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Review Article

Therapeutic applications of ginseng for skeletal muscle-related disorder management

Syed Sayeed Ahmad [a, b], Hee Jin Chun [a], Khurshid Ahmad [a, b], Inho Choi [a, b, *]

[a] Department of Medical Biotechnology, Yeungnam University, Gyeongsan, Republic of Korea
[b] Research Institute of Cell Culture, Yeungnam University, Gyeongsan, Republic of Korea

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ABSTRACT

Skeletal muscle (SM) is the largest organ of the body and is largely responsible for the metabolism required to maintain body functions. Furthermore, the maintenance of SM is dependent on the activation of muscle satellite (stem) cells (MSCs) and the subsequent proliferation and fusion of differentiating myoblasts into mature myofibers (myogenesis). Natural compounds are being used as therapeutic options to promote SM regeneration during aging, muscle atrophy, sarcopenia, cachexia, or obesity. In particular, ginseng-derived compounds have been utilized in these contexts, though ginsenoside Rg1 is mostly used for SM mass management. These compounds primarily function by activating the Akt/mTOR signaling pathway, upregulating myogenin and MyoD to induce muscle hypertrophy, downregulating atrophic factors (atrogin1, muscle ring-finger protein-1, myostatin, and mitochondrial reactive oxygen species production), and suppressing the expressions of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in cachexia. Ginsenoside compounds are also used for obesity management, and their anti-obesity effects are attributed to peroxisome proliferator activated receptor gamma (PPARγ) inhibition, AMPK activation, glucose transporter type 4 (GLUT4) translocation, and increased phosphorylations of insulin resistance (IR), insulin receptor substrate-1 (IRS-1), and Akt. This review was undertaken to provide an overview of the use of ginseng-related compounds for the management of SM-related disorders.

1. Introduction

Skeletal muscle (SM) is a highly dynamic tissue that makes up around 40% of the total body weight and 50-75% of the body's protein content [1,2], and consumes around 80% of blood glucose. Furthermore, SM is essential for vital functions such as movement, postural support, and thermogenesis, and thus maintenance of SM mass is required to maintain metabolism and strength. The bulk of insulin-mediated glucose absorption is carried out by SM through glucose transporter type 4 (GLUT4) [3].

The enduring maintenance of muscle tissues is mediated by muscle satellite (stem) cells (MSCs), which are located close to muscle fibers [4]. The activities of these cells depend on myogenic regulatory factors (myoblast determination protein (MYOD), myogenin (MYOG), and muscle regulatory factor 4 (MRF4) [5]), certain growth factors (insulin-like GFs (IGF-1 and -2), fibroblast GF, and hepatocyte GF) [6], and cytokines (TNF-α and LIF (leukemia inhibitory factor) [7,8]. Under normal conditions, MSCs are present in an inactive form and remain dormant until injury or exercise [9], when they become activated and trigger SM tissue formation through myogenesis. The term myogenesis refers to the process leading to the formation of SM tissue and involves MSC activation and proliferation and the fusion of differentiating myoblasts into mature myofibers [10]. Several MRFs were reported to participate in myogenesis. For example, IgLON4 promotes cell adhesion and maintains myotube orientation [11], whereas IgLON5 promotes myoblast adhesion and differentiation and regulates myogenesis [12]. On the other hand, fibromodulin (FMOD) is an extracellular matrix protein involved in the conservation of myoblast stemness and function [13] and controls myoblast differentiation by

Abbreviations: SM, Skeletal muscle; MSCs, muscle satellite (stem) cells; MYOD, myoblast determination protein; MYOG, myogenin; MRF4, muscle regulatory factor 4; GFs, growth factors; IGF-1/2, Insulin growth factors; TNF-α, Tumour necrosis factor-alpha; FMOD, Fibromodulin; CC, cancer cachexia; MSTN, myostatin; DEX, Dexamethasone; MyHC, myosin heavy chain; MuRF1, muscle ring-finger protein-1; KRG, Korean Red Ginseng.

* Corresponding author. Department of Medical Biotechnology, Yeungnam University, Gyeongsan, 38541, Republic of Korea.
E-mail address: inhochoi@ynu.ac.kr (I. Choi).

