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The potential effects of isoflavones on nuclear receptor modulation in bone remodeling: A review

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ABSTRACT

Isoflavones are plant-based compounds that act as phytoestrogens by mimicking the action of estrogen. Osteoblasts and osteoclasts are the key cells for bone remodeling, a process that includes bone proliferation, differentiation, deposition, and resorption. Studies have demonstrated that isoflavones, a class of flavonoids found almost exclusively in soybeans, could prevent bone loss. Recent findings revealed that isoflavones could activate nuclear receptors (NRs) and regulate bone formation and resorption processes. This current research discussed the principal actions of isoflavones mediated by NRs on bone remodeling such as steroid receptors (estrogen receptor, estrogen-related receptor, and androgen receptor) and metabolic receptors including peroxisome proliferator-activated receptor-γ. Isoflavones modulate osteogenesis by fine-tuning physiological responses on NR sensors and their transcriptional networks. Hence, this present review will dive deep into the use of several isoflavones as potential osteoporosis treatment through NR-controlling gene regulation.

INTRODUCTION

Physiological bone remodeling plays a pivotal role in coordinating structural bone integrity, as well as preserving bone mass and systemic mineral homeostasis. This process involved a delicate balance between bone resorption by osteoclasts and bone formation by osteoblasts (Kenkre and Bassett, 2018; Kim and Koh, 2019). Excessive bone resorption or reduced bone formation causes an imbalance of this coupling process, leading to bone diseases such as osteoporosis and osteopetrosis (Lombardi and Delvin, 2022; Terkawi *et al*., 2022). Therefore, direct communication between osteoblasts and osteoclasts is essential for consenting activation signals through cell-cell contact, cytokines secretion, hormone signaling pathway, and nuclear receptor (NR) pathway, and regulating cell differentiation and activities (Kim and Koh, 2019; Weivoda *et al*., 2020).

Various endogenous (hormones, growth factors, and cytokines) and exogenous (nutrients, drugs, and phytoestrogens) regulators are vital in their direct actions toward bone development, growth, and maintenance (Kang *et al*., 2021; Macías *et al*., 2021; Zhou *et al*., 2021). These regulators act as ligands of NRs, a distinct set of DNA transcription factors that modulate gene expression in bone cells, particularly osteoblast and osteoclast cells at specific stages (Imai *et al*., 2013; Lee and Park, 2018). NRs bind to DNA response elements in specific regulatory regions of target genes that markedly lead to respective ligand signaling pathways. Following binding specific cognate ligands, NRs modulate the expression of specific target genes at the transcription level (Frigo *et al*., 2021; Jin *et al*., 2015; Li *et al*., 2022a, 2022b, 2022c). The physiology of NRs has been extensively studied via the development of novel genetic manipulation and experimental animal models in which certain NR genes were mutated in specific cell types.

NRs are specific targets of genes that can bind to synthetic ligands (drugs or chemical compounds), which can be

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effectively used to attenuate the initiation and development of bone diseases, particularly in the case of estrogen deficiency-induced osteoporosis in postmenopausal women (Burr and Phipps, 2022; Li *et al*., 2022a, 2022b, 2022c). For instance, selective estrogen receptor modulators (SERMs) and non-steroidal compounds are exogenous partial estrogen receptor (ER) agonists which are clinically proven for osteoporosis treatment. The effects of SERMs on bone metabolism are similar to endogenous estrogen. SERMs have been shown to subtly bind to ERs and subsequently to estrogen response elements (EREs) to activate or repress the transcriptional activation of estrogen target genes. SERMs could extraordinarily act as agonists or antagonists in specific target genes and their transcriptional regulation produces unique physiologic effects on bone (Goldstein, 2022).

Isoflavones are flavonoid compounds acting as phytoestrogens owing to their structural similarity to 17-β estradiol (Jiang *et al*., 2013). In Asian countries, soy foods enriched with isoflavones include tofu, tempeh, miso, natto, cheonggukjang, kinema, hawaijar, and tungrymbai, while in Western countries, isoflavones are mainly found in dairy substitutes, such as soy milk, soy cheese, and soy yogurt. The most recognized isoflavones are genistein, daidzein, S-equol, biochanin A, and coumestrol (do Prado *et al*., 2022; Kim, 2021; Mutha *et al*., 2021). Soy is the main dietary source of isoflavones, the most prevalent type of phytoestrogen. Genistein and daidzein, the two primary isoflavones found in soybean as D-glycosides, are not physiologically active. These glycosides are first hydrolyzed by bacterial glucosidases in the digestive tract to produce the equivalent bioactive aglycones, genistein, and daidzein, which are then absorbed into the bloodstream. Although some genistein and daidzein are available in plasma as an aglycone, plasma conjugates genistein and daidzein for the most part (never glucoside). Daidzein, genistein, and o-desmethylangolensin (O-DMA) can all be extensively metabolized in the digestive system producing dihydrodaidzein, equol, and p-ethyl phenol (Chen *et al*., 2018, 2022a; Gonzales *et al*., 2015). Notably, S-equol is the most prevalent and active metabolite of daidzein found in the digestive tract. All rodents make equol, but only 30% of people can convert daidzein to equol in their bodies (Pawlowski *et al*., 2015).

