Review

Sarcopenic Obesity: Involvement of Oxidative Stress and Beneficial Role of Antioxidant Flavonoids

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Abstract: Sarcopenic obesity, which refers to concurrent sarcopenia and obesity, is characterized by decreased muscle mass, strength, and performance along with abnormally excessive fat mass. Sarcopenic obesity has received considerable attention as a major health threat in older people. However, it has recently become a health problem in the general population. Sarcopenic obesity is a major risk factor for metabolic syndrome and other complications such as osteoarthritis, osteoporosis, liver disease, lung disease, renal disease, mental disease and functional disability. The pathogenesis of sarcopenic obesity is multifactorial and complicated, and it is caused by insulin resistance, inflammation, hormonal changes, decreased physical activity, poor diet and aging. Oxidative stress is a core mechanism underlying sarcopenic obesity. Some evidence indicates a protective role of antioxidant flavonoids in sarcopenic obesity, although the precise mechanisms remain unclear. This review summarizes the general characteristics and pathophysiology of sarcopenic obesity and focuses on the role of oxidative stress in sarcopenic obesity. The potential benefits of flavonoids in sarcopenic obesity have also been discussed.

Keywords: sarcopenic obesity; pathophysiology; oxidative stress; flavonoids

1. Introduction

Obesity epidemics and aging are two major health concerns in developed countries. Over the last decade, obesity has become a worldwide pandemic [1]. Coupled with a rapidly aging population, obesity in the elderly is considered a major public health issue [2–4]. In general, obese elderly people have characteristics indicative of sarcopenia, such as loss of muscle mass, strength, and performance [5]. Although not clearly defined, the common definition of sarcopenic obesity is the coexistence of obesity and sarcopenia. The prevalence of sarcopenic obesity varies between 2% and 85% because of ambiguous criteria regarding its definition and diagnostic methods of sarcopenia and obesity [6–9]. Its prevalence is high among elderly people with comorbidities, such as type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), dyslipidemia, and cardiovascular disease. Although the prevalence of sarcopenic obesity increases with age, younger generations are also at risk, especially when they have comorbidities [10,11].

Sarcopenic obesity can lead to various health problems such as metabolic syndrome, functional disability, osteoarthritis, osteoporosis, lung disease, renal disease, and depression [12–15]. Several mechanisms, including insulin resistance, inflammation, hormonal changes, behavioral problems, and oxidative stress, have been implicated in the pathophysiology of sarcopenic obesity [16–19]. To effectively prevent and treat sarcopenic obesity-related health problems, it is crucial to better understand sarcopenic obesity.

Recently, there has been increasing interest in the therapeutic use of flavonoids for sarcopenic obesity. Flavonoids are bioactive molecules present in many plants including fruits, vegetables, grains, and spices. They provide a diverse range of health benefits including antioxidant, anti-inflammatory, anti-viral, anti-diabetic, anti-cancer, cardioprotective, and neuroprotective properties [20]. There is evidence showing that some flavonoids have

the potential to prevent and treat sarcopenia and obesity via multiple mechanisms [21,22]. This article provides an overview of sarcopenic obesity, its underlying pathophysiological mechanisms, and the potential benefits of flavonoids for the prevention and treatment of sarcopenic obesity.

2. General Characteristics

A rational consideration of sarcopenia and obesity is required to diagnose and treat sarcopenic obesity.

2.1. Sarcopenia

Sarcopenia is characterized by the loss of skeletal muscle mass, strength, and physical function, which can lead to physical disability, lower quality of life, and a higher mortality rate [23–25]. Although age-related changes in skeletal muscle are the primary causes of sarcopenia, they can also occur due to various factors, such as limited mobility, malnutrition, and obesity [26,27]. According to the definition provided by the European Working Group on Sarcopenia in Older People (EWGSOP), the diagnostic criteria for sarcopenia include low muscle strength (an early indicator of sarcopenia), low muscle mass, and low physical performance [26]. Specifically, subjects with low muscle strength may have sarcopenia, and low muscle quantity or quality should be confirmed before diagnosis. Subjects who fulfil all three criteria are considered to have a severe sarcopenia. Various tests and tools are used to diagnose sarcopenia in clinical practice and research. Grip strength and chair stand tests are two commonly used tests of skeletal muscle strength. Muscle quantity can be determined using various tools, including magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry, and bioelectrical impedance analysis. Gait speed is commonly used for the assessment of physical performance, and a short physical performance battery and the timed up-and-go test are alternatives to the gait speed test. Recently, the importance of muscle strength (assessed by grip strength) and physical performance (assessed by gait speed) over muscle mass in the definition of sarcopenia is being emphasized [28].

Sarcopenia is a known risk factor for various health issues, including chronic disease progression, physical disability, falls, osteoporosis, and postoperative complications (both infections and noninfectious complications) [29–34]. Therefore, it is associated with increased hospital costs, length of hospital stay, and recurrence [35]. Although early diagnosis is key to preventing and treating sarcopenia-related health problems, there is no global consensus on the definition and diagnostic criteria for sarcopenia.

2.2. Obesity

Obesity is defined as abnormal or excessive fat accumulation that may be a health hazard [36]. According to the World Health Organization, a body mass index (BMI) $\geq 30\ \text{kg/m}^2$ in adults indicates obesity. However, it is recommended to use a lower BMI cut-off point for defining obesity ($\geq 25\ \text{kg/m}^2$) in the Asian population, due to a higher risk of obesity-related diseases such as diabetes [37]. Waist circumference, another index of obesity, is the most frequently used to measure abdominal adiposity. Abdominal obesity is defined as a waist circumference ≥ 88 cm and ≥ 102 cm for women and men, respectively [38]. Waist circumference criteria for diagnosis of abdominal obesity also differ depending on ethnicity. It occurs when energy intake exceeds energy expenditure, which is influenced by genetic and environmental factors (e.g., nutrition, exercise, viruses, microbiome, and circadian rhythms). Obesity is an important risk factor for metabolic abnormalities, including insulin resistance, type 2 diabetes, dyslipidemia, NAFLD, and cardiovascular diseases. It is also associated with cancer, osteoarthritis, pulmonary dysfunction (e.g., obstructive sleep apnea), and cognitive impairment [39–41]. Recently, obesity has been reported to be a risk factor for severe coronavirus disease 2019 (COVID-19) [42].

