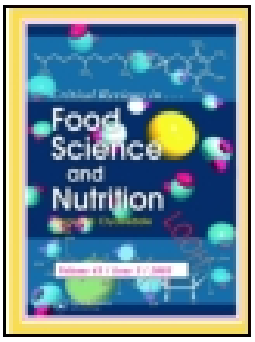

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REVIEW

Dietary interventions for better management of osteoporosis: An overview

Danjun Guo[a,b]*, Mengge Zhao[a]*, Wei Xu[b], Hui He[a], Bin Li[a], and Tao Hou[a]

[a]College of Food Science and Technology, Huazhong Agricultural University, Wuhan, China; [b]College of Food Science & Engineering, Wuhan Polytechnic University, Wuhan, China

ABSTRACT
Osteoporosis is a public health concern and a cause of bone loss, increased risk of skeletal fracture, and a heavy economic burden. It is common in postmenopausal women and the elderly and is impacted by dietary factors, lifestyle and some secondary factors. Although many drugs are available for the treatment of osteoporosis, these therapies are accompanied by subsequent side effects. Hence, dietary interventions are highly important to prevent osteoporosis. This review was aimed to provide a comprehensive understanding of the roles of dietary nutrients derived from natural foods and of common dietary patterns in the regulation of osteoporosis. Nutrients from daily diets, such as unsaturated fatty acids, proteins, minerals, peptides, phytoestrogens, and prebiotics, can regulate bone metabolism and reverse bone loss. Meanwhile, these nutrients generally existed in food groups and certain dietary patterns also play critical roles in skeletal health. Appropriate dietary interventions (nutrients and dietary patterns) could be primary and effective strategies to prevent and treat osteoporosis across the lifespan for the consumers and food enterprises.

KEYWORDS
dietary nutrients; dietary patterns; osteoporosis; processed foods

Introduction

Bones are dynamic tissues essential to human body, which are constantly remodeled throughout life. Firstly, osteoblasts and osteoclasts contribute to maintaining the balance between bone formation and resorption. Once this balance is destroyed because of a decrease in bone formation and an increase in bone resorption, bone loss is induced, elevating the risk of bone fracture. Additionally, bone mesenchymal stem cells (MSCs) can differentiate into osteoblasts and adipocytes. Certain regulators such as steroids and cytokines can stimulate the suppression of osteogenic processes and increase the incidence of osteoporosis (Pino, Rosen, and Pablo Rodríguez 2012). Osteoporosis is commonly defined as a reduction in bone mass and disruption of its microstructure, followed by an increased risk of bone fracture. Approximately 53 million individuals suffer from the risk of bone loss in the USA (Looker et al. 2017). Simultaneously, osteoporosis is also considered a heavy economic burden worldwide. It has been estimated that the cost of prevention and management of osteoporosis in the EU is €37 billion, which might be increased by 25% until 2025 (Hernlund et al., 2013).

Multiple factors, categorized as modifiable and non-modifiable, can affect bone mass and health. Non-modifiable factors including age, gender, race, and genetics cannot be altered. Modifiable factors including dietary factors, and lifestyles, such as cigarette smoking, alcohol intake, and physical activity, can be altered (Rajput, Wairkar, and Gaud 2018). Currently, pharmacological and non-pharmacological interventions are two approaches employed to prevent and/or treat osteoporosis. The former is further categorized into approaches involving anti-resorption, anabolic, and dual-effect drugs including bisphosphonates, estrogen, denosumab, teriparatide, and strontium ranelate (Ip et al. 2013). However, the use of these agents causes several side effects such as reactions at the injection site, hypercalcemia, and orthostatic hypotension (Khosla and Hofbauer 2017). Non-pharmacological treatments mainly include the consumption of proper diets, adopting healthy lifestyles, and regular physical exercise, which may assist clinical treatments and prevent osteoporosis.

Since the symptoms of osteoporosis are not evident at an early stage, their prevention and management are crucial for reducing its incidence. Dietary intervention is considered a convenient approach to improve bone health. Many nutrients in our diets such as unsaturated fatty acids (UFAs), proteins, minerals, peptides, phytoestrogens, and prebiotics, which are derived from natural sources, have shown beneficial effects on bone health. Meanwhile, food groups or dietary patterns are also considered valuable approaches to balance the association between dietary interventions and bone health. Therefore, this review summarizes the effects of single nutrient from daily diets on bone health with their respective mechanisms, and discusses the benefits and risks of four common dietary patterns (Mediterranean, Eastern, Western and Modern diets). It is hoped that this

CONTACT Tao Hou houtao@mail.hzau.edu.cn
*These authors contributed equally.

Table 1. An overview of representative dietary nutrients affecting bone health.

Categories	Nutrients	Effects	Potential mechanism
Macronutrients			
Fatty acids	SFAs	Enhancing osteoclasts survival, inducing the apoptosis of osteoblasts and MSCs, decreasing bone mineral content and cancellous bone in rats	Increasing MIP-1 level, activating TLR4-mediated NF-κB signaling pathway (Yaghooti, Mohammadtaghvaei, and Mahboobnia 2019; Oh et al. 2010), and activating MAPK pathways (Yaghooti, Mohammadtaghvaei, and Mahboobnia 2019) and Fas/JNK pathway (Gunaratnam et al. 2013).
	UFAs	ω-6 FAs decreased hip and trochanter BMD in postmenopausal women, and increased the risk of osteoporosis; ω-6 FAs decreased total fracture risk, hip fracture risk, and increased the total body BMD (Orchard et al. 2010; Järvinen et al., 2012)	Decreasing calcium absorption due to the formation of calcium-fatty acid soaps (Ilesanmi-Oyelere et al. 2019), inducing the release of inflammatory cytokines (Kelly et al. 2013);
		ω-3 FAs could inhibit osteoclast differentiation and formation, enhance osteoblast activity, inhibit osteoclastogenesis, and facilitate calcium transport in the gut.	Activating FFAR4-βarr2 signaling pathway (Kasonga, Kruger, and Coetzee 2019), activating PPARγ and RANKL-mediated NF-κB pathway (Nakanishi and Tsukamoto 2015; Sun et al. 2003), increasing the activity of Ca^{2+}-ATPase, and positively affecting lipid rafts in plasma membrane (Maggio et al. 2009).
Proteins	Proteins	Inducing calcium loss in the bone;	Inducing chronic metabolic acid load, and increasing urinary calcium (Riond 2001).
		Attenuating age-related BMD, decreasing and reducing bone turnover marker levels in the elderly, and decreasing the risk of osteoporotic fractures in the elderly	Increasing IGF-1 levels (Rizzoli et al., 2018), enhancing intestinal calcium absorption (Kerstetter, Kenny, and Insogna 2011), increasing lean body and physical performance (Meng et al. 2009; Beasley et al. 2013), and increasing amino acids profiles for the synthesis of bone matrix (Bawa 2011).
Bioactive food components			
Bioactive peptides	Milk-derived peptides	Increasing BMD in healthy adult women, stimulating the proliferation and differentiation of osteoblasts, inhibiting bone resorption, and protecting from the apoptosis of osteoblasts.	Increasing the absorption of calcium (Ahn and Je 2019), activating L-type (Perego et al. 2012) and TRPV6 calcium channels (Perego et al. 2013), activating pAkt signaling cascade, suppressing the cytokines (Reddi et al. 2019), decreasing the production of ROS and LPO (Mada et al., 2017a), and augmenting the antioxidant defense systems (Mada et al., 2017b).
	Collagen peptides	Increasing the mechanical strength of the bone and BMD in OVX rats, enhancing collagen synthesis, and promoting the proliferation of osteoblasts	Activating TGF-β/Smad and ERK/MAPK signaling pathways (Song et al. 2019; Zhang et al. 2018), and interacting with EGFR (Ye et al. 2019).
Phytoestrogens	Isoflavones, Lignans, coumestans	Increasing bone strength and quality in a rat osteopenia model, increasing BMD, and alleviating bone loss in the spines of menopausal women	Upregulating the levels of ERβ, increasing the production of Runx2/Cbfa1 (De Wilde et al. 2004), activating the cAMP-mediating signaling pathways (Jiang et al. 2019; Jia et al. 2003), suppressing RANKL signaling pathways (Wei et al. 2019; Kanno, Hirano, and Kayama 2004; Karieb and Fox 2011), and enhancing intestinal calcium absorption (Zafar et al. 2004).
Prebiotics	FOS, GOS, inulin, polydextrose, etc.	Maintaining skeletal health, improving mineral absorption and bioavailability, preventing form bone loss, and anti-inflammatory effects	Altering the composition of the microbial communities (Wang, Wang, et al. 2017; Tanabe et al. 2019; Hou et al. 2017), increasing short-chain fatty acids content, and subsequently increasing calcium absorption, enhancing the epithelial barrier and morphological characteristics of the intestine (Hou et al. 2017; Whisner and Castillo 2018), increasing calbindin D9k levels (Fukushima, Aizaki, and Sakuma 2012), and activating anti-inflammatory signaling pathways (Singh et al. 2014; Iraporda et al. 2015).

review could provide new strategies for the prevention and treatment of osteoporosis.

Dietary nutrients

Dietary interventions could affect bone health through multiple mechanisms, which potentially contribute to reducing the risk of osteoporosis. Thereinto, numerous dietary nutrients derived from natural foods play important roles in bone health, such as fatty acids, proteins, peptides, phytoestrogens, prebiotics, minerals and vitamins. Several reviews have profoundly summarized the effects of minerals and vitamins on bone health, as well as their potential mechanisms (Maioli, Tagliabue, and Cioni 2018). Therefore, this section would focus on the effects of macronutrients (fatty acids and proteins), food components (peptides, phytoestrogens, prebiotics) on bone metabolism, which has been shown in Table 1.

