Journal of Ethnic Foods

REVIEW ARTICLE

Open Access

Soybean isoflavones potentially prevent sarcopenia: a systematic review

Sang-Yeob Lee[1,2] and Jun-Il Yoo[3*]

Abstract

Background Soybean is an important food resource that has been used for centuries in Korean cuisine. Soybean is considered a good source of protein and a nutritional powerhouse. Isoflavone, one of the components of soybean, has been investigated for its nutritional role and physiological effects. As soybean can supply sufficient proteins for muscle and soybean isoflavone might have a direct effect on muscle, soybean could be a potential nutritional treatment for muscle atrophy. However, the effect of isoflavone on muscle atrophy is controversial.

Methods Four in vitro studies and four in vivo studies were selected from the literature to determine the potential capacity of isoflavones as preventers of sarcopenia.

Results In vitro and in vivo studies, there have been studies that isoflavone extracted from soybean is effective in preventing muscle atrophy. Research on soybean isoflavone and muscle loss included in this study showed that soybean isoflavone may prevent myotube atrophy by blocking the expression of MuRF1 or by regulating androgen receptors. Isoflavone has been shown to increase the diameter of myoblasts and increase muscle mass.

Conclusion The present study showed the potential of soy isoflavones as a preventer of sarcopenia by preventing muscle loss.

Keywords Soybean, Isoflavones, Genistein, Daidzein, Sarcopenia

Introduction

Rich flavors, vivid colors, and distinctive culinary traditions are hallmarks of Korean food. One of the Korean foods is soybean, which has played a pivotal role in shaping Korean cuisine for centuries reflecting both nutritional and cultural value [1]. They have been developed in a variety of fermented items, including sauces and pastes [2].

In Korean cuisine, soybean serves to enhance flavor. One of the most well-known examples is a soy sauce called Kanjang. Kanjang is a crucial ingredient in Korean cooking because it gives dishes a savory depth of flavor and a distinct umami flavor. Doenjang, a different fermented soybean paste, is additionally used as a foundation for soups and stews adding a potent umami flavor that enhances the flavor profile of these foods [1].

Korea is also considered the origin of soybean. This is because wild soybeans, medium soybeans, and cultivated soybeans grow in one place in the Korean Peninsula and Manchuria, and carbonized soybeans, the remains of soybeans, have been consistently excavated from the Korean Peninsula from the Neolithic Age to the Bronze Age [3]. This indicates that not only were soybeans being grown, but they had also spread to the point where Koreans were eating food made with them [4]. As a result, Korea could

*Correspondence:
Jun-Il Yoo
furim@daum.net
[1] Department of Biomedical Research Institute, Gyeongsang National University Hospital, Jinju, South Korea
[2] Department of Theriogenology and Biotechnology, College of Veterinary Medicine, Gyeongsang National University, Jinju, South Korea
[3] Department of Orthopaedic Surgery, Inha University Hospital, 27 Inhang-Ro, Jung-Gu, Incheon, South Korea

© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

create meals made from soybeans like tofu, Doenjang, and Kanjang since ancient times [5].

Soybean is considered a nutritional powerhouse as it contains dietary fiber, vitamins, and minerals, including iron, calcium, and B vitamins [6]. The composition of general soybean seeds is carbohydrates (31.7–31.85%), proteins (32–43.6%), fat (15.5–24.7%), water (5.6–11.5%), crude ash (4.5–6.4%), neutral detergent fiber (10–14.9%), and acid detergent fiber (9–11.1%) [7]. Isoflavone, one of the components of soybean, has been investigated for its nutritional role and physiological effects [8]. Isoflavones have a limited natural distribution. They are only found in physiologically meaningful concentrations in soybeans and foods derived from this legume among regularly consumed foods [9]. Isoflavones including the 3 aglycones genistein (4',5,7-trihydroxyisoflavone), daidzein (4',7-dihydroxyisoflavone), and glycitein (7,4'-dihydroxy-6-methoxyisoflavone) are found in about 25 mg per serving of traditional soy foods (Fig. 1) [10, 11].

Isoflavones have a phenolic ring with agonistic and antagonistic effects on the estrogen receptor (ER) α and ERβ [12, 13]. There have been concerns raised about the potential negative consequences of soy consumption on men, such as feminization and infertility [14, 15]. Isoflavones have nongenomic effects that regulate a variety of intracellular signaling cascades in addition to estrogen receptor binding [16]. Isoflavones also may alter the activity of enzymes involved in hormone production and metabolism [17]. Therefore, isoflavone has been considered as having the potential to be a natural alternative to conventional hormone therapy for postmenopausal women [18].

There are 12 soybean isoflavone isomers belonging to three aglycones of different conjugated forms (β-glucoside, acetylglucoside, and malonylglucoside): genistein, daidzein, and glycitein [19]. Abundantly present in soy products, they are well known for their estrogenic action. Isoflavone might have a direct influence on muscle by structurally and weakly binding affinity for estrogen receptor (ER), which is 100–1000 times lower than estradiol [20, 21]. In both smooth and skeletal muscle cells, ERs have been measured [22]. It has been demonstrated that estrogen can decrease skeletal muscle energy loss and improve cell membranes [23]. Therefore, isoflavones can bind to and transactivate estrogen receptors. They have molecular structures comparable to estrogen [24]. The study of Ji et al. [25] has shown that genistein can limit L8 myoblast proliferation, fusion, and myotube protein synthesis. In contrast, the study of Pan et al. [26] has demonstrated that genistein, daidzein, and glycitein can inhibit smooth cell proliferation.