2.3. Sarcopenic Obesity

The obesity epidemic is increasing worldwide [43]. The obesity epidemic is prevalent not only in industrialized but also in developing countries [43]. In addition to the prevalence of obesity in the general population, the incidence of obesity in the elderly has been increasing and poses a serious threat to the health of elderly individuals in both developed and developing countries [44]. It is particularly noteworthy that the prevalence of sarcopenic obesity is increasing with the rising population of senior citizens and has become an important health issue. Recently, sarcopenic obesity has been considered a health risk in younger and older populations [10,11].

Sarcopenia commonly occurs with aging and is often accompanied a relative or absolute increase in adiposity. However, it can strike anyone with obesity, regardless of age. Obesity can independently cause sarcopenia, because underlying factors contributing to obesity such as inflammation, insulin resistance, and oxidative stress can adversely affect sarcopenia [45]. Meanwhile, sarcopenia can promote fat accumulation due to decreased physical activity and energy expenditure. Thus, obesity and sarcopenia may affect each other. Although the definition of sarcopenic obesity remains under discussion, most studies have defined it based on the concomitant presence of sarcopenia and obesity. For example, based on a recent consensus statement by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO), sarcopenic obesity is defined as abnormal and excessive adiposity and low skeletal muscle mass and function [46]. The ESPEN and EASO recommended following diagnostic criteria. Screening for sarcopenic obesity is performed to verify the presence of both high BMI or waist circumference (based on ethnic cut-off points) and surrogate indicators of sarcopenia (clinical symptoms, clinical suspicion, or questionnaires). After positive screening results, both altered skeletal muscle functional parameters (e.g., hand grip strength) and altered body composition (increase in % fat mass and decrease in muscle mass) are required to make a firm diagnosis of sarcopenic obesity. Once a diagnosis of sarcopenic obesity is confirmed, it can be classified into two stages depending on the presence or absence of complications (e.g., metabolic diseases, functional disabilities, and cardiovascular and respiratory diseases). Since an internationally agreed definition and diagnostic criteria for sarcopenic obesity have not been established, further efforts are needed to reach a consensus on an appropriate definition and diagnostic criteria.

3. Pathophysiological Mechanisms: Involvement of Oxidative Stress

Obesity and sarcopenia have common pathophysiological characteristics, including insulin resistance, inflammation (increased secretion of pro-inflammatory markers and decreased anti-inflammatory markers), hormonal changes (a decline in growth hormone, testosterone, and estrogen), lack of physical activity, and oxidative stress [16–19]. As a result of their synergistic interactions, sarcopenic obesity may have deleterious effects on health compared with those of either condition alone [47–57]. Several studies have suggested that sarcopenic obesity is linked to an increased risk of functional disability, cardiometabolic diseases (cardiovascular disease, type 2 diabetes, and hypertension, among others), and other comorbidities, such as liver disease, osteoarthritis, osteoporosis, pulmonary disease, renal disease, mental health problems (cognitive impairment and depression, among others), postoperative complications, and severe COVID-19 [47–57] (Figure 1).

Oxidative stress is a critical factor that links sarcopenic obesity with related comorbidities [17]. It is also associated with other factors contributing to sarcopenic obesity, such as insulin resistance, inflammation, hormonal changes, and behavioral problems [17]. Oxidative stress is caused by an imbalance between the formation of free radicals (highly reactive molecules containing one or more unpaired electrons) and antioxidant defenses, which can damage many tissues and lead to various diseases, including sarcopenic obesity [58]. Free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), are derived from endogenous and exogenous sources. Endogenous antioxidants (e.g., superoxide dismutase, catalase, glutathione peroxidase, and bilirubin) and exoge-

nous antioxidants (e.g., ascorbic acid, β-carotene, α-tocopherol, and phenolic compounds) can defend against free radical-induced damage [58]. However, insufficient antioxidant capacity and increased ROS and RNS generation can cause oxidative damage to organelles, carbohydrates, proteins, nucleic acids, and lipids, leading to dysfunction and disease development [59]. In elderly individuals, oxidative stress elicits sarcopenia and obesity through mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and imbalances in muscle mass control [17]. In this section, we focused on the effects of oxidative stress on the development of sarcopenic obesity.
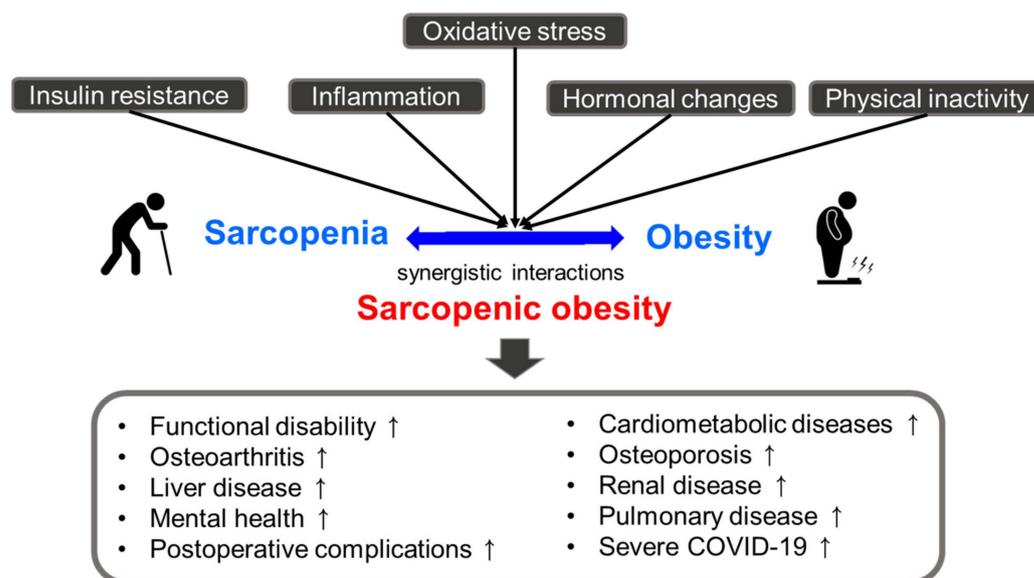
Figure 1. Pathophysiologic characteristics and consequence of sarcopenic obesity.

3.1. Mitochondrial Dysfunction

Mitochondrial dysfunction can increase ROS production [60] because mitochondria are important sites for ROS formation [61]. The release of ROS from mitochondria increases with aging, resulting in increased oxidative damage to mitochondrial and cellular proteins, lipids, and DNA, which consequently causes a decline in mitochondrial function, including mitochondrial protein synthesis, respiration, and maximal ATP production rate [62–65].