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regulating the expressions of COL1α1 and integral membrane protein 2 A at the gene level [14].

Given the importance of SM, loss of SM function and its regenerative properties underlie debilitating musculoskeletal disorders [10]. Novel therapies are urgently required that promote the maintenance of SM, and ginseng is known to have curative effects on several diseases. The aim of this review was to explore ginseng-related compounds with potential use for the management of SM-related disorders. Furthermore, several peptides (MIF1 and MIF2) [15] and natural compound (dithymoquinone) [16] are known to enhance SM mass.

Herbal remedies have been used for millennia to treat disease, whereas, over the past century, the trend has been toward the use of allopathic/synthetic drugs. Currently, most patients favor allopathic drugs over herbal treatments, but long-term treatments with these drugs are invariably associated with side effects. As a result, patients' perceptions are changing in favor of natural therapies and traditional medicines with minimal side effects. Ginseng has been consumed as an herbal medicine for thousands of years and today is commercially available as pills and teas [17]. Intriguingly, one clinical study reported that patients who took ginseng after curative surgery had a 38% higher overall survival rate than those who did not and a 35% higher 5-year disease-free rate [18].

Ginsengs belong to the Araliaceae family (*genus Panax*), and there are two ginseng types, namely, Asian [*Panax ginseng*] and American ginseng [*Panax quinquefolius*]). The roots part of these plants contain steroidal saponins called ginsenosides and are the roots are the most widely used plant part in natural remedies [19]. The active compounds in ginseng have been reported to act on the central nervous system [20], have antioxidant [21] and anti-inflammatory properties [22], maintain body homeostasis, improve brain function, enhance the immune system and liver function, modulate blood pressure, improve libido, and have pain-relieving, anti-tumor activity, anti-diabetic, anti-fatigue, anti-stress, anti-aging [23,24], and anti-type 2 diabetes (T2D) mellitus effects [25]. Ginseng is also used to treat neurodegenerative diseases such as Alzheimer's disease [26], Parkinson's disease, Huntington's disease, and brain ischemia [27]. Furthermore, ginseng is generally recognized as safe (GRAS) by the FDA [19].

Ginseng is frequently delivered in dried or steamed form because it degrades quickly when it is fresh [27]. Peak plasma concentrations are reached around 4 hours after oral administration [28], and pharmacokinetic studies in rabbits have shown that certain ginsenosides have half-lives ranging from 0.8 to 7.4 hours, while longer-acting ginsenosides have elimination half-lives ranging from 19 to 21 hours. Thus, discontinuation should occur at least 24 hours [28,29]. Ginseng is most effective when taken in doses of 0.5 to 2g of dried ginseng root for short-term use and 1g for long-term use, which corresponds to approximately 200 to 600 mg of extract [30]. There are some known side effects of ginseng use, including headaches, diarrhea, blood pressure changes, skin irritations, and vaginal bleeding [19].

Ginseng has long been used in Korean medicine to reenergize the body and mind, delay aging, and boost vitality and strength. Several compounds in ginseng (Table 1) have been used for SM mass regulation. In particular, ginsenoside Rg1, a major component of *P. ginseng*, has been shown to have an anti-inflammatory effect on human SM during exercise [31]. *P. ginseng* is broadly categorized as raw, red, white, or black. The main contents of ginseng are ginsenosides, flavonoids, phenols, polysaccharides, and steroids [32]. *P. ginseng* has a number of beneficial pharmacological and physiological effects on chronic fatigue [21], cancer [33], hypertension [34], diabetes [35], obesity [36], cardiovascular diseases and stroke [37], sarcopenia [38,39], muscle-wasting conditions [40], muscle

Table 1
Therapeutic application of different ginseng compounds in skeletal muscle management/improvement

