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Review

Potential of Laurel (*Laurus nobilis* L.) Leaf Polyphenols for Modulation of Body Composition

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Featured Application: Based on the properties evaluated in this review, laurel leaf polyphenols could promote healthy aging by preventing or abating various metabolic disorders and modulating body composition. They could also be therapeutic for noncommunicable diseases characterized by inflammation and oxidative stress in younger individuals triggered by sedentary lifestyle and nonoptimal dietary patterns.

Abstract: Due to increased life spans and senescence in society, there is a growing need for supplements that enable healthy aging. Aging is accompanied by changes in body composition such as loss of bone and muscle mass and increase/redistribution of adipose tissue. These changes may, at least in part, be alleviated by exercise, adequate diet and possibly some natural adjuvants. Laurel (*L. nobilis* L.) leaves are rich in secondary metabolites, especially polyphenols (mostly flavonols, phenolic acids and flavones) which have recently showed potential for modulation of body composition that could allow healthier aging. Therefore, the aim of this paper was to evaluate the potential of laurel leaf polyphenols for modulating body composition. We searched the literature available on the PubMed electronic database related to the main polyphenolic representatives of laurel leaf extracts (namely, kaempferol, hydroxycinnamic acids and apigenin) and their modulation of bone, skeletal muscle and adipose tissue. The search yielded 135 articles showing that the main laurel leaf polyphenols exhibit various positive effects on bones, skeletal muscle and adipose tissue. These effects could ameliorate metabolic disorders related to modern lifestyles and result in an improvement of body composition and function, resulting in healthier aging, but more evidence-based research in humans is needed.

Keywords: body composition; bone health; skeletal muscle; adipose tissue; healthy aging; polyphenols; *Laurus nobilis*

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1. Introduction

In the last 5 years, there have been more people over the age of 65 than children younger than 5 years [1]. Consequently, there is growing interest in finding optimal physiological, endocrinological, nutritional, and lifestyle milieus for promoting healthy aging. Generally, normal aging involves changes in body composition including the loss of bone (osteoporosis) and muscle (sarcopenia) mass and increased and/or redistributed body fat [2]. A new syndrome, osteosarcopenic obesity/adiposity, has been identified to describe impairments of all three tissues [3,4]. The syndrome has been widely studied, and findings have revealed that the combined condition is characterized by more damaging health outcomes than any one or two of the conditions (e.g., osteoporosis, sarcopenia, or obesity alone) [5].

The ultimate goal of research endeavors is to find ways in which optimal lifestyle modifications, namely food choices and physical activity, could be used to either prevent or ameliorate the inevitable changes of aging [6,7], including body composition deterioration. There is increasing evidence about the relationship between body composition and some

bioactive components [8–11] that could enhance the positive effects of healthy food choices and physical activity and lead to improved health during aging. In this context, different plant sources are being considered as sources of polyphenols that could be used for food fortification or as supplements.

Laurel (*L. nobilis* L) or bay leaf is a Mediterranean bush best known for the culinary use of its leaves, as well as for some medicinal purposes (e.g., treating various gastrointestinal and respiratory diseases), since ancient times [12]. Therefore, the leaves have been researched to a greater extent than other plant parts. They contain several metabolites, such as polyphenols, norisoprenoids, alkaloids, organic acids and volatile oils, which exhibit various biological activities responsible for the leaves' beneficial effects [13]. Among these, polyphenols are of special interest, since the laurel leaves contain a variety of such compounds, including flavonoids (flavonols, flavones, flavan-3-ols, flavanones), phenolic acids, proanthocyanidins and lignans. According to a previous literature review [14], flavonols represent nearly 50% of laurel leaf polyphenols, kaempferol glycosides being the most abundant flavonols. Phenolic acids (predominantly hydroxycinnamic acids) and flavones (mainly apigenin and its glycosides) account for around 20% and 15% of the laurel leaf polyphenols, respectively, while other phenolic groups are present in lower proportions. The rich polyphenolic content of this Mediterranean plant indicates that the leaf extracts could possibly be used to benefit some health issues, including modulation of body composition, mainly through their proven antioxidant [15–17] and anti-inflammatory activity [18,19], since oxidative stress and inflammation play a significant role in the deterioration of body composition [20–25].

Therefore, the aim of this paper was to evaluate the potential of laurel leaf extracts for modulating body composition, including bone, muscle and adipose tissues. We focused on the main components, such as kaempferol, hydroxycinnamic acids and apigenin.

2. Review Method

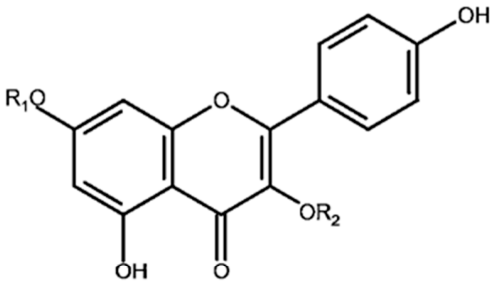
In order to find literature related to the effect of the main laurel leaf polyphenols on body composition, the electronic database PubMed was searched. The following keywords were used: "kaempferol", "hydroxycinnamic acids", "apigenin", "bones", "bone health", "skeletal muscle", "adipose tissue", and combinations of these. During the search, filters related to the year of publication (2012–2022), type of article (research articles) and the language of the publication (English) were applied. The search resulted in 135 publications (45 for kaempferol, 50 for hydroxycinnamic acids and 40 for apigenin). All publications that appeared as a result of the search with available full texts or abstracts were reviewed, and relevant ones that included compounds present in laurel leaves and effects related to body composition were included in this review and systematically sorted in the following subsections.

3. Overview of Main Laurel Leaf Polyphenols' Components

3.1. Kaempferol

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is a widely distributed flavonol that has a diphenylpropane structure (C6-C3-C6) (Figure 1) and is synthetized through the condensation of 4-coumaroyl-CoA with three molecules of malonyl-CoA. It is most often bonded with sugars such as glucose, galactose, rhamnose and rutinose to form glycosides [26].

Laurel leaves contain a variety of biologically active kaempferol glycosides formed by simple and complex biosynthesis pathways, such as the commonly detected kaempferol-3-O-glucoside (astragalin), kaempferol-3-O-rutinoside and kaempferol-3-O-α-L-(2″,4″-di-E-*p*-coumaroyl)-pyranorhamnoside [13,14].

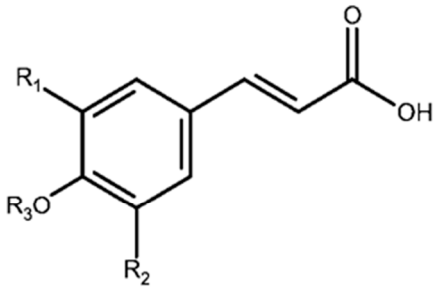


Kaempferol(R_1=H; R_2=H); Kaempferol-3-O-glucoside (R_1=H; R_2=glucopyranoside);Kaempferol-3-O-α-L-(2″,4″-di-E-p-coumaroyl)-pyranorhamnoside (R_1=H; R_2=α-L-(2″,4″-di-E-p-coumaroyl)-pyranorhamnoside); kaempferol-3-O-rutinoside(R_1=H, R_2=rutinoside); kaempferol-3,7-di-O-a-L-thamnosidę (R_1=H; R_2=α-L-thamnoside)

Figure 1. Chemical structure of kaempferol and commonly detected glycosides (adapted from [27]).

3.2. Hydroxycinnamic Acids

Phenolic acids are a group of polyphenols that possess a carboxylic acid as the main functional group and are divided into two groups—hydroxybenzoic and hydroxycinnamic acids. Hydroxycinnamic acids are more common phenolic acids that have a phenylpropanoid C6-C3 structure as the main chemical scaffold and are characterized by the presence of hydroxyl groups at different positions on the aromatic rings and a carboxyl group in the lateral chain [28]. Some of the most commonly found hydroxycinnamic acids in laurel leaves are caffeic, sinapic, ferulic and *p*-coumaric acid (Figure 2) [13,27,29].



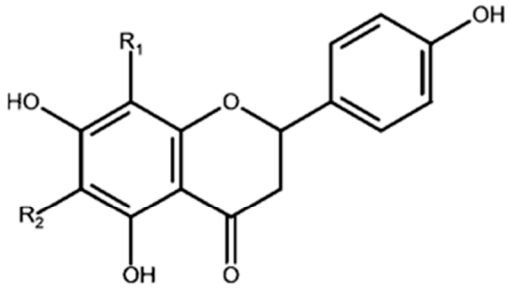
Caffeic acid (R_1=OH, R_2=R_3=H); *p*-coumaric acid (R_1=R_2=R_3=H); ferulic acid (R_1=OCH_3, R_2=R_3=H); sinapic acid (R_1=R_2=OCH_3,R_3=H)

Figure 2. Chemical structure of hydroxycinnamic acids commonly detected in laurel leaves (adapted from [13,27]).

3.3. Apigenin

Apigenin (5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one) is a widely distributed flavone substituted by three hydroxy groups at positions 4′, 5′ and 7 (Figure 3). In plants, it is most often present in the form of O- or C- glucosides, followed by the aglycone form and its methylated or acetylated derivatives [30].

The aglycone form of apigenin and four different glycosides (apigenin 8-C glucoside, apigenin-6,8-di-C-hexoside, apigenin-6-C-hexoside and apigenin-6-C-(2″-O-deoxyhexosyl)-hexoside) have all been detected in laurel leaves [13].



Apigenin (R_1=R_2=H); apigenin-8-C-glucoside (R_1=glucoside, R_2=H; apigenin-6,8-di-C-hexoside (R_1=hexoside, R_2=hexoside); apigenin-6-C-(2″-O-deoxyhexosyl)-hexoside (R_1=H, R_2= hexosyl-2″-O-deoxyhexosyl; apigenin-6-C-glucoside (R_1=H, R_2=glucoside)

Figure 3. Chemical structure of apigenin and its glycosides detected in laurel leaves (adapted from [13]).

4. Influence of Laurel Leaf Polyphenols on Body Composition

Physiological intracellular redox homeostasis is a balance between the levels of prooxidants (ROS and RNS) and their elimination by antioxidants [31]. This balance is disrupted by the increased production of free radicals during physiological processes (aging and hormonal changes) and pathological events paired with the reduced production of endogenous antioxidants resulting in a state of oxidative stress and enhanced inflammation [32], which results in modified transcriptomal activity, cellular signaling pathways, reduced mitochondrial function, altered protein formation and decreased cellular metabolism linked to different human disorders [31,33]. Oxidative stress and inflammation can be considered some of the main contributors to age-related changes in bones, skeletal muscle and adipose tissue. For example, it has been shown that oxidative stress and inflammation lead to an imbalance between osteoclast and osteoblast activity in bones by interfering with complex molecular pathways [20,22], which can lead to metabolic bone diseases and contribute to pathogenesis of the skeletal system. In skeletal muscle, chronic low-grade inflammation disrupts the muscle protein metabolism, leading to a progressive loss of skeletal muscle mass [24], while oxidative stress has been connected with the inability of aged satellite cells to maintain the homeostatic activity of skeletal muscle [21]. Adipose tissue is severely affected by inflammation and oxidative stress, which has been shown to affect cellular aspects of adipocyte differentiation [25,34] and the endocrine and metabolic functions of the adipose tissue [25]. For this reason, the antioxidant and anti-inflammatory activity of polyphenols through their involvement in different signaling pathways in the human body represent the most likely mechanisms by which the polyphenols alleviate age-related changes in body composition.

Several antioxidant mechanisms of polyphenols have been proposed. First, polyphenols can directly scavenge ROS due to the hydroxyl groups in their structure, the number and position of which, paired with substitution pattern and glycosylation, determine the strength of antioxidant activity [35]. The second possible mechanism is the upregulation of endogenous antioxidant and oxidase enzyme activity (SOD1 in the cytosol and SOD2 in the mitochondria) [35]. Polyphenols may also enhance cellular antioxidant activity through the regulation of the Nrf2-mediated pathways included in the regulation of genes responsible for cell survival, metabolism, and adipocyte differentiation (e.g., FoxO1), as well as detoxifying enzymes such as SOD, GSH, NQO1, GST and HO-1 by binding to AREs in the gene promoter regions of the enzymes [36,37]. There is also emerging evidence that the polyphenols counteract ROS through regulation of microRNAs (endogenous non-coding short RNAs) that regulate various biological pathways [35]. The main molecular mechanisms related to the anti-inflammatory activity of polyphenols include: (a) the inhibition of proinflammatory enzymes (COX-2, LOX, iNOS) through the activation of PPARγ; (b) the inhibition of mitogen-activated protein kinases (MAPK), phosphoinositide 3-kinase (PI3K), and tyrosine

kinases (NF-κB); (c) activation of endogenous antioxidant enzymes; and (d) modulation of cell survival genes [38]. A general overview of the polyphenols' molecular targets related to their antioxidant and anti-inflammatory activity is shown in Figure 4, while the specific effects of laurel leaf polyphenols are discussed further in the text.

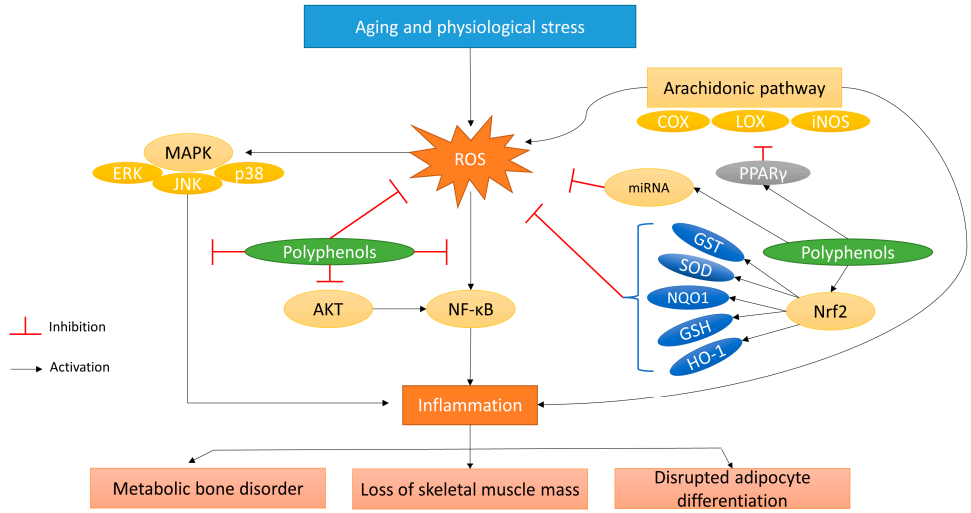


Figure 4. Overview of potential molecular targets for polyphenols' antioxidant and anti-inflammatory activity. MAPK, mitogen-activated kinase; ERK, extracellular signal-regulated kinase; p38, p38 MAPK; AKT, protein kinase B; NF-κB, nuclear factor-kappa β; ROS, radical oxygen species; COX, cyclooxigenase; LOX, lipoxygenase; iNOS, inducible nitrogen oxide synthase; PPARγ, peroxisome proliferator-activated receptor γ; miRNA, micro ribonucleic acid; Nrf2, nuclear factor erythroid 2-related factor 2; GST, glutathione S-transferase; SOD, superoxide dismutase; NQO1, NADP(H) quinone oxidoreductase 1; GSH, glutathion; HO-1, heme oxygenase-1.

4.1. Influence of Laurel Leaf Polyphenols on Bones

Bone is a composite structure that consists of inorganic mineral (calcium, phosphorus) crystals, an organic matrix represented mainly by collagen type I, other proteins, water, and some lipids. The majority of bone cells are mesenchymal-originated chondrocytes (osteoblasts and osteocytes), which are responsible for the deposition and remodeling of the growth plate, while hematopoietic multinucleated osteoclasts are responsible for bone resorption [39]. These processes are regulated by multiple molecular pathways including systemic (e.g., growth and sex hormones, calcitriol, calcitonin, IGF-1, glucocorticoids) and local (e.g., the osteoprotegerin—receptor activator of NFκ-B ligand) factors [40], yielding opportunities for the action of some exogenous bioactive components. A pathway regulated by the wingless-type MMTV integration site (Wnt) genes was shown to regulate aging in all cells, as well as in bone cells, where it was first observed that decreased expression of the Wnt genes resulted in lower osteoblast formation [39]. Aside from these, physiological redox status also seems to play an important role in the maintenance of balanced osteoclast and osteoblast activity and bone turnover [41]. In addition to the imbalance in bone turnover in favor of bone resorption, aging results in changes in collagen structure and increase in non-collagenous proteins, which regulate cell-matrix and mineral-matrix interactions leading to fragile bones [42]. Moreover, the mineral content of bones increases with age (in relation to the protein part of the bone volume), leading to the exponential loss of bone toughness and increased susceptibility to breaking [39]. The potential role of polyphenols in maintaining bone health mainly originates from their aforementioned antioxidant and anti-inflammatory activity but could also be exerted by other unknown and/or unclarified mechanisms [40]. The search on the PubMed database yielded 30 studies (8 for kaempferol, 10 for hydroxycinnamic acids and 12 for apigenin) published in the last ten years. The main observed effects of the selected laurel leaf polyphenols on bones are summarized in Table 1 and discussed below.

Table 1. Summary of main laurel leaf polyphenols' effects on bones.

Compound(s)	Effects	Reference
Kaempferol	Induction of SaOS-2 osteoblast differentiation	[43]
	Promotion of osteoblast survival in glucocorticoid induced osteonecrosis on human bone microvascular endothelial cells and in vivo in female ovariectomized rats	[44,45]
	Promotion of bone regeneration in rat bone marrow stromal cells and in vivo in rat femur bones	[46]
Hydroxycinnamic acids	Supression of bone erosion and osteoporosis in murine bone marrow cells and RAW 264.7 macrophage cell line; in vivo in neonatal rats with induced osteoporosis	[47,48]
	Promotion of bone regeneration in a critical-sized rat calvarial bone defect model system and in a rat model of critically sized mandible defects	[49,50]
	Inhibition of oxidative stress and inflammation related to arthritis and disc degradation in nucleus pulposus cells and in acute and chronic models of inflammation	[51,52]
Apigenin	Reduction of epidural fibrosis after spine surgery in human fibroblasts and in vivo in Sprague-Dawley rats	[53]
	Treatment of osteoporosis in ovariectomy-induced osteoporosis rats	[54]

4.1.1. Kaempferol

As shown in Table 1, one of the main effects of kaempferol on bones was the induction of osteoblast differentiation achieved by mediating the activation of the Wnt signaling pathway through the estrogen signaling pathway in SaOS-2 osteoblasts [43]. The observed effects included increased osteogenic markers during the early and late phases of the signaling processes. The results of osteoblast survival promotion were observed in studies where glucocorticoid-induced bone loss was alleviated by kaempferol, resulting in higher expression of osteogenic markers and lower damage to bone microvascular endothelial cells isolated from a human femoral head or femoral neck in vitro [44], and improved callus formation at injured sites in female ovariectomized rats in vivo [45]. The induced bone regeneration was observed in a study where kaempferol was used for formulation of titanium-dioxide implants used for promoting bone formation [46]. The titanium dioxide implants promoted osteogenic differentiation of mesenchymal stem cells, alkaline phosphatase activity and calcium deposition in vitro on rat bone marrow stromal cells, while histological analysis revealed stimulation of new bone formation around implants on rat femur bones. In another study, zein-coated 58S glass-based scaffolds showed desirable mechanical and release properties, showing the potential of these scaffolds for bone tissue engineering; however, their application needs further exploration [55].

4.1.2. Hydroxycinnamic Acids

As shown in Table 1, several positive outcomes of hydroxycinnamic acids on bones were reported. Doss et al. [27] showed beneficial effects on osteoporosis and bone erosion related to rheumatoid arthritis, in which treatment with ferulic acid resulted in significant decrease in osteoclast activity and downregulation of the inflammatory NF-κB pathway in vitro tested on albino Wistar rats' bone marrow cells and a murine RAW 264.7 macrophage cell line. Another study showed an increase in bone mineral density along with increased mRNA and SIRT-1 levels and the reduction of NF-κB in vivo in neonatal rats with glucocorticoid-induced osteoporosis [48]. Another observed effect was the promotion of bone regeneration by the application of sinapic acid-loaded chitosan nanoparticles, which showed activation of osteogenesis molecular pathways in vitro on mouse mesenchymal stem cells and bone formation in vivo in a critical-sized rat calvarial bone defect model system [49]. In addition, a *p*-coumaric acid-conjugated collagen scaffold applied in a rat

model of critically sized mandible defects showed enhancement of bone regeneration by activating osteogenic, anti-osteoclastic and angiogenic responses [50]. Ferulic acid incorporated into a gelatin–chitosan–glycerol phosphate hydrogel showed downregulation of metalloproteinase activity and upregulation of type II collagen and inhibited oxidative-stress-induced apoptosis of nucleus pulposus cells related to disc degeneration [52]. An ethyl ester of *p*-coumaric acid showed inhibition of the inflammatory pathways involved in the pathogenesis of arthritis on acute and chronic models of inflammation, showing potential for application in treatment of arthritis [51].

4.1.3. Apigenin

Even though the initial results of the PubMed search yielded 12 studies by using the keywords "apigenin" and "bones", only two studies were related to the potential effects of the apigenin (glycosides) present in laurel leaves on human bone health. In a study carried out by Jie et al. [53], it was shown that apigenin can reduce epidural fibrosis, a common post-laminectomy complication, by suppressing the Wnt signaling pathway in human fibroblasts, and this finding was supported by histological and immunohistochemical analysis of Sprague-Dawley rats' bone tissue [53]. Vicenin-2 (apigenin 6,8-di-C-glucoside) improved bone turnover markers, body mass and inflammatory markers, and increased the presence of calcium in ovariectomy-induced osteoporosis rats' serum, showing potential for osteoporosis treatment [54].

Overall, these are promising findings, but the studies have been done only in cell cultures or animal models. Therefore, more research in humans and supplementation with specific derivatives is needed for evidence-based findings about the effects of laurel leaf polyphenols on bones.

4.2. Influence of Laurel Leaf Polyphenols on Skeletal Muscle

The human body consists of over 500 skeletal muscles, which support the skeletal system and are controlled by the nervous system. These muscles are built from muscle fibers formed from the smallest repeating functional units, called sarcomeres, which are responsible for the contraction and relaxation of the muscles [56]. Besides supporting the bones, skeletal muscles are involved in numerous metabolic processes, including being the site of action for fatty acid metabolism and glycogen synthesis [57]. In addition, muscles interact with other organs through the excretion of myokines, which support the metabolic function of different tissues, such as the bones, pancreas, liver, and adipose tissue, by exerting autocrine, paracrine, or endocrine effects [4,58]. For this reason, metabolic disturbances (e.g., hormonal disruption, inflammation, or gene expression) can result in insulin resistance, metabolic syndrome, obesity, or other problems, showing the importance of the muscles in maintaining overall health. Skeletal muscle atrophy (decrease of muscle mass and strength), also known as sarcopenia/dynapenia, can occur in numerous situations. For example, reduced protein synthesis or accelerated protein degradation due to various illnesses and aging may result in mitochondrial dysfunction, inflammation and oxidative stress, which modulate the signaling pathways included in muscle homeostasis [59]. The PubMed database search yielded 42 studies (16 for kaempferol, 17 for hydroxycinnamic acids and 9 for apigenin) published in the last ten years. The main observed effects of the selected laurel leaf polyphenols on skeletal muscle are summarized in Table 2 and discussed below.

Table 2. Summary of main laurel leaf polyphenols' effects on skeletal muscle.

Compound(s)	Effects	Reference
Kaempferol	Antidiabetic on L6 murine skeletal muscle cells and in vivo in streptozotocin-induced diabetic rats	[60–64]
	Increase of ATP content in myotubes at hypoxic conditions	[65]
Hydroxycinnamic acids	Muscle growth promotion on C2C12 murine skeletal muscle cells and in vivo in zebrafish models	[66–68]
	Modification of muscle fiber type on C2C12 murine skeletal muscle cells and in vivo in weaned piglets	[69,70]
	Influence on skeletal muscle differentiation in C2C12 murine skeletal muscle cells	[68,71]
	Antidiabetic on L6 murine skeletal muscle cells	[72–75]
Apigenin	Suppression of muscle atrophy on C2C12 murine skeletal muscle cells and in vivo in mice	[76–80]

4.2.1. Kaempferol

As shown in Table 2, the antidiabetic activity of kaempferol was the most researched subject related to skeletal muscle. It was shown that oral administration of kaempferol to diabetic mice promoted glucose metabolism in skeletal muscle by restoring hexokinase activity while inhibiting gluconeogenesis in the liver through the suppression of pyruvate carboxylase activity [60]. Another mechanism of action was shown to be the influence on the JAK 2-dependent pathway resulting in an increased glucose uptake in L6 myotubes (developmental stage of muscle fiber) and an increased GLUT-4 translocation, resulting in the prevention of hyperglycemia [63]. In another study, kaempferol was among the most active ligands from *Carica papaya* extract in the acceleration of GLUT-4 and insulin receptor expression, confirming the hypoglycemic effect in diabetic skeletal muscle [64]. Kaempferol-3-rutinoside also showed stimulating effects on glucose uptake through the induction of SIRT-1, which is included in the metabolic pathway and insulin signaling, along with increased GLUT-4 translocation in myotubes [62]. Among five kaempferol glycosides, kaempferitrin (kaempferol 3,7-dirhamnoside) was dominant in modulation of the glycolytic enzyme 6-phosphofructo-1-kinase tested in murine skeletal muscles, adipose and liver tissue. This was attributed to the presence of two rhamnosyl moieties directly related to the hypoglycemic activity [61]. Apart from the antidiabetic activity, Aikajima et al. [65] showed that kaempferol can increase the content of ATP in myotubes under low oxygen conditions by suppressing the hypoxia-inducible factor-1α responsible for the switch from the mitochondrial respiration to glycolysis. This can be useful, since altered metabolism in the muscles can occur regardless of oxygen presence, often due to a sedentary lifestyle [65].

4.2.2. Hydroxycinnamic Acids

Research on hydroxycinnamic acids showed several effects on skeletal muscle. Ferulic acid was the most investigated of the hydroxycinnamic acids, exhibiting muscle growth through promotion of upregulation of myogenic transcriptional factors and their target genes and resulting in elevated levels of myosin heavy chain and overall muscle mass in a zebrafish model [66,67]. Ferulic acid was also shown to regulate muscle fiber type formation through the SIRT-1/AMP-activated protein kinase/PGC-1α signaling pathway in mouse C2C12 myotubes [70], as well as in weaned piglets where fast-twitch muscle fibers switched to slow-twitch [69]. In addition, ferulic acid was shown to modulate the differentiation of L6 skeletal muscle cells by activating the ERK 1/2 and AKT signaling cascades, osteogenic genes and myogenic protein markers [68]. In contrast, coumaric acid inhibited skeletal muscle differentiation through the AMPK-α mediated pathway, which decreased the expression of early myogenic differentiation markers in L6 skeletal muscle cells [71]. However, coumaric acid showed potential for modulating glucose metabolism

by increasing the phosphorylation of AMP-activated protein kinase in L6 skeletal muscle cells [75]. Ferulic acid exhibited similar effects in L6 skeletal muscle and in hyperglycemia-induced human liver cells (HepG2). In addition, it also upregulated GLUT-2 and GLUT-4 transporters and inhibited c-Jun N-terminal protein kinase by increased phosphorylation. These findings showed the potential for the treatment of hyperglycemia of both coumaric and ferulic acid [64]. Ferulic acid also ameliorated insulin resistance by promoting glucose uptake and glycogen synthesis in muscle cells (that were insulin-resistant) through the enhancement of transferrin receptor-containing endosomal compartment activities [73]. Another mechanism by which ferulic acid may modulate insulin resistance is by blocking the phospho-PKCε via prevention of saturated fatty acid-induced impairment of insulin signaling molecules in skeletal muscle cells [72].

4.2.3. Apigenin

The only effect of apigenin that was investigated in the published studies included in this review was the suppression of muscle atrophy through different mechanisms. It was shown that apigenin can ameliorate obesity- and sciatic nerve denervation-induced skeletal muscle atrophy by reducing the expression of atrophic genes (MuRF1 and Atrogin-1), increasing mitochondrial function in obese mice and upregulating myosin heavy chain in sciatic nerve-denervated mice [77,78]. Apigenin also repressed age-related skeletal muscle atrophy in mice by activating antioxidant and mitochondrial respiratory enzymes, enhancing the expression related to mitochondrial biogenesis and inhibiting Bcl-2/adenovirus E1B 19kD-interacting protein 3 and DNA fragmentation characteristic of mitophagy and apoptosis [80]. Apigenin also inhibited lipopolysaccharide-mediated expression of atrophic genes by inhibiting the JNK-2 molecular pathway in murine C2C12 myotubes, resulting in suppressed muscle atrophy [76]. In addition, apigenin enhanced skeletal muscle hypertrophy and myoblast differentiation in mice through the regulation of the Prmt7-PGC-1α-GPR56 and Prmt7-p38-myoD molecular pathways, indicating the possibility of prevention of other forms of skeletal muscle weakness and atrophy, such as sarcopenia and dynapenia [79].

Overall, like the effects on bones, the laurel leaves components' biological effects on muscle need more investigation, as all the studies were performed on animal models or in vitro. However, these are all encouraging leads and beginnings for human studies.

4.3. Influence of Laurel Leaf Polyphenols on Adipose Tissue

Adipose tissue is the largest endocrine organ, as well as a site for energy storage. It plays an important role in metabolic processes and energy homeostasis by releasing factors that regulate appetite, insulin sensitivity, glucose metabolism, inflammation and tissue (dis)repair [81]. It is typically divided into white adipose tissue, which is the dominant lipid storage with a role in multiple endocrine and immune responses, and brown adipose tissue, which enhances energy release and thermogenesis and is responsible for maintaining body temperature during cold exposure [82,83]. Also, white adipose tissue is categorized as subcutaneous and visceral fat. The latter increases during aging, and its redistribution is phenotypically visible as intraabdominal (visceral) fat [84]. During aging, the dysregulation of endocrine factors results in reduced ability of the adipose tissue to buffer the excess of ingested energy, which, in addition to numerous other factors, leads to higher obesity prevalence in older individuals [85]. In addition, dysfunctional adipose tissue with a dysregulated secretome is correlated with various age-related disorders regulated by hormones and inflammatory pathways and characterized by states of low-grade chronic inflammation and oxidative stress [81,86]. The search of the PubMed database resulted in 63 studies (21 for kaempferol, 23 for hydroxycinnamic acids and 19 for apigenin) published in the last ten years. The main observed effects of the selected laurel leaf polyphenols on adipose tissue are summarized in Table 3 and discussed further below.

Table 3. Summary of main laurel leaf polyphenols' effects on adipose tissue.

Compound(s)	Effects	Reference
Kaempferol	Antiobesity on murine adipocytes and in vivo in obese mice	[87–92]
	Antidiabetic on murine adipocytes and in vivo in obese C57BL/6 mice	[87,89,93]
	Anti-inflammatory on macrophage-like cell line J774.1 and in vivo in obese mice	[92,93]
Hydroxycinnamic acids	Antiobesity on human and murine adipocytes and in vivo in obese mice	[94–103]
	Antidiabetic on murine adipocytes and in vivo in obese and diabetic mice	[72,95,100,101]
	Anti-inflammatory on murine 3T3-L1 adipocytes and lipopolysaccharides (LPS)-induced macrophages; in vivo in obese mice	[72,95,97]
	Management of NAFLD [a] in vivo in obese mice	[95]
Apigenin	Antiobesity on murine 3T3-L1 and human adipocytes and in vivo in obese mice	[104–111]
	Anti-inflammatory on human adipocytes and in vivo in obese mice	[106,107,112]
	Antidiabetic in vivo in obese mice	[109,112]

[a] non-alcoholic fatty liver disease.

4.3.1. Kaempferol

Kaempferol showed several beneficial effects on adipose tissue. The most researched one was the antiobesity effect, which is closely related to confirmed antidiabetic and anti-inflammatory effects. The antiobesity effect was achieved through different mechanisms. For example, it was shown that kaempferol can inhibit lipid accumulation and increase fatty acid oxidation by suppressing adipogenic transcription factors and activating PPAR-α in murine adipocytes [87]. In the same study, kaempferol suppressed the GLUT-4 glucose transporter in adipocytes exhibiting antidiabetic potential. Kaempferol also showed multiple effects in obese mice, including the reduction of inflammatory cytokine expression, reduced metabolic syndrome, reduced dysbiosis of cecal microbiota and improvement of gut inflammation and intestinal barrier integrity by reducing activation of the TLR4/NF-κB signaling pathway [92]. Intraperitoneal treatment of obese mice with an extract containing kaempferol showed anti-inflammatory effects through induction of the strong anti-inflammatory CD11b+, Gr-1+ myeloid-derived suppressor cells (MDSC) in visceral adipose tissue. In vitro analysis showed that kaempferol was responsible for this effect, since among the compounds isolated from the extract, only kaempferol showed an exclusive effect on the MDSC [93]. It was also shown that supplementation of Wistar rats with kaempferol during pregnancy and lactation can reduce adiposity of the offspring and increase somatic growth without influencing feeding patterns, thus showing potential for antiobesity effects from the earliest age [90]. Kaempferol-3-O-glucoside (astragalin) showed antiadipogenic activity on 3T3-L1 adipocyte cells by downregulating adipogenic transcription factors and regulatory proteins [91]. In another study, the same glycoside (astragalin) had no effect on glucose homeostasis or reduction of insulin resistance or thiobarbituric acid reactive substances (indicators of oxidative stress) in obese mice compared with kaempferol, which exhibited all of the mentioned effects, indicating its role in insulin resistance and oxidative stress management [89].

4.3.2. Hydroxycinnamic Acids

Hydroxycinnamic acids have shown several beneficial effects on adipose tissue. As was the case with skeletal muscle, ferulic acid was the most investigated among the hydroxycinnamic acids, showing suppressing effects on obesity and obesity-related metabolic disorders and diseases. For example, administration of ferulic acid to obese mice resulted in reduced visceral fat accumulation, adipocyte size and body weight. In addition, there was improvement in different metabolic parameters including levels of serum lipid profiles,

blood glucose, insulin and inflammatory mediators like TNF-α and MCH-1, showing the multifunctional role of this acid in management of obesity [103]. In addition, ferulic acid was shown to contribute to the self-renewal of embryonic stem cells and adipose-derived mesenchymal stem cells from mouse abdominal adipose tissue, showing potential for therapeutic effects [102].

The reducing effects of ferulic acid on blood glucose and serum lipid profiles in obese mice were also observed in another study [101], in which the expression of hepatic lipogenic genes and gluconeogenic enzymes was reduced and the hepatic CPT1a gene and PPARα proteins were activated, showing the improvement of both lipid and glucose homeostasis. Another suggested mechanism for the ferulic acid's modulation of glucose homeostasis in mice was the phosphorylation and inactivation of the transcription factor FoxO1, which is responsible for the expression of gluconeogenic and orexigenic genes [100]. In a study by Kuppusamy et al. [98], the ferulic acid treatment on 3T3-L1 adipocytes and lipid homeostasis showed downregulation of the adipocyte differentiation factors PPAR-γ, CCAT enhancer binding-proteins-α (C/EBP-α), its downstream targets and adipokines, along with upregulation of lipolysis-related factors. Another study suggested a specific anti-inflammatory effect of ferulic acid, in which administration to obese mice resulted in a reduced expression of the Fet-A gene, which is otherwise involved in adipose tissue inflammation. This ferulic acid treatment resulted in a decreased circulatory level of Fet-A followed by an attenuation of proinflammatory cytokines [72].

The *p*-coumaric acid also showed beneficial effects on metabolic disorders related to obesity, including non-alcoholic fatty liver disease in C57BL/6J mice through increased blood glucose regulation and decreased activity of inflammatory cytokines and hepatic lipogenic enzymes, resulting in increased fecal lipid excretion and decreased levels of liver weight, hepatic lipid, plasma lipid and aspartate aminotransferase [95]. Both coumaric and sinapic acid showed activating effects on thermogenesis in brown adipose tissue, which is related to antiobesity effects. Additionally, *p*-coumaric acid activated thermogenesis in the brown adipose tissue of obese mice by upregulating the uncoupling protein 1 (UCP1) and accelerating the breakdown of glucose and fatty acids, resulting in higher energy expenditure and thermogenesis. These effects were also related to the rapamycin complex 1 (mTORC1)-RPS6 signaling pathway in in vitro studies [94]. Sinapic acid also showed effects on UCP1 as well as other genes related to the expression of brown-adipocyte activation proteins (PGC-1α and Prdm16). In addition, sinapic acid activated thermogenesis of human adipose tissue through phosphorylation of protein kinase A and cyclic AMP response element-binding protein signaling and promoted lipolysis by the protein kinase A/p38 signaling pathway [99].

4.3.3. Apigenin

Apigenin showed mostly antiobesity and anti-inflammatory effects related to adipose tissue. It was shown that apigenin can reduce visceral adiposity in obese mice by reducing the phosphorylation of the signal transducer and activator of the transcription 3 (STAT3) in adipocytes and its target genes, resulting in reduced expression of the PPAR-γ receptor, which is the critical nuclear factor in adipogenesis [110]. In addition, apigenin ameliorated insulin resistance and glucose intolerance in obese mice and produced increased energy expenditure and activation of lipolysis without higher cycling of free fatty acids due to the upregulated oxidation, thermogenesis and browning of the adipose tissue [109]. The stimulating effects of apigenin on the browning of white adipose tissue were connected with the expression of vascular endothelial growth factor A and upregulation of Prdm16 signaling cascade in murine white adipocytes [111]. It was also shown that apigenin can reverse the inflammatory suppression of human adipose tissue browning through the activation of the COX-2–PGE2 axis, which results in UCP1 induction [107]. In the same study, IL-1β-induced inflammation in adipocytes was repressed by apigenin's inhibitory effects on inflammatory markers and the NF-κB signaling pathway. In another study [112], apigenin activated PPARγ, which resulted in blocked p65 translocation into nuclei and

consequently decreased NF-κB activation, resulting in decreased levels of proinflammatory cytokines in obese mice. In addition, levels of hepatic enzymes, triglycerides, total cholesterol, and liver and muscular steatosis were reduced and glucose resistance was improved. In another study [106], apigenin prevented colonic inflammation and motor dysfunctions in obese mice through reduction of the levels of malondialdehyde and proinflammatory cytokines, eosinophil infiltration, substance P and iNOS expression and the normalization of electrically evoked tachykininergic and nitergic contractions [106]. Also, antiobesity effects of apigenin glycoside were observed in which vitexin (apigenin-8-C-glucoside) ameliorated adipogenesis and obesity in male C57BL/6J mice by affecting AMP-activated protein kinase-α, CAATT element binding protein-α and fatty acid synthase in white adipose tissue [108].

The animal studies clearly point to the beneficial effects of the reviewed components of the laurel leaves. However, studies in humas are warranted in order to switch from translation research to clinical trials and prove the noted benefits.

5. Conclusions and Future Perspectives

This review revealed that the main laurel leaf polyphenols exhibit various positive effects on bones, skeletal muscle and adipose tissue in animal and in vitro studies. However, in order to obtain benefits related to the amelioration of metabolic disorders related to aging and modern lifestyle, ultimately leading to an improved body composition and function, much more needs to be done. Further research is needed in order to evaluate the potential of laurel leaf extracts as a whole, since they contain a variety of polyphenols that could contribute to the observed effects, including quercetin, whose effects on bones [113], muscles [114] and adipose tissue [115] are well researched. In addition, more clinical studies in humans should be performed in order to confirm the observed effects in translational studies. The focus should be on investigating the bioavailability of the extracts, which is crucial for achieving systemic effects in the human body. Moreover, since the polyphenols are subjected to biotransformations during the digestion process, the influence of their metabolites on bones, skeletal muscles and adipose tissue should be investigated, since the effects of metabolites are not necessarily the same as their precursors'. Nevertheless, the potential of laurel leaf extract in modulation of body composition was confirmed in this review, thereby opening a road to further research on this valuable plant.

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Abbreviations

AKT, protein kinase B; AMPK, AMP activated protein kinase-α; ARE, antioxidant-response elements; Bcl-2, B-cell lymphoma 2; C2C12, subclone of the mouse myoblast cell line; COX-2, cyclooxygenase-2; CPT, carnitine palmitoyltransferase; ERK, extracellular signal-regulated kinases; Fet-A, fetuin-A; FoxO1, Forkhead box protein O1; GLUT, glucose transporter; GPR56, G protein-coupled receptor 56; GSH, glutathione; GST, glutathione S-transferase; HO-1, heme oxygenase-1; IGF-1, insulin-like growth factor 1; iNOS, inducible nitric oxide synthase; JAK-2, Janus kinase-2; L6, lumbar-6; LOX, lipoxygenase; mTOR, mammalian target of rapamycin; MCH-1, major histocom-

patibility complex 1; MMTV, mouse mammary tumor virus; MuRF1, muscle RING-finger protein-1; myoD, myoblast determination protein 1; NFκ-B, nuclear factor-kappa β; NQO1, NADP(H) quinone oxidoreductase 1; Nrf 2, nuclear factor erythroid 2-related factor 2; RNS, reactive nitrogen species; ROS, reactive oxygen species; PGE2, prostaglandin E2; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1α; PKCε, protein kinase C ε; PPAR, peroxisome proliferator-activated receptor; Prdm16, positive regulatory domain-containing protein 16; Prmt7, protein arginine methyltransferase 7; SaOS-2, sarcoma osteogenic-2; SIRT-1, sirtuin 1; SOD, sodium oxide dismutase; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α.

References

1. United Nations, Department of Economic and Social Affairs, Population Division. *World Population Prospects 2019: Highlights (ST/ESA/SER.A/423)*; United Nations, Department of Economic and Social Affairs, Population Division: New York, NY, USA, 2019.
2. Jafari Nasabian, P.; Inglis, J.E.; Reilly, W.; Kelly, O.J.; Ilich, J.Z. Aging human body: Changes in bone, muscle and body fat with consequent changes in nutrient intake. *J. Endocrinol.* **2017**, *234*, R37–R51. [CrossRef]
3. Ilich, J.Z.; Gilman, J.C.; Cvijetic, S.; Boschiero, D. Chronic Stress Contributes to Osteosarcopenic Adiposity via Inflammation and Immune Modulation: The Case for More Precise Nutritional Investigation. *Nutrients* **2020**, *12*, 989. [CrossRef] [PubMed]
4. Ilich, J.Z.; Kelly, O.J.; Inglis, J.E.; Panton, L.B.; Duque, G.; Ormsbee, M.J. Interrelationship among muscle, fat, and bone: Connecting the dots on cellular, hormonal, and whole body levels. *Ageing Res. Rev.* **2014**, *15*, 51–60. [CrossRef] [PubMed]
5. Kelly, O.; Gilman, J.; Ilich, J. Utilizing Dietary Nutrient Ratios in Nutritional Research: Expanding the Concept of Nutrient Ratios to Macronutrients. *Nutrients* **2019**, *11*, 282. [CrossRef] [PubMed]
6. Eckstrom, E.; Neukam, S.; Kalin, L.; Wright, J. Physical Activity and Healthy Aging. *Clin. Geriatr. Med.* **2020**, *36*, 671–683. [CrossRef]
7. Mafra, D.; Ugochukwu, S.A.; Borges, N.A.; Cardozo, L.F.M.F.; Stenvinkel, P.; Shiels, P.G. Food for healthier aging: Power on your plate. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 1–14. [CrossRef]
8. Llaha, F.; Zamora-Ros, R. The Effects of Polyphenol Supplementation in Addition to Calorie Restricted Diets and/or Physical Activity on Body Composition Parameters: A Systematic Review of Randomized Trials. *Front. Nutr.* **2020**, *7*, 84. [CrossRef]
9. Gaamouri, N.; Zouhal, H.; Hammami, M.; Hackney, A.C.; Abderrahman, A.B.; Saeidi, A.; El Hage, R.; Ounis, O. Ben Effects of polyphenol (carob) supplementation on body composition and aerobic capacity in taekwondo athletes. *Physiol. Behav.* **2019**, *205*, 22–28. [CrossRef]
10. Shen, C.-L.; Cao, J.J.; Dagda, R.Y.; Chanjaplammootil, S.; Lu, C.; Chyu, M.-C.; Gao, W.; Wang, J.-S.; Yeh, J.K. Green tea polyphenols benefits body composition and improves bone quality in long-term high-fat diet–induced obese rats. *Nutr. Res.* **2012**, *32*, 448–457. [CrossRef]
11. Farhat, G.; Drummond, S.; Al-Dujaili, E.A.S. Polyphenols and Their Role in Obesity Management: A Systematic Review of Randomized Clinical Trials. *Phyther. Res.* **2017**, *31*, 1005–1018. [CrossRef]
12. Sharma, A.; Singh, J.; Kumar, S. Bay leaves. In *Handbook of Herbs and Spices*; Peter, K.V., Ed.; Woodhead Publishing Ltd.: Oxford, UK, 2012; pp. 73–85.
13. Alejo-Armijo, A.; Altarejos, J.; Salido, S. Phytochemicals and biological activities of laurel tree (*Laurus nobilis*). *Nat. Prod. Commun.* **2017**, *12*, 743–757. [CrossRef]
14. Dobroslavić, E.; Repajić, M.; Dragović-Uzelac, V.; Elez Garofulić, I. Isolation of Laurus nobilis Leaf Polyphenols: A Review on Current Techniques and Future Perspectives. *Foods* **2022**, *11*, 235. [CrossRef] [PubMed]
15. Brahmi, N.; Scognamiglio, M.; Pacifico, S.; Mekhoukhe, A.; Madani, K.; Fiorentino, A.; Monaco, P. ^{1}H NMR based metabolic profiling of eleven Algerian aromatic plants and evaluation of their antioxidant and cytotoxic properties. *Food Res. Int.* **2015**, *76*, 334–341. [CrossRef] [PubMed]
16. Dias, M.I.; Barros, L.; Dueñas, M.; Alves, R.C.; Oliveira, M.B.P.P.; Santos-Buelga, C.; Ferreira, I.C.F.R. Nutritional and antioxidant contributions of *Laurus nobilis* L. leaves: Would be more suitable a wild or a cultivated sample? *Food Chem.* **2014**, *156*, 339–346. [CrossRef]
17. Muñiz-Márquez, D.B.; Rodríguez, R.; Balagurusamy, N.; Carrillo, M.L.; Belmares, R.; Contreras, J.C.; Nevárez, G.V.; Aguilar, C.N. Phenolic content and antioxidant capacity of extracts of *Laurus nobilis* L., *Coriandrum sativum* L. and *Amaranthus hybridus* L. *CYTA J. Food* **2014**, *12*, 271–276. [CrossRef]
18. Mazzio, E.A.; Li, N.; Bauer, D.; Mendonca, P.; Taka, E.; Darb, M.; Thomas, L.; Williams, H.; Soliman, K.F.A. Natural product HTP screening for antibacterial (*E. coli* 0157:H7) and anti-inflammatory agents in (LPS from *E. coli* O111:B4) activated macrophages and microglial cells; focus on sepsis. *BMC Complement. Altern. Med.* **2016**, *16*, 467. [CrossRef]
19. Matsuda, H.; Kagerura, T.; Toguchida, I.; Ueda, H.; Morikawa, T.; Yoshikawa, M. Inhibitory effects of sesquiterpenes from bay leaf on nitric oxide production in lipopolysaccharide-activated macrophages: Structure requirement and role of heat shock protein induction. *Life Sci.* **2000**, *66*, 2151–2157. [CrossRef]
20. Domazetovic, V.; Marcucci, G.; Iantomasi, T.; Brandi, M.L.; Vincenzini, M.T. Oxidative stress in bone remodeling: Role of antioxidants. *Clin. Cases Miner. Bone Metab.* **2017**, *14*, 209. [CrossRef]

21. Dalle, S.; Rossmeislova, L.; Koppo, K. The Role of Inflammation in Age-Related Sarcopenia. *Front. Physiol.* **2017**, *8*, 1045. [CrossRef]
22. Epsley, S.; Tadros, S.; Farid, A.; Kargilis, D.; Mehta, S.; Rajapakse, C.S. The Effect of Inflammation on Bone. *Front. Physiol.* **2021**, *11*, 511799. [CrossRef]
23. Kawai, T.; Autieri, M.V.; Scalia, R. Adipose tissue inflammation and metabolic dysfunction in obesity. *Am. J. Physiol. Physiol.* **2021**, *320*, C375–C391. [CrossRef] [PubMed]
24. Scicchitano, B.M.; Pelosi, L.; Sica, G.; Musarò, A. The physiopathologic role of oxidative stress in skeletal muscle. *Mech. Ageing Dev.* **2018**, *170*, 37–44. [CrossRef] [PubMed]
25. Masschelin, P.M.; Cox, A.R.; Chernis, N.; Hartig, S.M. The Impact of Oxidative Stress on Adipose Tissue Energy Balance. *Front. Physiol.* **2020**, *10*, 1638. [CrossRef] [PubMed]
26. Calderón-Montaño, J.M.; Burgos-Morón, E.; Pérez-Guerrero, C.; López-Lázaro, M. A Review on the Dietary Flavonoid Kaempferol BenthamScience. *Mini Rev. Med. Chem.* **2011**, *11*, 298–344. [CrossRef] [PubMed]
27. Stefanova, G.; Girova, T.; Gochev, V.; Stoyanova, M.; Petkova, Z.; Stoyanova, A.; Zheljazkov, V.D. Comparative study on the chemical composition of laurel (*Laurus nobilis* L.) leaves from Greece and Georgia and the antibacterial activity of their essential oil. *Heliyon* **2020**, *6*, e05491. [CrossRef]
28. Sova, M.; Saso, L. Natural sources, pharmacokinetics, biological activities and health benefits of hydroxycinnamic acids and their metabolites. *Nutrients* **2020**, *12*, 2190. [CrossRef]
29. Dobroslavić, E.; Elez Garofulić, I.; Šeparović, J.; Zorić, Z.; Pedisić, S.; Dragović-Uzelac, V. Pressurized Liquid Extraction as a Novel Technique for the Isolation of *Laurus nobilis* L. Leaf Polyphenols. *Molecules* **2022**, *27*, 5099. [CrossRef]
30. Sirotkin, A.V.; Kolesarova, A. Plant molecules and their influence on health and female reproduction. In *Environmental Contaminants and Medicinal Plants Action on Female Reproduction*; Elsevier: Amsterdam, The Netherlands, 2022; pp. 245–399.
31. Aguiar, S.S.; Sousa, C.V.; Deus, L.A.; Rosa, T.S.; Sales, M.M.; Neves, R.V.P.; Barbosa, L.P.; Santos, P.A.; Campbell, C.S.; Simões, H.G.; et al. Oxidative stress, inflammatory cytokines and body composition of master athletes: The interplay. *Exp. Gerontol.* **2020**, *130*, 110806. [CrossRef]
32. El-Missiry, M.A.; Fekri, A.; Kesar, L.A.; Othman, A.I. Polyphenols are potential nutritional adjuvants for targeting COVID-19. *Phyther. Res.* **2021**, *35*, 2879–2889. [CrossRef]
33. Yahfoufi, N.; Alsadi, N.; Jambi, M.; Matar, C. The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients* **2018**, *10*, 1618. [CrossRef]
34. Findeisen, H.M.; Pearson, K.J.; Gizard, F.; Zhao, Y.; Qing, H.; Jones, K.L.; Cohn, D.; Heywood, E.B.; de Cabo, R.; Bruemmer, D.; et al. Oxidative Stress Accumulates in Adipose Tissue during Aging and Inhibits Adipogenesis. *PLoS ONE* **2011**, *6*, e18532. [CrossRef]
35. Luo, J.; Si, H.; Jia, Z.; Liu, D. Dietary anti-aging polyphenols and potential mechanisms. *Antioxidants* **2021**, *10*, 283. [CrossRef]
36. Kobayashi, M.; Yamamoto, M. Molecular Mechanisms Activating the Nrf2-Keap1 Pathway of Antioxidant Gene Regulation. *Antioxid. Redox Signal.* **2005**, *7*, 385–394. [CrossRef] [PubMed]
37. Pallauf, K.; Duckstein, N.; Hasler, M.; Klotz, L.-O.; Rimbach, G. Flavonoids as Putative Inducers of the Transcription Factors Nrf2, FoxO, and PPAR γ. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 1–11. [CrossRef]
38. Santangelo, C.; Varì, R.; Scazzocchio, B.; di Benedetto, R.; Filesi, C.; Masella, R. Polyphenols, intracellular signalling and inflammation. *Ann. Ist. Super. Sanita* **2007**, *43*, 394–405. [PubMed]
39. Boskey, A.L.; Coleman, R. Aging and bone. *J. Dent. Res.* **2010**, *89*, 1333–1348. [CrossRef] [PubMed]
40. Austermann, K.; Baecker, N.; Stehle, P.; Heer, M. Putative Effects of Nutritive Polyphenols on Bone Metabolism In Vivo—Evidence from Human Studies. *Nutrients* **2019**, *11*, 871. [CrossRef]
41. Banfi, G.; Iorio, E.L.; Corsi, M.M. Oxidative stress, free radicals and bone remodeling. *Clin. Chem. Lab. Med.* **2008**, *46*, 1550–1555. [CrossRef]
42. Grzesik, W.J.; Frazier, C.R.; Shapiro, J.R.; Sponseller, P.D.; Robey, P.G.; Fedarko, N.S. Age-related Changes in Human Bone Proteoglycan Structure. *J. Biol. Chem.* **2002**, *277*, 43638–43647. [CrossRef]
43. Sharma, A.R.; Nam, J.-S. Kaempferol stimulates WNT/β-catenin signaling pathway to induce differentiation of osteoblasts. *J. Nutr. Biochem.* **2019**, *74*, 108228. [CrossRef]
44. Xu, X.; Fan, X.; Wu, X.; Shi, L.; Wang, P.; Gao, F.; Sun, W.; Li, Z. Protective effect of Kaempferol on endothelial cell injury in glucocorticoid induced osteonecrosis of the femoral head. *Chin. J. Reparative Reconstr. Surg.* **2022**, *36*, 1277–1287. [CrossRef]
45. Adhikary, S.; Choudhary, D.; Ahmad, N.; Karvande, A.; Kumar, A.; Banala, V.T.; Mishra, P.R.; Trivedi, R. Dietary flavonoid kaempferol inhibits glucocorticoid-induced bone loss by promoting osteoblast survival. *Nutrition* **2018**, *53*, 64–76. [CrossRef] [PubMed]
46. Tsuchiya, S.; Sugimoto, K.; Kamio, H.; Okabe, K.; Kuroda, K.; Okido, M.; Hibi, H. Kaempferol-immobilized titanium dioxide promotes formation of new bone: Effects of loading methods on bone marrow stromal cell differentiation in vivo and in vitro. *Int. J. Nanomed.* **2018**, *13*, 1665–1676. [CrossRef]
47. Doss, H.M.; Samarpita, S.; Ganesan, R.; Rasool, M. Ferulic acid, a dietary polyphenol suppresses osteoclast differentiation and bone erosion via the inhibition of RANKL dependent NF-κB signalling pathway. *Life Sci.* **2018**, *207*, 284–295. [CrossRef]
48. Hou, T.; Zhang, L.; Yang, X. Ferulic acid, a natural polyphenol, protects against osteoporosis by activating SIRT1 and NF-κB in neonatal rats with glucocorticoid-induced osteoporosis. *Biomed. Pharmacother.* **2019**, *120*, 109205. [CrossRef]

49. Balagangadharan, K.; Trivedi, R.; Vairamani, M.; Selvamurugan, N. Sinapic acid-loaded chitosan nanoparticles in polycaprolactone electrospun fibers for bone regeneration in vitro and in vivo. *Carbohydr. Polym.* **2019**, *216*, 1–16. [CrossRef]
50. Bhattarai, G.; Jeon, Y.-M.; Choi, K.-C.; Wagle, S.; Sim, H.-J.; Kim, J.-I.; Zhao, S.; Kim, J.-G.; Cho, E.-S.; Kook, S.-H.; et al. Functional improvement of collagen-based bioscaffold to enhance periodontal-defect healing via combination with dietary antioxidant and COMP-angiopoietin 1. *Biomater. Adv.* **2022**, *135*, 112673. [CrossRef]
51. Filho, A.C.M.L.; Silva, I.S.; Sousa, F.B.M.; de Souza, L.K.M.; da Gomes, B.S.; Gonçalves, R.L.G.; de Rezende, D.C.; Cunha, F.V.M.; Wong, D.V.T.; Júnior, R.C.P.L.; et al. Inhibition of neutrophil migration and reduction of oxidative stress by ethyl p-coumarate in acute and chronic inflammatory models. *Phytomedicine* **2019**, *57*, 9–17. [CrossRef]
52. Cheng, Y.-H.; Yang, S.-H.; Liu, C.-C.; Gefen, A.; Lin, F.-H. Thermosensitive hydrogel made of ferulic acid-gelatin and chitosan glycerophosphate. *Carbohydr. Polym.* **2013**, *92*, 1512–1519. [CrossRef]
53. Jiao, R.; Chen, H.; Wan, Q.; Zhang, X.; Dai, J.; Li, X.; Yan, L.; Sun, Y. Apigenin inhibits fibroblast proliferation and reduces epidural fibrosis by regulating Wnt3a/β-catenin signaling pathway. *J. Orthop. Surg. Res.* **2019**, *14*, 258. [CrossRef]
54. Zhang, Z.; Zhao, Q.; Liu, T.; Zhao, H.; Wang, R.; Li, H.; Zhang, Y.; Shan, L.; He, B.; Wang, X.; et al. Effect of Vicenin-2 on ovariectomy-induced osteoporosis in rats. *Biomed. Pharmacother.* **2020**, *129*, 110474. [CrossRef]
55. Ranjbar, F.E.; Foroutan, F.; Hajian, M.; Ai, J.; Farsinejad, A.; Ebrahimi-Barough, S.; Dehghan, M.M.; Azami, M. Preparation and characterization of 58S bioactive glass based scaffold with Kaempferol-containing Zein coating for bone tissue engineering. *J. Biomed. Mater. Res. B Appl. Biomater.* **2021**, *109*, 1259–1270. [CrossRef]
56. Tieland, M.; Trouwborst, I.; Clark, B.C. Skeletal muscle performance and ageing. *J. Cachexia Sarcopenia Muscle* **2018**, *9*, 3–19. [CrossRef] [PubMed]
57. Stump, C.S.; Henriksen, E.J.; Wei, Y.; Sowers, J.R. The metabolic syndrome: Role of skeletal muscle metabolism. *Ann. Med.* **2006**, *38*, 389–402. [CrossRef]
58. Schnyder, S.; Handschin, C. Skeletal muscle as an endocrine organ: PGC-1α, myokines and exercise. *Bone* **2015**, *80*, 115–125. [CrossRef] [PubMed]
59. Nikawa, T.; Ulla, A.; Sakakibara, I. Polyphenols and Their Effects on Muscle Atrophy and Muscle Health. *Molecules* **2021**, *26*, 4887. [CrossRef] [PubMed]
60. Alkhalidy, H.; Moore, W.; Wang, Y.; Luo, J.; McMillan, R.; Zhen, W.; Zhou, K.; Liu, D. The Flavonoid Kaempferol Ameliorates Streptozotocin-Induced Diabetes by Suppressing Hepatic Glucose Production. *Molecules* **2018**, *23*, 2338. [CrossRef]
61. Da Silva, D.; Casanova, L.M.; Marcondes, M.C.; Espindola-Netto, J.M.; Paixão, L.P.; de Melo, G.O.; Zancan, P.; Sola-Penna, M.; Costa, S.S. Antidiabetic activity of Sedum dendroideum: Metabolic enzymes as putative targets for the bioactive flavonoid kaempferitrin. *IUBMB Life* **2014**, *66*, 361–370. [CrossRef] [PubMed]
62. Kashyap, B.; Saikia, K.; Samanta, S.K.; Thakur, D.; Banerjee, S.K.; Borah, J.C.; Talukdar, N.C. Kaempferol 3-O-rutinoside from Antidesma acidum Retz. Stimulates glucose uptake through SIRT1 induction followed by GLUT4 translocation in skeletal muscle L6 cells. *J. Ethnopharmacol.* **2022**, *301*, 115788. [CrossRef]
63. Kitakaze, T.; Jiang, H.; Nomura, T.; Hironao, K.; Yamashita, Y.; Ashida, H. Kaempferol Promotes Glucose Uptake in Myotubes through a JAK2-Dependent Pathway. *J. Agric. Food Chem.* **2020**, *68*, 13720–13729. [CrossRef]
64. Roy, J.R.; Janaki, C.S.; Jayaraman, S.; Periyasamy, V.; Balaji, T.; Vijayamalathi, M.; Veeraraghavan, V.P. Carica papaya Reduces Muscle Insulin Resistance via IR/GLUT4 Mediated Signaling Mechanisms in High Fat Diet and Streptozotocin-Induced Type-2 Diabetic Rats. *Antioxidants* **2022**, *11*, 2081. [CrossRef] [PubMed]
65. Akiyama, M.; Mizokami, T.; Miyamoto, S.; Ikeda, Y. Kaempferol increases intracellular ATP content in C_2C_{12} myotubes under hypoxic conditions by suppressing the HIF-1α stabilization and/or by enhancing the mitochondrial complex IV activity. *J. Nutr. Biochem.* **2022**, *103*, 108949. [CrossRef]
66. Wen, Y.; Ushio, H. Ferulic Acid Promotes Hypertrophic Growth of Fast Skeletal Muscle in Zebrafish Model. *Nutrients* **2017**, *9*, 1066. [CrossRef] [PubMed]
67. Yin, X.; Liu, W.; Chen, H.; Qi, C.; Chen, H.; Niu, H.; Yang, J.; Kwok, K.W.H.; Dong, W. Effects of ferulic acid on muscle development and intestinal microbiota of zebrafish. *J. Anim. Physiol. Anim. Nutr.* **2022**, *106*, 429–440. [CrossRef]
68. Kuppusamy, P.; Soundharrajan, I.; Kim, D.H.; Hwang, I.; Choi, K.C. 4-hydroxy-3-methoxy cinnamic acid accelerate myoblasts differentiation on C_2C_{12} mouse skeletal muscle cells via AKT and ERK 1/2 activation. *Phytomedicine* **2019**, *60*, 152873. [CrossRef] [PubMed]
69. Wang, Y.; Chen, X.; Huang, Z.; Chen, D.; Yu, B.; Chen, H.; Yu, J.; Luo, Y.; Zheng, P.; He, J. Effects of dietary ferulic acid supplementation on growth performance and skeletal muscle fiber type conversion in weaned piglets. *J. Sci. Food Agric.* **2021**, *101*, 5116–5123. [CrossRef] [PubMed]
70. Chen, X.; Guo, Y.; Jia, G.; Zhao, H.; Liu, G.; Huang, Z. Ferulic acid regulates muscle fiber type formation through the Sirt1/AMPK signaling pathway. *Food Funct.* **2019**, *10*, 259–265. [CrossRef]
71. Ilavenil, S.; Kim, D.; Srigopalram, S.; Arasu, M.; Lee, K.; Lee, J.; Lee, J.; Renganathan, S.; Choi, K. Potential Application of p-Coumaric Acid on Differentiation of C_2C_{12} Skeletal Muscle and 3T3-L1 Preadipocytes—An in Vitro and in Silico Approach. *Molecules* **2016**, *21*, 997. [CrossRef]
72. Gogoi, B.; Chatterjee, P.; Mukherjee, S.; Buragohain, A.K.; Bhattacharya, S.; Dasgupta, S. A polyphenol rescues lipid induced insulin resistance in skeletal muscle cells and adipocytes. *Biochem. Biophys. Res. Commun.* **2014**, *452*, 382–388. [CrossRef]

73. Kang, B.; Chiang, B. Amelioration of insulin resistance using the additive effect of ferulic acid and resveratrol on vesicle trafficking for skeletal muscle glucose metabolism. *Phyther. Res.* **2020**, *34*, 808–816. [CrossRef] [PubMed]
74. Singh, S.S.B.; Patil, K.N. Trans-ferulic acid attenuates hyperglycemia-induced oxidative stress and modulates glucose metabolism by activating AMPK signaling pathway in vitro. *J. Food Biochem.* **2022**, *46*, e14038. [CrossRef] [PubMed]
75. Yoon, S.-A.; Kang, S.-I.; Shin, H.-S.; Kang, S.-W.; Kim, J.-H.; Ko, H.-C.; Kim, S.-J. P-Coumaric acid modulates glucose and lipid metabolism via AMP-activated protein kinase in L6 skeletal muscle cells. *Biochem. Biophys. Res. Commun.* **2013**, *432*, 553–557. [CrossRef] [PubMed]
76. Shiota, C.; Abe, T.; Kawai, N.; Ohno, A.; Teshima-Kondo, S.; Mori, H.; Terao, J.; Tanaka, E.; Nikawa, T. Flavones Inhibit LPS-Induced Atrogin-1/MAFbx Expression in Mouse C2C12 Skeletal Myotubes. *J. Nutr. Sci. Vitaminol.* **2015**, *61*, 188–194. [CrossRef] [PubMed]
77. Choi, W.H.; Jang, Y.J.; Son, H.J.; Ahn, J.; Jung, C.H.; Ha, T.Y. Apigenin inhibits sciatic nerve denervation–induced muscle atrophy. *Muscle Nerve* **2018**, *58*, 314–318. [CrossRef]
78. Choi, W.H.; Son, H.J.; Jang, Y.J.; Ahn, J.; Jung, C.H.; Ha, T.Y. Apigenin Ameliorates the Obesity-Induced Skeletal Muscle Atrophy by Attenuating Mitochondrial Dysfunction in the Muscle of Obese Mice. *Mol. Nutr. Food Res.* **2017**, *61*, 1700218. [CrossRef]
79. Jang, Y.J.; Son, H.J.; Choi, Y.M.; Ahn, J.; Jung, C.H.; Ha, T.Y. Apigenin enhances skeletal muscle hypertrophy and myoblast differentiation by regulating Prmt7. *Oncotarget* **2017**, *8*, 78300–78311. [CrossRef]
80. Wang, D.; Yang, Y.; Zou, X.; Zhang, J.; Zheng, Z.; Wang, Z. Antioxidant Apigenin Relieves Age-Related Muscle Atrophy by Inhibiting Oxidative Stress and Hyperactive Mitophagy and Apoptosis in Skeletal Muscle of Mice. *J. Gerontol. Ser. A* **2020**, *75*, 2081–2088. [CrossRef]
81. Ou, M.Y.; Zhang, H.; Tan, P.C.; Zhou, S.B.; Li, Q.F. Adipose tissue aging: Mechanisms and therapeutic implications. *Cell Death Dis.* **2022**, *13*, 300. [CrossRef]
82. Cinti, S. Anatomy and physiology of the nutritional system. *Mol. Aspects Med.* **2019**, *68*, 101–107. [CrossRef]
83. Cannon, B.; Nedergaard, J. Brown Adipose Tissue: Function and Physiological Significance. *Physiol. Rev.* **2004**, *84*, 277–359. [CrossRef]
84. Kuk, J.L.; Saunders, T.J.; Davidson, L.E.; Ross, R. Age-related changes in total and regional fat distribution. *Ageing Res. Rev.* **2009**, *8*, 339–348. [CrossRef]
85. Ouchi, N.; Parker, J.L.; Lugus, J.J.; Walsh, K. Adipokines in inflammation and metabolic disease. *Nat. Rev. Immunol.* **2011**, *11*, 85–97. [CrossRef]
86. Ilich, J.Z.; Kelly, O.J.; Kim, Y.; Spicer, M.T. Low-grade chronic inflammation perpetuated by modern diet as a promoter of obesity and osteoporosis. *Arch. Ind. Hyg. Toxicol.* **2014**, *65*, 139–148. [CrossRef] [PubMed]
87. Lee, B.; Kwon, M.; Choi, J.S.; Jeong, H.O.; Chung, H.Y.; Kim, H.-R. Kaempferol Isolated from Nelumbo nucifera Inhibits Lipid Accumulation and Increases Fatty Acid Oxidation Signaling in Adipocytes. *J. Med. Food* **2015**, *18*, 1363–1370. [CrossRef]
88. Li, H.; Kang, J.-H.; Han, J.-M.; Cho, M.-H.; Chung, Y.-J.; Park, K.H.; Shin, D.-H.; Park, H.-Y.; Choi, M.-S.; Jeong, T.-S.; et al. Anti-Obesity Effects of Soy Leaf via Regulation of Adipogenic Transcription Factors and Fat Oxidation in Diet-Induced Obese Mice and 3T3-L1 Adipocytes. *J. Med. Food* **2015**, *18*, 899–908. [CrossRef]
89. Mehanna, E.T.; El-sayed, N.M.; Ibrahim, A.K.; Ahmed, S.A.; Abo-Elmatty, D.M. Isolated compounds from *Cuscuta pedicellata* ameliorate oxidative stress and upregulate expression of some energy regulatory genes in high fat diet induced obesity in rats. *Biomed. Pharmacother.* **2018**, *108*, 1253–1258. [CrossRef]
90. Chaves, W.F.; Pinheiro, I.L.; da Silva, L.O.; Lima-Oliveira, D.P.; de Muniz, G.S.; do Barreto, Á.N.; da Silva, B.J.; Manhães-de-Castro, R.; da Silva Aragão, R. Neonatal administration of kaempferol does not alter satiety but increases somatic growth and reduces adiposity in offspring of high-fat diet dams. *Life Sci.* **2020**, *259*, 118224. [CrossRef]
91. Barge, S.; Deka, B.; Kashyap, B.; Bharadwaj, S.; Kandimalla, R.; Ghosh, A.; Dutta, P.P.; Samanta, S.K.; Manna, P.; Borah, J.C.; et al. Astragalin mediates the pharmacological effects of *Lysimachia candida* Lindl on adipogenesis via downregulating PPARG and FKBP51 signaling cascade. *Phyther. Res.* **2021**, *35*, 6990–7003. [CrossRef] [PubMed]
92. Bian, Y.; Lei, J.; Zhong, J.; Wang, B.; Wan, Y.; Li, J.; Liao, C.; He, Y.; Liu, Z.; Ito, K.; et al. Kaempferol reduces obesity, prevents intestinal inflammation, and modulates gut microbiota in high-fat diet mice. *J. Nutr. Biochem.* **2022**, *99*, 108840. [CrossRef] [PubMed]
93. Kitamura, H.; Saito, N.; Fujimoto, J.; Nakashima, K.; Fujikura, D. Brazilian propolis ethanol extract and its component kaempferol induce myeloid-derived suppressor cells from macrophages of mice in vivo and in vitro. *BMC Complement. Altern. Med.* **2018**, *18*, 138. [CrossRef]
94. Han, X.; Guo, J.; You, Y.; Zhan, J.; Huang, W. p-Coumaric acid prevents obesity via activating thermogenesis in brown adipose tissue mediated by mTORC1-RPS6. *FASEB J.* **2020**, *34*, 7810–7824. [CrossRef]
95. Yoon, D.S.; Cho, S.Y.; Yoon, H.J.; Kim, S.R.; Jung, U.J. Protective effects of p-coumaric acid against high-fat diet-induced metabolic dysregulation in mice. *Biomed. Pharmacother.* **2021**, *142*, 111969. [CrossRef] [PubMed]
96. Wang, W.; Pan, Y.; Wang, L.; Zhou, H.; Song, G.; Wang, Y.; Liu, J.; Li, A. Optimal Dietary Ferulic Acid for Suppressing the Obesity-Related Disorders in Leptin-Deficient Obese C57BL/6J -ob/ob Mice. *J. Agric. Food Chem.* **2019**, *67*, 4250–4258. [CrossRef] [PubMed]

97. Seo, S.H.; Jo, S.-M.; Truong, T.T.M.; Zhang, G.; Kim, D.-S.; Lee, M.; Lee, Y.; Kang, I. Peanut sprout rich in p -coumaric acid ameliorates obesity and lipopolysaccharide-induced inflammation and the inhibition of browning in adipocytes via mitochondrial activation. *Food Funct.* **2021**, *12*, 5361–5374. [CrossRef]
98. Kuppusamy, P.; Ilavenil, S.; Hwang, I.H.; Kim, D.; Choi, K.C. Ferulic Acid Stimulates Adipocyte-Specific Secretory Proteins to Regulate Adipose Homeostasis in 3T3-L1 Adipocytes. *Molecules* **2021**, *26*, 1984. [CrossRef]
99. Hossain, M.; Imran, K.M.; Rahman, M.S.; Yoon, D.; Marimuthu, V.; Kim, Y.-S. Sinapic acid induces the expression of thermogenic signature genes and lipolysis through activation of PKA/CREB signaling in brown adipocytes. *BMB Rep.* **2020**, *53*, 142–147. [CrossRef]
100. Kinyua, A.W.; Ko, C.M.; Doan, K.V.; Yang, D.J.; Huynh, M.K.Q.; Moh, S.H.; Choi, Y.-H.; Kim, K.W. 4-hydroxy-3-methoxycinnamic acid regulates orexigenic peptides and hepatic glucose homeostasis through phosphorylation of FoxO1. *Exp. Mol. Med.* **2018**, *50*, e437. [CrossRef]
101. Naowaboot, J.; Piyabhan, P.; Munkong, N.; Parklak, W.; Pannangpetch, P. Ferulic acid improves lipid and glucose homeostasis in high-fat diet-induced obese mice. *Clin. Exp. Pharmacol. Physiol.* **2016**, *43*, 242–250. [CrossRef]
102. Cho, J.; Park, E. Ferulic acid maintains the self-renewal capacity of embryo stem cells and adipose-derived mesenchymal stem cells in high fat diet-induced obese mice. *J. Nutr. Biochem.* **2020**, *77*, 108327. [CrossRef] [PubMed]
103. De Melo, T.S.; Lima, P.R.; Carvalho, K.M.M.B.; Fontenele, T.M.; Solon, F.R.N.; Tomé, A.R.; de Lemos, T.L.G.; da Cruz Fonseca, S.G.; Santos, F.A.; Rao, V.S.; et al. Ferulic acid lowers body weight and visceral fat accumulation via modulation of enzymatic, hormonal and inflammatory changes in a mouse model of high-fat diet-induced obesity. *Braz. J. Med. Biol. Res.* **2017**, *50*, e5630. [CrossRef] [PubMed]
104. Van den Hoek-Hil, E.F.; van Schothorst, E.M.; van der Stelt, I.; Swarts, H.J.M.; van Vliet, M.; Amolo, T.; Vervoort, J.J.M.; Venema, D.; Hollman, P.C.H.; Rietjens, I.M.C.M.; et al. Direct comparison of metabolic health effects of the flavonoids quercetin, hesperetin, epicatechin, apigenin and anthocyanins in high-fat-diet-fed mice. *Genes Nutr.* **2015**, *10*, 23. [CrossRef] [PubMed]
105. Guo, X.; Liu, J.; Cai, S.; Wang, O.; Ji, B. Synergistic interactions of apigenin, naringin, quercetin and emodin on inhibition of 3T3-L1 preadipocyte differentiation and pancreas lipase activity. *Obes. Res. Clin. Pract.* **2016**, *10*, 327–339. [CrossRef] [PubMed]
106. Gentile, D.; Fornai, M.; Colucci, R.; Pellegrini, C.; Tirotta, E.; Benvenuti, L.; Segnani, C.; Ippolito, C.; Duranti, E.; Virdis, A.; et al. The flavonoid compound apigenin prevents colonic inflammation and motor dysfunctions associated with high fat diet-induced obesity. *PLoS ONE* **2018**, *13*, e0195502. [CrossRef]
107. Okla, M.; Al Madani, J.O.; Chung, S.; Alfayez, M. Apigenin Reverses Interleukin-1β-Induced Suppression of Adipocyte Browning via COX2/PGE2 Signaling Pathway in Human Adipocytes. *Mol. Nutr. Food Res.* **2020**, *64*, 1900925. [CrossRef] [PubMed]
108. Peng, Y.; Sun, Q.; Xu, W.; He, Y.; Jin, W.; Yuan, L.; Gao, R. Vitexin ameliorates high fat diet-induced obesity in male C57BL/6J mice via the AMPKα-mediated pathway. *Food Funct.* **2019**, *10*, 1940–1947. [CrossRef] [PubMed]
109. Sun, Y.-S.; Qu, W. Dietary Apigenin promotes lipid catabolism, thermogenesis, and browning in adipose tissues of HFD-Fed mice. *Food Chem. Toxicol.* **2019**, *133*, 110780. [CrossRef]
110. Su, T.; Huang, C.; Yang, C.; Jiang, T.; Su, J.; Chen, M.; Fatima, S.; Gong, R.; Hu, X.; Bian, Z.; et al. Apigenin inhibits STAT3/CD36 signaling axis and reduces visceral obesity. *Pharmacol. Res.* **2020**, *152*, 104586. [CrossRef]
111. Sreekumar, S.; Vijayan, V.; Singh, F.; Sudhakar, M.; Lakra, R.; Korrapati, P.S.; Kiran, M.S. White to brown adipocyte transition mediated by Apigenin via VEGF-PRDM16 signaling. *J. Cell. Biochem.* **2022**, *123*, 1793–1807. [CrossRef]
112. Feng, X.; Weng, D.; Zhou, F.; Owen, Y.D.; Qin, H.; Zhao, J.; Yu, W.; Huang, Y.; Chen, J.; Fu, H.; et al. Activation of PPARγ by a Natural Flavonoid Modulator, Apigenin Ameliorates Obesity-Related Inflammation Via Regulation of Macrophage Polarization. *Ebio Med.* **2016**, *9*, 61–76. [CrossRef]
113. Wong, S.K.; Chin, K.-Y.; Ima-Nirwana, S. Quercetin as an Agent for Protecting the Bone: A Review of the Current Evidence. *Int. J. Mol. Sci.* **2020**, *21*, 6448. [CrossRef]
114. Lin, W.; Zhao, Y.; Liu, C.; Yan, Y.; Ou, Q. Quercetin supplementation and muscular atrophy in animal models: A systematic review and meta-analysis. *Int. J. Food Prop.* **2022**, *25*, 2166–2183. [CrossRef]
115. Sato, S.; Mukai, Y. Modulation of Chronic Inflammation by Quercetin: The Beneficial Effects on Obesity. *J. Inflamm. Res.* **2020**, *13*, 421–431. [CrossRef] [PubMed]