Macronutrients

Dietary fatty acids

Saturated fatty acids (SFAs). Dietary SFAs are mainly derived from animal fats and plant oils, including meat, butter fat, and oils of palm, palm kernel, and coconut. In the last few decades, it has been revealed that a close

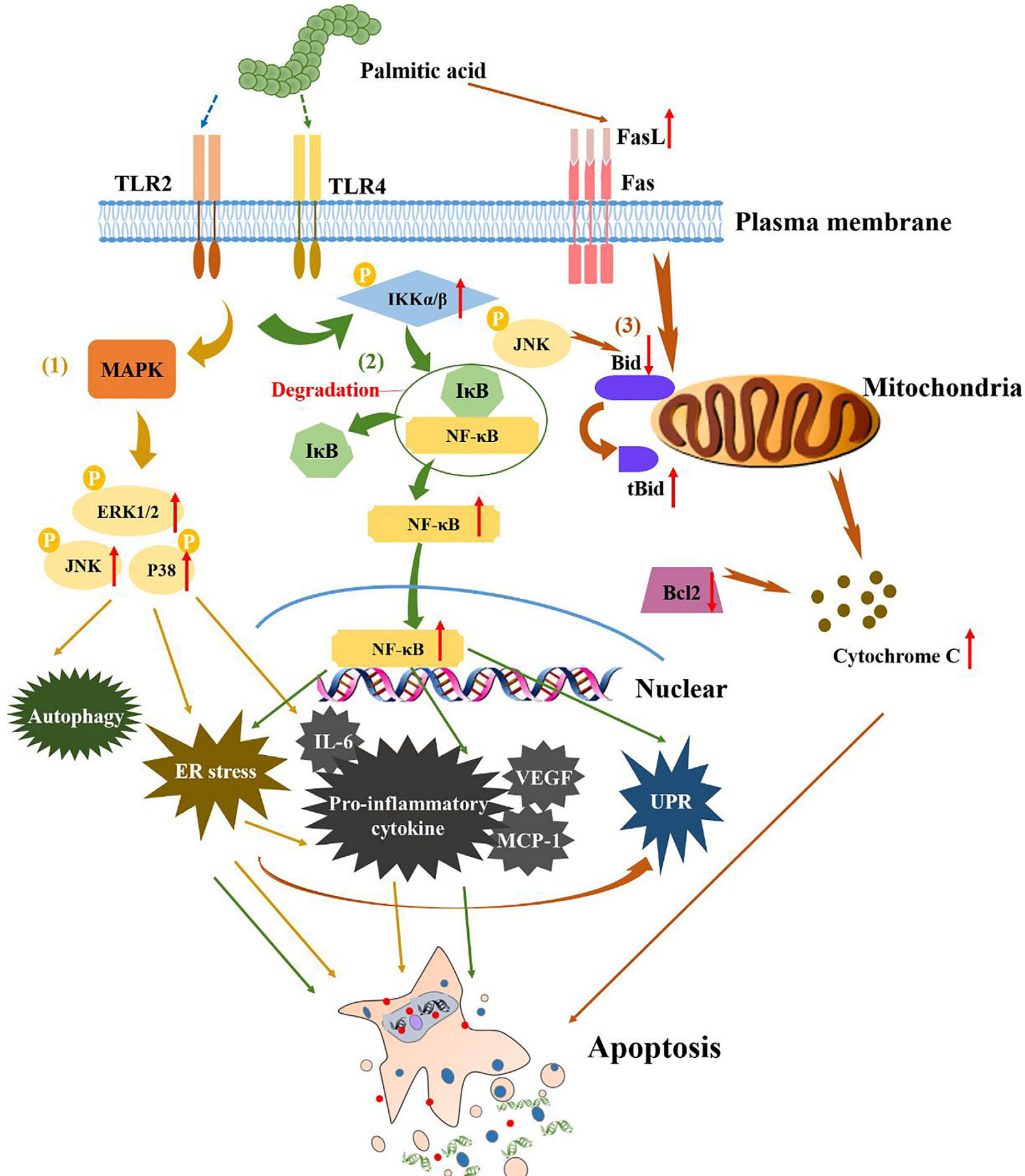

Figure 1. Mechanisms underlying the adverse effects of palmitic acid on bone health. Orange, green, and brown arrows indicate involvement of palmitic acid in mediating the MAPK, NF-κB, and Fas/JNK pathways, respectively. Red arrows pointing up and down indicate the mean promotion and inhibitory effects, respectively. Dotted arrow indicates indirect relationship or no direct evidence.

relationship exists between the bone and lipid metabolism, particularly in the human bone marrow (Muruganandan, Govindarajan, and Sinal 2018). A study by the Women's Health Initiative has indicated that the consumption of SFAs could significantly increase the risk of hip fracture (Orchard et al. 2010). The Dietary Guidelines for Americans (DGA) recommend that the consumption of saturated fat should be less than 10% of calories per day (DeSalvo et al. 2016).

Palmitic acid, a 16-C SFA, is one of the most common SFAs found in the human body and diet. Palmitic acid was reported to induce the apoptosis of osteoblasts (Zhong et al. 2011) and human MSCs, and enhance the survival of osteoclasts by preventing apoptosis (Oh et al. 2010). Palmitate is a ligand of toll-like receptors 2 (TLR2) and TLR4 in the human monocytes, which subsequently activates mitogen-activated protein kinases (MAPK) and nuclear factor κB (NF-κB) signaling pathways (Tian et al. 2015; Snodgrass et al. 2013). However, Lancaster et al. (2018) have proven that TLR4 is not a receptor for palmitate, although it could induce an inflammatory response in the human marrow cells (Lancaster et al. 2018). Moreover, the expressions of TLR2 and TLR4 are upregulated by palmitate (Gillet et al. 2015). Therefore, the relationship between TLR2 and/or TLR4 and palmitate in MSCs needs to be investigated further.

As shown in Figure 1, three major molecular mechanisms are involved in mediating the effects of palmitate on bone loss and osteoporosis. The first mechanism involves the MAPK pathways, in which, palmitate increases the phosphorylation of extracellular signal-regulated protein kinases

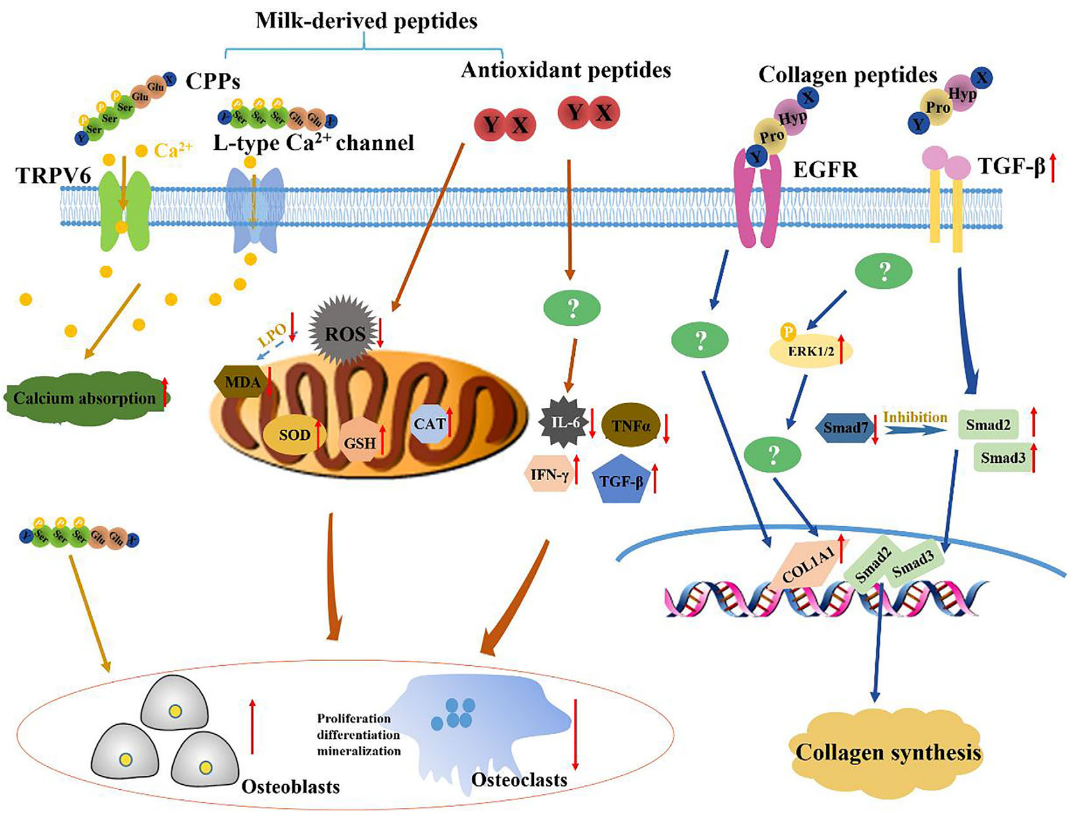

Figure 2. Underlying mechanisms of bioactive peptides in mediating the beneficial effects of bone health. Orange, and brown arrows indicated the effects of CPPs and milk-derived antioxidant peptides on bone health, respectively. Blue arrows indicated collagen peptides mediating the pathways involved in its synthesis. Red arrows pointing up and down indicated the mean promotion and inhibitory effects, respectively. White question marks indicated the unknown pathways or proteins involved in the processes.

(ERK) 1/2, p38, and c-Jun N-terminal kinase (JNK) (Yaghooti, Mohammadtaghvaei, and Mahboobnia 2019). It has been suggested that p38 might be involved in inducing endoplasmic reticulum (ER) stress in human bone MSCs (Lu et al. 2012). The release of palmitate-induced pro-inflammatory cytokines, such as vascular endothelial growth factor (VEGF), interleukin (IL)-6, and monocyte chemo-attractant protein (MCP)-1, are linked to the p38/ERK/JNK MAPK pathway (Yaghooti, Mohammadtaghvaei, and Mahboobnia 2019). It has also been shown that palmitate-induced autophagy and apoptosis of MSCs are dependent on the ERK/p38 MAPK pathway (Liu et al. 2018). The second mechanism involves the NF-κB pathway through the induction of a pro-inflammatory response. Palmitate increased the phosphorylation of inhibitory kappa kinase (IKK) α-IKKβ (Yaghooti, Mohammadtaghvaei, and Mahboobnia 2019), which led to the phosphorylation and degradation, dissociation, and activation and nuclear translocation of the inhibitor of NF-κB (IκB), IκB/NF-κB complex, and NF-κB, respectively (Wang et al. 2009). NF-κB pathway contributed to the apoptosis of MSCs and it was involved in unfolded protein response (UPR) and ER stress (Gillet et al. 2015), and the release of pro-inflammatory cytokines (Yaghooti, Mohammadtaghvaei, and Mahboobnia 2019). The third mechanism is linked to the Fas/JNK pathway in the osteoblasts (Gunaratnam et al. 2013). The expression of the Fas ligand (FasL) was improved by palmitate, which led to the activation of Fas and decreased the levels of BH3-interacting domain death agonist (Bid) due to the alteration in the Bid protein to its truncated form. Then, cytochrome c (pro-apoptotic factor) was released from the mitochondria. A significant decrease of Bcl2 could also promote the release of cytochrome c, thereby activating apoptosis. Additionally, the activation of the JNK pathway could induce the truncation of Bid protein (Westphal et al. 2011).

Unsaturated fatty acids (UFAs). It has been revealed that free fatty acid receptor 4 (FFAR4), also known as G protein-coupled receptors 120, which is a specific cell surface receptor of ω-3 FAs, is expressed in the osteoblasts, osteoclasts, and MSCs (Gao, Huang, et al. 2015). The activation of FFAR4 can induce various cellular responses and signals. Minimally, three mechanisms mediating the effect of ω-3 FAs on bone health are known, including the β-arrestin 2 (βarr2) signaling pathway, peroxisome proliferator-activated receptors (PPAR) γ, and calcium absorption (Figure 2). (1) Eicosapentaenoic acid (EPA) and docosahexenoic acid (DHA) present anti-osteoclastogenesis and pro-osteoblastogenesis effects through FFAR4-βarr2 signaling pathway (Kasonga, Kruger, and Coetzee 2019). FFAR4 recruits βarr2 to the plasma membrane in response to ω-3 FAs, which results in the formation and internalization of the FFAR4/βarr2 complex. βarr2 can prevent the formation of the transforming growth factor β-activated kinase 1/TAK1-binding protein-1 (TAK1/TAB1) complex. Then, MAPK and NF-κB signaling pathways were inhibited by inhibiting the phosphorylation of p38, JNK-1, ERK 1, IKK, and IκB/NF-κB (Kim et al. 2016). Consequently, nuclear factor of activated T-cells c1 (NFATc1) was downregulated (Kasonga, Kruger, and Coetzee 2019). (2) ω-3 FAs are the natural ligands of PPARγ, which can negatively regulate BMD and bone microstructure (Bonnet, Somm, and Rosen 2014). EPA and DHA have also been reported to inhibit osteoclastogenesis through the PPARγ-mediated suppression of NF-κB activation in MSCs (Nakanishi and Tsukamoto 2015), followed by the decrease of tumor necrosis factor (TNF)-α and IL-6 (Nakanishi, Iitsuka, and Tsukamoto 2013). Additionally, DHA and EPA suppressed osteoclastogenesis by inhibiting the expression of receptor activator of nuclear factor-kappa B ligand (RANKL), thus decreasing its binding to receptor activator of nuclear factor-kappa B (RANK). Consequently, NF-κB was inhibited (Sun et al. 2003). (3) Treatment with ω-3 FAs promoted calcium transport in Caco-2 cell models (Gilman and Cashman 2007). ω-3 FAs increased the absorption of calcium by increasing the activity of Ca^{2+}-ATPase, which contributed to an active absorption of calcium in the basolateral membrane (Haag and Kruger 2001). The activation of protein kinases A and C (PKA and PKC) by ω-3 FAs could induce protein phosphorylation, and the activity of Ca^{2+}-ATPase was improved (Haag and Kruger 2001). Additionally, it has been reported that ω-3 FAs could positively affect the structures and dimensions of membranes, particularly those of the lipid rafts, which play roles in the passive uptake of calcium (Maggio et al. 2009).

Recently, increasing evidence has indicated that ω-3 FAs play a beneficial role in bone formation, maintenance of bone quality (Koren et al. 2014), and bone remodeling (Farina et al. 2011). However, the effect of ω-6 FAs on bone health still remains inconsistent. It was reported that ω-6 FAs and their derivatives could induce the release of pro-inflammatory cytokines and subsequently stimulated bone resorption and loss (Chang and Chang 2003). Both prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) are metabolites of ω-6 FAs, which induce the release of inflammatory cytokines and lead to the development of osteoporosis (Kelly et al. 2013). Nevertheless, several large cohorts of postmenopausal women and men with high consumption of ω-6 FAs were associated with a decrease of total fracture (Orchard et al. 2010) and an increase of total body BMD (Järvinen et al., 2012). Additionally, ω-3 and ω-6 FAs share the common enzymes and their metabolites possess the anti- and pro-inflammatory effects, respectively, which suggesting the importance of the ratio of ω-3 and ω-6 FAs in the diets. Several results from the Women's Health Initiative and Nurses' Health Study indicated no significant relationship between the ratio of ω-3 and ω-6 FAs and fracture risk (Orchard et al. 2010). The scale range of ω-3 to ω-6 FAs in these researches might be inappropriate to detect any significant differences in fracture risk. Nowadays, the appropriate ratio of ω-3 to ω-6 FAs for the protection of bone health is clear, upper and lower limits of the ratio of ω-3 to ω-6 still remain unknown. Therefore, more prospective studies are required to address these questions and to subsequently establish a comprehensive understanding of the appropriate recommendations for the consumption of UFAs. If such efforts can be achieved, UFAs consumption might be a prospective approach to protect from excessive bone loss. High-quality fatty acid supplements (such as EPA and DHA) are required for several specific individuals, such as the elderly (Moon et al. 2012), pregnant mothers (Weichselbaum et al. 2013), and children (Parks et al. 2017).

Dietary proteins

Proteins, particularly collagen, make up 22% of the bone mass. However, the role of dietary proteins in bone health remains controversial. Early studies reported that high protein intake could negatively affect bone health owing to the chronic metabolic acid load, the subsequent increase in the levels of urinary calcium, and the induction of calcium loss in the bone (Riond 2001). Dietary proteins are mainly responsible for the dietary acid load because of the metabolism of sulfur-containing amino acids. Meanwhile, longitudinal, epidemiological, and population-based studies on osteoporosis have indicated that dietary protein consumption above the current recommended dietary allowance (RDA) (0.8 g/kg body weight/day) can maintain the BMD and decrease the risk of osteoporotic fractures in the elderly (Groenendijk et al. 2019). There are four underlying mechanisms supporting the positive relationship between high protein intake and bone health when other nutrients are adequate. (1) Increased dietary protein intake could increase the levels of serum insulin-like growth factor (IGF)-1 (Kazemi et al. 2020), which is regarded as a beneficial mediator of bone formation and health. (2) There was a positive association between dietary protein intake and intestinal calcium absorption (Kerstetter, Kenny, and Insogna 2011). (3) High protein intake could increase lean body mass in postmenopausal women (Meng et al. 2009) and physical performance (Beasley et al. 2013). (4) Dietary protein consumption could effectively provide amino acid profiles for the synthesis of collagen and non-collagen in the bone matrix (Bawa 2011). Herein, another heterogeneity between animal and plant protein with respect to osteoporosis arises. It has been reported that the consumption of animal protein increased the BMD in elderly women, while plant protein reduced the BMD (Evans et al. 2007). However, a meta-analysis revealed no differences in the consumption of animal and plant proteins in the prevention of bone loss (Wallace and Frankenfeld 2017). Though data linking the source of dietary protein and bone health are inconsistent and scarce, dairy sources of protein are confirmed to exert superior effects on skeleton than other nondairy proteins, which might be due to the high quality of dairy protein, and partly to the high content of calcium and vitamin D. A debate on the relationship between dietary protein and bone health has been going on for several years, which might, in part, be due to several intrinsic factors such as the population, baseline BMD, dietary patterns, lifestyle, and intake of other nutrients. Overall, evidence from human and animal studies showed that high dietary protein (>0.8 g/kg body weight/day) intakes had moderate or beneficial effects on the

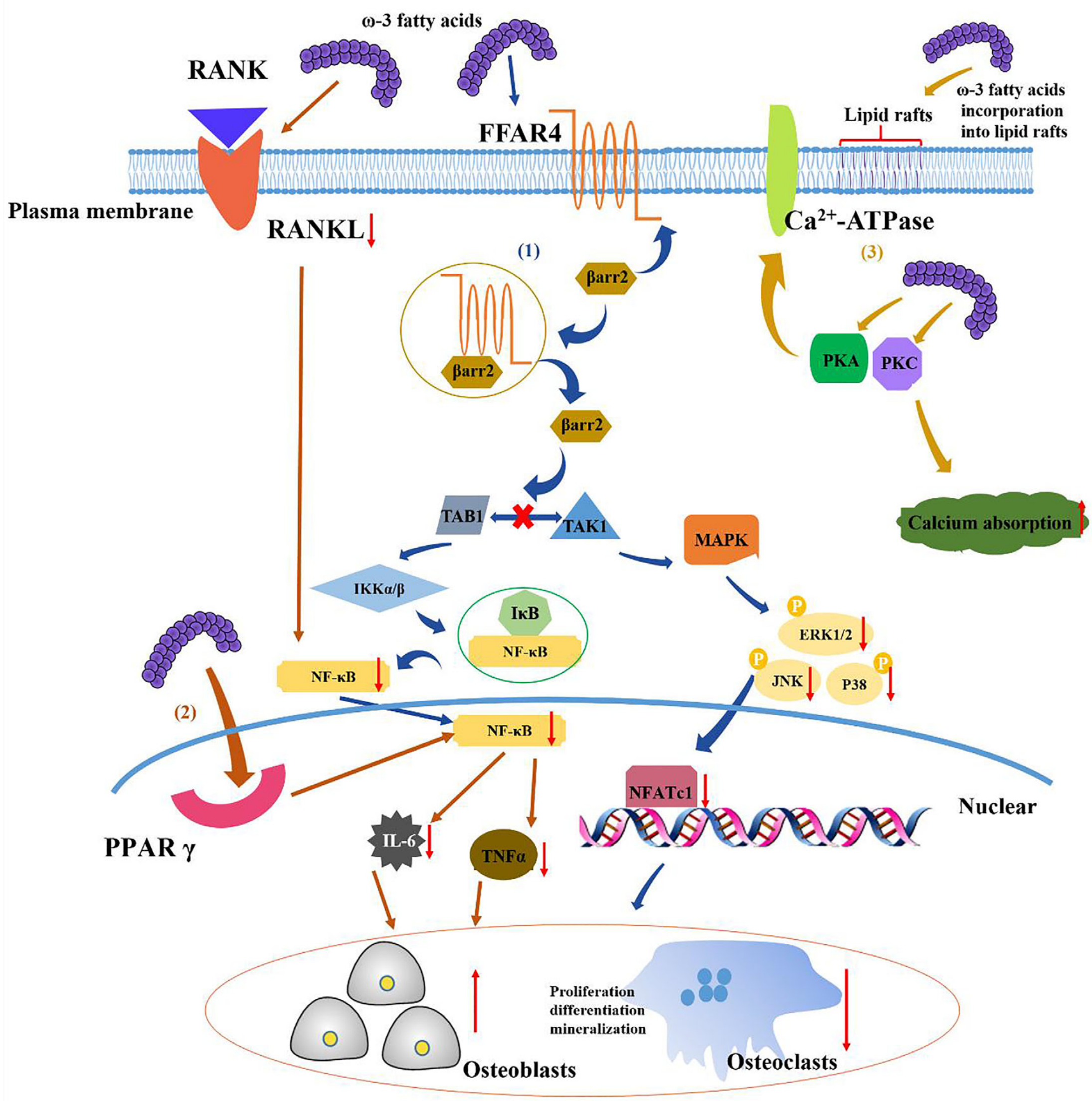

Figure 3. Underlying mechanisms involving ω-3 fatty acids in promoting bone health. Blue, brown, and orange arrows indicate the involvement of ω-3 fatty acids in mediating the βarr2 signaling pathway, PPARγ pathway, and calcium absorption, respectively. Red arrows pointing up and down indicate the mean promotion and inhibitory effects, respectively.

skeleton. Additionally, protein deficiency (20 g/day) had detrimental effects on bone mass and strength, especially for the elderly (Hannan et al. 2000). Therefore, adequate protein consumptions are highly important in bone and body health, especially for dairy protein intakes. However, current studies on the effects of high protein consumption (>0.8 g/kg body weight/day) on bone metabolism are not sufficient for now. It is hard to recommend high protein intake as the management for osteoporosis. More prospective studies are needed to consider these intrinsic factors with greater statistical power.

Bioactive food components

Bioactive peptides

Food-derived bioactive peptides are generally considered as healthy and safe cofactors owing to their ease of absorption and superior biological activities (Chakrabarti et al., 2018). Peptides promoting bone health have been discovered in various protein sources such as milk, collagen, ark shell, and duck egg white (Ahn and Je 2019). Peptides derived from milk and collagen are described in details in this section.

(Chakrabarti et al., 2018). Peptides promoting bone health have been discovered in various protein sources such as milk, collagen, ark shell, and duck egg white (Ahn and Je 2019). Peptides derived from milk and collagen are described in details in this section.

Milk-derived peptides

Milk is rich in proteins and minerals, and its consumption is considered to contribute to bone health. The results of a controlled trial have indicated that the daily intake of basic milk protein supplements mainly containing lactoferrin, lactoperoxidase (40 mg per day) could increase BMD in healthy adult women (Aoe et al. 2001). Milk contains approximately 3.5% of protein, which comprises 80% casein and 20% whey proteins. To date, it has been confirmed that various milk-derived peptides confer beneficial effects to bone health. Several potential mechanisms might help demonstrate the favorable effects of milk-derived peptides on bone health (Figure 3).

Casein phosphopeptides (CPPs) are obtained from milk casein protein through tryptic hydrolysis. CPPs share an 'acidic motif' (Ser(P)-Ser(P)-Ser(P)-Glu-Glu) with superior binding sites for minerals such as calcium. Therefore, CPPs could increase the absorption of calcium by preventing its precipitation in the intestine (Ahn and Je 2019). CPPs are also regarded as the calcium absorption promotors owing to their interaction with L-type (Perego et al. 2012) and transient receptor potential vanilloid subfamily member 6 (TRPV6) calcium channels (Perego et al. 2013). Furthermore, CPPs directly affected the proliferation, differentiation, and mineralization of human osteoblasts (Tulipano et al. 2010) and elevated the bioavailability of other minerals in the intestinal lumen (Sun et al. 2018).

Currently, several antioxidative peptides from buffalo casein and whey hydrolysates are identified (Reddi et al. 2018). VLPVPQK (PEP) derived from casein protected osteoblasts from H_2O_2-induced oxidative stress by decreasing the production of reactive oxygen species (ROS) and related lipid peroxidation (LPO), thereby decreasing the levels of malonaldehyde (MDA) (Mada et al., 2017b). PEP also augmented the levels of antioxidant defense systems in osteoblasts such as intracellular superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) (Mada et al., 2017a). PEP could also inhibit the expressions of TNF-α, IL-6, and RANKL, and prevent bone loss in OVX rats (Mada et al., 2017b). Additionally, whey-derived antioxidant peptides (YVEEL) and angiotensin-converting enzyme inhibitory peptides (YLLF) could enhance the bone formation and improve its microarchitectural parameters owing to a reduction in the levels of inflammatory cytokines (TNF-α) and the formation of anti-inflammatory cytokines (TGF-β, IFN-γ) (Pandey et al. 2018).

Collagen-derived peptides

Collagen is one of the most critical proteins present in the human body. Approximately 28 types of collagens have been identified, of which, type I collagen is the most common, providing structure and flexibility to the bone. Therefore, adequate consumption of products containing collagen is beneficial for maintaining the bone mass and its architecture in postmenopausal women (König et al. 2018). Moreover, the hydrolysates of collagen are more absorbable than the protein (Fu et al. 2019).

Various studies have demonstrated the beneficial effects of collagen peptides on the proliferation, differentiation, and formation of a mineralized bone matrix of osteoblasts (Liu et al. 2015). Supplementation with collagen peptides increased the mechanical strength of the bone and BMD in OVX rats (Zhang et al. 2014). As shown in Figure 3, various mechanisms are potentially involved in the regulation of bone health through the involvement of collagen peptides. Firstly, collagen peptides activate the pathways related to collagen synthesis, which include the TGF-β/Smad and ERK/MAPK signaling pathways. The expressions of TGF-β, Smad2, and Smad3 are upregulated, and the levels of type I procollagen and osteopontin (OPN) are increased to enhance collagen synthesis. It has been observed that collagen peptides could decrease the levels of Smad7, an inhibitor of Smad2 and Smad3 (Song et al. 2019). Collagen peptides could also increase the phosphorylation levels of extracellular regulated proteins kinases (ERK)1/2 and the *COL1A1* gene (related to collagen synthesis) (Kim, Kim, and Leem 2013). Secondly, GPSGPAGKDGRIGQPG (GP-16) and GDRGETGPAGPAGPIGPV (GD-18), identified and selected from the yak bone, promoted the proliferation of osteoblasts by bonding strongly with the epidermal growth factor receptor (EGFR) through hydrogen bonds (Ye et al. 2019). EGFR, a transmembrane glycoprotein, could improve collagen fibrils and decrease the degradation of the extracellular matrix in the growth plate (Zhang et al. 2011).

Bioactive peptides have been considered potential functional foods in recent years, as well as a new source of medical development. Though an increasing number of bone-beneficial peptide products are available as functional foods or food matrixes in the market, limited studies are being conducted in this field. Firstly, numerous studies described above were mainly conducted in cell lines (osteoblasts, osteoclasts, and MSCs) and animals, while the digestion, absorption, distribution and allergenicity of peptides have not been taken into account in the body. Further clinical trials are required to evaluate their bioavailability and pharmacodynamic parameters in human intervention studies. Secondly, bone-beneficial peptides in the market are still expensive for the general population owing to the lack of advanced technologies. It is urgent to develop innovative facilities focusing on the separation and enrichment of high-quality bone-beneficial peptides for industrial-scale production. Thirdly, the processing characteristics of peptides, such as thermostability and storage stability, are critical for their application in food systems. The interactions between food matrixes and peptides should be considered during processing and storage. Nowadays, chemical, synthetic, or genetic recombinant peptides with desirable structure and activity are easier and stable alternatives of traditional protein hydrolysates.

Phytoestrogens

Phytoestrogens are a group of natural substances with structures similar to that of estradiol. Increasing evidence has revealed that treatment with phytoestrogens can decrease the levels of bone turnover markers, increase BMD, and potentially protect from osteoporosis (Fu et al. 2014). Additionally, dietary phytoestrogens usually exist in foods in their glycoside form and can be hydrolyzed by intestinal microorganisms to produce corresponding metabolites. It has been reported that the estrogenic activities of the metabolites of phytoestrogens are higher than that of phytoestrogens, and variations are depended on the metabolisms of the individual (Gil-Izquierdo et al. 2012). Isoflavones, lignans, and coumestans are three main classes of phytoestrogens available in human diets (Poluzzi et al. 2014). Among these three phytoestrogens, isoflavones are the most common

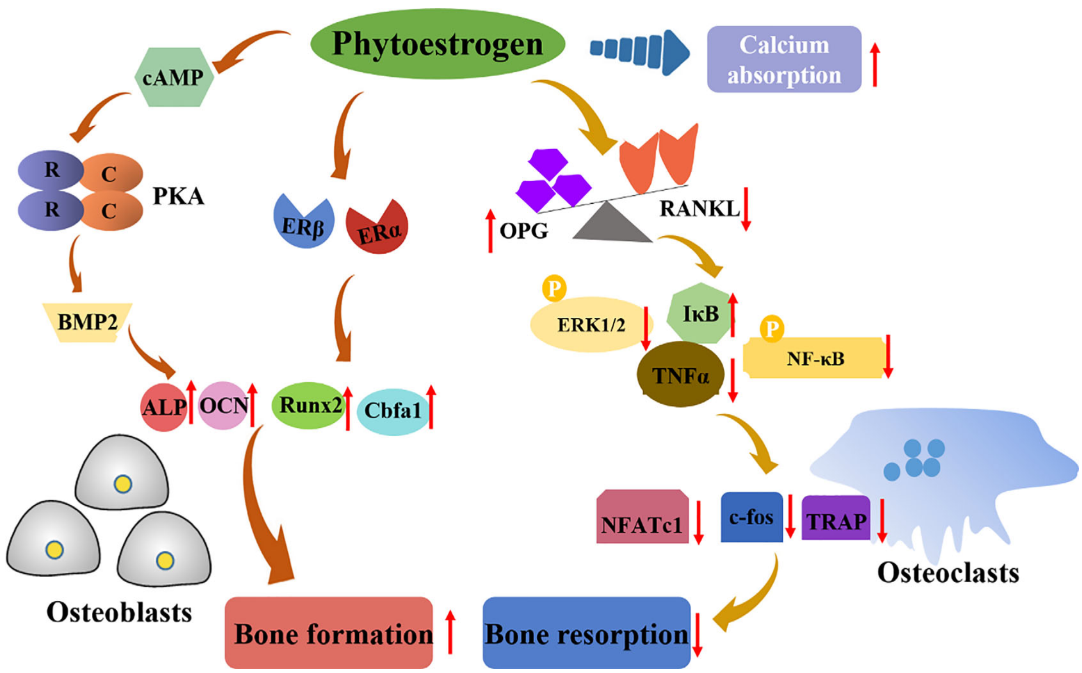

Figure 4. Underlying mechanisms of phytoestrogens in promoting bone health. Brown arrows were involved in phytoestrogen-mediated bone formation; orange arrows were associated with phytoestrogen-mediated bone resorption. Red arrows indicated the mean promotion effect. Red arrows indicated the mean inhibitory effect.

phytoestrogens available in the diet, comprising mainly of daidzein and genistin.

To our knowledge, the beneficial effects of these phytoestrogens on bone health and their related mechanisms are shown in Figure 4. Firstly, phytoestrogens possess similar chemical structures with estradiol, hence they could bind to the estrogen receptor (ERα and ERβ) and positively regulate endogenous estrogens and downstream signaling pathways. It is reported that daidzein can exert estrogen actions and upregulate the levels of ERβ, with the subsequent production of runt-related transcription factor 2/core-binding factor alpha 1 (Runx2/Cbfa1) (De Wilde et al. 2004). Secondly, phytoestrogens could activate the cyclic adenosine monophosphate (cAMP)-mediating signaling pathways. Pinoresinol, which is abundantly present in olive oil and the precursors of lignans, promoted the differentiation and mineralization of osteoblasts. This action is involved in the activation of the cAMP/PKA signaling pathway, followed by enhancing the expressions of bone morphogenetic protein (BMP)-2 and Runx2 (Jiang et al. 2019). Daidzein could also induce an increase in alkaline phosphatase (ALP) activity and OCN synthesis by increasing the production of BMP-2 (Jia et al. 2003). Thirdly, the ratio of RANKL to osteoprotegerin (OPG) plays a vital role in phytoestrogens mediating the activity of osteoclasts. Daidzein suppressed RANKL-induced IκB degradation and NF-κB phosphorylation, and the expressions of several osteoclast marker genes such as NFATc1, c-fos, and tartrate-resistant acid phosphatase (TRAP), subsequently inhibiting the resorption by osteoclasts (Wei et al. 2019). Treatment with coumestrol can reduce the phosphorylation of extracellular ERK1/2 induced by RANKL, which could lead to the suppression of osteoclast differentiation (Kanno, Hirano, and Kayama 2004). Moreover, the direct inhibition of TNF-α-induced osteoclastogenesis by coumestrol might be attributed partly to a decrease in the levels of c-fos, followed by the prevention of NFATc1-mediated osteoclast differentiation (Karieb and Fox 2011).

Numerous studies have demonstrated that phytoestrogens possessed promising effects on the maintenance of bone health and the prevention of osteoporosis fracture. Meanwhile, they are easier and safer options than hormonal therapy. However, several controversies still exist and limit the development and applications of phytoestrogen products. Firstly, given the metabolism of the individual phytoestrogens, it is essential to carry out comprehensive analysis and evaluation of individual nutritional health status, dietary survey and genetic polymorphism, contributing to a precise recommendation for the individuals needed for prevention, treatment or management of osteoporosis. Besides, age, estrogen status, and background diet are also important for establishing the intake of phytoestrogens for individuals. Secondly, the effects of phytoestrogens on skeletal health lack consistent conclusions. The adverse effects of phytoestrogens might be regarded as endocrine disruptors and lead to adverse health effects (Rietjens, Louisse, and Beekmann 2017).

Prebiotics

Prebiotics are generally defined as the substances that can be selectively utilized by the host flora and then converted into substances that are beneficial to the health of the host (Gibson et al., 2017). Prebiotics comprise various structural components such as fructo-oligosaccharides (FOS), inulin, galacto-oligosaccharides (GOS), xylo-oligosaccharides, and polydextrose. Over the past 25 years, the beneficial roles of prebiotics in the growth of microorganisms in the intestine

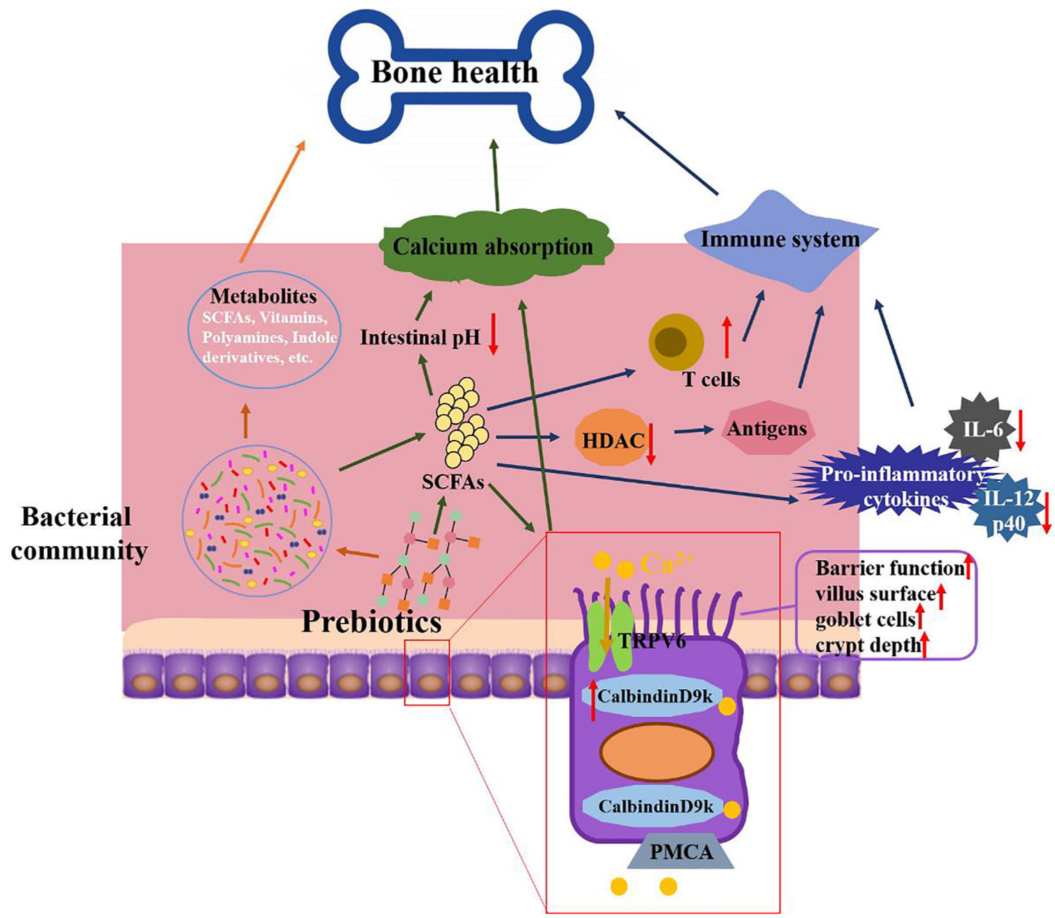

Figure 5. Underlying mechanisms of prebiotics in promoting bone health. Orange arrows indicated that prebiotics impacted the microbial community. Green and blue arrows indicated the effects of SCFAs on calcium absorption and immune signaling pathways, respectively. Red arrows pointing up and down indicated the mean promotion and inhibitory effects, respectively.

and prevention of chronic diseases have been confirmed (Tsai et al. 2019). Increasing evidence has indicated that prebiotics are highly important in maintaining skeletal health (McCabe, Britton, and Parameswaran 2015). For instance, the mixture of GOS/FOS can significantly improve mineral absorption and prevent bone loss in OVX rats consuming low calcium diets (Seijo et al. 2019). A randomized pilot study demonstrated that diets enriched with 10 g inulin for three months could increase bone formation and decrease bone resorption, respectively in children with celiac disease (Drabińska et al. 2019). However, the exact mechanisms through which prebiotics mediate their beneficial effects on bone health remain poorly understood.

As shown in Figure 5, prebiotics can alter the composition of the microbial communities in the intestine. It is commonly accepted that the structures and diversities of bacterial communities will be changed due to age, sex, diet, genetics, and the effect of prebiotics (Rizzoli 2019). For instance, the percentages of *Firmicutes*, *Bacteroidetes*, and eight other phyla in the communities were significantly different in healthy individuals than those detected in patients with primary osteoporosis (Wang, Wang, et al. 2017). Meanwhile, dietary prebiotics significantly enhanced the population of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, which could increase the calcium uptake (Tanabe et al. 2019; Hou et al. 2017), regulate the immune response (Jang et al. 2019) and thereby prevent bone loss. Differences in the compositions of the gut microbiota might also affect their metabolites, such as vitamins (Patterson et al. 2014), polyamines, and indole derivatives, which are involved in bone metabolism and health. Additionally, gut microbiota compositions are also essential for the development of intestinal mucosal barrier and adaptive immune response, which leads to the host's immune balance (Ma et al. 2018; Heeney et al. 2019) and bone metabolism balance.

Secondly, the consumption of prebiotics leads to the production of short-chain fatty acids (SCFAs) in the gut, which mainly produced by *Bifidobacterial*, *Lachnospiraceae*, *Ruminococcaceae*, *Propionibacteria* and *Bacteroidetes*, respectively (Yang et al. 2013). SCFAs have been beneficially associated with calcium absorption through the involvement of several mechanisms. SCFAs could lower the intestinal pH and prevent the precipitation of calcium induced by phytates and oxalates. Moreover, the consumption of SCFAs could enhance the properties of the epithelial barrier and improve the morphological characteristics of the intestine, such as crypt depth, blood flow (Whisner and Castillo 2018), goblet cell diameter, and villus surface (Hou et al. 2017), thus providing a wider intestinal surface and increased absorption of calcium in the gut. These morphological changes might be attributed to the role of SCFAs, such as butyrate, which acts as energy sources for colonocytes (Donohoe et al. 2011).

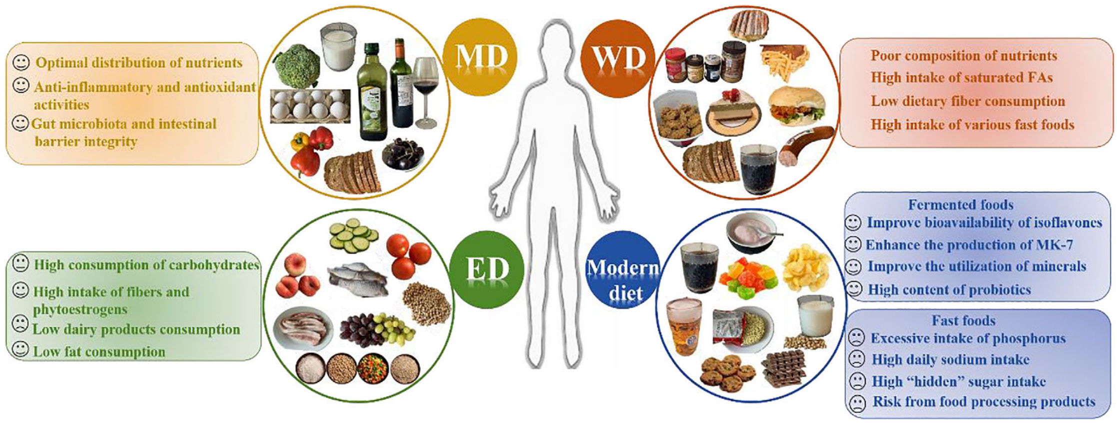

Figure 6. **A diagrammatic overview depicting the effects of common dietary patterns on bone health.** Happy face (☺) indicated the beneficial effects on bone health. Sad face ([N/A]) indicated the detrimental activities on skeletal health. Poker face () indicated inconsistent conclusions on bone health.

Additionally, the levels of calbindin D9k, a critical calcium transport protein, can be elevated by FOS (Fukushima, Aizaki, and Sakuma 2012). SCFAs could also beneficially affect bone health *via* the involvement of the immune signaling pathways. On the one hand, SCFAs enhanced the differentiation of T cells through the activation of G protein-coupled receptor 109 A (GPR109A) (Singh et al. 2014). On the other hand, SCFAs could modulate the production of pro-inflammatory cytokines, such as IL-6 and IL-12p40 in the epithelial cells (Iraporda et al. 2015), and the regulate antigen presentation by suppressing histone deacetylase (HDAC) (D'Amelio and Sassi 2018).

Nevertheless, much more efforts are required in providing nutritional strategies of prebiotics for the public. Firstly, over-consumption of prebiotics has been reported to induce negative effects such as dehydration, vomiting, and osmotic diarrhea (Nath et al. 2018). Therefore, the establishment of an optimum dose, form, timing, and duration of prebiotic intake is a prerequisite for its wide application. More prospective studies with human models are also needed to explore the bioavailability and limitations of various prebiotics. Secondly, the biological activities of prebiotics are mainly based on the existing intestinal microbiota. In fact, the basic colonization and establishment of intestinal microbiota occur before age 18 months. But the composition of the microbiota is partially affected by daily nutrient consumption, especially prebiotics. However, the microbial populations in the intestine are quite vast and complex, which are not fully understood to date. Hence, a specialized effort should emphasize the relationship and mechanism between exact species of bacteria and prebiotics. Besides extracted or purified prebiotics, systematic studies could also focus on the assessment of high prebiotic diets as an approach to improve skeletal health.

Dietary patterns

Various nutrients are present together in foods and might interact with each other in our diets. Meanwhile, the synergetic effect of several dietary foods contributes more than the impact of a single nutrient. Therefore, it is of great importance to take the relationship between dietary patterns and bone health into consideration. The formation of a dietary pattern is generally related to the natural environment, culture, customs, and the development of economic status. There are three famous dietary patterns worldwide, which are the Mediterranean (nutrient-dense), Western (energy-dense), and Eastern (plant-based) diets. Additionally, people of today have gradually adapted to a new system of food consumption, which is the Modern diet. The effects of these four dietary patterns on bone health and the potential strategies for maintaining bone mass are expounded in details (Figure 6).

Mediterranean diet

Mediterranean diet (MD) is regarded as one of the healthiest dietary patterns around the world, which possesses the characteristics of high consumption of vegetables, fruits, nuts, cereals, legumes, fish, and olive oil, as well as modest intake of wine and dairy products and low intake of meat and poultry. It is well known that the MD has beneficial effects on cardiovascular diseases, diabetes, and visceral obesity (Sofi et al. 2014). It is proposed that a relatively low incidence of osteoporosis occurred in the Mediterranean countries or people who adhere to the MD pattern (Rivas et al. 2013). Currently, numerous studies have indicated that adherence to the MD exhibited a positive association with higher bone mass in premenopausal women (Pérez-Rey et al. 2019), decreased hip fracture incidence in older adults (Benetou et al., 2018), and lowered risk of falling among the elderly (Ballesteros et al. 2020).

According to previous studies, the possible beneficial effects of the MD on bone health are derived from its four properties. First of all, the MD pattern contained the optimal distribution of nutrients for the public, that is, 45–60% of daily calories came from carbohydrates, less than 30% of daily calories came from fats, and 12–18% of daily calories came from proteins (Migliaccio et al. 2018). Besides, almost 85% of fats in the MD were furnished by olive oil with low SFAs and high monounsaturated fatty acids (MUFAs). Secondly, numerous foods in the MD had anti-inflammatory and antioxidant activities. The increased oxidative stress and impairment of antioxidant systems were critical pathogenic factors of age-related bone loss (Almeida 2012). The representative compounds are UFAs (ω-3 FAs and oleic acid), which were abundant in fish, vegetable and olive oils. Other components in the MD are represented by phenolic compounds (hydroxytyrosol, oleuropein and resveratrol), which are mainly contained in olive oil, fruits, vegetables and wine. Among the phenolic compounds, hydroxytyrosol, the major polyphenol in olive oil, could prevent oxidative damage *via* the activation of mitochondrial biogenesis and phase II detoxifying enzyme systems (Zhu et al. 2010), and contribute to the protection of preosteoblasts by activating the Keap1/Nrf2 pathway (Gao, Huang, et al. 2015). Moreover, vitamins C and E enriched in fruits and vegetables, and phytoestrogens enriched in legumes also played an antioxidant role in the protection of bone health. Thirdly, long-term adherence to the MD had a considerable effect on gut microbiota and intestinal barrier integrity. High adherence to the MD could increase the ratio of *Bifidobacterial* to *E. coli*, and the SCFA contents in adults (Mitsou et al. 2017). Recent studies have also indicated that adherence to the MD can positively affect the diversity, composition, and activity of the gut microbiota as well as its metabolites (Krznarić, Vranešić Bender, and Meštrović 2019; Moszak, Szulińska, and Bogdański 2020). This action might result in the high consumption of carbohydrates, fibers, UFAs, and antioxidants, and low intake of processed foods. Fourthly, the MD promoted the consumption of alkalinizing food. It has been reported that metabolic acid load had a detrimental effect on bone health (Riond 2001). Therefore, alkaline precursors (K, Ca, and Mg), which were abundant in the MD, could neutralize the acid burden, maintain the acid-base balance in the body, and subsequently contribute to skeletal health (Lambert et al. 2015).

Currently, the traditional MD is changing with the developments in the food industry and preparation techniques. Refined salted, processed fruits, sweetened cereals, baked, and canned beans are gradually replacing the raw materials of the food groups in the MD (Hoffman and Gerber 2013). Despite the slight changes in the MD, recent studies have demonstrated that higher adherence to the MD is a protective approach to maintain bone mass for the public population (Savanelli et al. 2017). Importantly, some studies have failed to show any associations between the MD and bone health in the elderly (Erkkilä et al. 2017; Feart et al. 2013). This inconsistency may be attributed to a variety of research factors, such as research scale and study periods. Therefore, more large-scale and long-term studies are required to clarify the effects of the modified MD on bone health, which will provide reliable strategies for the management of osteoporosis.

Eastern diet

Eastern diet (ED) is characterized by the plant-based dietary pattern, which involves high consumption of grains, fruits, vegetables, legumes, and fish as well as modest intake of red meat, eggs, soybean oil and low intake of dairy products. Several past studies had investigated the association of adherence to the ED and health (Zhu et al. 2013; García-Bailo et al. 2012). A dietary pattern with high intake of plant-based and low intake of animal-based food are also recommended in Dutch food-based guidelines (Kromhout et al., 2016). Nevertheless, studies focusing on bone health in relation to the ED are scarce. To the best of our knowledge, four potential factors in the ED might be involved in its effect on skeletal health. Firstly, high consumption of carbohydrates is a major feature of the ED, and almost 70% of daily energy comes from carbohydrates. From the limited studies, whether high-carbohydrate diets could regulate bone health remains inconsistent. It has been reported that a high intake of carbohydrates could evoke the oxidative stress response (Gregersen et al. 2012), and increase the rate of bone turnover (Nowson, Patchett, and Wattanapenpaiboon 2009). Recent studies have indicated that there was no relationship between carbohydrate intake and fracture risk (Mozaffari, Daneshzad, and Azadbakht 2020). Additionally, a high intake of carbohydrates might lead to low consumption of other nutrients (such as high-quality of proteins), which could indirectly affect bone metabolism. Secondly, bone-beneficial nutrients exist abundantly in the ED owing to the high intake of grains, fruits, vegetables, and legumes such as fibers and phytoestrogens. An observational study indicated that postmenopausal women with a diet enriched in phytoestrogens had a lower risk of osteoporosis fracture (Coxam 2008). Thirdly, dairy product consumption in the ED is far lower than the recommended intake. This phenomenon might lead to the deficiency of calcium in the population, and subsequently, cause low bone mass peak and bone loss. Additionally, though the ED contains the lowest fat consumption among these three diets, the incidence of chronic diseases related to high-fat intake was not low in the ED (He et al. 2016). The predominant reason might be the high consumption of pork in the ED, which contains abundant SFAs and thereby have negative effects on bone health.

Nowadays, with globalization, western highly-processed food consumption has been rapidly incorporated into the ED. However, studies focusing on the effects of the traditional or modified ED on bone health are very limited compared with those focusing on the MD and WD. More prospective studies are required to explore their relationship and provide beneficial strategies for the population with the ED. A better understanding of bone metabolism and representative nutrients in the ED, such as high consumption of carbohydrates and low intake of animal proteins, may pave the way for the prevention and/or management of osteoporosis in the ED. Moreover, it is highly necessary to educate the public on how to effectively select suitable diets that benefit bone health, especially in developing countries.

Western diet

Western diet (WD) possesses the features of high consumption of red meat, processed meat, refined grains, high-fat dairy products, high-sugar drinks, fried foods and sweets as well as low intake of fruits, vegetables, fish, nuts, and whole grains (Halton et al. 2006). Preliminary epidemiological studies have indicated that the WD was positively associated with numerous chronic metabolic diseases, such as obesity, type-2 diabetes mellitus, and cardiovascular diseases (Medina-Remón et al. 2018). Currently, increasing evidence has indicated that the WD had a detrimental effect on bone mass and potentially leaded to the incidence of osteoporosis (Fabiani, Naldini, and Chiavarini 2019; Wang, Wang, et al. 2017).

The adverse effects of the WD on bone health could be discussed in several aspects. (1) The poor composition of nutrients exists in the WD, especially the high consumption of protein and low intake of fruits and vegetables. Deficiency of dietary potassium and alkaline minerals due to the limited fruit and vegetable consumption failed to balance the excessive acidity (Macdonald et al. 2005). To maintain the systemic pH balance, alkaline salts (such as calcium and magnesium phosphates) were released from the bone, leading to the bone loss and high risk of fracture (Tylavsky, Spence, and Harkness 2008). (2) A typical WD is associated with high amounts of saturated FAs, and their detrimental effects have been described above. (3) Low dietary fiber consumption in the WD is due to the low intake of fruits, vegetables, and whole grains. Dietary fiber has numerous beneficial effects on bone health, and low intake of fiber could rapidly and profoundly affect the composition of the intestinal microbiota (David et al. 2014). (4) The WD is heavily furnished by various highly-processed foods. These highly-processed foods supply an increased amount of fat and sugar, as well as a variety of food additives, which would be a considerable factor affecting bone health.

Nowadays, WD with high-energy and low-nutrient dense types of food is generally considered an unhealthy diet. Whereas, a growing number of people have a preference for western food style in growing economies. The health professions should also emphasize the importance of adjusted and balanced diets, and provide nutritional guidance for the public. These actions might improve the awareness of bone health and reduce the burden of osteoporotic fractures. Moreover, further studies are needed to comprehensively explore the underlying mechanism of the interactions between the components in the WD and the gut microbiota, and their effects on skeletal health of the host. Additionally, increasing the daily intake of fruits and vegetables in the WD might be an additional strategy for managing osteoporosis. Hence, more longer-term intervention studies are needed to fully evaluate the exact daily amount and type of fruits and vegetables on bone metabolism in the WD. These studies are also required to take into account the needs of different age groups, especially for the adolescents, postmenopausal women and the elderly.

Modern diet

The modern diet emerged and was incorporated into these traditional dietary patterns after the Industrial Revolution, which introduced new methods of food processing. Generally, highly-processed foods are the major hallmark of modern diets. Highly-processed foods are a big category of foods that have been cooked, frozen, packaged, fermented, canned, or changed in nutrition composition in different ways. On the one hand, processed foods bring us convenient and nutrient-dense foods, such as modern fermented foods. On the other hand, many studies have noted that processed foods, especially for highly-processed foods are associated with numerous chronic health problems, such as obesity (Nardocci et al. 2019), cardiovascular disease (Srour et al. 2019), and osteoporosis.

Modern fermented foods

Modern fermented foods, differing from traditional fermented food regarding production, functionality and nutrition, are regarded as convenient and nutrient-dense foods. Microbial fermentation, widely used in the food industry, can potentially decrease the concentrations of anti-nutritional factors, induce biological activities, and improve the bioavailability of the ingredients in modern fermented foods (Shiferaw Terefe and Augustin 2020). Many modern fermented products, including those derived from soybean and soymilk, have been reported to promote bone health.

Firstly, microbial fermentation improves the bioavailability of isoflavones. Fermentation bacteria enriched with β-glucosidase can hydrolyze glucosides to form aglycones. It has been reported that supplementation with fermented soybean could increase BMD and prevent bone loss in a senile osteopenia model (Nirmala et al. 2019) and OVX mice (Kim et al. 2019). Secondly, microbial fermentation enhances the production of menaquinoe-7 (MK-7), which is considered as the most potent form of vitamin K. Several studies have reported that MK-7 stimulated bone formation in elderly rats (Yamaguchi, Uchiyama, and Tsukamoto 2002), inhibited bone resorption (Yamaguchi, Uchiyama, and Tsukamoto 2003), and increased BMD in elderly men (Fujita et al. 2012). MK-7 rarely exists in natural foods, but is abundant in modern fermented foods such as natto, cheese, and Cheonggukjang (Mahdinia, Demirci, and Berenjian 2017). It has been reported that vitamin K played a critical role in the γ-carboxylation of matrix Gla-protein, osteocalcin, and protein S, which were closely related to bone metabolism (Sogabe et al. 2007). Thirdly, the utilization of minerals in the intestine is enhanced to some extent. Phytase was produced during fermentation hydrolyzes phytate in plant foods, and subsequently could prevent the precipitation of minerals and enhance their bioavailability (Humer and Schedle 2016). Moreover, poly-γ-glutamic acid (γ-PGA) was usually produced by *Bacillus* species in fermented soybeans, which suppressed the formation of insoluble calcium complexes (Tanimoto et al. 2001). Importantly, probiotics are abundantly present in modern fermented foods and beverages such as cheese, yogurt, kimchi, and beer. Three mechanisms mediating the effects of probiotics on bone health were explored as microbial composition, immune system, and intestinal barrier function (McCabe and Parameswaran 2018).

Highly-processed foods

Highly-processed foods mentioned here does not only refer to the foods in the food restaurant, but also include chips, cookies, candy, soda, burgers, pizza, and all other high-calorie, low-nutrient processed foods (Fuhrman 2018). High consumption of highly-processed foods was associated with lower BMD in college students (Lim et al. 2018), and poor bone health in young children (Vogel et al. 2016). Highly-processed foods possess the following features: high fat, sugar, phosphorus, and sodium content, as well as low content of various nutrients, resulting in a negative effect on bone health.

Excessive intake of phosphorus because of the increased consumption of processed foods with phosphate additives is becoming a concern. A high intake of phosphorus is linked to the suppression of bone formation and promotion of bone resorption in young females (Kemi, Kärkkäinen, & Lamberg-Allardt, 2006). It has also been found to reduce the growth of bone and impact its structural properties in growing male rats (Huttunen et al., 2006). Additionally, the daily intake of cola was associated with low BMD in women (Tucker et al. 2006). Phosphorus-based food additives could interfere bone and mineral metabolism in humans (Gutiérrez et al. 2015). Excess amounts of phosphorus could interact with calcium and disturb calcium absorption, elevating the levels of parathyroid hormone (PTH), and subsequently inducing a loss of calcium in the bone (Maioli, Tagliabue, and Cioni 2018). Therefore, the ratio of calcium to phosphorus in diets could be regarded as an indicator to predict bone mass (Lee et al. 2014).

Daily sodium intake is usually higher than the recommended daily intake (1500 mg/d). For instance, the average intake of sodium by the population of America is 3330 mg/d (Hoy, Goldman, Murayi, Rhodes, & Moshfegh, 2011). Many studies have indicated that a high daily intake of sodium can negatively affect bone mass in postmenopausal women (Fatahi et al. 2018; Kwon, Ha, and Park 2017). This phenomenon might be attributed to an increase in PTH levels and calciuria (Heaney 2006). A longitudinal study has shown that diets with low sodium could significantly decrease the excretion of calcium and bone turnover, benefiting the bone health of postmenopausal women (Carbone, et al., 2005). Additionally, the effect of a high intake of sodium on bone health could also be associated with the consumption of potassium (Harrington and Cashman 2003). A high intake of potassium could alleviate the adverse effects on bone induced by high sodium consumption (Heaney 2006).

High 'hidden' sugar exists in the processed foods mainly because of the addition of sweeteners. The DGA recommend a limitation of added sugar to less than 10% of calories per day, contributing to a healthy dietary pattern of the public (DeSalvo et al., 2016). There was a complex relationship between sugar intake and bone health (Tian and Yu 2017). On the one hand, a high-sugar diet exerted a detrimental effect on both bone formation and resorption, leading to a decrease in bone mass and strength, which might be attributed to the impairment of mitochondrial respiration (Shi et al. 2020). Aspartame, saccharin, and acesulfame K could induce DNA damage in MSCs, and thereby present a potential risk to bone health (Bandyopadhyay, Ghoshal, and Mukherjee 2008). On the other hand, several sweeteners play a beneficial role in skeletal health. For instance, a high-fructose diet improved the bone microstructure and strength in rats (Bass et al. 2013). Xylitol could also increase BMD and suppress the activity of osteoclasts in OVX and normal rats (Sato et al. 2012; Sato et al. 2011), particularly owing to its prebiotic properties involving the intestinal microbiota, SCFAs, mineral absorption, inflammatory cytokines, and isoflavone metabolism (Tamura, Hoshi, and Hori 2013; Salli et al. 2019). Therefore, a better understanding of the relationship between various sweeteners and bone health is required to enable a conclusion before any recommendations.

Undoubtedly, processed foods are contributing to numerous changes in the modern diet and also improving the overall quality of the diet of individuals. However, processed foods have a bad reputation owing to the increase in obesity and high blood pressure in recent years. Therefore, three key problems need to be addressed regarding the relationship between modern diet and bone health. (1) The precise effects of ingredients or food processing in the modern diet on bone health remain unclear. On the one hand, numerous prospective studies are needed to assess and consider their association in terms of providing nutritional strategies. On the other hand, the food matrix is mainly digested and absorbed in the gastrointestinal tract and does not directly enter or affect the skeleton. Hence, further studies should be aimed to more human intervention studies instead of cell models. (2) A multi-pronged approach is required in the food industry to address the issues of high phosphorus, sodium, fat, sugar, and the 'hidden' risk of AGEs in processed foods. Exploring novel and safe food processing technologies has created opportunities for a healthier diet for the public. (3) Widespread health education is needed to improve the awareness of the public on the benefits and risks of processed foods on bone health. It is crucial to clarify the roles of processed foods in the modern diet. Meanwhile, health professionals should focus on the optimization of the modern diet aiming at different stages, especially for children and the elderly.

Conclusion and future research

As the number of patients with osteoporosis increases, a variety of therapies for osteoporosis is available. The adverse effects and heavy economic burden can subsequently result in enormous physical and mental pressure. There are two primary strategies for improving skeletal health: promoting the peak of bone mass in earlier years, and maintaining it and decreasing bone loss after the peak reached. Thereinto, dietary intervention is a promising strategy for the management of osteoporosis across the lifespan. On the one hand, numerous nutrients derived from daily diets have been reported to exert a beneficial role in bone balance and mass, which provides an essential understanding of our diets and bone health. Meanwhile, the nutrients alone or their combination with therapeutic agents for osteoporosis are a potential alternative for the management of osteoporosis. Therefore, a comprehensive understanding of the nutrients and additional clinical studies for their deployment need to be conducted in future studies. On the other hand, compared with a single nutraceutical, dietary patterns or the overall quality of diets are of great importance in promoting bone health. Nevertheless, these four common dietary patterns (Mediterranean, Eastern, Western and Modern diets) have either beneficial or adverse effects on bone health. Owing to the complex interactions in the food matrix, scientifically defined healthy diets for maintaining bone health could be designed for people with different needs, which include those requiring prevention and patients undergoing treatment. If such efforts are effective, the osteoporosis-induced dual pressures may be ameliorated through the achievement of a high bone mass peak, early prevention based on dietary intervention, consumption of scientifically defined diets during treatments, and adjuvant therapies using nutrients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contribution

Danjun Guo, Mengge Zhao, Wei Xu, Hui He, Bin Li and Tao Hou conducted the literature research, synthetized information. Danjun Guo and Mengge Zhao wrote the manuscript. Tao Hou revised the manuscript and was responsible for the supervision of the whole manuscript.

Abbreviations

MSCs	Mesenchymal stem cells
PTH	Parathyroid hormone
BMD	Bone mineral density
RANKL	Receptor activator of nuclear factor-kappa B ligand
RANK	Receptor activator of nuclear factor-kappa B
UFAs	Unsaturated fatty acids
SFAs	Saturated fatty acids
MUFAs	Monounsaturated fatty acids
TLR2/4	Toll-like receptors 2/4
NF-κB	Nuclear factor κB
MAPK	Activate mitogen-activated protein kinases
ERK1/2	Extracellular regulated proteins kinases 1/2
JNK	c-jun N-terminal kinase
ER	Endoplasmic reticulum
VEGF	Vascular endothelial growth factor
IL-6/ IL-12p40	Interleukin-6/ interleukin-12 subunit beta
MCP-1	Monocyte chemoattractant protein
IKK α/β	Inhibitory kappa kinase α/β
IκB	Inhibitor of NF-κB
UPR	Unfolded protein response
FasL	Fas ligand
Bid	BH3-interacting domain death agonist
FFAR4	Free fatty acids receptor 4
βarr2	β-arrestin 2
PPAR γ	Peroxisome proliferator-activated receptors
EPA	Eicosapentaenoic acid
DHA	Docosahexenoic acid
TAK1	Transforming growth factor β-activated kinase 1
TAB1	TAK1-binding protein-1
NFATc1	Nuclear factor of activated T-cells c1
TNFα/β	Tumor necrosis factor-α/β
PKA/PKC	Protein kinases A/C
IGF-1	Insulin-like growth factor-1
ALP	Alkaline phosphatase
CPPs	Casein phosphopeptides
TRPV6	Transient receptor potential vanilloid subfamily member 6
ROS	Reactive oxygen species
LPO	Related lipid peroxidation
MDA	Malonaldehyde
SOD	Superoxide dismutase
CAT	Catalase
GSH	Glutathione
IFN-γ	Interferon-γ
OPN	Osteopontin
EGFR	Epidermal growth factor receptor
ERα/ERβ	Estrogen receptor α/β
Runx2	Runt-related transcription factor 2
Cbfa1	Core-binding factor alpha 1
BMP2	Bone morphogenetic protein 2
TRAP	Tartrate-resistant acid phosphatase
cAMP	Cyclic adenosine monophosphate
OPG	Osteoprotegerin
FOS	Fructo-oligosaccharides
GOS	Galacto-oligosaccharides
SCFAs	Short-chain fatty acids
HDAC	Histone deacetylase
MK-7	Menaquinoe-7
γ-PGA	Poly-γ-glutamic acid

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ORCID

Tao Hou http://orcid.org/0000-0002-7567-2800

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