Ginseng	Types/condition	Components (molecular formula)	Upregulation	Downregulation	Models	References
Ginsenosides	Protopanaxadiol (PPD)	20(R)-ginsenoside Rh2 ($C_{36}H_{62}O_8$)	Akt1/PKB phosphorylation	cyclin-dependent kinase inhibitor 1B (p27Kip1)	C2C12 Murine myoblasts	[42]
		Ginsenoside Rb1 ($C_{54}H_{92}O_{23}$)	Akt/mTOR signaling	TNF-α and IL-6	C2C12 myoblasts,	[43]
		Ginsenoside Rb1 ($C_{54}H_{92}O_{23}$)	Akt/mTOR signaling pathway, myogenin, MyoD	———	C2C12 myoblasts,	[43]
		Ginsenoside Rb1 ($C_{54}H_{92}O_{23}$)	———	TNF-α and IL-6	C26-induced cancer cachexia model	[44]
		Compound K ($C_{38}H_{47}N_5O_5$)	Myogenin, MyoD, Akt and p38 phosphorylation	Atrogin1, MuRF1, and MSTN	Mouse SM C2C12	[40]
		Ginsenoside Rb1 ($C_{54}H_{92}O_{23}$)	Akt/mTOR Signaling, myogenin	Atrogin-1	C2C12 myoblasts	[45]
	Malonylginsenosides	Ginsenoside Rd ($C_{48}H_{82}O_{18}$)	———	STAT3 phosphorylation, Atrogin-1, MuRF-1, and myostatin	C2C12 myoblasts	[46]
	Protopanaxatriol	Ginsenoside Rg1 ($C_{42}H_{72}O_{14}$)	Akt/mTOR signaling	MuRF-1 and atrogin-1	C2C12 muscle cells	[47]
Ginseng extract	Fresh ginseng	Mountain ginseng	Increase diameter of myotubes, MyHC, HSP90, p-Akt, and follistatin	MuRF1, atrogin1 and myostatin	Rat myoblast (L6) cells	[48]
	Red Ginseng	Ginsenoside Rg3 ($C_{42}H_{72}O_{13}$)	Akt/mTOR activation	inhibits the production of mitochondrial ROS	C2C12 cells	[45]
		Ginsenoside Rb2 ($C_{53}H_{90}O_{22}$)	Akt/mTOR activation	———	C2C12 myoblasts	[43]
	Black ginseng	Ginsenoside Rh4 ($C_{36}H_{60}O_8$) Ginsenoside Rg5 ($C_{42}H_{70}O_{12}$)	Akt/mTOR/p70S6K activation	———	C2C12 cells	[49]
Mountain ginseng			———	atrogin1	L6 rat	[48]
Korean Red Ginseng			increased amount of lysosomal β-galactosidase	———	C2C12 myoblasts	[38]

aging, and cancer cachexia (CC) [41]. Based on a review of the literature, we provide an overview of the effects of ginseng components on SM-related disorders such as atrophy, sarcopenia, cachexia, and obesity.

2. Use of ginseng as a treatment for muscle atrophy

Imbalance between protein synthesis and breakdown is the main cause of muscle atrophy (Fig. 1), and results in reductions in SM fiber size and mass [50] and is associated with several diseases and conditions, such as aging, fasting, metabolic disorders, and cancer [51]. Dexamethasone (DEX), a synthetic glucocorticoid, causes muscle atrophy as a side effect because it downregulates MYOG and increases the synthesis of myostatin (MSTN), which prevents myogenesis. MSTN is mainly responsible for downregulating the proliferation and differentiation of MSCs and thus inhibits muscle mass development [52,53]. In this context, ginseng has been reported to protect against muscle atrophy in mice, rats, and C2C12 myotubes [54,55]. Ginsenoside Rg1 (Table 2) was found to prevent muscle protein degradation in C2C12 myotubes via the AKT/mTOR/FoxO signaling pathway [47] and to prevent myotube atrophy by activating the Akt/mTOR pathway [56]. L6 cells (rat myoblast cell) were differentiated for 7 days, and the myotubes obtained were treated with mountain ginseng (30% ethanol extract) and DEX (20 nmol/L for 12 h). DEX significantly decreased L6 cell numbers, and mountain ginseng treatment significantly increased myotube diameters versus DEX-treated cells. Mountain ginseng treatment also increased myosin heavy chain (MyHC) levels in differentiated myoblasts [48], whereas DEX reduced MyHC levels [57]. The expression of MSTN was higher in DEX-induced L6 cells than in non-treated controls. The treatment with mountain ginseng inhibited this effect. In L6 cells, a 30% ethanol extract (0.2 or 1.0 mg/mL) of mountain ginseng significantly reduced the expressions of MuRF1 (muscle ring-finger protein-1) and atrogin1 [48], which are both transcriptionally upregulated under atrophic conditions [58]. Overall, the increased expressions of MuRF1, atrogin1, and MSTN by DEX were attenuated by mountain ginseng.