The removal of dysfunctional mitochondria via mitophagy (a selective form of autophagy) is critical for maintaining the redox balance and muscle health. A lack of capacity of muscles to effectively remove dysfunctional mitochondria can contribute to excessive ROS formation and a consequent decrease in mitochondrial quantity and quality, which can lead to the development of muscle fiber atrophy in sarcopenia [66]. Muscle atrophy resulting from aging can occur due to a decrease in the total number of muscle fibers and a simultaneous decrease in the size of individual fibers [67,68]. Aging-related muscle loss was mainly attributed to a decrease in type II muscle fibers, probably because type II fibers embedded with less mitochondria are more vulnerable to aging-induced processes [69,70].

Oxidative stress associated with obesity can also trigger disturbances in mitochondrial function, resulting in increased ROS production. Although white adipose tissue (WAT) is not a mitochondria-rich tissue, mitochondria in WAT have a critical role in maintaining metabolic homeostasis, including adipogenesis, lipogenesis, lipolysis, and adipokine production [71,72]. Obesity caused by excess energy intake, such as HFD, could lead to mitochondrial dysfunction in adipocyte partly due to ROS-induced oxidative damage to the adipocyte. Consequently, mitochondrial dysfunction caused by oxidative stress in obesity can induce insulin resistance, inflammation, dyslipidemia, and other adverse effects [71,72]. Although the mechanism underlying adipocyte mitochondrial dysfunction in obesity is unclear, hypertrophic adipocytes (enlargement of adipocyte size) in obesity is associated with mitochondrial dysfunction [73]. Another possibility is that a rise in mitochondrial

substrate overload in conditions of overnutrition increases electron transport chain activity in the mitochondria and subsequently ROS generation, leading to oxidative stress [74]. Nutrient overload in obesity can also lead to ER stress, which promotes oxidative stress and contributes to mitochondrial dysfunction in adipocyte [75].

The protein kinase A (PKA)/liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK) signaling pathway plays essential roles in improving mitochondrial dysfunction and inhibiting oxidative stress [76,77]. PKA activates AMPK, a crucial cellular energy sensor, via LKB1, which promotes mitochondrial biogenesis and antioxidant capacity in the skeletal muscles [76,77].

3.2. ER Stress

The ER performs many functions, particularly in protein synthesis and folding. The excessive formation of unfolded or misfolded proteins in the ER can lead to ER stress [78]. As redox homeostasis is crucial for protein folding in the ER, oxidative stress can generate misfolded proteins by disrupting protein folding and thus elicits ER stress. ER stress is a major source of ROS, which accelerates oxidative stress. ER stress affects cellular homeostasis and morphology, leading to various diseases, including obesity and sarcopenia.

ER stress is commonly observed in obese subjects and in genetically modified or high-energy diet-induced obese animals [79–81]. Chronic ER stress in the liver, skeletal muscle, and adipose tissue impairs insulin sensitivity and contributes to inflammation, leptin resistance, and steatosis [79–83]. By contrast, weight loss in obese individuals decreases ER stress and increases insulin sensitivity [84]. Moreover, a reduction in ER stress in the adipose tissue and liver using chemical or molecular chaperones was found to improve inflammation, hepatic steatosis, and glucose homeostasis in obese mice [85,86], suggesting that prolonged ER stress may be involved in obesity-associated tissue dysfunction and metabolic disturbances.

ER stress is also an important contributor to sarcopenia development. Skeletal muscle contains the ER, which plays a critical role in the regulation of calcium storage and protein homeostasis. ER stress is increased in the skeletal muscles of both aged people and rodents [87–90], and oxidative stress is involved in the induction of ER stress in obese subjects with and without comorbidities [91]. Increased ER stress was found to cause diaphragm contractile dysfunction in a muscle atrophy mouse model due to sepsis [92]. In contrast, the inhibition of ER stress protected against muscle atrophy in a hind-limb-unloaded mouse model, which showed skeletal muscle atrophy and weakness [93].

3.3. Imbalance in Muscle Mass Control

The balance between the anabolic and catabolic pathways is important for maintaining muscle mass. Oxidative stress causes muscle wasting by activating the catabolic pathways and inhibiting the anabolic pathway [59].

3.3.1. Anabolic Pathway

In skeletal muscle, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway is one of the major anabolic pathways controlling protein synthesis [94,95]. The activation of PI3K phosphorylates and activates AKT, which regulates several downstream molecules, including mTOR [96]. mTOR is a key regulator of protein synthesis in addition to having a role in other biological functions, such as the regulation of cell growth and survival. It regulates the anabolic and catabolic signaling pathways in skeletal muscles and thus modulates muscle hypertrophy and muscle wasting [97]. According to the free radical theory of aging [98], ROS damage mitochondrial proteins and reduce ATP generation, resulting in the inhibition of the mTOR pathway and subsequent down-regulation of protein synthesis. Furthermore, the impairment of the mTOR pathway has been observed in patients with sarcopenia [99]. Other studies also support the deleterious effect of mTOR inhibitors on muscle mass and growth [100,101].

The PI3K/Akt/mTOR pathway is activated by several upstream triggers, such as insulin-like growth factor 1 (IGF-1), insulin, and physical activity, all of which are associated with obesity or aging [95,102]. Circulating IGF-1 levels are lower in sarcopenic subjects than in non-sarcopenic subjects, and its levels are associated with sarcopenia in the elderly as well as fat mass and the prevalence of comorbidities in obese subjects [103–105]. Moreover, insulin and IGF-1 stimulate protein synthesis in the skeletal muscles of mice [106], and impaired insulin activity in skeletal muscles is linked to obesity and sarcopenia [107]. Type 2 diabetic db/db mice show an impaired PI3K/Akt pathway along with increased protein degradation, resulting in muscle atrophy, whereas an improvement in insulin-sensitivity using rosiglitazone protects against muscle loss [108,109]. Physical activity is most effective in preventing sarcopenia in elderly individuals [109]. Exercise can mitigate a decline in autophagy in skeletal muscles of aged rats by regulating the mTOR pathway, resulting in improved aging-induced skeletal muscle atrophy [110]. However, the role of the mTOR pathway in sarcopenia remains controversial [111]. Aging is influenced by mTOR hyperactivation [112].