Sarcopenia is a muscle atrophy caused by the loss of muscular mass, strength, and function that occurs as people age [27]. Muscle atrophy is caused by a decrease in protein synthesis and an increase in proteolysis [28]. Because muscle is an endocrine organ, muscle atrophy of sarcopenia is directly involved in metabolic disease. Decreased secretion of sex hormones such as estrogen

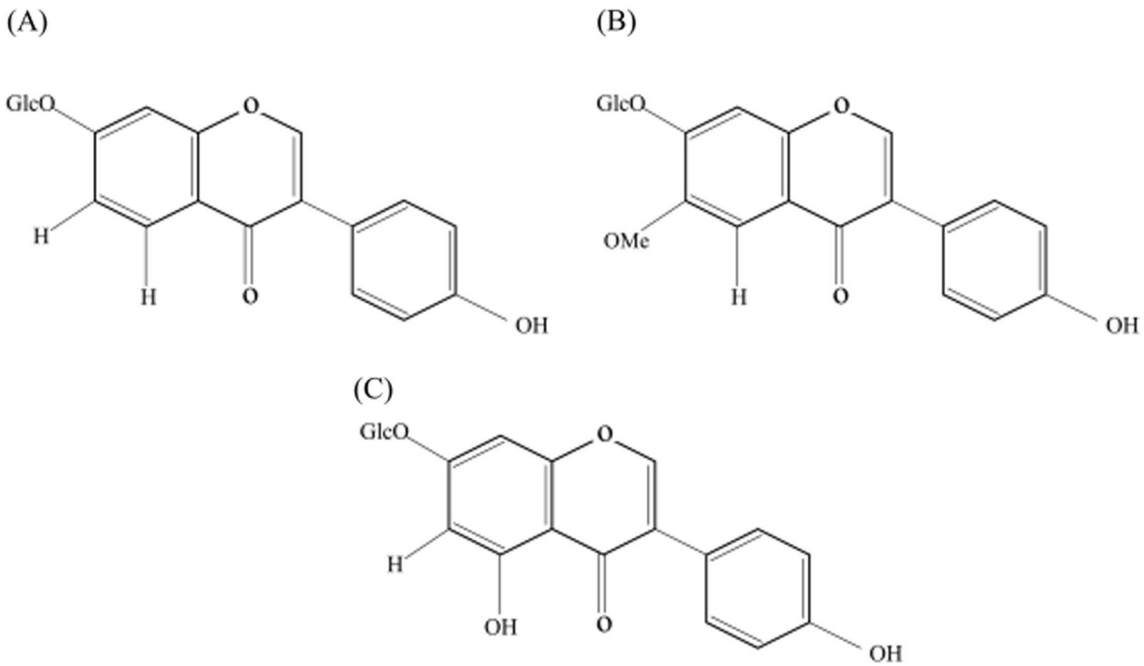

Fig. 1 Structure of isoflavone. **A** Daidzin; **B** Glycitin; **C** Genistin. Glc = Glycoside

and testosterone is related to skeletal muscle loss [29, 30]. Intake of soybean isoflavone might be a potential nutritional treatment for muscle atrophy as soybean isoflavone has a capacity toward estrogen receptors (ERs). As soybean can supply sufficient proteins for muscle and soybean isoflavone might have a direct effect on muscle, soybean could be a potential nutritional treatment for muscle atrophy. However, the effect of isoflavone on muscle atrophy is controversial.

Soybeans and Soybean isoflavones have been studied for their potential role in preventing the age-related muscle loss associated with sarcopenia. Overall understanding of the relationship between soybean isoflavones and muscle loss could develop the potential usability of Korean soybean. This study systematically reviews the previous in vitro and in vivo studies in determining the effect of soybean isoflavone on muscle. Four in vitro and four in vivo studies were selected for the present systematic review.

Materials and methods

The literature search was conducted in PubMed/MEDLINE database to identify relevant studies. The search was carried out between January 1st, 2005 and September 30th, 2021. This study used the following search terms: ("soybean s"[All Fields] OR "soybeans"[MeSH Terms] OR "soybeans"[All Fields] OR "soybean"[All Fields]) AND ("muscle, skeletal"[MeSH Terms] OR ("muscle"[All Fields] AND "skeletal"[All Fields]) OR "skeletal muscle"[All Fields] OR ("skeletal"[All Fields] AND "muscle"[All Fields])). MeSH (Medical Subject Headings) serves as the National Library of Medicine's controlled vocabulary thesaurus, used for indexing of articles for PubMed. The terms in [] are commands to search the relevant area (or term). [MeSH Terms] is a command to perform a search in the MeSH area, and [All Fields] is a term to search in all saved areas of the paper without limitation. A total of 463 articles were identified from the database (Fig. 2), and 352 articles were removed by title and abstract screening. After the full-text screening, 85 articles that have no relation to soybean and skeletal muscle were also removed. 18 records were excluded additionally because they did not describe detailed application methods for soybean or isoflavones and failed to provide sufficient data for muscle atrophy. Finally, 8 unique articles were included in the present study (Fig. 3).

Additionally, we sorted out articles that included content about the association of soybean isoflavone with muscle change. Articles were divided into two groups: a group of in vitro studies and a group of in vivo studies.

Results and discussion

In vitro studies

Four in vitro studies about the association of soybean isoflavone with muscle change were included (Table 1) [28, 31–33]. According to the study of Jones et al. [31], soy isoflavones including genistein, daidzein, glycitein are associated with endogenous estrogens. In that study, a proliferation of Rat L6 myogenic cells was inhibited by a supplement with genistein. Additionally, genistein, daidzein, and glycitein slightly stimulated protein synthesis. Genistein, which has the capacity