SM mass is highly regulated by Akt/mTOR signaling (Fig. 2) initiated by IGF-1 to IGF-1R binding [59], which is responsible for hypertrophy through protein synthesis. Ginsenoside Rg1-treated C2C12 cells form larger myotubes than the control. Ginsenoside Rg1 at 10nM was also reported to enhance myotube thickness by up to 2.45-fold [56]. The roles played by Ginsenoside Rg1 in SM management are shown in Table 2.

3. Use of ginseng in sarcopenia

Age-related progressive loss of SM mass, strength, and function is termed sarcopenia [60]. Denervation, mitochondrial dysfunction, inflammatory processes, and hormonal changes are some of the pathophysiological processes believed to be involved in sarcopenia and may cause falls, functional decline, frailty, and mortality due to loss of lean body mass [61,62]. Decreases in MSC and type II muscle fiber numbers and intramuscular and intermuscular fat infiltration are the main causes of cellular changes in sarcopenic muscles. MSC functional decline in sarcopenic SM is due to alterations in MSC niche factors and MYOG, which induces myogenesis. In addition, MSTN is also responsible for SM deterioration [53,63,64]. Several biomarkers of sarcopenia have been reported, namely, follistatin (mediates muscle growth by suppressing MSTN and activin A) [65], growth and differentiation factor 15 (GDF-15) [66], sex hormone binding globulin (responsible for the transport and activation of sex hormones) [67], and Troponin T (a muscle injury marker) [68]. In adults, obesity occurs in parallel with age-related muscle mass loss (sarcopenia), which results in a syndrome called "sarcopenic obesity" [69]. Korean Red Ginseng (KRG) has been shown to have beneficial effects on aging, insulin resistance, dyslipidemia, inflammation, and cancer [70–72], and was reported to increase follistatin levels significantly. In one study, KRG was administered to female patients aged over 55 for 24 weeks and increased