3.3.2. Catabolic Pathway

The loss of skeletal muscle occurs in a state of protein degradation that exceeds its synthesis. In skeletal muscle, protein degradation is mainly mediated by two catabolic pathways: the ubiquitin–proteasome pathway and the autophagic/lysosomal pathway. The ubiquitin–proteasome pathway is crucial for protein degradation in striped muscles [113]. FoxO activates the expression of the genes involved in the ubiquitin-proteasome pathway, including atrogin-1, muscle atrophy F-box (MAFbx), and muscle RING-finger protein-1 (MuRF1), which are up-regulated in muscle atrophy [114,115]. FoxO also regulates the activation of autophagic/lysosomal pathway-related genes (LC3, Bnip3, and Bnip3l) during muscle atrophy in vivo [116]. The activation of Akt not only induces mTOR signaling but also inhibits FoxO through phosphorylation, thereby inhibiting the catabolic process of skeletal muscle [117]. Autophagy is a catabolic pathway that removes dysfunctional organelles and denatured proteins in a lysosome-dependent process [118]. With aging, abnormal autophagy causes the accumulation of damaged cellular constituents, such as damaged mitochondria, which increases ROS generation and further damage [119]. Dysregulated autophagy in muscles also causes ER stress, impaired sarcomeric protein turnover, and cell death, resulting in the loss of muscle mass [120]. Both a lack of and excessive autophagy are associated with muscle atrophy [119,120].

Multiple triggers including oxidative stress and inflammatory cytokines affect protein degradation. Oxidative stress-induced atrophy is associated with the up-regulation of FoxO1 and MuRF1 expression in muscle cells, whereas treatment with ascorbic acid, an antioxidant, counteracts oxidative stress-induced atrophy by down-regulating FoxO1, MuRF1, and atrogin-1 expression [121]. ROS also activates autophagy through multiple mechanisms, leading to protein breakdown [122]. Another important factor controlling protein degradation and skeletal muscle loss is nuclear factor-kappa B (NF-κB). The activation of NF-κB results in skeletal muscle atrophy by increasing the expression of ubiquitin–proteasome pathway protein (e.g., MuRF1), pro-inflammatory cytokines (e.g., TNF-α and IL-1), and chemokines contributing to muscle loss [123]. Increased levels of NF-κB and pro-inflammatory cytokines are observed in elderly people with sarcopenia, as well as in obese individuals [124–127].

3.3.3. Satellite Cells

Satellite cells, also known as muscle stem cells, are the primary source for muscle re-generation. It is critical for muscle fiber maintenance, repair, and remodeling [128]. Age-related reductions in the number and function of satellite cells occur, especially in type II fibers, although conflicting results have been reported [129–132]. In addition, patients with sarcopenia frequently exhibit aberrant satellite cell homeostasis [133]. Although its role in the development of sarcopenia and sarcopenic obesity is not completely clear,

exercise-induced satellite cell activation, along with the provision of sufficient nourishment, appears to offer effective protection against sarcopenia and sarcopenic obesity [134].

Considerable evidence suggests that excess ROS and diminished antioxidant capacity can impair muscle regeneration, primarily by affecting satellite cell homeostasis [135,136]. An increase in ROS occurs in the satellite cells of aged muscles, and antioxidant capacity is decreased in aged satellite cells [136,137]. Oxidative stress not only leads to impaired removal of misfolded proteins but also dysregulates basal autophagy, which is vital for the maintenance of the stem cell quiescent state, contributing to stem cell resilience [138], thereby affecting muscle regeneration [135,136,139,140]. In addition, redox-sensitive signaling pathways, such as Notch, Wnt, p38/MAPK, and JAK/STAT3, are aberrantly expressed in satellite cells during aging, causing abnormal satellite cell functions, including proliferation, fibrosis, and differentiation [141–144].

Myogenic regulatory factors (e.g., Myf5, MyoD, Myogenin, and MRF4) play a critical role in controlling the myogenesis via satellite cells. The expression of myogenic regulatory factors is up-regulated during myogenesis and influences the activation and differentiation of stem cells [145]. By contrast, myostatin, a myokine secreted by myocytes, functions as a negative regulator of muscle growth and regeneration by reducing satellite cell number and regeneration, inhibiting the Akt/mTOR pathway, and activating FoxO [146]. Although the role of myostatin in aging and other muscle-wasting conditions is unclear, skeletal muscle myostatin mRNA expression is higher in overweight and obese middle-aged and older adults with sarcopenia than in those without sarcopenia, and myostatin mRNA expression is positively correlated with BMI, fat mass, and mid-thigh intra-muscular fat area [147]. Genetic and pharmacological inhibition of myostatin ameliorates sarcopenic obesity by increasing muscle mass and improving glucose homeostasis [147–152].

4. Effects of Antioxidant Flavonoids on Sarcopenic Obesity

Flavonoids are among the most abundant phenolic compounds in edible plants [153]. More than 5000 flavonoids have been reported to date [154]. They have a C6-C3-C6 backbone and are generally subdivided into different subgroups based on their chemical structures: flavones, flavonols, flavan-3-ols, chalcones, flavanones, and isoflavonoids (Figure 2). Flavonoids possess many bioactivities, such as antioxidant, anti-inflammatory, and anti-viral effects, and protect against various diseases, including cardiovascular diseases, diabetes, neurodegenerative diseases, osteoporosis, and cancer [20]. In addition, in vitro and in vivo studies have reported their anti-obesity potential via stimulation of energy expenditure, appetite suppression, inhibition of adipocyte differentiation and digestive enzymes, promotion of adipocyte apoptosis and lipolysis, and regulation of lipid metabolism and gut microbiota [21]. Recently, flavonoids have received renewed attention as candidates for improving muscle atrophy and muscle health [22]. Some flavonoids have been reported to provide effective protection against sarcopenic obesity; therefore, their anti-sarcopenic effects and mechanisms are summarized.
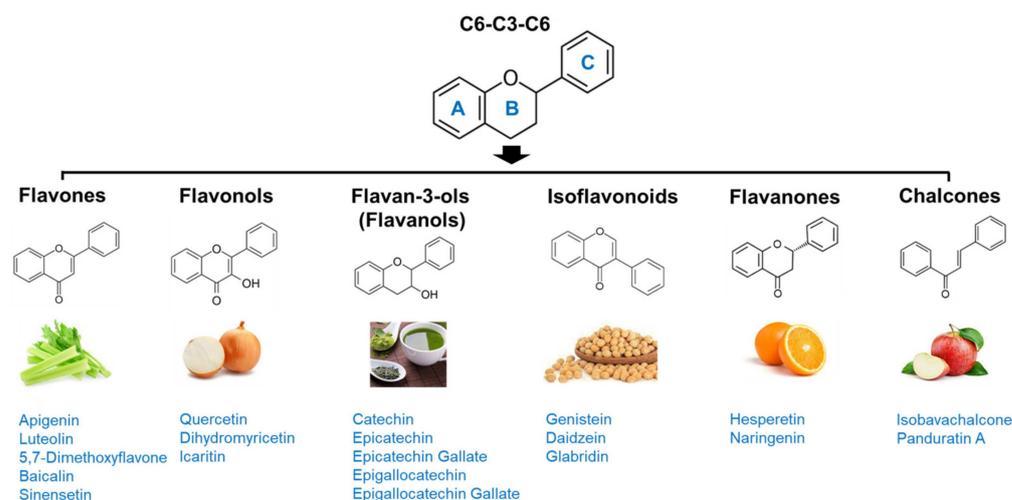
Figure 2. Subgroups of flavonoids and their chemical structures.