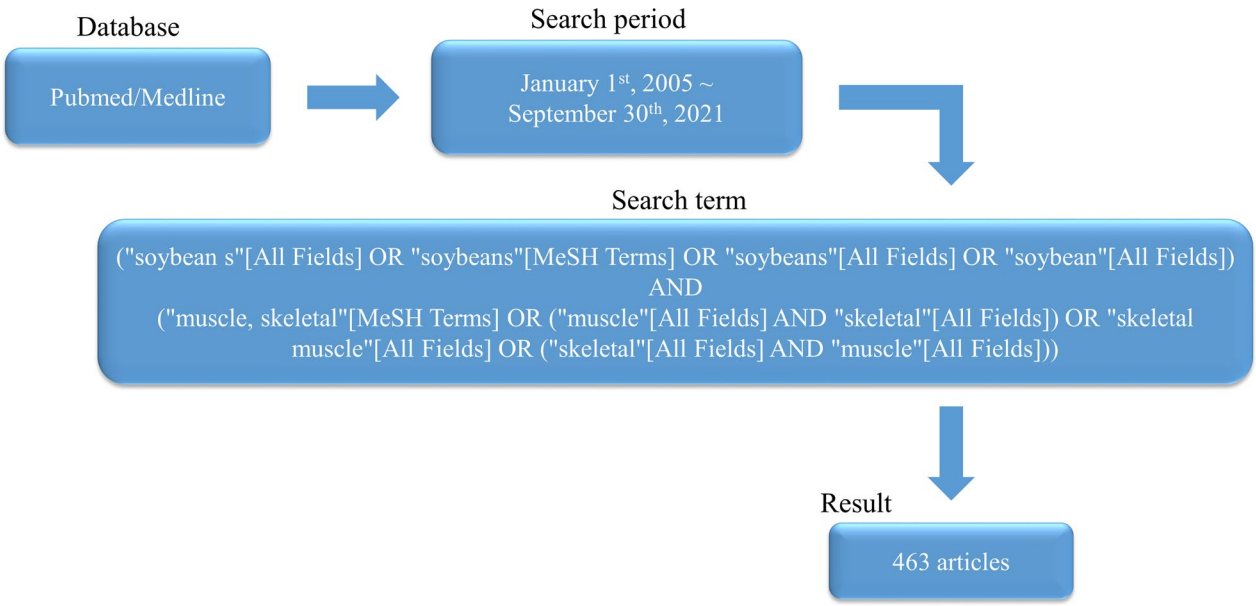

Fig. 2 The results obtained from the PubMed/Medline search

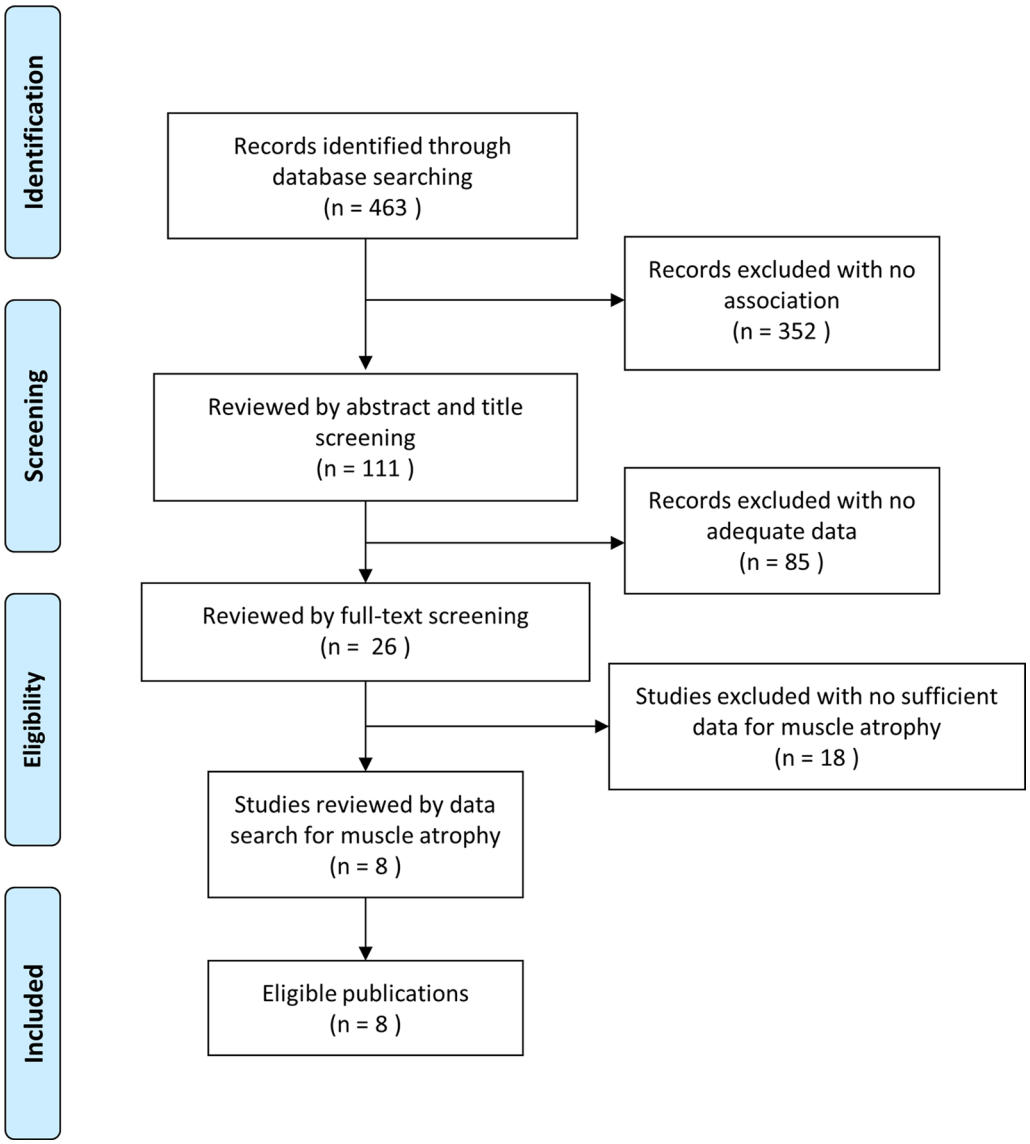

Fig. 3 Flowchart of literature selection process

as an inhibitor of receptor tyrosine kinase, could affect cell growth [34]. Genistein might be involved in the cell cycle by inhibiting tyrosine kinases, which could affect the mitosis-promoting factor complex. This could obstruct the cell cycle, thus inhibiting proliferation [34]. Compared to genistein, other isoflavones such as daidzein and glycitein might not have as strong affinity for ER binding sites. For binding to the ER, genistein competes with E2, preferring estrogen receptor α (ERα) over estrogen receptor β (ERβ). In addition, it has been observed that glycitein has little influence on muscle cell proliferation [24]. As ERs in skeletal muscle cells have not been precisely characterized, the present study could contribute to the understanding of whether the response of one ER is more prevalent than that of another receptor.