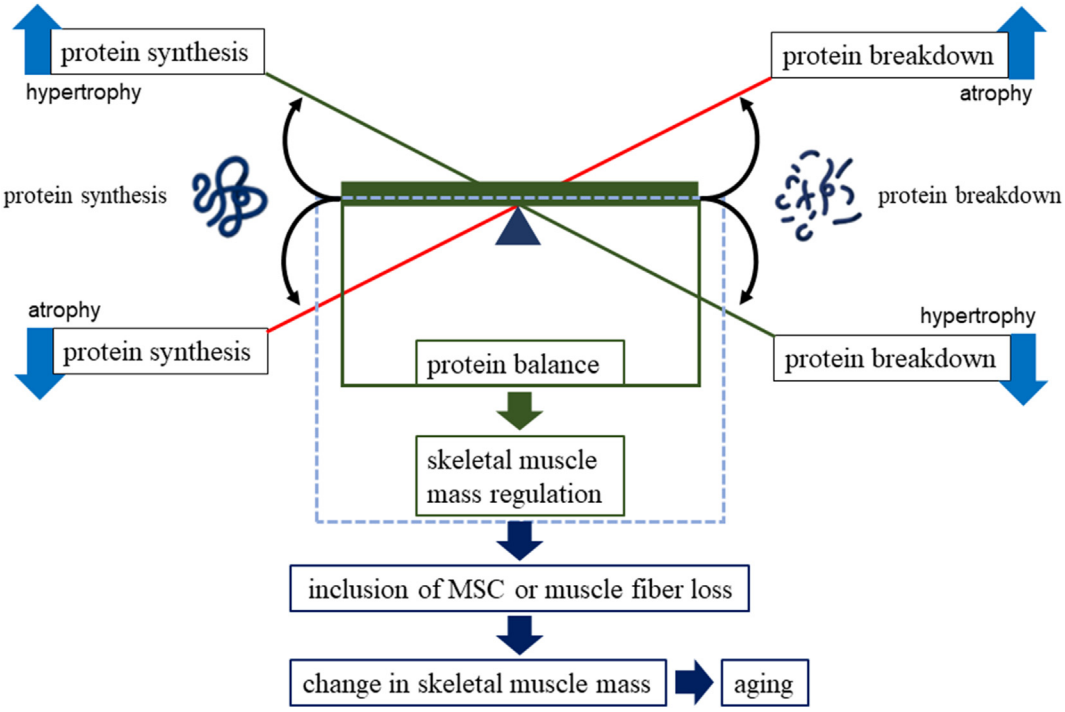
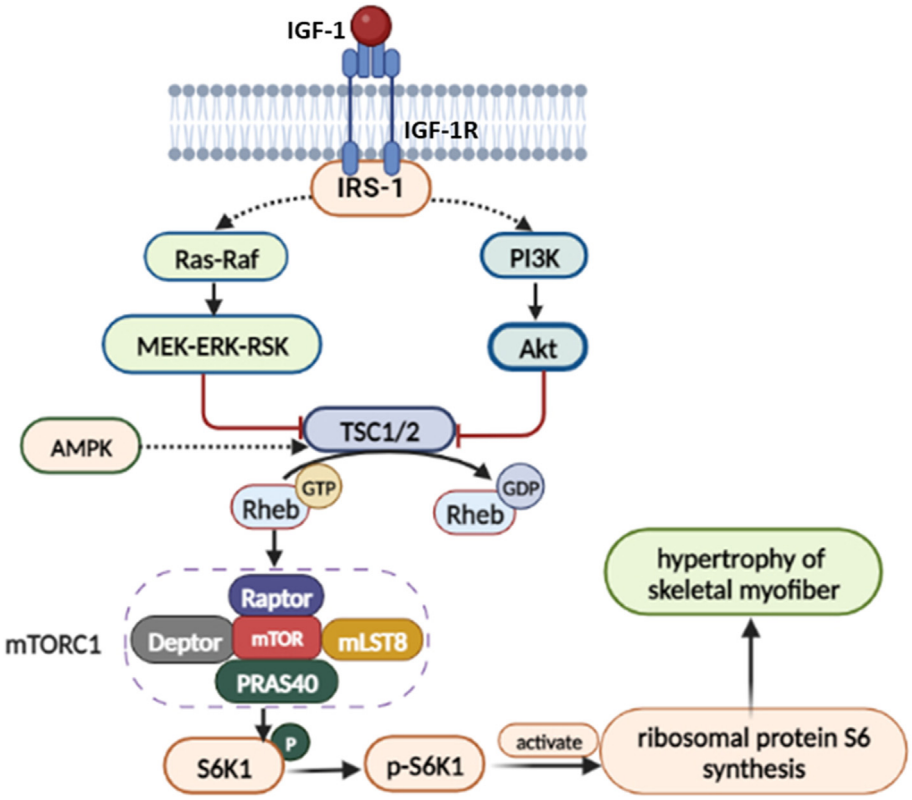


Fig. 1. Skeletal muscle management via protein synthesis and degradation. Protein synthesis is primarily responsible for hypertrophy, whereas protein degradation is a cause of muscle atrophy.

Table 2
Therapeutic Application of ginsenoside Rg1 in skeletal muscle management

Compounds name	Activity	Mode of action	References
Ginsenoside Rg1	prevents muscle protein degradation	regulating Akt/ mTOR/FoxO signaling in C2C12 myotubes	[47]
	prevents myotube atrophy	through activating the Akt/mTOR pathway	[56]
	C2C12 cells viability increase	MuRF-1 and atrogin1 expression inhibited	[47]
	upregulates promyogenic kinases (Akt)	myoblast differentiation and myotube growth enhanced	[56]
	conversion of embryonic fibroblasts into myoblasts enhanced	prevention of muscle atrophy	[56]