4.1. Apigenin

Apigenin (4′,5,7-trihydroxyflavone) is a flavone that is plentiful in edible plants such as parsley, celery, celeriac, oranges, and chamomile [155]. There is evidence that it has positive health effects, owing to its anti-inflammatory, antioxidant, anti-steatotic, anti-diabetic, anti-cancer, and neuroprotective properties [156–161]. Apigenin also possesses anti-obesity properties associated with decreased food intake, increased energy expenditure, activated lipolysis, fatty acid oxidation, and control of gut microbiome composition [162–164].

In addition, apigenin exerts a protective effect against sarcopenia. In lipopolysaccharide (LPS)-treated mouse skeletal muscle cells, it decreases the expression of the atrophic genes atrogin-1 and MAFbx [165]. This anti-atrophic effect was supported by the findings of an in vivo study in which apigenin increased muscle mass and enhanced muscle function in mice by enhancing skeletal muscle hypertrophy and myoblast differentiation [166]. Apigenin also alleviates sciatic nerve denervation-induced muscle atrophy by inhibiting muscle inflammation [167]. Moreover, apigenin not only decreases fat mass but also prevents muscle loss and increases exercise capacity by down-regulating atrogin-1 and MuRF1 in the skeletal muscle of high-fat diet (HFD)-induced obese mice [168], which suggests that it can ameliorate HFD-induced sarcopenic obesity. Interestingly, a recent study reported that apigenin improves muscle atrophy by decreasing oxidative stress and activating mitophagy and apoptosis in aged mice [169].

4.2. Luteolin

Another flavone luteolin (3′,4′,5′,7′-tetrahydroxyflavone), commonly occurring in edible plants such as celery, parsley, and broccoli [170], has a protective effect on sarcopenic obesity [171]. Long-term supplementation with luteolin not only decreases body weight and fat mass but also increases muscle mass, muscle fiber size and number, and muscle function in HFD-induced obese mice. The beneficial effects of luteolin on sarcopenic obesity are associated with suppressed protein degradation, decreased muscular lipid accumulation, and attenuated inflammation. The anti-atrophic properties of luteolin are supported by other in vitro and in vivo studies using LPS- and cachexia-induced muscle atrophy models [165,172].

4.3. Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a flavonol abundantly present in various vegetables and fruits [173]. It can protect against multiple diseases, such as osteoporosis, cancer, memory impairment, and cardiovascular diseases, and these promising effects are achieved partly through its antioxidant and anti-inflammatory actions [174–177]. Quercetin also has a positive influence on decreasing body weight and adiposity in diet-induced

obese animals, and multiple mechanisms, such as the activation of lipolysis, inhibition of lipogenesis and adipogenesis, and browning effects, have been implicated in its anti-obesity effects in vivo and in vitro [178–184]. In particular, quercetin inhibits oxidative stress and NF-κB and thus limits immune activation and inflammation, which results in an improvement in mitochondrial functions in the adipose tissue of HFD-induced obese mice [185]. Clinical trials have supported the anti-obesity effects of quercetin. Quercetin administration reduces BMI and fat mass in overweight or obese individuals [186]. In another study conducted on overweight/obese subjects with various apolipoprotein E genotypes, reductions in waist circumference and triglyceride levels were observed after quercetin administration [187]. However, quercetin slightly increases pro-inflammatory TNF-α levels [187], and high doses of quercetin do not affect oxidative stress in obese people [188]. Further clinical studies are required to investigate its anti-obesity effects.

The protective effects of quercetin on obesity-induced skeletal muscle atrophy have also been demonstrated in vivo [189,190]. In the skeletal muscle of HFD-fed mice, quercetin was found to reverse the increase in levels of mRNA and protein of atrophic markers (atrogin-1, MuRF1) and pro-inflammatory markers (TNF-α, MCP-1) induced by HFD [189]. The anti-atrophic effect of quercetin is reported in another study showing that it suppresses muscle atrophy in HFD-induced obese mice via up-regulation of Nrf2-mediated heme oxygenase-1 and antioxidant capacity and down-regulation of pro-inflammatory NF-κB [190]. Therefore, quercetin may protect against obesity-induced sarcopenia and metabolic dysregulation.

Its anti-atrophic effects have been observed in other animal models [181–184]. Quercetin increases muscle mass and suppresses unloading-induced disused muscle atrophy and lipid oxidation in mice [191]. Mukai et al. [192] have also found that quercetin inhibits denervation-induced muscle loss by increasing p-Akt, IGF-1, and PGC-1α in mice, despite having no effect on MuRF1. A recent study demonstrated the protective role of quercetin in cancer- and chemotherapy-induced muscle loss by maintaining mitochondrial homeostasis [193]. It is particularly noteworthy that quercetin promotes behavioral functional recovery by hastening the recovery of weight in damaged muscles and increasing neuronal intrinsic growth capacity following sciatic nerve crush injury in mice [194]. In addition, in middle-aged and older adults, the administration of quercetin glycoside together with low-intensity resistance exercise improves muscle quality (an increase in muscle stiffness) and independent muscle quantity [195].

4.4. Dihydromyricetin

Dihydromyricetin, also known as ampelopsin, is a flavonol present in medicinal herbs, vegetables, and fruits, including grapes and berries [196]. It has multiple biological and pharmacological properties, including antioxidant, anti-inflammatory, anti-cancer, neuroprotective, and hepatoprotective actions [197–201]. Some studies have also demonstrated that dihydromyricetin prevents obesity in HFD-fed and ob/ob mice and that its role in adipogenesis inhibition, adipocyte browning activation, and gut microbiota regulation is related to its anti-obesity effect [202–205].