The study of Hirasaka et al. [28] showed that myotube atrophy induced by TNF-α could be blocked by genistein and daidzein. These isoflavones could inhibit muscle RING-finger protein 1 (MuRF1) promoter activity which is stimulated by TNF-α inflammatory cytokines. They also reported that genistein and daidzein could induce the phosphorylation of AMP-activated protein kinase (AMPK) in C2C12 myotubes. AMPK has been demonstrated to be able to indirectly activate SIRT1 by increasing intracellular NAD+levels [28]. This suggests that inhibitory effects of isoflavones are mediated not just by estrogen receptor-mediated activation of sirtuin

Table 1 In vitro studies about the influence of soybean isoflavone on muscle

References	Cell lines used in research	Type of soybean or isoflavones	Model of test	Results	Discussion
Jones et al. [31]	Rat L6 myogenic cell lines	Genistein, daidzein, glycitein	Experiments examined cell proliferation and cell protein synthesis stimulation or inhibition The media for cell proliferation experiment consisted of DMEM with FBS supplemetned with insulin, estradiol, genistein, daidzein and glycitein, at 0, 0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 5, 10, or 20 uM concentration The media for cell protein synthesis consisted of DMEM with 2% FBS alone or supplemented with 1uM insulin, 1 uM estradiol, 1 uM genistein, 1 uM daidzein, 1 uM glycitein, or 0.1 uM dexamethasone	Genistein and estradiol inhibit cellular proliferation at a concentration of 5uM and greater Daidzein and glycitein showed no significant difference compared with the control Genistein, daidzein, and glycitein slightly stimulated the protein synthesis, but there were no significant effects	Soy isoflavones may potentially modulate growth and development in humans and animals who consume soy-based products
Hirasaka et al. [28]	TNF-α treated atrophied C2C12 myoblastic cell	Genistein, daidzein	TNF-α (10 ng/mL) treated atrophied C2C12 myoblastic cells were transfected with pGL3-MuRF1 promoter and pRL-TK and cells were treated with 100 uM of isoflavones (genistein and daidzein)	Genistein and daidzein blocked TNF-α induced myotube atrophy	TNF-α treatment resulted in a decreased myotube thickness and upregulated MuRF1 promoter activity Inhibitory effect of Isoflavones (genistein and daidzein) in upregulated MuRF1 promotor blocked TNF-α induced myotube atrophy
Saneyasu et al. [32]	C2C12 myoblasts	Soyaflavone RS extract (SRE), Soybean meal extract (SME), Soybean-germ protein extract (SGE)	Soybean meal: defatted soybean, protein content about 45% Soybean-germ protein: protein content about 65% Soyaflavone RS: Roasted soybean-germ powder, protein content about 40% C2C12 cells were treated with SRE, SME, SGE at 1 mg/ml as protein concentration. And gene expressions of MyH7, MyH2, MyH1, MyH4 were measured by PCR	SRE upregulated MyH7 and downregulated MyH4 SME upregulated Myh7 and downregulated Myh4 and Myh1 SGE upregulated Myh7	The soybean protein cause the increase of Myh7 which is slow-type myosin heavy chain

Table 1 (continued)

References	Cell lines used in research	Type of soybean or isoflavones	Model of test	Results	Discussion
Zheng et al. [33]	C2C12 myotubes	Soy extract (SoyEx)	SoyEx: 5.3 mg/g genistein, 10.4 mg/g daidzein, 3.2 mg/g glycitein C2C12 Myotubes were incubated for 48 h in the presence of SoyEx (0.0005–50 µg/mL), E2 (1 or 10 nM), antiestrogen ZK191703 (1 µM), AR antagonist DHT (1 µM), flutamide (1 µM), genistein (0.001 µM), daidzein (0.0021 µM), glycitein (0.0006 µM), or control (0.1% DMSO only) The diameter of C2C12 myotubes, IGF-1 mRNA expression, IGF-1R mRNA expression, and MuRF1 mRNA expression was measured	The effect of 48 h SyoEx treatment significantly increased myotube diameter at the concentration of 0.05 ug/mL The increased diameter induced by the treatment of either E2 or SoyEx for 48 h was antagonized by an antiestrogen ZK191703 IGF-1R expression was increased by E2, SoyEx, and genistein in C2C12 myotubes	SoyEx increases the diameter of C2C12 myotubes Isoflavone aglycones from SoyEx induce anabolic effects on C2C12 myotubes by binding to ER and increasing IGF-1. Among the tested aglycones, genistein seems to have the strongest anabolic bioactivity

1 (SIRT1), but also by additional routes that activate AMPK phosphorylation in C2C12 myotubes.

In mammals, skeletal muscle is made up of four types of fibers, including oxidative slow-twitch type I, oxidative fast-twitch IIA, glycolytic fast-twitch IIB, and IIX/D [35]. In these types of fibers, the isoform of myosin heavy chain (MyHC) is expressed. Saneyasu et al. [32] have shown that soy isoflavones can increase Myh7, which is a slow type of myosin heavy chain in C2C12 cells. According to their study, roasted soybean-germ powder (containing 40% protein), soybean meal (containing 45% protein), and soybean-term protein (containing 65% protein) upregulated mRNA expression levels of MyH7 in C2C12 myotubes [32]. In contrast, mRNA levels of Myh4, a fast-type myosin heavy chain, were decreased by isoflavone. Their study also showed that soy isoflavones extracted from soybean-germ could significantly increase MyHC1, which is encoded by Myh7 in the extensor digitorum longus. These results show that isoflavone is closely related to muscle fiber.