IGF-1: Insulin-like growth factor 1; IGF-1R: Insulin-like growth factor type 1 receptor; IRS-1: Insulin receptor substrate-1; PI3K: Phosphatidylinositol 3-kinase; TSC1/2: Tuberous sclerosis complex1/2; AMPK: AMP-activated protein kinase; mTORC1: Mammalian target of rapamycin complex 1; S6K1: Ribosomal protein S6 kinase B1

Fig. 2. The IGF-1 dependent mTOR pathway of protein synthesis. IGF-1 is a well-known stimulator of mTOR for muscle growth and regeneration. Binding of IGF-1 to its receptor (IGF-1R) results in the activation of insulin receptor substrate-1 (IRS-1), which is responsible for the activation of the Ras-Raf-MEK-ERK pathway. TSC1/2 is phosphorylated by Akt, which inhibits the GTPase-activation of small G protein Rheb. GTP-bound Rheb activates mTORC1, resulting in S6K1 phosphorylation, which promotes protein synthesis by activating ribosomal protein S6 leading to hypertrophy of skeletal myofibers.

follistatin and significantly decreased GDF-15 levels [72]. Red ginseng was also found to reduce troponin T1 and T3 levels, which suggested its possible use for treating sarcopenia [72]. In addition, treatment of C2C12 cells with black ginseng (BG) activated MyoD by triggering Akt to facilitate the heterodimerization of MyoD and E proteins. This subsequently promoted the expressions of major histocompatibility complex (MHC) and MYOG to promote myoblast differentiation and the formation of multinucleated myotubes [49]. Moreover, BG extract delayed muscle atrophy in T2D by activating the Akt/mTOR/p70S6K signaling and stimulating SM protein synthesis [73]. These findings suggest that KRG promotes the upregulations of sarcopenia biomarkers such as follistatin and downregulates MSTN.

4. Use of ginseng in cachexia

Cachexia is a wasting syndrome allied with chronic disease (cancer, chronic heart disease, renal failure, and autoimmune diseases) and characterized by body and SM weight losses and white adipose tissue dysfunction. Cachexia is most common in advanced cancer patients [74,75], and cancer cachexia (CC) affects ~50-80% of cancer patients and is responsible for nearly one-fifth of cancer-related deaths [76]. Furthermore, CC is associated with a variety of cytokines, such as interleukins, interferons, and TNFs. TNF-α and IL-6 are two important cytokines and are responsible for proteolysis and energy expenditure [77]. Presently, no treatment is available for CC, but patients have been treated using complementary and alternative medicines [78]. Therefore, researchers are interested in traditional therapies based on natural compounds, and *P. ginseng* offers a means of overcoming immunomodulatory issues, which have noteworthy adverse effects on physical strength [79]. Furthermore, ginsenosides Rg1, Rg3, Rh2, Re, and Rb1 have strong immunoregulatory, anticancer, anti-inflammatory, and antioxidant effects. In particular, ginsenoside Rb1 has been reported to reduce TNF-α and IL-6 levels in a rat model of cancer-induced bone pain [80] and to inhibit intestinal ischemia/

reperfusion injury inductions of TNF-α and IL-6 in rats [81]. These observations suggest some ginseng compounds might be useful in cachexia by reducing elevated TNF-α and IL-6 levels.

5. Use of ginseng in the obesity

Obesity is a metabolic disorder characterized by excessive fat accumulation caused by an energy intake versus expenditure imbalance [82]. WHO reported that rates of overweight and obesity among adults worldwide increased almost threefold between 1975 and 2016, that ~70% of American adults are obese, and that the prevalence of obesity in Europe is likely to exceed 20% by 2025 [83,84]. Several diseases, such as dyslipidemia, insulin resistance, and diabetes mellitus, and other metabolic disorders, are strongly associated with obesity (Fig. 3), and inflammation is thought to be the primary mechanism [82]. Fat accumulation triggers the productions of pro-inflammatory mediators (TNF-α and IL-6), which reduce the secretion of adiponectin, a hormone that regulates

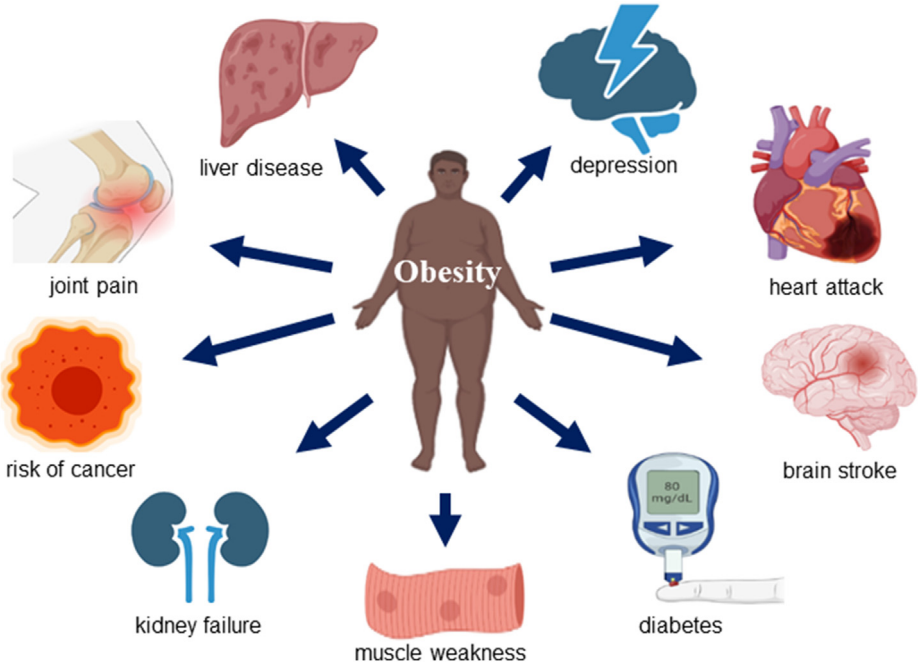


Fig. 3. Obesity-associated diseases.