Pharmacokinetic studies have proved that healthy adults absorb isoflavones quickly and efficiently (Chen *et al*., 2022a, 2022b). The aglycones in phytoestrogen-rich foods typically take 4–7 hours to reach plasma concentrations after consumption (Chen *et al*., 2022a, 2022b; Křížová *et al*., 2019). According to research conducted by Chang and Choue (2013) on South Korean women, soy-based diets with a high isoflavone aglycone content are more efficient at increasing plasma isoflavone levels. For this point, bioavailability increases as the percentage of aglycones increases. Therefore, isoflavone aglycone-rich foods such as fermented soybeans promote beneficial impacts in improving human health (do Prado *et al*., 2022). Moreover, isoflavones are reported to have numerous health benefits such as reducing the risk of menopausal syndrome (Chen and Chen, 2021), cardiovascular diseases (Barańska *et al*., 2021; Sathyapalan *et al*., 2018), cancer (Aboushanab *et al*., 2021; Fan *et al*., 2022), neurodegenerative diseases (Li *et al*., 2022a, 2022b, 2022c), osteoporosis (Zheng *et al*., 2016), and diabetes mellitus (Laily *et al*., 2022). These beneficial effects arise from the estrogen-like structure of isoflavones such as genistein (Elsayed *et al*., 2022), daidzein (Mayo *et al*., 2019), S-equol (Wang *et al*., 2014), and 8-prenylgenistein (8-PG) (Li *et al*., 2019a, 2019b).

In recent times, most isoflavones have been enormously employed to prevent estrogen-deficient bone loss. Due to their structural similarity to 17-β estradiol, they have binding affinities to ER and may exert estrogenic activities as either an estrogen agonist or antagonist. Many experimental studies demonstrated the ability of isoflavones to inhibit the loss of bone mineral density (BMD). *In vitro*, *in vivo,* and human studies have demonstrated the bone protective properties of isoflavones by increasing osteoblasts number, trabecular thickness, and osteocalcin (OCN) level, as well as diminishing osteoclasts number and C-telopeptide of type I collagen level (Bellavia *et al*., 2021; Cao *et al*., 2022; Zheng *et al*., 2016). However, the potential underlying mechanism of isoflavones at the upstream transcriptional level is not well established.

Efforts to identify the roles of isoflavones in the upstreaming of genetic pathways have generated new insights into the mechanism of action that is critical for ideal drug targets in regulating proper bone remodeling. It is now clear that other NRs such as androgen receptor (AR), peroxisome proliferator-activated receptor (PPAR), and estrogen-related receptor (ERR) are also the targets of isoflavones' biological actions. Isoflavones manifest their biological action by binding to NRs, modulating their transcriptional responses, and entering the signaling pathways regulated by endogenous receptor ligands (Maldonado-Rojas *et al*., 2021). This is highly warranted to develop better therapeutic options for bone-related disorders. Therefore, this review highlights recent study findings to better understand the unique nature of isoflavones' actions on the regulation of NRs involved in bone remodeling.

DATA SOURCES AND SEARCHES

This review was based on data obtained from PubMed, Google Scholar, and EBSCOhost Medline databases from their inception to November 2022. Special attention was given to the mechanisms of particular isoflavones on NRs in the regulation of bone remodeling (summarized in Table 1).

ROLES OF NRs IN BONE REMODELING

NRs, a superfamily comprising 48 members in humans, are activated by lipophilic ligands including steroid hormones, thyroid hormones, lipophilic vitamins, and cholesterol metabolites (Gustafsson, 2016). They are mainly composed of a DNA-binding domain (DBD), a ligand-binding domain (LBD), an N-terminal domain, and a variable C-terminal domain. The binding of ligands causes conformational changes in the NR that initiate binding to chromatin within the nucleus. NRs subsequently bind to their responsive elements in the promoters and other regulatory regions (co-regulators) of target genes to intricately orchestrate an appropriate gene expression. Following binding to co-regulators, NRs exhibit their transcription by stimulation (co-activators) or repression (co-repressors) of transcription. In addition, ligands serve as agonists or antagonists, leading to up- or downregulation of target genes. NRs are involved in all key biological processes including development, cell growth, and differentiation, metabolism, immunity, reproduction, circadian

Table 1. Summary findings of isoflavones on modulation of bone remodelling through nuclear receptor mediated pathway. The parameter for these findings are statistically significant ($p < 0.05$).

Isoflavone compounds	Nuclear receptor	Summary findings	Author
Daidzein	ER	Daidzein promoted osteogenesis by facilitating proliferation, differentiation and anti-apoptosis in human osteoblast-like MG-63 cells through ER-dependent MEK/ERK and PI3K/Akt activation.	Jin *et al*. (2017)
Genistein	ER	Genistein promoted osteoblastogenesis in ER dependent manner by increasing extracellular collagen deposition and alkaline phosphatase activity	Cepeda *et al*. (2020)
Daidzein and genistein	ER	Treatment with soybean extracts promoted the secretion of OPG and inhibited RANKL expression-induced osteoclast differentiation through the suppression of nuclear factor of activated T cells c1 (NFATc1) activation and ER dependent manner.	Park *et al*. (2014)
Genistein	ER	Genistein promoted bone healing by triggering ERα-mediated expressions of osteogenesis-associated genes.	Wu *et al*. (2020)
Isoflavone	ER	Oral administration of isoflavone effectively inhibited uterus atrophy by increasing 17β- oestradiol level and bone mineral density (BMD) in femur and tibia of ovariectomised mice.	Kim *et al*. (2022)
Equol	ER	Equol promoted rat osteoblast proliferation and differentiation through estrogen receptor activation.	Wang *et al*. (2014)
Equol	ER	Equol improves bone formation by promoting proliferation and differentiation of osteoblasts through ER-PKCα signalling pathway.	Tousen *et al*. (2015)
Equol	ER	Equol improved trabecular bone volume of femoral distal metaphysis in ovariectomised rats through suppression of inflammatory cytokines production by bone marrow cells	Nishide *et al*. (2013)
8-prenylgenistein	ER	8-PG exerted oestrogenic effects in immature female mice with upregulation of ERα expression without affecting oestrus cycle and histology of uterus and vagina.	Li *et al*. (2019)
8-prenylgenistein	ER	8-PG improved trabecular bone properties in OVX mice without exerting uterotrophic effects and its estrogenic actions were distinct from those of genistein.	Zhang *et al*. (2018)
Daidzein	ER and PPARγ	Low-dose daidzein mainly acted on ERs, whereas high-dose daidzein mainly acted on PPARγ. Activation of ERs promoted the proliferation of osteoblasts. Activation of PPARγ inhibited proliferation of osteoblasts .	Bao *et al*. (2011)
Genistein	ER and PPARγ	At low concentrations (<1 μM), genistein bound to ER, stimulating osteogenesis and inhibiting adipogenesis. At high concentrations (>1 μm), genistein acts as a ligand of PPARγ, leading to up-regulation of adipogenesis and down-regulation of osteogenesis.	Dang *et al*. (2003)

rhythm, and behavior control (Gopi *et al*., 2021; Gustafsson, 2016; Papageorgiou *et al*., 2021). However, failure of translational regulation of NRs in terms of mutations, misfolding, or alteration of the ligand-signaling pathway can lead to numerous diseases such as obesity, diabetes, osteoporosis, and cancer (Anbalagan *et al*., 2012; Wang *et al*., 2017).

The members of the steroid receptors include the ER (α and β), AR, glucocorticoid receptor, and progesterone receptor. Vitamin D, thyroid hormone receptor (TR), PPAR (α, δ/β, and γ), and liver X receptor are classified as non-steroid receptors (Gopi *et al*., 2021; Gustafsson, 2016; Papageorgiou *et al*., 2021). Orphan receptors that lack endogenous ligands include ERRs (α, β, and γ) (Tanida, 2022). For orphan receptors, once their endogenous ligands are discovered, these receptors are called "adopted orphans" (de Vera, 2018; Tanida, 2022).

In bone-related disorder treatment especially osteoporosis, many researchers have focused on the ability to selectively modulate the receptors, which led to the preferable drug targets including SERMs (Clarke, 2020) and selective AR modulators (SARMs) that target steroid receptors (Solomon *et al*., 2019; Xie *et al*., 2022), selective PPAR modulators that aim at the non-steroid receptor (Liu *et al*., 2015; Marciano *et al*., 2015), and selective NR modulators (Sturm's) that target orphan receptors (Gallet and Vanacker, 2010; Kim *et al*., 2019; Zuo and Wan, 2017). Selective drug targets can be discovered by activating specific NRs with a specific set of target genes initiated by a specific ligand, which causes allosteric conformational changes in the NR. Herein, the NRs subfamilies that display pivotal roles in bone remodeling are discussed, particularly in promoting bone deposition and inhibiting bone resorption.

Estrogen receptor

ERα and ERβ are two steroid receptors whose ligand-activated transcription factors are detected by immunohistochemistry in osteoblasts, osteocytes, and osteoclasts. Both ERs regulate bone deposition and resorption through ligand or non-ligand-dependent nuclear mechanism or membrane-associated (DNA-independent) mechanism (Jiang *et al*., 2021; Khalid and Krum, 2016). They can transduce the physiological functions of estrogen, particularly on bone metabolism. Following binding to estrogen, activated ERs are translocated into the nucleus. They then transcriptionally regulate an appropriate gene

expression by associating with estrogen response elements (EREs) or binding to non-ligand ER of other DNA transcription factors and subsequent associated binding in ER/specificity protein and ER/activating protein 1 (Fuentes and Silveyra, 2019; Palaniappan *et al*., 2019).

Previous studies demonstrated that ER deletion in osteoclast lineage initiates more loss of trabecular than cortical bone, showing that ER indirectly inhibits osteoclast differentiation and resorption (Nicks *et al*., 2016; Melville *et al*., 2014). Interestingly, ERα has been reported to be expressed more than ERβ and ameliorated the progression of fracture healing in ovariectomized (OVX) rats by promoting osteoblast proliferation (Haffner-Luntzer *et al*., 2018; Melville *et al*., 2015). The level of estrogen ERα was elevated during bone restoration by eliciting chromosomal osteogenesis-related gene expressions such as Runx2, alkaline phosphatase (ALP), and OCN, which promote osteoblast maturation (Almeida *et al*., 2012). In addition, an immunohistochemistry study demonstrated that ERα and ERβ produced opposite effects with ERα highly expressed in cortical bone and ERβ highly expressed in trabecular bone (Bord *et al*., 2001).

A pioneering study in the 2000s used ER knockout murine models that are completely deficient of ERα and/or ERβ (ERα −/− and/or ERβ −/−) to study the roles of each receptor in bone by measuring BMD and cortical thickness. Findings showed that the deletion of both receptors (ERα −/− and ERβ −/−) caused a reduction of bone turnover and trabecular bone volume in both genders. The deletion of ERα (ERα −/−) was associated with declined bone turnover but increased bone volume of trabecular bone for both genders. Meanwhile, the deletion of ERβ (ERβ −/−) produced similar results as ERα but only occurred in females (Sims *et al*., 2002). To understand the roles of estrogen and its corresponding receptor on bone turnover and its underlying mechanism, gonadectomy was performed in the knockout mice. It was shown that estrogen treatment in orchidectomized ERα–/– mice failed to prevent bone loss. In contrast, estrogen treatment impeded ovariectomy and orchidectomy-induced bone loss in ERβ –/– mice. Collectively, these studies demonstrated that ERα is the central player of estrogen effects on bone (Sims *et al*., 2003).

SERMs are synthetic pharmacological compounds with less estrogen steroidal structure and exhibiting a tertiary structure. They can bind to ERs to produce estrogen's beneficial effects on bone and the cardiovascular system without producing adverse effects on the uterus or mammary glands after menopause (Burr and Phipps, 2022). Conceptually, SERMs differentially express multiple genes and the transcription activity is regulated by ER. The expression of agonist or antagonist activity by SERMs genes was determined by either co-activators or co-repressors' preferential binding to SERM/ER NR transcription complex (Puranik *et al*., 2019).

An ideal SERM can thus be utilized for the treatment and prevention of breast cancer (Makar *et al*., 2020) and osteoporosis (Goldstein, 2022) or to provide relief of hot flashes and other menopause symptoms (Mehedintu *et al*., 2021). The classical SERM, tamoxifen, is a selective ER blocker in the breast and is an effective agent for treating breast cancer (Cha *et al*., 2021; Slanař *et al*., 2021). It has also been indicated to prevent bone loss (Genant, 2011) and provide cardioprotective benefits (Ebrahimi *et al*., 2020). However, it is associated with a significantly higher incidence of venous thromboembolic events (Lin *et al*., 2018). The newer SERMs including raloxifene (Nagai *et al*., 2018), lasofoxifene (Cummings *et al*., 2010), and bazedoxifene (Cho *et al*., 2021) have been approved as osteoprotective agents in postmenopausal women with a favorable uterine and breast safety profile. However, they produce adverse effects such as hot flashes and symptoms of vaginal atrophy including dyspareunia (Pinkerton and Thomas, 2014).

Estrogen-related receptors

ERRs, termed ERRα, ERRβ, and ERRγ, belong to the subfamily of orphan NRs that act as transcription factors. As ERRs are orphan NRs, no natural ligands have been identified for them. ERRs have a similar molecular structure to that of other NRs and act as ligand-independent transcription factors (Goher and Elgendy, 2021). Their transcriptional activities are regulated by post-translational modification or the availability of transcriptional co-regulators (Goher and Elgendy, 2021; Huss *et al*., 2015). ERRs recruit co-regulators to modulate gene expression transcription and play a part in various physiological functions including energy metabolism, embryonic stem cell pluripotency, bone metabolism, and cancer progression (Huang and Sun, 2021; Ranhotra, 2018). In terms of ERRs activities on bone metabolism, ERRα and ERRγ are potential targets to protect against bone loss (Bonnelye, 2016; Feng *et al*., 2022; Gallet and Vanacker, 2010).

In vitro experiments have shown that ERRα was strongly expressed in mesenchymal cell commitment, and when upregulated, they promote early osteoblast and adipogenic differentiation. Several findings pointed to the role of ERRα as a switch that suppresses the differentiation of MSCs into osteoblasts of the bone formation pathway while favoring the adipocytic pathway (Bonnelye, 2016; Gallet and Vanacker, 2010). ERRα constructively modulates the key proteins in osteoblastogenesis including Runt-related transcription factor (Runx2), osteopontin (OPN), and OCN transcription. This regulation is dependent on respective PPAR, gamma coactivator-1 alpha (PGC-1α), and PGC-1β expression levels (Chen *et al*., 2022a, 2022b; Feng *et al*., 2022; Kammerer *et al*., 2013; Wang and Wang, 2013). The prominent role of ERRα in osteoblast differentiation was underlined by a demonstration that ERRα acted as a transcriptional activator of Runx2-I in the presence of PGC-1α and as a transcriptional repressor of Runx2-I in the presence of PGC-1β (Kammerer *et al*., 2013). ERRα has also been found to interact mutually with PGC-1α and increase OCN promoter activity (Wang and Wang, 2013). In addition, high ERRα expression has been found in the ossification zones (long and flat bones) during mouse embryonic development, suggesting that this receptor may promote endochondral and intramembranous ossifications (Bonnelye, 2022).

There is evidence that ERRα may also regulate osteoclastogenesis activity (Bae *et al*., 2017; Kim *et al*., 2021; Yang and Wan, 2019). A study by Yang and Wan (2019) verified that ERRα deletion disrupted bone hemopoiesis, as seen in ERRα knockout mice which exhibited osteopetrosis due to decreased bone resorption and high bone mass. Since ERRα is an orphan receptor, it can bind to any synthetic compounds including cholesterol. Cholesterol has been identified as a potential agonist to modulate ERRα activities and stability (Casaburi *et al*.,

2018). Cholesterol binding to ERRα synergistically promoted downstream osteoclastogenesis. Furthermore, the study by Wei *et al*. (2016) revealed that cholesterol enhanced the interaction between ERRα and PGC-1α in osteoclasts, thus promoting bone resorption activity. Following these study findings, several other studies reported low BMD in dyslipidemia patients (Kim *et al*., 2013) and post-menopausal women with high lipid profiles (Yang *et al*., 2018). Thus, dyslipidemia could accelerate the bone resorption process and lead to bone-related disorders such as osteopenia and osteoporosis.

Accordingly, statins are the most prescribed cholesterol-lowering drugs that block 3- hydroxy-3-mthylglutaryl-coenzyme A reductase activity and inhibit the synthesis of mevalonate, the precursor of cholesterol (Zhang *et al*., 2021). Besides their cardioprotective properties, statins produce pleiotropic osteoprotective effects, which affect bone formation rather than bone resorption (Murphy *et al*., 2020). The lipophilic structure of statin and its capability of modulating the transcriptional activity of ERRα in bones have been reported. Statins have been shown to act as an endogenous agonist of ERRα to suppress osteoclastogenesis by decreasing the free cholesterol bioavailability (Casaburi *et al*., 2018; Wei *et al*., 2016). Concomitantly, statin has been found to inhibit the receptor of nuclear factor κβ ligand (RANKL) in macrophages, which caused a reduction in free cholesterol and prevented ERRα from stimulating osteoclastogenesis (Climent *et al*., 2021). The osteoprotective effects of statin was also associated with increased expression of the bone morphogenetic protein-2 gene that promotes osteoblast differentiation (Kuwahara *et al*., 2022; Li *et al*., 2022a, 2022b, 2022c). Congruously, in human studies, BMDdecreases with an increase in statin dose (Fadheel and Naser, 2022; Zheng *et al*., 2020). Thus, these findings implied the importance of ERRα in the pathogenesis of osteoporosis, leading to enormous interest in this protein as a novel therapeutic target.

Peroxisome proliferator-activated receptor-γ (PPAR-γ)

PPARs are adopted orphan NRs, which consist of three isoforms, PPAR-α, PPAR-γ, and PPAR-δ/β (Grygiel-Górniak, 2014; Palomer *et al*., 2018). In the DNA-dependent pathway, PPARs form heterodimers with retinoid X receptors and are associated with peroxisome proliferator response elements in the promoter of their target genes (Kilu *et al*., 2021). PPAR-γ has been markedly established as the master regulator of adipocyte differentiation, which plays a role in adipogenic and lipogenic pathways (Ma *et al*., 2018). However, PPAR-γ activities have also been addressed in osteoblasts (Li *et al*., 2019a, 2019b), osteoclasts (Guo *et al*., 2019), and chondrocytes (Chen *et al*., 2015). In these cells, PPAR-γ suppressed bone formation and stimulated bone resorption by favoring adipogenesis (Guo *et al*., 2019; Li *et al*., 2019a, 2019b). PPAR-γ agonists such as thiazolidinediones (TZDs) (Ahsan, 2019), lobeglitazone (Rocha *et al*., 2020), and pioglitazone (Tomlinson *et al*., 2022) are potent treatments of type II diabetes but may cause adverse effects of increased fracture risk. The PPAR-γ activated by TZDs causes disproportionate bone remodeling, which led to increased bone resorption and decreased bone formation. The use of selective PPAR-γ modulators can reduce the harmful effects of the PPAR-γ on bones (Wei and Wan, 2011).

Noteworthily, homozygous PPAR-γ-deficient embryonic stem cells failed to differentiate into adipocytes but displayed an increased number of osteoblasts (Akune *et al*., 2004). The deletion of PPAR-γ in mesenchymal progenitors' cells has also been shown to improve BMD, bone volume, trabecular bone number, and osteoblasts cell number (Cao *et al*., 2020). In addition, PPAR-γ deletion in osteoclast and endothelial cells increased bone mass due to reduced osteoclast differentiation (Zou *et al*., 2016). Physiologically, it is worth noting that PPAR-γ could act as a pro-osteoclastogenesis regulator (Cao *et al*., 2020; Li *et al*., 2019a, 2019b; Zou *et al*., 2016). Therefore, the molecular mechanisms of PPAR-γ that link adipogenic signaling molecules and osteoclast differentiation need to be elucidated. This is important to determine if PPAR-γ modulators may provide therapeutic strategies for the treatment of metabolic diseases especially cardiovascular disease and osteoporosis (Muruganandan *et al*., 2020)

Androgen receptor

AR is a ligand-inducible transcription factor and a member of the nuclear steroid TR gene superfamily. Androgen hormone specifically binds to AR which causes conformational changes in AR and the recruitment of specific promoter elements. This is followed by transcription activation or repression of various target genes. Since AR is on chromosome X, the deficiency of AR mostly affects males (Davey and Grossmann, 2016; Levine and Garabedian 2014). Androgen is also essential for conversion to estrogen by aromatase activity; therefore, androgen is competent for activating both ERs and ARs expression (Bianchi *et al*., 2021; Rosati *et al*., 2021).

Osteoblasts and osteocytes in bone tissues express AR to modulate several gene expressions that encode various growth factors and cytokines to control bone remodeling (Chen *et al*., 2019; Gong *et al*., 2021). AR in osteoblasts is stimulated by estrogen, androgen, and 1,25-dihydroxy vitamin D to accelerate osteoblast proliferation, differentiation, and synthesis of extracellular matrix protein to initiate mineralization (Chen *et al*., 2019; Chinetti and Neels, 2021). AR that presents on osteocytes has a pivotal role in improving skeletal integrity and bone quality (Sinnesael *et al*., 2012). Impaired AR signaling can lead to irregular bone cell activities (Russell *et al*., 2012). A study by Kawano *et al*. (2003) revealed that the upregulation of RANKL expression in osteoblasts of AR-deficient mice augmented osteoclastogenesis . Furthermore, AR activation in osteoblasts inhibited bone resorption in the cancellous compartment (Sinnesael *et al*., 2015). These findings also showed that osteoclasts in AR knockout (ARKO) mice did not show changes in their proliferation and differentiation and there were no changes in bone microarchitecture (Kawano *et al*., 2003; Sinnesael *et al*., 2015). These two findings evidently illustrated that osteoclast function is mainly regulated by estrogens and ER, not AR.

To outline the physiological roles of AR on bone metabolism, AR transgenic and ARKO models were designed through the deletion of exon 3 of AR, which encode the 2nd zinc finger of the DBD (Chang *et al*., 2013). In ARKO mice, the DNA-binding-dependent AR pathway is abolished but the non-DNA pathway remains functional (Rana *et al*., 2014). The clinical phenotype of ARKO mice is consistent with hypogonadism in human males, with high-fat mass but low bone and muscle mass

(Rana *et al*., 2014; Sebo *et al*., 2021). Previous studies showed that ARKO murine displayed osteopenia, retarded growth curves, and increased trabecular bone resorption. Since AR affects both osteoblast and osteoclast cells, mature osteoblast ARKO and mature osteoclast ARKO were developed. The study by Kawano *et al*. (2003) revealed that AR deletion in mature osteoblasts increased RANKL expression, followed by enhanced osteoclast differentiation. This has been further supported by subsequent studies demonstrating that deletion of exon 3 of the AR gene in osteoblast cells led to pronounced trabecular bone loss in adult male mice (Notini *et al*., 2007; Wu *et al*., 2019;). On the other hand, Jardi *et al*. (2019) demonstrated that 46-week-old neuronal ARKO mild mice displayed pronounced loss of cortical thickness and strength. The study concluded that AR in neurons retains bone mass and strength in aging mice.

SARMs are anabolic steroids that bind to AR by a DNA-dependent pathway and display pronounced tissue selectivity. Examples of SARMs currently available are ostarine and andarine (Solomon *et al*., 2019). The understanding of AR interactions with various co-activators and co-suppressors is therefore crucial.

Interaction of isoflavones to ER

Upon ingestion, the isoflavones are deconjugated to their respective aglycone in the gastrointestinal tract. These aglycones are extensively metabolized during absorption to become glucuronidated and/or sulfated conjugates before entering the bloodstream (Chen *et al*., 2018, 2022a, 2022b; Gonzales *et al*., 2015). These conjugates have been demonstrated to be agonistic ligands of both ER-LBD and ER-LBD to stimulate ER-LBD-coregulator interaction and exhibit their transcription (Morito *et al*., 2002). Examples of these conjugates include dihydrodaidzein, dihydrogenistein, equol, and O-DMA (Gaya *et al*., 2016; Islam *et al*., 2015). Isoflavones' ER-binding abilities have the ability to induce intracellular signaling processes, which are crucial for cellular growth (Lee *et al*., 2013).

Isoflavones and estradiol are competitively binding on ERs. According to Beekmann *et al*. (2015) *'s* findings, isoflavone aglycones were less effective than E2 at activating the LBDs of ERα and ERβ, and genistein was more effective than daidzein. This is consistent with other studies showing that genistein and daidzein have a lower affinity for binding to ERα and ERβ than E2 (Jiang *et al*., 2013) and that they can induce ERα and ERβ-mediated gene transcription as well as cell proliferation at concentrations higher than E2 with genistein frequently being more potent than daidzein (Islam *et al*., 2015). ERβ-LBD was shown to be more responsive to genistein activation than ERα-LBD (Beekmann *et al*., 2015). This is consistent with observations in the literature that show that genistein preferentially binds to and activates ERβ over ERα during transcription (Jiang *et al*., 2013).

ERs are widely distributed in reproductive organs, particularly the uterus and breast. The affinity of 17β-estradiol for ERα and ERβ receptors is equal, whereas the affinity of isoflavones for ERβ receptor is higher (Lee *et al*., 2021; Mbachu *et al*., 2020). When a phytoestrogen binds to a receptor, the receptor may be partially activated (have an agonistic impact) or become less activated (have an antagonistic effect), depending on the effect of the estrogen molecule being displaced by the phytoestrogen (Khan *et al*., 2022; Wang *et al*., 2021). Researchers are interested in tissue-specific phytoestrogens because estrogenic (agonist) activity in some tissues can help maintain BMDand enhance blood lipid profiles while antiestrogenic (antagonist) activity in reproductive tissues can help lower the risk of hormone-related tumors (such as those of the breast, uterus, and prostate) (Hsieh *et al*., 2018). Isoflavones can also exert a biphasic scheme by acting as estrogen agonists at low concentrations but as an antagonist at high concentrations (Erguc *et al*., 2021; Manayi, 2021). For instance, isoflavones inhibit the growth of breast cancer cells at higher doses while stimulating the growth of positive ER breast cancer cells at low concentrations (Martinkovich *et al*., 2014).

EFFECTS OF ISOFLAVONES ON BONE REMODELING THROUGH ER PATHWAY

Various *in vitro* and *in vivo* studies on bone remodeling demonstrated that isoflavones positively stimulate osteoblastic bone formation and inhibit osteoclastic bone resorption (Fig. 1). Daidzein and genistein have been found to stimulate osteoblastogenesis in rat and human osteoblast cells. These isoflavones facilitated osteoblast proliferation, differentiation, and anti-apoptosis via the activation of phosphoinositide 3-kinase/protein kinase B or PKB (PI3K/Akt) in an ER-dependent manner (Cepeda *et al*., 2020; Jin *et al*., 2017). The osteoblastogenic effects of these isoflavones were confirmed with increased levels of osteoblast differentiation markers such as ALP, type 1 collagen, bone sialoprotein, OPN, and OCN (Cepeda *et al*., 2020). On the other hand, daidzein and genistein exerted anti-resorptive effects by increasing the osteoprotegerin (OPG) level and decreasing the RANKL level. This was achieved through the suppression of the nuclear factor of activated T cells c1 expression in the ER-dependent manner (Park *et al*., 2014).

More remarkably, in *in vivo* studies, genistein was capable of promoting fracture healing by stimulating osteoblast maturation via an ERα-dependent mechanism (Wu *et al*., 2020). This suggested that genistein has the potential to be developed as drug therapy for osteoporosis and osteoporotic fracture. Additionally, Kim *et al*. (2022) showed that oral administration of isoflavone to OVX mice increased 17β-estradiol level and effectively inhibited uterus atrophy and promoted BMD of femora and tibiae. In line with these findings, isoflavone was found to enhance the ratio of serum OPG/RANKL in OVX mice, conceivably improving bone remodeling (Kim *et al*., 2022).

Previous studies reported that equol, the active metabolite of daidzein, showed greater affinity for ERβ and has a longer half-life and greater bioavailability than daidzein and genistein (Mayo *et al*., 2019). Equol promoted the proliferation and differentiation of osteoblasts through the ER -protein kinase C alpha (ER-PKCα) signaling pathway, suggesting its ability to improve bone formation (Wang *et al*., 2014). In addition, Tousen *et al*. (2015) indicated that equol was more efficient than daidzein to increase the BMD of growing females by enhancing bone formation without affecting the weight of reproductive organs. Furthermore, equol was revealed to improve the femoral trabecular bone volume of OVX rats through suppression of inflammatory cytokines production by bone marrow cells (Nishide *et al*., 2013).

Prenylated isoflavone is characterized by the presence of a prenylated side chain in the flavonoid skeleton. The substitute for genistein, 8-PG, is found in the flower of hops (*Humulus lupulus*

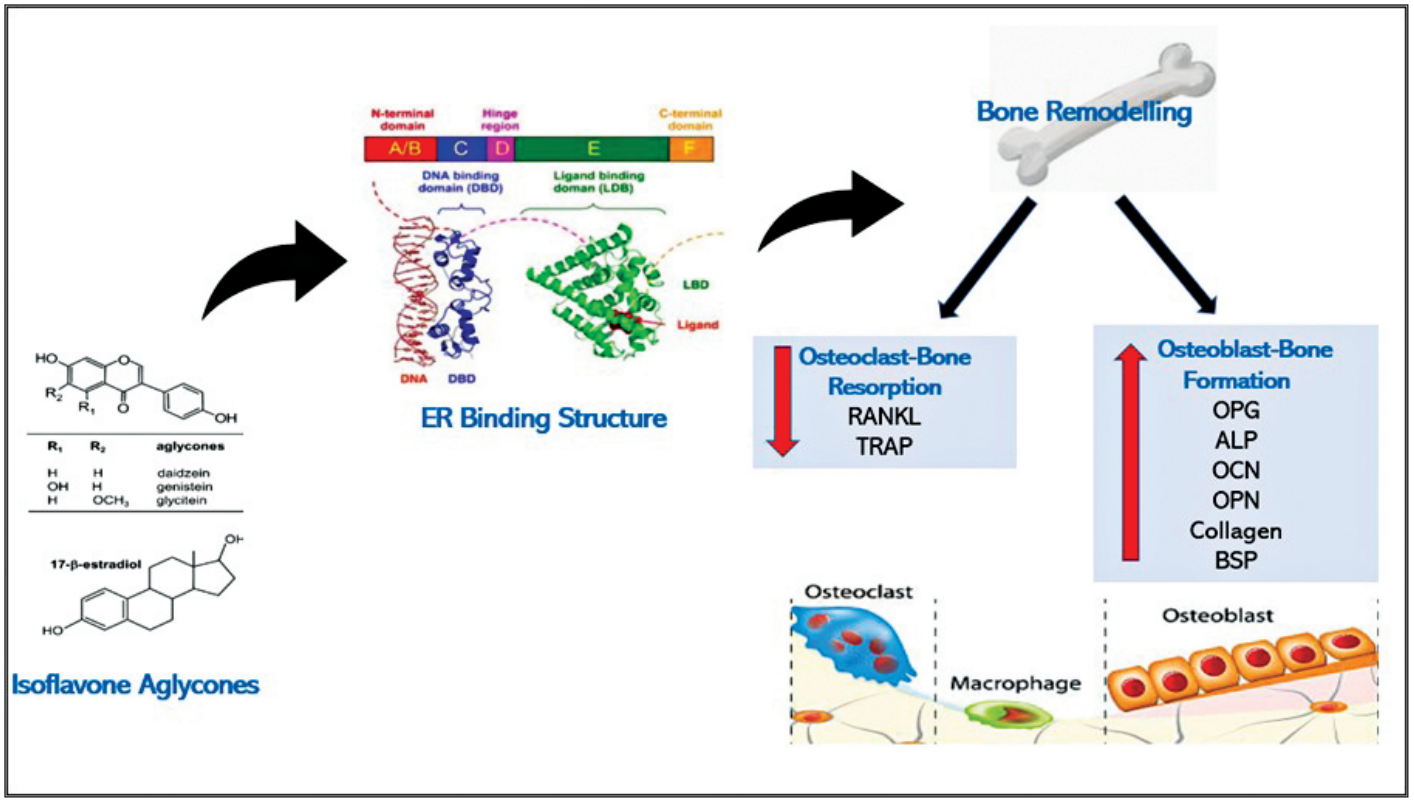

Figure 1. Isoflavones aglycones bind to either ERα or ERβ, increase osteoblast bone formation markers such as OPG, ALP, OCN, OPN, collagen, and BSP, and reduce osteoclast bone resorption markers such as RANKL and TRAP via ER-dependent signaling pathway. ER: Estrogen receptor; OPG: *Osteoprotegerin*; ALP: Alkaline phosphatase; OCN: Osteocalcin; OPN: *Osteopontin; BSP: Bone sialoprotein;* RANKL: Receptor activator of the nuclear factor-κB ligand; OPG: Osteoprotegerin; TRAP: Tartrate-resistant acid phosphatase.

L.). Multiple *in vitro* and *in vivo* studies have regarded 8-PG as one of the potent isoflavones with estrogenic activities. Interestingly, Kretzschmar *et al*. (2010) demonstrated that 8-PG was able to induce responsive reporter activities in yeast and ALP activities in Ishikawa cells much greater than other phytoestrogens such as genistein, daidzein, and coumestrol. The high estrogenic activity of 8-PG was confirmed in an *in vivo* study by the upregulation of ERα in bone cells of immature female mice without altering ERα level in the uterus (Li *et al*., 2019a, 2019b). Intriguingly, prenylated isoflavones displayed an essential role in bone remodeling. 8-PG was reported to improve trabecular bone properties in OVX mice through an ERα-dependent mechanism without exerting uterotrophic effects (Zhang *et al*., 2018). Moreover, 8-PG displayed a more pronounced ability than naringenin in enhancing osteoblast differentiation and mineralization (Ming *et al*., 2012). These studies clearly indicated that prenylation modification in the isoflavone compound is essential for inducing osteogenesis.

The beneficial effects of soy isoflavones on BMD of postmenopausal women have been discussed in a systematic review (Barańska *et al*., 2022).

EFFECTS OF ISOFLAVONES ON BONE REMODELING THROUGH ERR PATHWAY

Suetsugi *et al*. (2003) demonstrated that the activation of ERRα by genistein and daidzein was comparable to the activation of ERα and ERβ. Note that even though ERRα is structurally similar to ERα, it is not activated by 17β-estradiol. Concomitantly, daidzein reduced lipid deposition in muscle cells through the ERRα pathway and not the ER pathway (Kitamura *et al*., 2020). The important role of ERRα in bone remodeling is well accepted. ERRα exhibits diverse functions in osteogenesis, especially in regulating osteoblast and osteoclast differentiation (Feng *et al*., 2022). A study is required to determine the effects of isoflavones on bone remodeling through the ERRα-mediated pathway.

EFFECTS OF ISOFLAVONES ON BONE REMODELING THROUGH PPARY DOWNREGULATION

In a study on murine mesenchymal progenitor cell lines, low concentration of isoflavones stimulated osteogenesis and inhibited adipogenesis. Conversely, a high concentration of isoflavones inhibited osteogenesis and accelerated adipogenesis. It is interesting to note that when ERs were blocked by ICI182780, an ER antagonist, daidzein could activate PPARγ signaling pathway to modulate adipogenesis and osteogenesis signaling pathway (Bao *et al*., 2011). In line with this, the bone marrow mesenchymal stem cell of PPARγ knockout mice exhibited abolishment of adipogenesis and increased osteoblastogenesis (Cao *et al*., 2015). Further, genistein at low concentration (<1 μM) was shown to act as an inhibitor of PPARγ by promoting osteogenesis and inhibiting adipogenesis (Dang *et al*., 2003). The inhibition of PPARγ could also inactivate bone resorption activities (Guo *et al*., 2019; Li *et al*., 2018). Thus, blockage of the PPARγ-mediated signaling pathway by isoflavones could increase bone formation and attenuate bone resorption. In summary, the biphasic dose-dependent modulation

of osteogenesis and adipogenesis by isoflavones is crucial for the treatment of metabolic disorders and osteoporosis.

EFFECTS OF ISOFLAVONES ON BONE REMODELING THROUGH AR PATHWAY

Isoflavones have been found to bind to ARs (Mahmoud *et al*., 2011). Multiple studies demonstrated that the binding to AR ligands would promote anabolic AR responses, which maintain muscle mass and bone integrity (Almeida *et al*., 2017; Chen *et al*., 2019; Lan *et al*., 2022). Isoflavones have been shown to downregulate AR expressions to suppress prostate cancer cells (Ajdžanovic *et al*., 2019; Sivoňová *et al*., 2019; Stanisławska *et al*., 2022). However, their actions toward bone remodeling via AR have yet to be elucidated.

CONCLUSION

This review offers up-to-date literature on the influence of isoflavones on bone remodeling, especially via osteoclast and osteoblast differentiation. Isoflavones have exemplified NRs regulation on bone osteoprotective effects. The classical steroid receptors recognized as regulators of bone remodeling include estrogen and AR, whereas recent studies have identified new NRs including ERR and PPAR-γ as novel regulators of osteogenesis. These NRs could be therapeutic targets that gain access to the mechanism controlling gene regulation in osteoporosis treatment. Therefore, this review has highlighted the potential of dietary isoflavones to prevent osteoporosis and exert beneficial effects on bone remodeling.

AUTHORS' CONTRIBUTIONS

Conceptualization was done by H. A. H. and A. N. S.; material searching was done by H. A. H., N. M., and P. A. J.; original draft preparation was contributed by H. A. H.; writing review and editing were contributed by H. A. H. and A. N. S. All authors have read and agreed to the published version of the manuscript.

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The authors declare that they have no conflicts of interest.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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LIST OF ABBREVIATIONS

8-PG, 8-Prenylgenistein; ALP, Alkaline phosphatase; AR, Androgen receptor; BMD, Bone mineral density; ER, Estrogen receptor; ERR, Estrogen-related receptor; NR, Nuclear receptor; OPG, Osteoprotegerin; OVX, Ovariectomized; PPAR, Peroxisome proliferator-activated receptor; RANKL, Receptor activator of nuclear factor-κB ligand; SERM, Selective estrogen receptor modulator.

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