Zheng et al. [33] have shown that soy extract (5.3 mg/g genistein, 10.4 mg/g daidzein, 3.2 mg/g glycitein) can increase the diameters of C2C12 myotubes. According to their study, isoflavone aglycones, especially genistein, can induce anabolic effects on C2C12 myotubes by binding to ER and increasing insulin-like growth factor 1 (IGF-1). Many studies have demonstrated that inactivation of IGF-1 can inhibit muscle growth by reducing muscle fiber number and size [36, 37]. IGF-1 is also known to be able to increase muscle mass by decreasing MuRF1. MuRF1 is a muscle-specific ubiquitin ligase that is thought to play a role in muscle atrophy [38]. Therefore, isoflavones of soy extracts can affect muscle fiber via IGF-1, not directly by regulating MuRF1 gene expression.

In vivo studies

There are four in vivo studies about the association of soybean isoflavone with muscle change (Table 2) [27, 39–41]. The study of Kataoka et al. [39] concluded that the soy germ protein concentrate diet (SGPC group) could enhance muscle hypertrophy than casein diet (C group) for Wistar rats. Weights of the gastrocnemius, plantaris, tibialis anterior, hindlimb muscle, and total hindlimb muscles were significantly higher in the SGPC group than in the C group. The study of Park et al. [27] showed that silk peptide was quickly absorbed, which might have protected against the reduction of grip strength in middle-aged female rats. However, their study was limited to middle-aged Sprague Dawley female obesity rats.

Qiang et al. [41] conducted an experiment with spinal and bulbar muscular atrophy (SBMA) transgenic mice and provided a soy-free diet or identical diet supplemented with genistein. Their results showed that genistein treatment promoted mutant androgen receptor (AR) degradation and increased survival rate, grip strength, and step distance. The study of Kurrat et al. [40] showed that lifelong intake of isoflavone could increase the muscle mass of soleus muscle (M. soleus) and gastrocnemius muscle (M. gastrocnemius) of OVX Wistar rats. As soy isoflavones are known as phytoestrogens, they might cause anabolic effects of estrogens on skeletal muscle mass [42, 43]. Because OVX Wistar rats represent a model of postmenopausal females, soy isoflavones might act as estrogenic compounds to stimulate myosin heavy chain I expression [44]. However, the molecular mechanisms of growing skeletal muscle mass are very complex. More investigation is warranted on growing skeletal muscle mass.

Because the amount of mutant AR is a well-known indicator of SBMA degeneration which is caused by a CAG repeat expansion with the AR gene, downregulation of mutant AR is an important factor for treatment [45, 46]. Studies showed that in an animal model of SBMA, mutant AR was susceptible to genistein treatment, indicating that genistein-mediated down-regulation of mutant AR could reduce motor impairments [45, 46].

Soybean, as a preventive food for sarcopenia

Nutritionally, because sarcopenia is caused by a deficiency in muscle protein, proper protein intake is one of the most important factors in the maintenance of muscle mass [47]. Studies investigating effects of dietary proteins are ongoing [48–50]. Healthy eating with proper protein sources is also important for preventing sarcopenia. Animal-based proteins also have a great ability to enhance muscle protein synthesis and plant-based protein sources are rich in fibers and minerals [51, 52]. Nowadays, excessive consumption of meat and meat products is frequently linked to excessive energy and fat accumulation, resulting in obesity, excess weight, and an increased risk of chronic diseases such as fatty liver disease and type 2 diabetes [53]. Therefore, soybean could be a great protein source for preventing muscle loss associated with aging instead of animal proteins today.

Research on soybean isoflavone and muscle loss included in this study showed that soybean isoflavone may prevent myotube atrophy by blocking the expression of MuRF1 or by regulating androgen receptors. Based on research findings, traditional soybean consumption in Korea may have helped prevent sarcopenia, even if soybean was not utilized exclusively to prevent sarcopenia in the local community.

Table 2 In vivo studies about the influence of soybean isoflavone on muscle

References	Animal used in research	Diet	Study design	Results	Discussion
Kataoka et al. [39]	Wistar rat	Casein (C), Soy protein concentrate (SPC), Soy germ protein concentrate (SGPC)	Rats were divided into three dietary groups (the C, SPC, and SGPC groups) and skeletal muscles of them were measured	The weights of the gastrocnemius, plantaris, tibialis anterior, hindlimb muscle, and total hindlimb muscles were significantly higher in the SGPC group than in the C group	SGPC diet can enhance muscle hypertrophy at higher levels than the C diet
Park et al. [27]	Sprague Dawley female rat (old ~ 12-month-old, young ~ 7-weeks-old)	(1) 0.5 g casein, (2) 0.15 g silk peptides (SPs) plus 0.35 g casein/kg BW/day(Low-SP), (3) 0.5 g SPs/kg BW/day (High-SP)	The skeletal muscle and grip strength of each group were measured	Relative loss of skeletal muscle mass was prevented in both SP groups compared to the Aged-group The Low-SP and High-SP groups exhibited forelimb grip strength similar to the Young-group	SP intake protected against the reduction of LBM and grip strength in middle-aged female rats
Kurrat et al. [40]	Wistar rat	(1) isoflavone(ISO)-free or ISO-rich control diet (CON ISO: 467 mg/kg diet) (2) Western diet (WD) in the absence or presence of ISO (WD ISO: 431 mg/kg diet)	Rats received a control diet in the absence or presence of ISO. female pubs were randomly grouped into either ovariectomized (OVX) group, which were ovariectomized, or intact group without surgery. Animals switched to WD (containing 20% sugar and 23% fat) in the absence or presence of ISO for 12 weeks	In WD OVX groups ISO increased soleus muscle weights by 20% ($p << 0.0001$) when compared to WD OVX	Lifelong ISO exposure increases muscle mass in OVX rats
Qiang et al. [41]	Spinal and bulbar muscular atrophy (SBMA) transgenic mouse	Soy-free diet, an identical diet supplemented with genistein (2.5 g/kg of food)	Treatments with genistein were initiated when mice reached 6 weeks of age and continued until the age of 25 weeks Mice received a soy-free diet or an identical diet supplemented with genistein AR expression in muscle, rotarod behavior, grip strength, and survival rate were calculated	Treatment with genistein diminished mutant AR monomer in the muscle Mice who received genistein exhibited less deterioration than control. And also, genistein increased the survival rate, grip strength, and step distance of SBMA transgenic mice	Genistein treatment promotes the dissociation of AR and thus induces AR protein degradation. Through promoting mutant AR degradation, genistein inhibits neuronal nuclear accumulation of mutant AR in neurons and considerably ameliorates the motor phenotypes in mouse models of SBMA