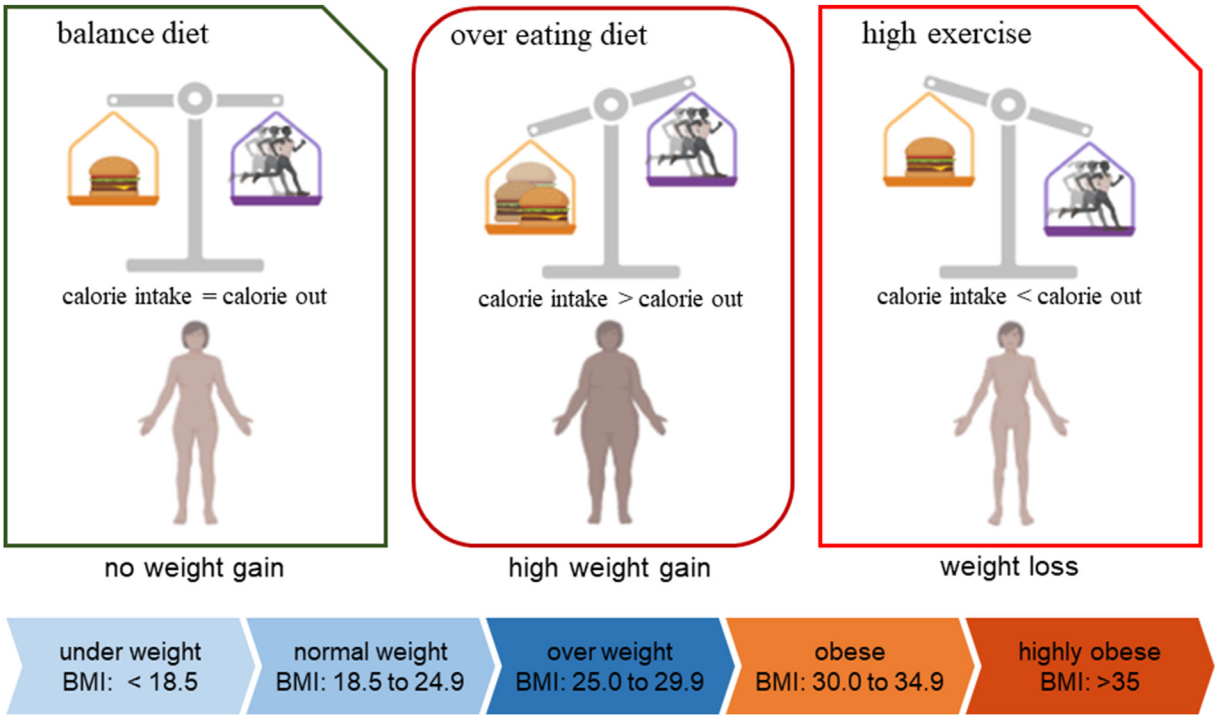


Fig. 4. The balance between calorie intake and exercise. BMI ranges used to categorize individuals as normal or obese.

Table 3
Therapeutic use of ginseng Compounds in obesity management

Compounds name	Targeted pathway	Function	Cell line/ models	References
Ginsenoside Rh2	PPARγ inhibition	inhibited adipocyte differentiation	cell culture systems	[92]
Ginsenoside Rh2	activate AMPK	anti-obesity	3T3-L1	[92]
Ginsenoside Rb1 and Rg1	activate PKA	reduced the triglyceride accumulation	3T3-L1	[93]
Ginsenoside Rb1 and Rg1	activation of phosphatidylinositol-3 kinase	insulin-stimulated glucose uptake was enhanced	———	[93]
Ginsenoside Rb1	regulate PPARγ	facilitate adipogenesis	3T3-L1	[94]
Ginsenoside Rg3	PPARγ inhibition and activate AMPK	anti-obesity	3T3-L1	[95]
Ginsenosides K and Rg1	GLUT4 translocation	significantly enhanced glucose uptake	3T3-L1	[96]
Ginsenoside Rh2	Activation of glucocorticoid receptor	promote preadipocytes differentiation	3T3-L1	[97]
fermented red ginseng	mRNA expressions of IR, GLUT1, GLUT4, PPAR-γ, in the liver and muscle were increased	improving insulin sensitivity, reducing body weight in old-aged ob/ob mice	old-aged, obese, leptin-deficient (B6.V-Lepob, "ob/ob") mice	[98]
Korean red ginseng	increased phosphorylation of IR, IRS-1, and Akt	antidiabetic and anti-obesity effects	Sprague-Dawley (SD) rats	[99]
Panax ginseng berry extract	activation of PI3K/Akt pathway	attenuated both obesity and sarcopenia	C57BL/6 mice	[100]

glucose and fatty acid metabolism [82]. Furthermore, weight gain and obesity were found to reduce serum adiponectin levels [85]. In addition, age-associated SM mass loss is connected with metabolic changes that trigger the development of obesity [86]. Dietary intake and lifestyle management are commonly used to manage obesity [87], and body mass index (BMI) measurements provide the easiest means of differentiating obese and normal conditions (Fig. 4). The beneficial effect of KRG on obesity has been demonstrated by human, animal, and *in vitro* studies [36]. KRG was found to downregulate triacyglycerol- and cholesterol synthesis, stimulate fatty acid oxidation and low-density lipoprotein clearance, and improve glucose uptake [36]. Furthermore, ginseng extract exhibited anti-hyperglycemic and anti-obesity effects in diabetic rodents (ob/ob and KKAy mice) [88,89]. MSTN acts as a negative regulator of SM mass and a potential therapeutic target for the treatment of obesity [90], and in high-fat diet (HFD) fed mice, MSTN inactivation reduced fat accumulation [91]. Overall, ginseng and its constituent compounds (Table 3) have been consistently reported to have beneficial effects on obesity and its associated diseases.

6. Conclusion

The world's population is aging rapidly at an alarming rate, and aging is associated with SM deterioration and muscle atrophy. Ginseng and several of its compounds, especially Korean red ginseng and ginsenoside Rg1, have been shown to suppress SM atrophy, increase SM mass, muscle fiber size, and exercise capacity, and reduce sarcopenic obesity. Therefore, we suggest clinical trials be undertaken to confirm the treatment efficacies of ginseng and its active compounds on atrophy, sarcopenia, cachexia, and obesity in the hope that they may prove to be potent in the treatment of SM-related disorders.

Acknowledgments

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