In addition, Zhou et al. [206] reported that dihydromyricetin improved skeletal muscle insulin resistance and reduced the proportion of type I fibers in HFD-induced obese and ob/ob mice. Type I fibers have more mitochondria and mostly involve fatty acid oxidative phosphorylation for energy generation compared to type II fibers [207]. Zou et al. [208] demonstrated that dihydromyricetin improved hypobaric hypoxia-induced mitochondrial dysfunction in rats, resulting in improved physical performance. The protective effects of dihydromyricetin on mitochondrial function and muscle atrophy are supported by another study, which showed that it ameliorates dexamethasone-induced muscle atrophy by improving mitochondrial dysfunction [209]. Accordingly, it down-regulated FoxO3a-mediated protein degradation and up-regulated Akt/mTOR pathway-dependent protein synthesis. Huang et al. [209] also observed that dihydromyricetin suppressed dexamethasone-induced oxidative stress in skeletal muscles, which might contribute to

protection against muscle atrophy because oxidative stress causes muscle wasting by activating the catabolic pathway and inhibiting the anabolic pathway [59]. Beneficial effects of dihydromyricetin on muscle atrophy induced by inflammation or D-galactose (a useful agent for accelerating aging) have also been reported in vitro and in vivo [210,211].

4.5. Epigallocatechin Gallate and Epicatechin

Epigallocatechin gallate (EGCG) is a flavanol abundantly present in tea, especially green tea, and is also present in small amounts in other plant foods, such as apples, carobs, berries, and avocados [212,213]. It possesses diverse bioactivities and pharmacological effects, including antioxidant, anti-inflammatory, cardioprotective, anti-diabetic, and anti-cancer effects [214–218]. EGCG also has positive effects on weight loss and fat reduction in HFD-induced obese animals [219–223]. The anti-obesity effect is linked to inhibited adipogenesis and lipogenesis, increased lipolysis, brown fat thermogenesis, mitochondria biogenesis, white fat autophagy, and improved gut microbiota homeostasis [219–225]. However, its potential benefits in obese individuals remain obscure [226–229].

The existing evidence indicates the beneficial effect of EGCG in alleviating sarcopenia. In aged rats, EGCG increases the recovery of muscle mass and function after disuse by decreasing apoptotic signaling and increasing satellite proliferation [230]. Takahashi et al. [231] reported that EGCG up-regulates autophagy signaling to improve the clearance of damaged organelles in resting and unloaded conditions but selectively inhibits autophagy-related proteins (Beclin1 and LC3) in reloaded muscles of aged rats, perhaps leading to the recovery of muscle mass and function. In another study using aged animals, EGCG prevented muscle loss by inhibiting protein degradation via the ubiquitin–proteasome pathway (atrogin-1, MuRF1, myostatin), along with the up-regulation of the anabolic factor IGF-1 [232,233]. In line with these findings, EGCG prevents cachexia-induced muscle loss via down-regulation of NF-κB, atrogin-1, and MuRF1 in mice [234], and it recovers muscle function impairment and damaged muscle fibers following nerve injury in rats by activating the anti-apoptotic signaling pathway [235]. Moreover, EGCG enhances endurance capacity in mice [236], decreases oxidative stress, and alleviates mitochondrial dysfunction by decreasing excessive autophagy in the skeletal muscles of rats with type 2 diabetes [237]. The anti-sarcopenic effect of EGCG is associated with not only decreased protein degradation but also increased protein synthesis in skeletal muscle [238].

Epicatechin, another flavanol found in green tea, also hinders aging-associated skeletal muscle degeneration and enhances physical activity in mice [239]. Similarly, supplementation of epicatechin in obese middle-aged mice (16 months of age) not only decreases fat mass but also enhances physical performance by increasing muscle growth and differentiation and by decreasing the ubiquitin–proteasome degradation pathway [240]. Interestingly, epicatechin reversed aging-induced oxidative stress and mitochondrial biogenesis in vivo [241]. In vitro studies also support its anti-atrophic effects via inhibition of protein degradation and improvements in mitochondrial biogenesis and muscle growth in skeletal muscle cells [242,243]. In addition, the administration of epicatechin together with resistance training increases skeletal muscle strength and growth factors in elderly individuals with sarcopenia [244]. The combination of tea catechins and exercise has a positive effect on maintaining muscle mass and physical function in the elderly compared to those without catechins [245]. However, there was no association between green tea consumption and sarcopenia in menopausal women [246]. Moreover, few studies have assessed the effects of EGCG on sarcopenic obesity in humans.

4.6. Others

5,7-dimethoxyflavone, a flavone found in Kaempferia parviflora, also exerts protective effects on sarcopenia and obesity [247,248]. Supplementation of 5,7-dimethoxyflavone to aged mice improves skeletal muscle function and increases muscle mass by increasing mitochondrial biogenesis, activating protein synthesis via the mTOR pathway, and suppressing

protein degradation via the FoxO pathway [247]. 5,7-dimethoxyflavone prevents obesity by suppressing adipogenesis in HFD-fed obese mice [248].

Glabridin, an isoflavan found in licorice, prevents glucocorticoid-induced muscle atrophy in vivo and in vitro [249]. Furthermore, it was found to ameliorate HFD-induced obesity by inhibiting lipid synthesis in the WAT and increasing muscular fatty acid oxidation via regulation of mitochondrial function as AMPK activator [250].

Hesperetin, a major flavanone abundant in citrus fruits, such as lemons and oranges, decreases body weight and fat mass in HFD-induced obese mice [251]. It also increases muscle fiber size and enhances running performance in aged mice [252]. These beneficial effects are associated with activation of PGC-1α and Nrf2 along with increased antioxidant capacity. Recently, Yeh et al. [253] reported that long-term oral administration of hesperetin improves age-associated energy expenditure decline, fat accumulation, and muscle loss in aged mice.

Another citrus flavanone, naringenin, reportedly protects against HFD-induced adiposity and inflammation in ovariectomized mice [254]. Moreover, it increases muscle mass and locomotor activity and decreases muscle lipid accumulation. Similarly, in ovariectomized mice fed a normal diet, naringenin improved estrogen deficiency-induced fat accumulation and muscle loss [255]. Previous studies suggest that naringenin increases energy expenditure, improves insulin resistance, and regulates skeletal muscle differentiation by controlling estrogen receptor α and β signal pathway [256,257].

Other flavonoids, such as daidzein (isoflavone), genistein (isoflavone), baicalin (flavone), sinensetin (flavone), icaritin (flavonol), isobavachalcone (chalcone), and panduratin A (chalcone), have the potential to attenuate obesity and sarcopenia [258–272].

5. Conclusions

Sarcopenic obesity has become a global epidemic affecting all generations, including the elderly. In addition to age-related diseases, multiorgan dysfunction and multiple mechanisms are implicated in the development of sarcopenic obesity. The development and progression of sarcopenic obesity are related to oxidative stress, inflammation, insulin resistance, hormonal changes, and behavioral problems. Accumulating evidence suggests that flavonoids may be effective in preventing and treating sarcopenic obesity, owing to their ability to control oxidative stress, inflammation, insulin resistance, mitochondrial dysfunction, anabolic and catabolic pathways, and satellite cells (Figure 3). Flavonoids having potential for improving sarcopenic obesity are summarized in Table 1.
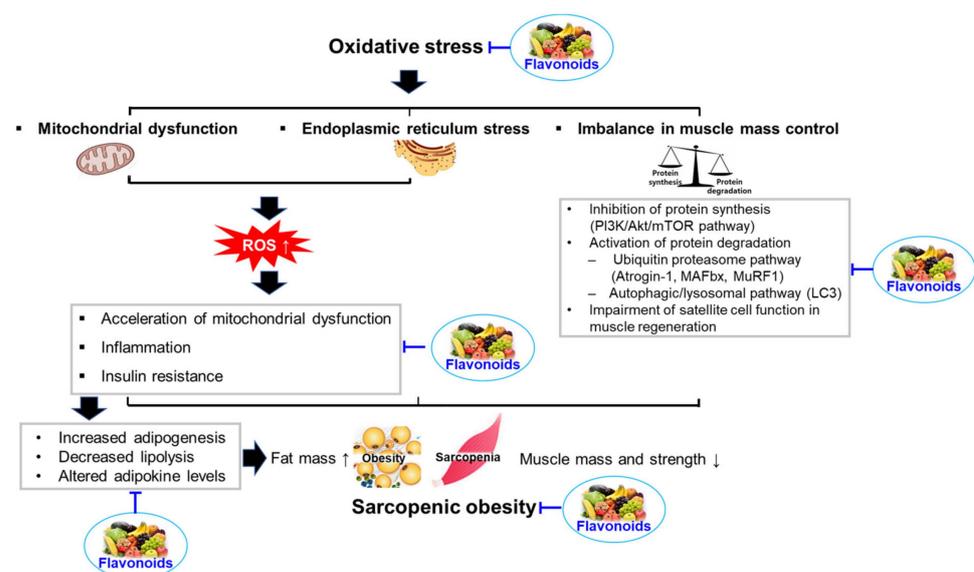

Figure 3. Summary of the influences of oxidative stress in the development of sarcopenic obesity and proposed mechanism by which flavonoids can protect against sarcopenic obesity.

Table 1. Summary of flavonoids having potential for improving sarcopenic obesity.

Subclass	Flavonoid Name	Experimental Model	Effects and Potential Mechanisms	References
Flavone	Apigenin	HFD-fed C57BL/6J mice	Body weight gain ↓, Food intake ↓	[162]
		HFD-fed C57BL/6J mice	Body weight gain ↓, Energy expenditure ↑, lipolysis ↑, fatty acid oxidation ↑	[163]
		HFD-fed C57BL/6J mice	Body weight ↓, gut microbiota regulation	[164]
		LPS-treated C2C12 myotubes	Protein degradation (atrogin-1, MAFbx) ↓	[165]
		C57BL/6J mice	Muscle mass ↑, muscle function ↑	[166]
		C2C12 myotubes	Stimulation of myogenic differentiation	[166]
		Denervated mice	Muscle mass ↑, protein degradation (MuRF1) ↓, Muscle inflammation ↓	[167]
		HFD-fed C57BL/6J mice	Fat mass ↓, muscle mass ↑, protein degradation (atrogin-1, MuRF1) ↓, mitochondrial dysfunction ↓, mitochondrial biogenesis ↑, AMPK ↑	[168]
		PA-treated C2C12 myotubes	Muscle atrophy ↓, mitochondrial dysfunction ↓, AMPK ↑	[168]
		Aged mice	Muscle mass ↑, muscle function ↑, mitochondrial function ↑, mitochondrial biogenesis ↑, oxidative stress ↓, hyperactive mitophagy and apoptosis ↓	[169]
Flavone	Luteolin	LPS-treated C2C12 myotubes	Protein degradation (atrogin-1, MAFbx) ↓	[165]
		HFD-fed C57BL/6J mice	Body weight ↓, fat mass ↓, muscle mass ↑, muscle fiber size and number ↑, muscle function ↑, protein degradation (atrogin, FoxO, MuRF) ↓, muscular lipid accumulation ↓, Muscle inflammation ↓	[171]
		Cachectic mice.	Muscle mass ↑, protein degradation (atrogin-1, MuRF1) ↓	[172]
Flavonol	Quercetin	HFD-fed ICR mice	Lipogenesis ↓, lipolysis ↑, WAT browning and thermogenesis ↑, AMPK ↑,	[180]
		HFD-fed aged mice	Body Weight ↓	[181]
		3T3-L1 cells	Adipogenesis ↓, AMPK ↑, apoptosis ↑	[182]
		HFD-fed C57BL/6J mice	Body Weight ↓, fat mass ↓, lipogenesis ↓	[183]
		Rat adipocytes	Lipolysis ↑	[184]
		Subjects with APOE genotype	Waist circumference ↓	[187]
		HFD-fed C57BL/6J mice	Fat mass ↓, Muscle mass ↑, muscle fiber size ↑, protein degradation (atrogin-1, MuRF1) ↓, Muscle inflammation ↓	[189]
		PA-treated cocultured C2C12 myotubes and Raw264.7 cells	Protein degradation (atrogin-1, MuRF1) ↓, inflammation ↓	[189]
		TNFα-treated myotubes	Protein degradation (atrogin-1, MAFbx, MuRF1) ↓, oxidative stress ↓, inflammation ↓	[190]
		HFD-fed C57BL/6J mice	Improvement in muscle atrophy, oxidative stress ↓, inflammation ↓	[190]
		Tail-suspension mice	Muscle mass ↑, protein degradation (atrogin-1, MuRF1) ↓, oxidative stress ↓	[191]
		Denervated mice	Muscle mass ↑, muscle fiber size ↑, protein synthesis (IGF-1, AKT) ↑	[192]
		Cachectic mice.	Muscle mass ↑, improvement in mitochondrial homeostatic balance	[193]
		Denervated mice	Improvement in muscle atrophy	[194]

Table 1. *Cont.*

Subclass	Flavonoid Name	Experimental Model	Effects and Potential Mechanisms	References
flavonol	Dihydromyricetin	3T3-L1 cells	lipid droplet formation ↓, Adipogenesis ↓	[202]
		HFD-fed C57BL/6J mice	Body weight ↓, Fat mass ↓, WAT browning ↑	[203]
		ob/ob mice	Body weight gain ↓, gut microbiota regulation	[205]
		HFD-fed C57BL/6J mice, ob/ob mice	Muscle insulin resistance ↓, proportion of type I fibers ↓	[206]
		SD rats under simulated high-altitude conditions	Muscle function ↑, hypobaric hypoxia-induced mitochondrial dysfunction ↓, mitochondrial biogenesis ↑	[208]
		SD rats	Muscle mass ↑, muscle fiber size ↑, mitochondrial biogenesis ↑, improvement in mitochondrial dysfunction, oxidative stress ↓	[209]
		D-gal-induced aging rats	Muscle mass ↑, muscle fiber size ↑, protein degradation (atrogin-1, MAFbx) ↓, AMPK ↑	[210]
		HFD-fed C57BL/6J mice	Fat mass ↓, muscle mass ↑, inflammation ↓, muscle function ↑, protein degradation (atrogin-1) ↓, protein synthesis (mTOR) ↑, AMPK ↑	[211]
		TNF-α-treated C2C12 myotubes	Inflammation ↓, protein degradation (atrogin-1, MuRF1) ↓, protein synthesis (mTOR) ↑, AMPK ↑	[211]
flavanol	EGCG	HFD-fed C57BL/6J mice	Body weight gain ↓, fat mass ↓, BAT thermogenesis and mitochondrial biogenesis ↑, AMPK ↑	[219]
		HFD-fed C57BL/6J mice	Body weight ↓, fat mass ↓, BAT thermogenesis ↑	[220]
		HFD-fed aged mice	Body weight ↓, fat mass ↓, food intake ↑, lipogenesis ↓, fatty acid oxidation ↑, gut microbiota regulation	[221]
		HFD-fed C57BL/6J mice	Fat mass ↓, lipogenesis ↓, lipolysis ↑, AMPK ↑	[222]
		HFD-fed C57BL/6J mice	Body weight ↓, fat mass ↓, lipogenesis ↓, lipolysis ↑, autophagy ↑, AMPK ↑	[223]
		3T3-L1 cells	Adipogenesis ↓	[224,225]
		Overweight men	Fatty acid oxidation ↑	[226]
		Aged rats (muscle disuse as hindlimb unloading)	Muscle mass ↑, muscle fiber size ↑, muscle function ↑, apoptosis ↓, satellite proliferation ↑	[230]
		Aged rats (muscle recovery after forced disuse)	Recovery from disuse, autophagy ↓, apoptosis ↓	[231]
		Aged rats	Muscle mass ↑, muscle fiber size ↑, protein degradation (MuRF1, MAFbx) ↓, myostatin ↓, protein synthesis (IGF-1) ↑,	[232]
		Aged mice	Muscle mass ↑, protein synthesis (IGF-1, AKT) ↑, protein degradation (atrogin-1, FoxO, MuRF) ↓	[233]
		Cachectic mice	Muscle mass ↑, protein degradation (MuRF, MAFbx) ↓, inflammation ↓	[234]
		Denervated rats	Muscle function ↑, apoptosis ↓	[235]
		Mice	Endurance capacity ↑, fatty acid oxidation ↑	[236]
		GK rats	Oxidative stress ↓, mitochondrial dysfunction ↓, autophagy ↓	[237]
		C2C12 myotubes	Protein degradation (MuRF1, MAFbx) ↓, protein synthesis (AKT) ↑	[238]
flavanol	Epicatechin	Aged mice	Muscle fiber size ↑, muscle function ↑	[239]
		Obese middle-aged mice	Body weight ↓, fat mass ↓, muscle function ↑, protein degradation (MuRF) ↓, muscle growth and differentiation ↑, oxidative stress ↓	[240]
		Aged mice	Oxidative stress ↓, mitochondrial biogenesis ↑	[241]
		C2C12 myotubes	Protein degradation (atrogin-1, MuRF1) ↓	[242]
		C2C12 myotubes	Mitochondrial biogenesis ↑	[243]
		Sarcopenic older adults (resistance training and epicatechin supplementation)	Muscle mass ↑, Skeletal muscle strength ↑, myostatin ↓, muscle growth factors ↑	[244]

Table 1. *Cont.*

Subclass	Flavonoid Name	Experimental Model	Effects and Potential Mechanisms	References
flavone	5,7-dimethoxyflavon	Aged mice	Muscle mass ↑, muscle fiber size ↑, muscle function ↑, protein synthesis (AKT, mTOR) ↑, protein degradation (atrogin-1, MuRF) ↓, mitochondrial biogenesis ↑, inflammation ↓	[247]
		3T3-L1 cell	Adipogenesis ↓	[248]
		HFD-fed C57BL/6J mice	Body weight gain ↓, fat mass ↓, adipogenesis ↓	[248]
isoflavan	Glabridin	Dexamethasone-treated C2C12 myotube	Protein degradation (MuRF1, FoxO) ↓,	[249]
		Dexamethasone-treated mice	Muscle mass ↑, protein degradation (MuRF1, FoxO) ↓,	[249]
		HFD-fed C57BL/6J mice	Body weight ↓, fat mass ↓, food intake ↓, energy expenditure ↑, inflammation ↓, lipogenesis ↓, fatty acid oxidation ↑, AMPK ↑	[250]
		C2C12 myotubes	Fatty acid oxidation ↑, AMPK ↑	[250]
flavanone	Hesperetin	HFD-fed C57BL/6J mice	Body weight gain ↓, fat mass ↓	[251]
		Aged mice	Muscle fiber size ↑, muscle function ↑, oxidative stress ↓	[252]
		Aged mice	Fat mass ↓, muscle mass ↑, muscle fiber size ↑, energy expenditure ↑	[253]
flavanone	naringenin	HFD-fed ovariectomized mice	Fat mass ↓, inflammation ↓	[254]
		Ovariectomized mice	Fat mass ↓, muscle mass ↑, muscle lipid accumulation ↓	[255]
		L6 myoblast, C2C12 myoblasts, satellite cells	Regulation of skeletal muscle differentiation	[256]
		HFHC diet-fed Ldlr−/− mice	Fat mass ↓, energy expenditure ↑, insulin resistance ↓	[257]

APOE, apolipoprotein E; D-gal, D-galactose; HFD, high-fat diet; HFHC, high fat and high cholesterol; LPS, lipopolysaccharide; PA, palmitic acid.

However, the underlying mechanisms of action remain obscure, and limited human clinical trials have investigated the effectiveness of flavonoids in sarcopenic obesity. Therefore, further studies are required to assess the potential impact and mechanism of flavonoid-mediated prevention of sarcopenic obesity. In addition, advancing the understanding of sarcopenic obesity may contribute to the emergence of novel therapies to prevent associated comorbidities, such as cardiometabolic diseases.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The author declares no conflict of interest.

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