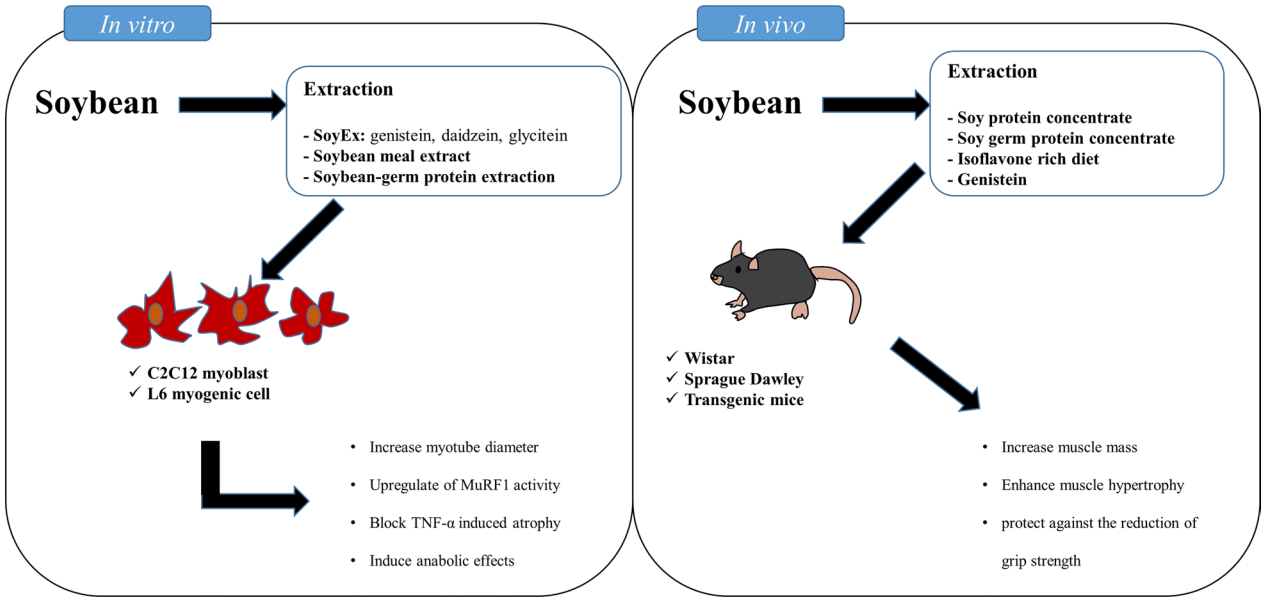

Fig. 4 Overall studies about effect of soybean-derived isoflavone on muscle

Conclusion

The present study showed the potential of soy isoflavones as preventers of sarcopenia by preventing muscle loss. Consumption of traditional soybean food in Korea could potentially help prevent sarcopenia. Overall studies are presented in Fig. 4. According to the results of this study, soybean consumption helps prevent muscle loss. Therefore, consistent consumption of soybean products may prevent muscle mass from decreasing with age. Further studies for the preservation of muscle by modifying the distribution of protein sources are needed to prevent sarcopenia and maintain health at the same time.

Limitations

The present study has several limitations. First, this study did not present remarkably comparable factors among the included studies. Second, the included studies were not enough to suggest other reliable results. More studies of in vitro and in vivo experiments about the relationship between soybean isoflavone and skeletal muscle are needed in the future.

Acknowledgements
Not applicable.

Author contributions
Writing—Original draft, investigation, Methodology: S.-Y.L. Writing—review & editing, Supervision, Conceptualization: J.-I.Y.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors consented for publication.

Competing interests
The authors declare that they have no competing interests.

Received: 19 June 2023 Accepted: 17 November 2023
Published online: 08 December 2023

References

1. Shin D, Jeong D. Korean traditional fermented soybean products: Jang. J Ethnic Foods. 2015;2:2–7. https://doi.org/10.1016/j.jef.2015.02.002.
2. Shin DH. Utilization of Soybean as Food Stuffs in Korea. Soybean and Nutrition. London: IntechOpen; 2011. https://doi.org/10.5772/21966.
3. Lee Y, Park T. Origin of legumes cultivation in korean peninsula by viewpoint of excavated grain remains and genetic diversity of legumes. Korean Jounal of Agricultural History. 2006;5:1–31.
4. Kim M, Ryu A. Fermented soybean and foodways of the three-kingdoms period. Korean Ancient Hist Soc. 2018;100:165–87. https://doi.org/10.18040/sgs.2018.100.165.
5. Berry SD, Lee Y, Cai S, Dore DD. Nonbenzodiazepine sleep medication use and hip fractures in nursing home residents. JAMA Intern Med. 2013;173:754–61. https://doi.org/10.1001/jamainternmed.2013.3795.
6. Hassan SM. Soybean, nutrition and health Soybean - bio-active compounds. London: IntechOpen; 2013. https://doi.org/10.5772/54545.
7. Banaszkiewicz T. Nutritional value of soybean meal soybean and nutrition. London: IntechOpen; 2011. https://doi.org/10.5772/23306.
8. Soy in Health and Disease Prevention. Routledge & CRC Press n.d. https://www.routledge.com/Soy-in-Health-and-Disease-Prevention/Sugano/p/book/9780367454050 (accessed October 8, 2021).
9. Messina M, Barnes S. The role of soy products in reducing risk of cancer. J Natl Cancer Inst. 1991;83:541–6. https://doi.org/10.1093/jnci/83.8.541.

