage of autophagy in disease. These studies would provide a better understanding of how this extract and its components could be used to treat diseases such as cancer. Conflicts of interest All authors declare no conflicts of interest.

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All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgr.2018.12.011.

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