10. Messina M, Nagata C, Wu AH. Estimated Asian adult soy protein and isoflavone intakes. Nutr Cancer. 2006;55:1–12. https://doi.org/10.1207/s15327914nc5501_1.
11. Murphy PA, Barua K, Hauck CC. Solvent extraction selection in the determination of isoflavones in soy foods. J Chromatogr B. 2002;777:129–38. https://doi.org/10.1016/S1570-0232(02)00342-2.
12. Setchell KD. Phytoestrogens: the biochemistry, physiology, and implications for human health of soy isoflavones. Am J Clin Nutr. 1998;68:1333S-1346S. https://doi.org/10.1093/ajcn/68.6.1333S.
13. Mueller SO, Simon S, Chae K, Metzler M, Korach KS. Phytoestrogens and their human metabolites show distinct agonistic and antagonistic properties on estrogen receptor alpha (ERalpha) and ERbeta in human cells. Toxicol Sci. 2004;80:14–25. https://doi.org/10.1093/toxsci/kfh147.
14. Martinez J, Lewi JE. An unusual case of gynecomastia associated with soy product consumption. Endocr Pract. 2008;14:415–8. https://doi.org/10.4158/EP.14.4.415.
15. Chavarro JE, Toth TL, Sadio SM, Hauser R. Soy food and isoflavone intake in relation to semen quality parameters among men from an infertility clinic. Hum Reprod. 2008;23:2584–90. https://doi.org/10.1093/humrep/den243.
16. Martin JHJ, Crotty S, Nelson PN. Phytoestrogens: perpetrators or protectors? Future Oncol. 2007;3:307–18. https://doi.org/10.2217/14796694.3.3.307.
17. Liu Z, Kanjo Y, Mizutani S. A review of phytoestrogens: their occurrence and fate in the environment. Water Res. 2010;44:567–77. https://doi.org/10.1016/j.watres.2009.03.025.
18. Eden JA. Managing the menopause: phyto-oestrogens or hormone replacement therapy? Ann Med. 2001;33:4–6. https://doi.org/10.3109/07853890109002054.
19. Messina M. Soybean isoflavone exposure does not have feminizing effects on men: a critical examination of the clinical evidence. Fertil Steril. 2010;93:2095–104. https://doi.org/10.1016/j.fertnstert.2010.03.002.
20. Shen M, Senthil Kumar SP, Shi H. Estradiol Regulates Insulin Signaling and Inflammation in Adipose Tissue. Horm Mol Biol Clin Investig. 2014;17:99–107. https://doi.org/10.1515/hmbci-2014-0007.
21. Harris HA, Bapat AR, Gonder DS, Frail DE. The ligand binding profiles of estrogen receptors alpha and beta are species dependent. Steroids. 2002;67:379–84. https://doi.org/10.1016/s0039-128x(01)00194-5.
22. Iafrati MD, Karas RH, Aronovitz M, Kim S, Sullivan TR, Lubahn DB, et al. Estrogen inhibits the vascular injury response in estrogen receptor alpha-deficient mice. Nat Med. 1997;3:545–8. https://doi.org/10.1038/nm0597-545.
23. Amelink GJ, Koot RW, Erich WB, Van Gijn J, Bär PR. Sex-linked variation in creatine kinase release, and its dependence on oestradiol, can be demonstrated in an in-vitro rat skeletal muscle preparation. Acta Physiol Scand. 1990;138:115–24. https://doi.org/10.1111/j.1748-1716.1990.tb08823.x.
24. Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology. 1998;139:4252–63. https://doi.org/10.1210/endo.139.10.6216.
25. Ji S, Willis GM, Frank GR, Cornelius SG, Spurlock ME. Soybean Isoflavones, Genistein and Genistin, Inhibit Rat Myoblast Proliferation, Fusion and Myotube Protein Synthesis. J Nutr. 1999;129:1291–7. https://doi.org/10.1093/jn/129.7.1291.
26. Pan W, Ikeda K, Takebe M, Yamori Y. Genistein, daidzein and glycitein inhibit growth and DNA synthesis of aortic smooth muscle cells from stroke-prone spontaneously hypertensive rats. J Nutr. 2001;131:1154–8. https://doi.org/10.1093/jn/131.4.1154.
27. Park S, Yuan H, Zhang T, Wu X, Huang SK, Cho SM. Long-term silk peptide intake promotes skeletal muscle mass, reduces inflammation, and modulates gut microbiota in middle-aged female rats. Biomed Pharmacother. 2021;137:111415. https://doi.org/10.1016/j.biopha.2021.111415.
28. Hirasaka K, Maeda T, Ikeda C, Haruna M, Kohno S, Abe T, et al. Isoflavones derived from soy beans prevent MuRF1-mediated muscle atrophy in C2C12 myotubes through SIRT1 activation. J Nutr Sci Vitaminol. 2013;59:317–24. https://doi.org/10.3177/jnsv.59.317.
29. Keller K. Sarcopenia. Wien Med Wochenschr. 2019;169:157–72. https://doi.org/10.1007/s10354-018-0618-2.
30. Anderson LJ, Liu H, Garcia JM. Sex differences in muscle wasting. In: Mauvais-Jarvis F, editor. Sex and Gender Factors Affecting Metabolic Homeostasis, Diabetes and Obesit. Cham: Springer; 2017. p. 153–97. https://doi.org/10.1007/978-3-319-70178-3_9.
31. Jones KL, Harty J, Roeder MJ, Winters TA, Banz WJ. In vitro effects of soy phytoestrogens on rat L6 skeletal muscle cells. J Med Food. 2005;8:327–31. https://doi.org/10.1089/jmf.2005.8.327.
32. Saneyasu T, Shindo H, Honda K, Kamisoyama H. The extract of soybean protein increases slow-myosin heavy chain expression in C2C12 myotubes. J Nutr Sci Vitaminol. 2018;64:296–300. https://doi.org/10.3177/jnsv.64.296.
33. Zheng W, Hemker ML, Xie M, Soukup ST, Diel P. Anabolic activity of a soy extract and three major isoflavones in C2C12 myotubes. Planta Med. 2018;84:1022–9. https://doi.org/10.1055/a-0598-4812.
34. Akiyama T, Ishida J, Nakagawa S, Ogawara H, Watanabe S, Itoh N, et al. Genistein, a specific inhibitor of tyrosine-specific protein kinases. J Biol Chem. 1987;262:5592–5.
35. Schiaffino S, Reggiani C. Fiber types in mammalian skeletal muscles. Physiol Rev. 2011;91:1447–531. https://doi.org/10.1152/physrev.00031.2010.
36. Musarò A, McCullagh K, Paul A, Houghton L, Dobrowolny G, Molinaro M, et al. Localized Igf-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. Nat Genet. 2001;27:195–200. https://doi.org/10.1038/84839.
37. Mavalli MD, DiGirolamo DJ, Fan Y, Riddle RC, Campbell KS, van Groen T, et al. Distinct growth hormone receptor signaling modes regulate skeletal muscle development and insulin sensitivity in mice. J Clin Invest. 2010;120:4007–20. https://doi.org/10.1172/JCI42447.
38. Sacheck JM, Ohtsuka A, McLary SC, Goldberg AL. IGF-I stimulates muscle growth by suppressing protein breakdown and expression of atrophy-related ubiquitin ligases, atrogin-1 and MuRF1. Am J Physiol Endocrinol Metab. 2004;287:E591-601. https://doi.org/10.1152/ajpendo.00073.2004.
39. Kataoka H, Saito S, Itoh A, Matsuo T. Soy germ protein concentrate diet decreased body fat weight and increased hindlimb muscle weight in rats. Biosci Biotechnol Biochem. 2012;76:1413–5. https://doi.org/10.1271/bbb.120217.
40. Kurrat A, Blei T, Kluxen FM, Mueller DR, Piechotta M, Soukup ST, et al. Lifelong exposure to dietary isoflavones reduces risk of obesity in ovariectomized Wistar rats. Mol Nutr Food Res. 2015;59:2407–18. https://doi.org/10.1002/mnfr.201500240.
41. Qiang Q, Adachi H, Huang Z, Jiang Y-M, Katsuno M, Minamiyama M, et al. Genistein, a natural product derived from soybeans, ameliorates polyglutamine-mediated motor neuron disease. J Neurochem. 2013;126:122–30. https://doi.org/10.1111/jnc.12172.
42. Velders M, Schleipen B, Fritzemeier KH, Zierau O, Diel P. Selective estrogen receptor-β activation stimulates skeletal muscle growth and regeneration. FASEB J. 2012;26:1909–20. https://doi.org/10.1096/fj.11-194779.
43. Enns DL, Tiidus PM. The influence of estrogen on skeletal muscle: sex matters. Sports Med. 2010;40:41–58. https://doi.org/10.2165/11319760-000000000-00000.
44. Velders M, Solzbacher M, Schleipen B, Laudenbach U, Fritzemeier KH, Diel P. Estradiol and genistein antagonize the ovariectomy effects on skeletal muscle myosin heavy chain expression via ER-beta mediated pathways. J Steroid Biochem Mol Biol. 2010;120:53–9. https://doi.org/10.1016/j.jsbmb.2010.03.059.
45. La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature. 1991;352:77–9. https://doi.org/10.1038/352077a0.
46. Adachi H, Katsuno M, Minamiyama M, Waza M, Sang C, Nakagomi Y, et al. Widespread nuclear and cytoplasmic accumulation of mutant androgen receptor in SBMA patients. Brain. 2005;128:659–70. https://doi.org/10.1093/brain/awh381.
47. Castaneda C, Charnley JM, Evans WJ, Crim MC. Elderly women accommodate to a low-protein diet with losses of body cell mass, muscle function, and immune response. Am J Clin Nutr. 1995;62:30–9. https://doi.org/10.1093/ajcn/62.1.30.
48. Arnarson A, Gudny Geirsdottir O, Ramel A, Briem K, Jonsson PV, Thorsdottir I. Effects of whey proteins and carbohydrates on the efficacy of resistance training in elderly people: double blind, randomised controlled trial. Eur J Clin Nutr. 2013;67:821–6. https://doi.org/10.1038/ejcn.2013.40.
49. Bos C, Benamouzig R, Bruhat A, Roux C, Valensi P, Ferrière F, et al. Nutritional status after short-term dietary supplementation in hospitalized

malnourished geriatric patients. Clin Nutr. 2001;20:225–33. https://doi.org/10.1054/clnu.2000.0387.
50. Symons TB, Sheffield-Moore M, Wolfe RR, Paddon-Jones D. A moderate serving of high-quality protein maximally stimulates skeletal muscle protein synthesis in young and elderly subjects. J Am Diet Assoc. 2009;109:1582–6. https://doi.org/10.1016/j.jada.2009.06.369.
51. Asif M, Rooney LW, Ali R, Riaz MN. Application and opportunities of pulses in food system: a review. Crit Rev Food Sci Nutr. 2013;53:1168–79. https://doi.org/10.1080/10408398.2011.574804.
52. Berrazaga I, Micard V, Gueugneau M, Walrand S. The role of the anabolic properties of plant-versus animal-based protein sources in supporting muscle mass maintenance: a critical review. Nutrients. 2019;11:1825. https://doi.org/10.3390/nu11081825.
53. Salter AM. The effects of meat consumption on global health. Rev Sci Tech. 2018;37:47–55. https://doi.org/10.20506/rst.37.1.2739.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions