ROLE OF POLYPHENOLS IN THE METABOLISM OF THE SKELETAL SYSTEM IN HUMANS AND ANIMALS – A REVIEW

Grzegorz Skiba¹, Stanisława Raj¹, Monika Sobol¹, Paweł Kowalczyk¹, Eugeniusz R. Grela^{2*}

¹The Kielanowski Institute of Animal Physiology and Nutrition Polish Academy of Sciences,
Instytutcka 3, 05-110 Jabłonna, Poland

²Institute of Animal Nutrition and Bromatology, University of Life Sciences in Lublin, Akademicka 13,
20-950 Lublin, Poland

*Corresponding author: eugeniusz.grela@up.lublin.pl

Abstract

Polyphenols are a group of compounds arousing enormous interest due to their multiple effects on both human and animal health and omnipresence in plants. A number of *in vitro* and animal model studies have shown that all polyphenols exhibit anti-inflammatory and antioxidant activities, and play a significant role against oxidative stress-related pathologies. They also exert gut promotory effects and prevent chronic degenerative diseases. However, less attention has been paid to the potential influence of polyphenols on bone properties and metabolism. It is well known that proper growth and functioning of the organism depend largely on bone growth and health. Therefore, understanding the action of substances (including polyphenols) that may improve the health and functioning of the skeletal system and bone metabolism is extremely important for the health of the present and future generations of both humans and farm animals. This review provides a comprehensive summary of literature related to causes of bone loss during ageing of the organism (in both humans and animals) and possible effects of dietary polyphenols preventing bone loss and diseases. In particular, the underlying cellular and molecular mechanisms that can modulate skeletal homeostasis and influence the bone modeling and remodeling processes are presented.

Key words: polyphenols, bone metabolism, bone health

Plant-based supplements and their secondary metabolites are alternative natural growth promoters that are widely used in livestock farming and nutrition (Wallace et al., 2010; Yesilbag et al., 2011). Phytochemicals that are found naturally in plants have attracted particular interest. They include polyphenols, i.e. common components of human and animal diets (Chiva-Blanch and Visioli, 2012; Lipiński et al., 2017). During the last decade, the interest in polyphenols has increased considerably, especially among food scientists, nutritionists, agricultural/food industry, and consumers. Chemically, polyphenols are a large heterogeneous group of compounds characterized by hydroxylated phenyl moieties (Singla et al., 2019). Based on their

chemical structure and complexity (i.e. the number of phenolic rings and substituting groups) polyphenols are generally classified into flavonoids, phenolic acids, lignans, and stilbenes (Neveu et al., 2010). Compounds representing polyphenols occur widely in plants and products contained in the human and animal diet (e.g. in fruit, vegetables, and cereals) (Ullah and Khan, 2008; Pieszka et al., 2015). They are present in various parts of plants, including roots, leaves, flowers, fruit, and seeds and can protect plants against pests and UV radiation (Petti and Scully, 2009). The absorption of polyphenols from food, their metabolism, and their subsequent impact on the organism depend on the natural microflora of the gastrointestinal tract (Paszkiwicz et al., 2012; Zhang et al., 2015; Żary-Sikorska et al., 2016; Memon et al., 2019). It has been estimated that only 5–10% of the total polyphenol intake are absorbed in the small intestine. The remaining part may accumulate in the large intestine up to a millimolar range where, together with conjugates excreted into the intestine through the bile, they are subjected to the enzymatic activities of the gut microbial community (Cardona et al., 2013; Bohn, 2014). Thus, the colonic microbiota are involved in the extensive breakdown of dietary polyphenols into a series of absorbable low-molecular-weight phenolic metabolites. In fact, they are responsible for the health effects, rather than polyphenols consumed with feed.

Flavonoids are a group of polyphenols arousing enormous interest due to their multidimensional effects on both human and animal health and omnipresence in plants. They are called “functional ingredients” and “health-promoting biomolecules” due to their potential role in health improvement. A number of *in vitro* and animal model studies have shown that all polyphenols exhibit anti-inflammatory (Law et al., 2016) and antioxidant (Pieszka et al., 2015; Cory et al., 2018) activities and play a significant role against oxidative stress-related pathologies/diseases (Ding et al., 2013). They also exert gut promotory effects (Zhang et al., 2013) and prevent chronic degenerative diseases (Nijveldt et al., 2001).

Less attention has been paid to the potential influence of polyphenols on bone properties and metabolism. Bone loss-related disease (osteopenia/osteoporosis) has become a public health concern, as the average life expectancy has increased. Recent data have indicated that approximately 200 million people in the world suffer from osteoporosis (Lampropoulos et al., 2012; Sözen et al., 2017). It has been known for decades that no symptoms of this disease are observed until a bone fracture occurs (Goulding et al., 1998). The main characteristics of osteoporosis are associated with low bone mass and micro-architectural deterioration of bone tissues as well as an increase in bone fragility and susceptibility to fracture (Clark et al., 2006). Osteoporosis is increasingly being recognized also in children and adolescents (Khalid and Khoshhal, 2011; Sheweita et al., 2019).

In fact, some researchers suggest that osteoporosis developing later in life may originate from childhood or adolescence years (Henwood and Binkovitz, 2009). Symptoms in children may include joint pain, physical deformity of the spine, a sunken chest, or chronic lameness. In older children and adolescents, osteoporosis can be caused by osteogenesis imperfecta, type 1 diabetes, type 2 diabetes, hyperthyroidism, or calcium and vitamin D deficiency (Sheweita et al., 2019). In recent years, research studies have shown that osteoporosis in children and

adolescents can be induced by obesity caused by overconsumption of a high-energy diet (with high content of unsaturated fatty acids and simple carbohydrates) or malnutrition (consumption of low energy diet) as well as lifestyle, e.g. low physical activity (Van Leeuwen et al., 2017; Fintini et al., 2020). Thus, it is obvious that the proper growth and functioning of the organism depends largely on bone growth and health. Therefore, understanding the action of chemicals (including polyphenols) that may improve bone metabolism and, consequently, the health and functioning of the skeletal system is extremely important for the health of the present and future generations of both humans and farm animals.

Metabolism of bone tissue (bone turnover)

Bones are multifunctional passive organs of movement that support soft tissue and directly attached muscles. They also protect internal organs and are a reserve of calcium, phosphorus, and magnesium. Bone is a metabolically dynamic tissue undergoing continual adaption during life to attain and preserve the skeletal size, shape, and structural integrity and to regulate mineral homeostasis. Bone modeling and bone remodeling are involved in this process. Bone modeling occurs in growing individuals and is stopped after reaching puberty (Domazetovic et al., 2017). Bone remodeling involves the removal and internal remodeling of existing bone (e.g. removal and repair of damaged tissue) and is responsible for maintaining tissue mass and architecture of mature bones (Akter and Ibanez, 2016). These processes determine the proper functioning of the skeleton, bone growth in young individuals, repair of bone fractures, and maintenance of the calcium-phosphorus balance (homeostasis) necessary for the health of the organism/body (Raggatt and Partridge, 2010).

Throughout life (both human and animal), bone turnover is regulated by the activity of two types of cells: osteoclasts responsible for bone resorption and osteoblasts responsible for bone formation, i.e. bone matrix synthesis and mineralization (Almeida and O'Brien, 2013). The main regulators of bone turnover include mechanical strain (Turner et al., 2004), systemic factors (e.g. calcitriol, calcitonin, growth hormone, insulin-like growth factor 1, glucocorticoids, sex hormones, and leptin), and local factors (e.g. osteoprotegerin [OPG], receptor activator of nuclear factor-kappa B ligand [RANKL]) (Hadjidakis and Androulakis, 2006; Christen et al., 2014; Wang et al., 2020). Moreover, the physiological equilibrium between body oxidants and antioxidants affecting the occurrence of oxidative stress also seems to be important for successful bone modeling and remodeling processes (Domazetovic et al., 2017).

Bone metabolism is determined using the following indicators/markers: 1) bone turnover markers, such as bone alkaline phosphatase (bAP), the aminoterminal propeptide of type I collagen (PINP), 2) bone resorption markers such as the C-telopeptide of type I collagen (CTX) and the N-telopeptide of type I collagen (NTX). Recent studies have revealed that, in addition to bone mineral density (BMD), these markers are good indicators of fracture risk (Cervellati et al., 2014). Moreover, changes in their concentration can be observed more rapidly than changes in bone mineral density (Eastell and Hannon, 2008).

Impact of oxidative stress and inflammation on the bone turnover process

Physiological equilibrium between body oxidants and antioxidants is important for supporting bone health. The redox state and its shifts are regulated by a physiological mechanism and depend on the ratio between the levels of pro-oxidants, oxidizing agents (reactive oxygen species, ROS), and antioxidants. Pro-oxidant species, in particular oxygen free radicals (ROS), are normally generated during cell metabolism. Intracellular ROS production occurs after the activation of mitochondrial oxidases, membrane enzymes (e.g. NADPH oxidases), cytoplasmic enzymes (e.g. superoxide dismutase), other enzymatic systems, and external stimuli (e.g. inflammatory cytokines) (Circu and Aw, 2010; Filaire and Toumi, 2012). The role of ROS (especially H_2O_2) in the regulation of physiological cellular function consists in mediating the transmission of intracellular signals in processes such as proliferation, differentiation, apoptosis, repair, and inflammation (Ray et al., 2012). Recent studies have also demonstrated that ROS generation is a key modulator in several signaling pathways in bone cells and that oxidative status influences the pathophysiology of mineralized tissues (Agidigbi and Kim, 2019).

Antioxidants are a group of chemical compounds that are able to stop or delay oxidation (a chemical reaction yielding free radicals, thereby leading to chain reaction that may damage organism cells). The term “antioxidant” is mostly used for substances (both industrial chemicals and naturally occurring compounds) that are able to prevent oxidation. The natural antioxidants in animals/humans are represented by thiol compounds e.g. glutathione (GSH, γ -glutamyl-cysteinyl-glycine), non-thiol compounds such as polyphenols, vitamins (e.g. ascorbic acid, alpha-tocopherol, vitamin A), various enzymes capable of elimination of ROS such as catalase, and enzymes that use GSH as a substrate (GSH-reductase, GSH peroxidase etc.) (Circu and Aw, 2010).

A steady-state redox status is maintained in equilibrium by various factors and mechanisms that regulate the activity of ROS-producing enzymes and antioxidants. In normal physiological conditions, ROS are produced at low levels and removed by endogenous antioxidant systems. Their steady-state concentrations are determined by the equilibrium between their production and removal (Valko et al., 2006, 2007). Imbalance of these intracellular processes leads to oxidative stress, which is characterized by an increased level of ROS. Oxidative stress has been related to tissue inflammation and degeneration. In the bone metabolism, oxidative stress promotes osteoclastic activity and inhibits osteoblastic differentiation resulting in bone resorption (Mody et al., 2001; Filaire and Toumi, 2012). Cervellati et al. (2014) showed that osteopenia and osteoporosis appeared to be associated with a worse oxidative balance, as women suffering from these conditions presented higher levels of the lipid oxidative damage marker, hydroperoxides, and lower levels of total antioxidant power. Oxidative stress often results in inflammatory processes. The degree of inflammation is determined e.g. using the following indicators/markers: pro-inflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). The results of a study conducted by McLean (2009) indicated that they are important regulators of bone resorption and may play a vital role in bone loss. As demonstrated by the authors, increases in pro-inflammatory cytokines are associated with decreased bone mass and greater fracture risk. However, the evidence is limited

and provides no clear indication of cytokines that may be most important for bone health. In a study conducted by Pino et al. (2010), osteoporotic women were characterized by higher content of pro-inflammatory and adipogenic cytokines in bone marrow fluid.

A crucial role in bone loss is attributed to osteoclasts, as evidenced in experiments with patients suffering from inflammatory diseases (e.g. arthritis). Such patients had elevated TNF- α levels and increased numbers of osteoclast precursor cells in the blood, which are strongly correlated with the extent of bone destruction (Ritchlin et al., 2003; Anandarajah and Schwarz, 2006). Besides TNF- α , a number of other cytokines (e.g. interleukins: IL-1 α , IL-1 β , IL-6, and IL-17) and other inflammatory mediators (e.g. macrophage colony stimulating factor M-CSF, parathyroid hormone related hormone related peptide – PTHrP) have a capacity to trigger the recruitment, differentiation, and activation of the osteoclast-induced process of bone resorption (Anandarajah and Schwarz, 2006). One of the possible mechanisms is a link between these cytokines and immune system activation. When the function of OPG/RANK/RANKL in bone remodeling is enhanced (e.g. in inflammatory arthritis), the activated T cells in the inflamed tissue promote production of RANKL (Gravallese et al., 2000). Nakashima and Takayanagi (2009) reported that IL-17-producing helper T cells (TH17) play a major role in bone destruction associated with inflammatory arthritis by inducing RANKL. Subsequently, RANKL stimulates osteoclastogenesis through the nuclear factor of activated T-cells cytoplasmic 1 (NFATc1), which is a crucial regulator of immune response. Moreover, investigations of the effects of oxidative stress on bone metabolism consists in measurement of markers of lipid oxidation (lipid damage) (e.g. malondialdehyde – MDA) (Leelarungrayub et al., 2011; Bloomer et al., 2013; Sirota et al., 2013) or markers of DNA damage (e.g. specific enzymes detecting oxidized purines and pyrimidines evidencing DNA damage) (Bichler et al., 2007; Langiea et al., 2014). Interestingly, a mechanical load can influence production of pro-inflammatory cytokines. The results reported by García-López et al. (2005) revealed that cyclic mechanical strain inhibits production of anti-inflammatory cytokines (IL-10) and stimulates production of their antagonist (IL-12) by osteoblasts. These two cytokines have the ability to decrease bone resorption, as IL-10 inhibits differentiation of osteoclast progenitors into preosteoclasts (Honma et al., 2014) and suppresses osteoblast differentiation by inhibition of TGF- β 1 production (Barron et al., 2010). In turn, IL-12 inhibits RANKL-induced osteoclast formation, an effect mediated by IFN- γ (Tortelli et al., 2009). Contrary data were obtained by Seferos et al. (2016) in a study on growing rats whose excessive physical activity (prolonged cold swimming) caused oxidative stress resulting in bone loss. However, interesting is the protective effect of the dietary supplementation of polyphenols (e.g. extract of *Hypericum perforatum* rich in the quercetin flavonoid) against the oxidative stress and the bone mass loss in the rats caused by the excessive physical activity (Seferos et al., 2016).

Causes of bone loss during body ageing

Bone mass accrual occurs with growth and is enhanced during pubertal growth in both pigs (Tanck et al., 2001) and humans (Baxter-Jones et al., 2003), however, somewhat earlier in females than in males. Thus, childhood and adolescence are very

important periods of life for bone development and mineralization. Along with body aging, the skeleton is more susceptible to oxidative stress induced by overproduction of reactive oxygen species (e.g. O_2^- , H_2O_2 , NOO^-) causing that the balance between bone resorption and formation is tipped towards enhanced resorption and decreased formation. Animal studies have demonstrated that reactive oxygen species formed by phagocytes (i.e. monocytes, macrophages, and neutrophils) contribute to bone resorption (Banfi et al., 2008). These radicals account for oxidation of specific enzymes, proteins, lipids, and DNA causing cell and tissue damage (Ames et al., 1993). Oxidative stress induces changes in the regulation of osteoblast and osteoclast differentiation resulting in predominance of osteoclastogenesis (Almeida and O'Brien, 2013) mainly via the RANK/RANKL and NF- κ B pathways. Reactive oxygen species produced in states of inflammation further enhance inflammation through stress-activated kinases (c-Jun N terminal kinase) (Haddad, 2002) and transcription factors such as NF- κ B and activator protein-1 (AP-1) (Rahman, 2000). Normally, the organism is able to prevent/mitigate the damaging effects of ROS through the natural antioxidant defense system by production of endogenous antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (Ighodaro and Akinloye, 2018), and by dietary antioxidants (Rao and Rao, 2012). Furthermore, the organism response to the prolonged action of negative agents is inflammation stimulated by pro-inflammatory cytokines and resulting in organ damage (Abbas et al., 2014). It has been known for decades that both chronic oxidative stress and inflammation during aging may cause bone loss (Filaire and Toumi, 2012). A link between bone loss and inflammation is the function of proinflammatory factors TNF- α , IL-1, IL-6, and ROS as bone resorbing cytokines. The intracellular immune response, inflammation, and cell cycle is regulated/modified by RANKL. This factor also regulates the expression of TNF- α , interleukin (IL)-1, and interleukin (IL)-6 among other important pro-inflammatory cytokines (Celec, 2004). Prolonged inflammation results in a chronic increase in the level of acute phase proteins and pro-inflammatory cytokines (TNF- α , IL-1, IL-6), C-reactive protein (CRP), fibrinogen, white blood cell (WBC), and ROS, resulting in bone loss (Yanbaeva et al., 2007). Examples of inflammation conditions associated with bone loss include periodontal disease (Van Dyke and Serhan, 2003), autoimmune diseases, rheumatoid arthritis, and multiple sclerosis (Di Munno et al., 2004), and osteoporosis (Ginaldi and De Martinis, 2016).

Mechanisms of age-related bone loss

Estrogen plays a fundamental role in skeletal growth and bone homeostasis in both males and females. It is known that estrogen deficiency causes bone loss, as it regulates bone homeostasis through regulatory effects on the immune system and oxidative stress as well as direct effects on bone cells (Weitzmann and Pacifici, 2006). Osteoblasts and osteoclasts have the functional estrogen receptors: $-\alpha$ (ER α) and $-\beta$ (ER β). These receptors are also expressed in bone marrow stromal cells, i.e. precursors of osteoblasts (Weitzmann and Pacifici, 2005). In humans, ER α dominates in cortical bone, while ER β dominates in trabecular bone. In general, ER α mediates most actions of estrogen on bone cells (Hall and McDonnell, 1999). As indicated by Streicher et al. (2017), the increase in bone resorption observed in

states of estrogen deficiency in mice is mainly caused by lack of estrogen receptor- α (ER α)-mediated suppression of RANKL expression in bone lining cells. Bone resorption is regulated by the activity of osteoclasts, and the essential cytokines required for osteoclast formation are RANKL and M-CSF (macrophage colony stimulating factor) produced primarily by bone marrow, osteoblasts, and activated T cells (Khosla, 2001). RANKL promotes the differentiation of osteoclast precursors from an early stage of maturation into fully mature multinucleated osteoclasts, thus stimulating these cells to resorb bone. RANKL binds to the transmembrane receptor RANK expressed on the surface of osteoclasts and their precursors. M-CSF enhances the production of RANKL by stromal cells and prolongs the functioning of osteoclasts by blocking their apoptosis. In contrast, the osteoclast activity is inhibited by osteoprotegerin (OPG), which binds to RANKL. Estrogen is critical for skeletal homeostasis and regulates bone remodeling in part by modulating (blocking) new osteoclast formation via down regulation of RANKL and other cytokines: IL-6, IL-1, and M-CSF. TNF- α is essential for bone resorption by osteoclasts (Teitelbaum, 2000) and other molecules (e.g. prostaglandin PG2), which are stimulators of ROS production (Manolagas and Jilka, 1995; Stein and Yang, 1995). Thus, estrogen deficiency creates an environment for increased inflammatory mediators and results in accelerated bone turnover with predominance of bone resorption over bone formation (Jagger et al., 2005), perforation of trabecular tissue, and loss of connection between the remaining trabeculae (Eriksen et al., 1990) followed by trabecular thinning, partly due to impaired osteoblastic activity secondary to increased osteoblast apoptosis (Riggs and Parfitt, 2005). Experiments conducted in ovariectomized animal models have demonstrated that, in states of depleted intracellular antioxidants, mainly glutathione and thioredoxin, osteoclast activity increases via up-regulation of TNF- α (Muthusami et al., 2005). Scavenging of ROS by estrogen has been found to be over two times higher than that of vitamin C and vitamin E (Ruiz-Larrea et al., 2000). Thus, this hormone has an ability to augment intracellular oxidant defenses by lowering the concentration of ROS within cells (Lean et al., 2003). As indicated by Nojiri et al. (2011), mice that were deficient in superoxide dismutase exhibited lower bone mass, lower osteoblast numbers, and higher ROS levels than wild type mice. Graef et al. (2018) reported that, in inflammatory conditions, inflammatory cytokines (e.g. TNF- α) suppressed alkaline phosphatase activity and tended to decrease nodule formation. This response coincided with suppressed gene expression of bone morphometric protein (Bmp2) and upregulation of an inhibitor of BMP signaling. In estrogen-deficient animal models, administration of antioxidants (e.g. ascorbic acid) has been shown to increase the levels of glutathione and thioredoxin and decrease TNF- α production (Lean et al., 2003). The same authors have shown in cell culture experiments that administration of glutathione and thioredoxin to osteoclasts protects against bone loss during estrogen deficiency. Lean et al. (2003) revealed that administration of a single dose of 17- β estradiol in ovariectomized rats resulted in normalization of previously decreased levels of the bone oxidant defense system (thiol antioxidant) within 24 hours; thus, it can also indirectly promote bone formation.

Estrogen deficiency leads to negative calcium balance by a decrease in intestinal calcium absorption (Gennari et al., 1990; Arjmandi et al., 1993) and reduction

of renal calcium reabsorption (McKane et al., 1995). It is believed that low calcium absorption and increased loss through kidneys are the main causes of bone loss resulting from estrogen deficiency/absence during menopause or after ovariectomy. Estrogen can exert an effect on bone condition indirectly, as its deficiency increases parathyroid hormone (PTH) levels and action leading to release of calcium from bones constantly into the bloodstream, which results in loss of bone mass (Reid, 2008). Bone loss may also be attributed to vitamin D deficiency due to decreased 1- α -hydroxylase activity in kidneys in females that do not get enough sunlight (Maetani et al., 2009).

Putative effects of nutritive polyphenols on bone metabolism

The peak bone mass is dependent mostly upon genetic factors (even in 80%), while others, e.g. diet and lifestyle (physical activity, etc.) and interactions between them, are regarded to be modifiable factors (Rizzoli et al., 2011). This suggests that modifiable factors largely contribute to attainment of the peak bone mass and the nutritional aspect is important in the development and maintenance of bone mass (Heaney, 2007). Thus, any modification of these factors during the time of the most intensive bone mass accrual (childhood and adolescence) might have an impact on the risk of skeletal system diseases later in life (Mølgaard et al., 1999).

Bone strength is determined by the material and structure components of skeletal tissue, e.g. minerals are responsible for bone stiffness (Weaver et al., 2016). Thus, knowledge of substances that may potentially influence the rate of nutrient absorption or help to minimize (or inhibit) bone loss after reaching the peak bone mass seems to be very important. Recent studies indicate a positive effect of diets rich in vegetables, fruit, whole grains, and nuts on bone health indicators in adolescents and adults as well as women during the menopause period.

This review is a comprehensive summary of literature describing the effects of polyphenols on bone in human, animal, and cell studies, in particular, the underlying cellular and molecular mechanisms that can modulate skeletal homeostasis and influence bone modeling and remodeling processes. Several studies have associated higher fruit intake with decreased fracture risk, greater formation markers, and bone mineral density (Shen et al., 2012). Many of the health-enhancing effects of fruit and vegetables have been attributed to flavonoids (polyphenols), i.e. a major class of phytochemicals found ubiquitously in fruit and vegetables (Hardcastle et al., 2011). Hassan et al. (2018) and Marwan and Saleh (2012) showed a significant correlation between the use of selected polyphenols and elevation of serum calcium, vitamin D, and osteocalcin levels as markers of modulation in bone mineralization. Based on the results of a cohort study, Hardcastle et al. (2011) found a significant association between flavonoid intake and bone mineral density in the hip and lumbar spine and a negative correlation with bone-resorption markers. New et al. (2000) reported higher mineral density in femoral neck bone in women who had consumed high amounts of fruit in their childhood than in women who had consumed medium or low amounts. In a study with orchidectomized rats, Deyhim et al. (2006) found that consumption of orange or grapefruit juice reversed orchidectomy-induced antioxidant suppression, decreased alkaline phosphatase and acid phosphatase activities,

moderately restored femoral density, increased femoral strength, and significantly delayed time-induced femoral fracture. The authors concluded that drinking citrus juice positively affects serum antioxidant status and bone strength. Data reported by Langsetmo et al. (2011) showed that a diet high in vegetables, fruit, and whole grains was associated with a reduced risk of fracture in both men and women. This was most evident in older women. However, it was independent of the body mass index, bone mineral density, falling (or other movement), and demographic variables. Slightly different data were presented by McTiernan et al. (2009), who revealed that a low-fat diet combined with increased consumption of fruit, vegetables, and grains only modestly reduced the risk of multiple falls and slightly lowered mineral density of hip bone but did not change the risk of fractures. Welch et al. (2012) concluded that habitual flavonoid intake was positively associated with bone mineral density in both the hip and spine regions. Hassan et al. (2018) found a strong association between an increase in the osteocalcin and elevation in serum calcium after administration of quercetin. This may indicate modulation of bone mineralization (Ducy et al., 1996). These findings suggest that polyphenols (e.g. quercetin) may be a potential drug of choice for reversal of impaired intestinal Ca^{2+} absorption in certain gut disorders that occur with oxidative stress and apoptosis. Studies conducted by Hohman and Weaver (2015) on ovariectomized rats indicate that consumption of grape products (rich in polyphenols) may improve calcium utilization and suppress bone turnover, leading to improvement in bone health (higher bone calcium retention, cortical thickness, and breaking strength). However, authors did not observe differences in femur bone mineral density and trabecular microarchitecture.

In a study on ovariectomized mice, Yamaguchi et al. (2011) indicated that quercetin potently suppressed osteoclastogenesis and NF- κ B (nuclear factor kappa B) activation induced by RANKL in osteoclast precursors; however, it had no effect on osteoblast mineralization and failed to significantly alleviate the inhibitory effect of NF- κ B induced by TNF α , even though quercetin potently suppressed NF- κ B activation in these cells. The results obtained in a previous study by Yamaguchi and Weitzmann (2009) indeed validated the potent suppressive effect of quercetin on TNF α -induced NF- κ B activation; however, this did not translate into a strong bone anabolic effect. The results reported by Xing et al. (2017) indicated that quercetin elevated bone mineral density in the distal femur and increased maximum energy absorption and maximum fracture load and stiffness in the femoral neck in ovariectomized female rats. In serum, analyses of minerals, osteogenic markers, and bone turnover markers revealed higher levels of calcium, phosphorus, osterix, runt-related transcription factor 2 (Runx-2), bone formation markers (ALP and N-terminal propeptide of type 1 procollagen (P1NP)) and lower levels of bone resorption markers (CTX and tartrate-resistant acid phosphatase (TRAP)) in the quercetin-treated ovariectomized rats. Moreover, this polyphenol is able to influence bone turnover via increased activity of bone synthesis markers and activity of osteoblasts (Abdelkarem et al., 2016) as well as inhibition of the mRNA expression of osteoclast-related genes (Guo et al., 2017) and osteoclast differentiation (Yamaguchi and Weitzman, 2009). Data obtained by Hooshmand et al. (2016) in a clinical study of postmenopausal women indicated that the consumption of dried plums daily increased serum

levels of bone formation markers, total alkaline phosphatase, bone-specific alkaline phosphatase, and insulin-like growth factor. In an osteoporotic rat model, Deyhim et al. (2005) found that consumption of dried plums, which are rich in polyphenols (caffeic acid, coumaric acid), restored bone density in femoral and tibial regions and significantly increased lumbar bone density. The increase in femoral bone density resulted in improved bone quality and strength. Varying doses of dried plums were also able to improve significantly trabecular microarchitecture properties in comparison with ovariectomized controls. The authors concluded that the improvement in the biomechanical properties of long bones induced by the consumption of dried plums may in part be related to the favorable microstructural changes such as tibial bone volume and connectivity even after losses have already occurred. Rendina et al. (2013) demonstrated that polyphenols from dried plums restored bone in osteopenic ovariectomized animals. They not only prevented bone loss but also induced an anabolic response, structural changes coinciding with local up-regulation of indicators of osteoblast activity, and down-regulation of osteoclastogenesis. These alterations in the mediators of bone metabolism occurred in conjunction with enhanced systemic glutathione peroxidase (GPx) activity. In turn, Mane et al. (2011) found that polyphenols from lingonberry increased superoxide dismutase and glutathione reductase activity while increasing the concentration of reduced glutathione in rats fed a diet inducing oxidative stress.

In another study conducted by Devareddy et al. (2008), blueberry polyphenols were able to prevent the loss of whole-body bone mineral density, compared to ovariectomized rats. This may have been related to suppression of an ovariectomy-induced increase in bone turnover, as evident by the reduced femoral mRNA levels of alkaline phosphatase, collagen type I, and tartrate-resistant acid phosphatase. Chiba et al. (2003) found that trabecular bone loss in ovariectomized mice could be prevented by flavonoids common to citrus fruit (hesperidin or α -glucosylhesperidin) through a reduction in the number of osteoclast cells. Hesperidin consumption also increased the femoral Ca concentration to a level slightly above that for mice in the control group. Chen et al. (2010) reported that blueberry polyphenols added to diet significantly promoted osteoblastic bone formation in rapidly growing male and female rats. Moreover, the same research team (Zhang et al. 2011 a, b) found that consumption of blueberry-containing diet before puberty can prevent ovariectomy-induced bone loss in adulthood. The molecular mechanisms underlying these effects involve stimulation of osteoblast differentiation and reduction of mesenchymal stromal cell senescence via increased myosin production.

As demonstrated by Villarreal et al. (2007), berry intake can improve the antioxidant status and reduce the level of inflammatory biomarkers *in vivo*. Cranberry juice significantly increased plasma antioxidant capacity, red blood cell oxidative resistance, and superoxide dismutase in ovariectomized rats, however, without an effect on bone health. Shen et al. (2012) reported that commonly consumed polyphenol-rich fruit have a pronounced effect on bone health. This effect is manifested by higher bone mass and trabecular bone volume (number and thickness) as well as lower trabecular separation through enhancement of bone formation and suppression of bone resorption, resulting in greater bone strength. Such osteoprotective effects

seem to be mediated via antioxidant or anti-inflammatory pathways and their downstream signaling mechanisms, leading to osteoblast mineralization and osteoclast inactivation. Karlsen et al. (2007) suggest that anthocyanin (bilberry polyphenols) supplementation may have a role in the prevention or treatment of chronic inflammatory diseases by inhibition of NF- κ B-transactivation and decreased plasma concentrations of pro-inflammatory chemokines, cytokines, and inflammatory mediators. Bilberry was also shown to decrease malondialdehyde levels (marker of lipid peroxidation) and decrease IL-6 and IL-15 (inflammatory mediators) in induced states of oxidative stress (Jakešević et al., 2011). Graef et al. (2018) demonstrated that a polyphenol extract induced 60–80% of the anabolic effect of dried plums on bone in osteopenic rats. However, the authors indicated that the response most closely mimicked that of dried fruit when the extract was combined with vitamin K and potassium (found in large amounts in dried plums).

In a cell culture study, Ko et al. (2009) investigated the effect of tea polyphenols (epigallocatechin, EGC) on bone metabolism using a cultured rat osteoblast-like osteosarcoma cell line. This polyphenol stimulated alkaline phosphatase activity and the level of mineralization mainly due to inhibition of osteoclast formation upon induction of the receptor activator of nuclear factor- κ B ligand and inhibition of the mRNA expression of tartrate-resistant acid phosphatase. The authors concluded that tea polyphenols had positive effects on bone metabolism through promotion of osteoblastic activity and inhibition of osteoclast differentiation. Smith et al. (2014) compared the effect of polyphenols from dried plums on bone in osteopenic animal models. Consumption of dried plums for 6 weeks restored the whole body and femoral bone mineral density to the level of the control group. The trabecular bone volume and cortical thickness were also improved. The mechanism of action was based on suppression of the ovariectomy-induced increase in bone turnover, as indicated by the bone formation marker (N-terminal procollagen type 1, P1NP) and the bone resorption marker (deoxypyridinoline, DPD). Histomorphometric analysis of the tibia revealed that the cancellous bone formation rate and mineralizing surface were increased. Moreover, up-regulation of bone morphogenetic protein (Bmp4) and insulin-like growth factor 1 (IGF-I) accompanied by down-regulation of the nuclear factor T cell activator 1 (Nfatc1) were detected. These findings demonstrate that the dried plum polyphenols primarily suppressed bone turnover in the adult osteopenic animal model induced by ovariectomy. Hooshmand et al. (2015) reported anti-inflammatory and antioxidative properties of these polyphenols in macrophage cells after induction of inflammation (by lipopolysaccharide–LPS stimulation) and lipid peroxidation (by a mixture of FeSO₄ and H₂O₂). A high dose of dried plum polyphenols was able to reduce nitric oxide (NO) production and expression of cyclooxygenase 2 (COX-2, a marker of inflammation); additionally, reduction of the product of lipid oxidation (MDA, malondialdehyde) was observed.

In recent years, researchers have investigated whether the bone-sparing actions of quercetin are mediated through its anti-inflammatory properties. An osteoblast and osteoclast co-culture treated with H₂O₂ showed an increased level of TNF- α , which was restored to a normal level when seeded on hydroxyapatite loaded with quercetin (Forte et al., 2017). Another experiment done by the same group of inves-

tigators revealed that quercetin-functionalized hydroxyapatite inhibited IL-6 production in a triculture model consisting of three types of cells, namely human osteoblast-like MG63 cells, osteoclast precursors 2T-110, and human umbilical-vein endothelial cells (HUVECs) (Forte et al., 2016). The concentrations of pro- and anti-inflammatory cytokines were also determined *in vitro* using RAW264.7 cells. Quercetin reduced the levels of IL-1 β , TNF- α , and IL-6 and increased those of IL-10 and Arg-1 in RAW264.7 cells exposed to M-CSF, RANKL, or LPS (Tang et al., 2019; Ge et al., 2020). *In vivo*, a reduction in TNF- α , IL-6, and CRP levels was observed following quercetin or quercetin-loaded phytosome nanoparticle interventions in ovariectomized (Abd El-Fattah et al., 2017) and zinc-oxide-nanoparticle-treated rats (Abdelkarem et al., 2016). Indeed, data indicate that the process of bone remodeling depends on the tight coupling between pro- and anti-inflammatory mediators. Quercetin helps to resolve overwhelming inflammatory responses by inhibiting pro-inflammatory cytokines and stimulating anti-inflammatory cytokines. The molecular machinery that underlies the anti-inflammatory action of quercetin remains a gap in this research field.

In the study conducted by Shahnazari et al. (2016) on young male adult and growing mice, the effects of polyphenols on bone were accompanied by a decline in interleukins, tumor necrosis factor (TNF), and monocyte chemoattractant protein-1 (MCP-1), suggesting that polyphenols act in part through the immune system to suppress inflammatory activity and reduce the size of the osteoclast precursor pool. This was accompanied by an increase in plasma phenolics, especially those that stimulate bone accrual. Moreover, in both investigated groups of animals (growing and adult), polyphenols from dried plums strongly increased bone volume, which demonstrates that dietary polyphenols are able to increase peak bone mass during growth. Moreover, the authors also suggest that bone turnover differed between the growing and adult animals. A decline in bone resorption was observed in the adult mice, whereas an increase in bone formation was evident in the young mice.

Estrogenic activity

The results of the study performed by Resende et al. (2013) indicate that many polyphenolic compounds have estrogenic activities. They exert effects primarily through binding to (ER). There are two variants of the estrogen receptor: alpha (ER- α) and beta (ER- β) and many polyphenol phytoestrogens display somewhat higher affinity for ER- β than ER- α (Křížová et al., 2019). Due to this ability, they have the potential to mimic estrogen and counteract the deleterious effects of estrogen deficiency on bone. The best-known effect on bone is assigned to isoflavones. However, their function depends on the exposure (type, matrix, concentration, and bioavailability), ethnicity, hormone levels (related to age, sex, and physiological condition), and health status of the consumer (Domínguez-López et al., 2020). In addition, phytoestrogens can act as intracellular regulators of the cell cycle and apoptosis. Moreover, due to their antioxidant, antiproliferative, antimutagenic, and antiangiogenic roles, phytoestrogens can improve the health of the organism (Desmawati and Sulastri, 2019). Therefore, a similar positive effect on bone should also be expected.

Most studies examining the impact of phytoestrogens on bone health measure osteocalcin (OC), i.e. a metabolic regulatory hormone secreted by osteoblasts, as it is

a sensitive biomarker of bone formation (Seibel, 2003). Human studies revealed the most significant increase in OC serum levels due to consumption of isoflavones in postmenopausal women, mainly due to stimulation of osteoblast activity (Chiechi et al., 2002). The results of a study conducted by Lambert et al. (2017 b) on postmenopausal women demonstrated that red clover-derived isoflavones combined with probiotics attenuated estrogen deficiency-induced loss of bone mineral density and improved bone turnover even in women suffering from osteopenia. Moreover, isoflavones can be effective in preserving bone mineral density and attenuating accelerated bone resorption (Lambert et al., 2017 a). The authors attribute this effect to the anti-resorptive properties of estrogen; thus, the beneficial effects may arise from the decreased bone resorption by osteoclasts rather than increased bone formation by osteoblasts.

However, there is little information on the estrogenic activities of other polyphenols. Prouillet et al. (2004) found that both quercetin and kaempferol significantly increased alkaline phosphatase activity in cultured human osteoblasts. This effect was markedly reduced by PD 98059, i.e. an inhibitor of the extracellular regulated kinase (ERK) pathway, and by ICI 182780, which is an antagonist of estrogen receptors. The authors found that the increase in alkaline phosphatase activity induced by flavonols in human osteoblasts involves a rapid stimulation of ERK activation as well as estrogen receptors and that the activation of ERK by flavonols occurs most likely downstream of the estrogen receptor activation. Taken together, these results suggest that flavonol derivatives such as quercetin and kaempferol can stimulate osteoblastic activity. Similar action of icarrin (a flavonoid glucoside isolated from *Herba epimedii*) was presented by Song et al. (2013).

Interaction with transporter proteins

Polyphenols have variable potencies to interact; hence, they alter the activities of various transporter proteins, many of them classified as anion transporting polypeptide-binding cassette transporters (Hussain et al., 2016). The application of quercetin in the study conducted by Hassan et al. (2018) on diabetic type 2 patients led to elevation of serum calcium. Similarly, Marwan and Saleh (2012) found that rats treated with quercetin had elevated serum calcium, vitamin D, and osteocalcin levels, indicating modulation in bone mineralization. The mechanism behind the elevation of serum calcium as a result of quercetin intake is not well understood, but it seems to be related to the potent antioxidant effect of this polyphenol that may correct the redox status in the small intestine at the cellular level, restoring the proper function of molecules involved in the transport and absorption of Ca^{+2} ions (de Barboza et al., 2015), activation of transient receptor potential vanilloid subfamily member 6 (TRPV6) gene expression, and activation of vitamin D receptor in the intestine (Inoue et al., 2010). As reported by Marchionatti et al. (2013), flavonoids (e.g. quercetin) may be useful in preventing inhibition of intestinal Ca^{2+} absorption in chicks caused by menadione-induced injury (or other substances that deplete GSH) by blocking the oxidative stress and, consequently, leading to improvement of calcium absorption. As suggested by Ding et al. (2013), all polyphenols have reducing properties; they can donate hydrogen to an oxidized cellular constituent and play a significant role against oxidative stress-related pathologies.

Table 1. Examples of the influence of polyphenols on bone metabolism

Source/type of polyphenols	Biological activity	References
1	2	3
Bilberry (anthocyanin compounds)	decrease in the MDA level	Jakesevic et al. (2011)
Blueberry (anthocyanin compounds)	prevention of chronic inflammatory diseases (inhibition of NF- κ B transactivation) decrease in plasma proinflammatory cytokines and inflammatory mediators suppression of ovariectomy-induced increased bone turnover by a decrease in ALP, collagen type I, TRAP promotion of osteoblastic bone formation stimulation of osteoblast differentiation reduction of mesenchymal stromal cells improvement of antioxidant status reduction of inflammatory biomarkers increase in antioxidant capacity increase in SOD activity no effect on bone health	Karlsen et al. (2007) Devareddy et al. (2008) Chen et al. (2010) Zhang et al. (2011 a) Zhang et al. (2011 b) Villarreal et al. (2007)
Berry, cranberry (anthocyanin compounds)		
Citrus fruit (quercetin, hesperidin, α -glucosylhesperidin)	prevention of trabecular bone loss caused by ovariectomy reduction of the number of osteoclasts increase in bone Ca content	Chiba et al. (2003)
Dried plum (caffeic acid, coumaric acid) Citrus (quercetin) Berry fruits (anthocyanin compounds)	increase in bone mass increase in trabecular bone volume increase in bone mineralization (osteoblast activity) increase in bone strength suppression of bone resorption (osteoclast inactivation)	Shen et al. (2012)

Dried plums (caffeic acid, coumaric acid)	restoration/increase in bone mineral density	Deyhim et al. (2005)
	increase in osteoblast activity	Rendina et al. (2013)
	decrease in osteoclast activity	
	enhancement of systemic GPx activity	
	increase in bone mineralization leading to improvement of trabecular bone volume and cortical thickness	Smith et al. (2014)
	suppression of ovariectomy-induced increase in bone turnover (based on levels of PINP and DPD markers)	
	increase in Bmp4, IGF-I, decrease in Nfatc1	
	decrease in oxidation and inflammation (reduction of NO and MDA production and expression of COX-2)	Hooshmand et al. (2015)
	increase in serum levels of bone formation markers (total ALP, bone-specific ALP)	Hooshmand et al. (2016)
	increase in IGF-I	
Flavonoids	suppression of inflammatory activity (by a decline in TNF- α , MCP-1)	Shahnazari et al. (2016)
	reduction of osteoclast precursor cells	
	increase in bone volume	
	decline in bone resorption (in adult individuals)	
	increase in bone formation (in young individuals)	
	increase in bone mineral density	Hardcastle et al. (2011)
	decrease in the level of bone-resorption markers	
	increase in SOD and GSR activity	Mane et al. (2011)
	increase in GSH content	
	decrease in ALP activity	Deyhim et al. (2006)
Lingonberry extract (anthocyanin compounds, hexoside derivatives)	decrease in ACP activity	
Orange or grapefruit juice (quercetin)	restoration of bone density	
	increase in bone strength	
	decrease in bone fracture indices	

Table 1 – contd.

1	2	3
Dried plums (caffeic acid, coumaric acid)	restoration/increase in bone mineral density	Deyhim et al. (2005)
	increase in osteoblast activity	Rendina et al. (2013)
	decrease in osteoclast activity	
	enhancement of systemic GPx activity	
	increase in bone mineralization leading to improvement of trabecular bone volume and cortical thickness	Smith et al. (2014)
	suppression of ovariectomy-induced increase in bone turnover (based on levels of PINP and DPD markers)	
	increase in Bmp4, IGF-I, decrease in Nfatc1	
	decrease in oxidation and inflammation (reduction of NO and MDA production and expression of COX-2)	Hooshmand et al. (2015)
	increase in serum levels of bone formation markers (total ALP, bone-specific ALP)	Hooshmand et al. (2016)
	increase in IGF-I	
Flavonoids	suppression of inflammatory activity (by a decline in TNF- α , MCP-1)	Shahnazari et al. (2016)
	reduction of osteoclast precursor cells	
	increase in bone volume	
	decline in bone resorption (in adult individuals)	
	increase in bone formation (in young individuals)	
	increase in bone mineral density	
	decrease in the level of bone-resorption markers	
	increase in SOD and GSR activity	Hardcastle et al. (2011)
	increase in GSH content	Mane et al. (2011)
	decrease in ALP activity	
Lingonberry extract (anthocyanin compounds, hexoside derivatives)	decrease in ACP activity	
	restoration of bone density	
	increase in bone strength	Deyhim et al. (2006)
	decrease in bone fracture indices	
Orange or grapefruit juice (quercetin)		

Tea (epigallocatechin)	stimulation of ALP activity	Ko et al. (2009)
	promotion of osteoblastic activity	
Quercetin	inhibition of osteoclast formation (by induction of nuclear factor- κ B ligand and inhibition of TRAP expression)	Yamaguchi et al. (2011)
	suppression of osteoclastogenesis by induction of NF- κ B activation in osteoclast precursors	
	inhibition of mRNA expression of osteoclast-related genes	
	increase in the activity of bone synthesis markers	
	increase in osteoblast activity	
	reduction of TNF- α , IL-6, CRP	
	decrease in inflammation processes (reduction of TNF- α , IL-6)	
	increase in serum Ca, vitamin D, and osteocalcin (markers of bone mineralization)	
	reduction of IL-1 β , TNF- α , IL-6	
	increase in IL-10, Arg-1	
	increase in bone mineral density	Xing et al. (2017)
	increase in bone flexibility	
	increase in bone strength	
	increase in the serum level of Ca, P, osterix, Runx2, ALP, P1NP	
	decrease in the level of CTX, TRAP	

Influence on cell membrane

Interactions of polyphenols with biological membranes (both lipid and protein compounds) alter their properties. Both the chemical structure and the nature of the interaction of polyphenols with bio-membranes are critical for their beneficial effects, and such an interaction represents the underlying mechanism through which they influence the functional properties of membrane-bound enzymes and transporter proteins, which alter the transmembrane potential for endogenous and exogenous molecules (Oteiza et al., 2005). During interactions, polyphenols decrease the fluidity of bio-membranes, thus limiting the penetration of free radicals to cells and reducing their damage. It is thus obvious that such interactions must influence the electric properties of membranes as well, consequently influencing the passage of anions and cations through the membrane (Okamoto et al., 2001). The main factor governing the strength of the flavonoid-lipid interactions seems to be the lipophilicity of flavonoid molecules. It also seems that the presence of the 3-hydroxyl group and the 2,3 double bond is of utmost importance for the antioxidative activity of flavonoids (Hendrich, 2006). The structural features of flavonoids that are propitious for their inhibitory properties are almost the same as those that bring about their antioxidative activity. In some cases, prenylation of the flavonoid molecule increases its inhibitory potency (Hussain et al., 2016).

Summary

Summing up, the main effects of bone loss during ageing and diseases causing bone loss include: a) increased oxidative stress and formation of reactive radicals both leading to decreased activity of osteoblasts and increased activity of osteoclasts and osteoblast apoptosis; b) decreased levels of estrogen and appearance of inflammatory cytokines; c) decreased absorption of Ca^{2+} in the intestine with a simultaneous increase in the excretion of calcium through kidneys; d) reduced activity of the vitamin D receptor; e) effects on parathyroid hormone. Studies carried out on both human and animal models indicate that all of these causes taken together lead to decreased content of minerals and decreased mineral density of bones and, consequently, to increased susceptibility to bone fracture.

However, it seems that polyphenols can modulate different signaling pathways and are able to target diverse bone cellular compartments, thus providing noticeable bone protection. The data presented in this review have shown that, thanks to their multiple beneficial mechanisms, polyphenols can protect the skeletal system from bone loss via: 1) decreasing the production of reactive oxygen species and increasing the level of body antioxidant factors and enzymes 2) interaction with biological membranes (both lipid and protein compounds) and alteration of their properties, 3) binding the β estrogen receptor, which creates a possibility of mimicking the estrogen role in bone health, 4) inhibition of the expression of pro-inflammatory cytokines and other pro-inflammatory molecules, 5) promotion of bone synthesis by enhancement of the expression of osteogenic protein, 6) inhibition of RANK-

induced osteoclast formation and inhibition of RANKL-stimulated expression of osteoclast-related genes.

Therefore, it can be concluded that the tangible (visible) effects of these actions include improved calcium and phosphorus absorption leading to increased deposition of minerals and mineral density in bones and, consequently, increasing bone strength. Thus, it can be concluded that polyphenols offer an interesting approach to prevent accelerated bone loss and improve their performance.

References

- Abbas A.K., Lichtman A., Pillai S. (2014). *Cellular and Molecular Immunology*. University of California, San Francisco, Philadelphia, USA, 8th ed., 544 pp.
- Abd El-Fattah A.I., Fathy M.M., Ali Z.Y., El-Garawany A.E.A., Mohamed E.K. (2017). Enhanced therapeutic benefit of quercetin-loaded phytosome nanoparticles in ovariectomized rats. *Chem. Biol. Interact.*, 271: 30–38.
- Abdelkarem H.M., Fadda L.M., Kamal O.R. (2016). Alleviation of bone markers in rats induced nano-zinc oxide by quercetin and α -lipoic acid. *Toxicol. Mech. Methods*, 26: 692–699.
- Agidigbi T.S., Kim C. (2019). Reactive oxygen species in osteoclast differentiation and possible pharmaceutical of ROS-mediated osteoclast diseases. *Int. J. Mol. Sci.*, 20: 3576–3592.
- Akter F., Ibanez J. (2016). Bone and cartilage tissue engineering. In: *Tissue engineering made easy*, Akter F. (ed.). 1st ed. New York, Elsevier Inc., pp. 77–98.
- Almeida M., O'Brien C.A. (2013). Basic biology of skeletal aging: Role of stress response pathways. *J. Gerontol. A. Biol. Sci. Med. Sci.*, 68: 1197–1208.
- Ames B.N., Shigenaga M.K., Hagen T.M. (1993). Oxidants, antioxidants, and the degenerative diseases of aging. *Proc. Natl. Acad. Sci.*, 90: 7915–7922.
- Anandarajah A.P., Schwarz E.M. (2006). Anti-RANKL therapy for inflammatory bone disorders: mechanisms and potential clinical applications. *J. Cell. Biochem.*, 97: 226–232.
- Arjmandi B.H., Salih M.A., Herbert D.C., Sims S.H., Kalu D.N. (1993). Evidence for estrogen receptor-linked calcium transport in the intestine. *Bone Miner.*, 21: 63–74.
- Banfi G., Iorio E.L., Corsi M.M. (2008). Oxidative stress, free radicals and bone remodelling. *Clin. Chem. Lab. Med.*, 46: 1550–1555.
- Barron M.J., Tsai C.J., Donahue S.W. (2010). Mechanical stimulation mediates gene expression in MC3T3 osteoblastic cells differently in 2D and 3D environments. *J. Biomech. Eng.*, 132: 041005.
- Baxter-Jones A.D., Mirwald R.L., McKay H.A., Bailey D.A. (2003). A longitudinal analysis of sex differences in bone mineral accrual in healthy 8-19-year-old boys and girls. *Ann. Hum. Biol.*, 30: 160–175.
- Bichler J., Cavin C., Simic T., Chakraborty A., Ferik F., Hoelzl C., Schulte-Hermann R., Kundi M., Haidinger G., Angelis K., Knasmüller S. (2007). Coffee consumption protects human lymphocytes against oxidative and 3-amino-1-methyl-5H-pyrido [4,3-b] indole acetate (Trp-P-2) induced DNA-damage: Results of an experimental study with human volunteers. *Food Chem. Toxicol.*, 45: 1428–1436.
- Bloomer R.J., Trepanowski J.F., Farney T.M. (2013). Influence of acute coffee consumption on postprandial oxidative stress. *Nutr. Metab. Insights*, 6: 35–42.
- Bohn T. (2014). Dietary factors affecting polyphenol bioavailability. *Nutr. Rev.*, 72: 429–452.
- Cardona F., Andrés-Lacueva C., Tulipani S., Tinahones F.J., Queipo-Ortuño M.I. (2013). Benefits of polyphenols on gut microbiota and implications in human health. *J. Nutr. Biochem.*, 24: 1415–1422.
- Celec P. (2004). Nuclear factor kappa B-molecular biomedicine: the next generation. *Biomed Pharmacother.*, 58: 365–371.
- Cervellati C., Bonaccorsi G., Cremonini E., Romani A., Fila E., Castaldi M.C., Ferrazzini S., Giganti M., Massari L. (2014). Oxidative stress and bone re-

- sorption interplay as a possible trigger for postmenopausal osteoporosis. *Biomed. Res. Int.*, 569563, 8 pp.
- Chen J.R., Lazarenko O.P., Wu X., Kang J., Blackburn M.L., Shankar K., Badger T.M., Ronis M.J.J. (2010). Dietary-induced serum phenolic acids promote bone growth via p38 MAPK/b-catenin canonical Wnt signaling. *J. Bone. Miner. Res.*, 25: 2399–2411.
- Chiba H., Uehara M., Wu J., Wang X., Masuyama R., Suzuki K., Kanazawa K., Ishimi Y. (2003). Hesperidin, a citrus flavonoid, inhibits bone loss and decreases serum and hepatic lipids in ovariectomized mice. *J. Nutr.*, 133: 1892–1897.
- Chiechi L.M., Secreto G., D'Amore M., Fanelli M., Venturelli E., Cantatore F., Valerio T., Laselva G., Loizzi P. (2002). Efficacy of a soy rich diet in preventing postmenopausal osteoporosis: The Menfis randomized trial. *Maturitas*, 42: 295–300.
- Chiva-Blanch G., Visioli F. (2012). Polyphenols and health: Moving beyond antioxidants. *J. Berry Res.*, 2: 63–71.
- Christen P., Ito K., Ellouz R., Boutroy S., Sornay-Rendu E., Chapurlat R.D., van Rietbergen B. (2014). Bone remodelling in humans is load-driven but not lazy. *Nature Communications*, 5: 4855–4860.
- Circu M.L., Aw T.Y. (2010). Reactive oxygen species, cellular redox systems, and apoptosis. *Free Radic. Biol. Med.*, 15: 749–762.
- Clark E.M., Ness A.R., Bishop N.J., Tobias J.H. (2006). Association between bone mass and fractures in children: A prospective cohort study. *J. Bone Miner. Res.*, 21: 1489–1495.
- Cory H., Passarelli S., Szeto J., Tamez M., Mattei J. (2018). The role of polyphenols in human health and food systems: A mini-review. *Front. Nutr.*, 5: 87.
- de Barboza G.D., Guizzardi S., de Talamoni N.T. (2015). Molecular aspects of intestinal calcium absorption. *World J. Gastroenterol.*, 21: 7142–7154.
- Desmawati D., Sulastri D. (2019). Phytoestrogens and their health effect. *Maced. J. Med. Sci.*, 7: 495–499.
- Devareddy L., Hooshmand S., Collins J.K., Lucas E.A., Chai S.C., Arjmandi B.H. (2008). Blueberry prevents bone loss in ovariectomized rat model of postmenopausal osteoporosis. *J. Nutr. Biochem.*, 19: 694–699.
- Deyhim F., Stoecker B., Brusewitz G., Devareddy L., Arjmandi B.H. (2005). Dried plum reverses bone loss in an osteopenic rat model of osteoporosis. *Menopause*, 12: 755–762.
- Deyhim F., Garica K., Lopez E., Gonzalez J., Ino S., Garcia M., Patil B.S. (2006). Citrus juice modulates bone strength in male senescent rat model of osteoporosis. *Nutrition*, 22: 559–563.
- Di Munno O., Mazzantini M., Delle Sedie A., Mosca M., Bombardieri S. (2004). Risk factors for osteoporosis in female patients with systemic lupus erythematosus. *Lupus*, 13: 724–730.
- Ding Y., Yao H., Yao Y., Fai L.Y., Zhang Z. (2013). Protection of dietary polyphenols against oral cancer. *Nutrients*, 5: 2173–2191.
- Domazetovic V., Marcucci G., Iantomasi T., Brand M.L., Vincenzini M.T. (2017). Oxidative stress in bone remodeling: role of antioxidants. *Clin. Cases. Miner. Bone Metab.*, 14: 209–216.
- Domínguez-López I., Yago-Aragón M., Salas-Huetos A., Tresserra-Rimbau A., Hurtado-Barroso S. (2020). Effects of dietary phytoestrogens on hormones throughout a human lifespan: *Nutrients*, 12: 2456–2481.
- Ducy P., Desbois C., Boyce B., Pinero G., Story B., Dunstan C., Smith E., Bonadio J., Goldstein S., Gundberg C., Bradley A., Karsenty G. (1996). Increased bone formation in osteocalcin-deficient mice. *Nature*, 382: 448–452.
- Eastell R., Hannon R.A. (2008). Biomarkers of bone health and osteoporosis risk. *Proc. Nutr. Soc.*, 67: 157–162.
- Eriksen E.F., Hodgson S.F., Eastell R., Cedel S.L., O'Fallon W.M.O., Riggs B.L. (1990). Cancellous bone remodelling in type I (postmenopausal) osteoporosis: quantitative assessment of rates of formation, resorption, and bone loss at tissue and cellular levels. *J. Bone Miner. Res.*, 5: 311–319.
- Filaire E., Hechmi T. (2012). Reactive oxygen species and exercise on bone metabolism: friend or enemy? *Joint Bone Spine*, 79: 341–346.

- Fintini D., Cianfarani S., Cofini M., Andreoletti A., Ubertini G.M., Cappa M., Manco M. (2020). The bones of children with obesity. *Front. Endocrinol.*, 11: 200–216.
- Forte L., Torricelli P., Boanini E., Gazzano M., Rubini K., Fini M., Bigi A. (2016). Antioxidant and bone repair properties of quercetin-functionalized hydroxyapatite: An in vitro osteoblast-osteoclast-endothelial cell co-culture study. *Acta Biomater.*, 32: 298–308.
- Forte L., Torricelli P., Boanini E., Rubini K., Fini M., Bigi A. (2017). Quercetin and alendronate multi-functionalized materials as tools to hinder oxidative stress damage. *J. Biomed. Mater. Res., A*, 105: 3293–3303.
- García-López S., Meikle M.C., Villanueva R.E., Montaña L., Massó F., Ramírez-Amador V., Bojalil R. (2005). Mechanical deformation inhibits IL-10 and stimulates IL-12 production by mouse calvarial osteoblasts in vitro. *Arch. Oral Biol.*, 50: 449–452.
- Ge Y.W., Feng K., Liu X.L., Zhu Z.A., Chen H.F., Chang Y.Y., Sun Z.Y., Wang H.W., Zhang J.W., Yu D.G., Mao Y.Q. (2020). Quercetin inhibits macrophage polarization through the p-38 α / β signalling pathway and regulates OPG/RANKL balance in a mouse skull model. *J. Cell. Mol. Med.*, 24: 3203–3216.
- Gennari C., Agnusdei D., Nardi P., Civitelli R. (1990). Estrogen preserves a normal intestinal responsiveness to 1, 25-dihydroxyvitamin D3 in oophorectomized women. *J. Clin. Endocrinol. Metab.*, 71: 1288–1293.
- Ginaldi L., De Martinis M. (2016). Osteoimmunology and beyond. *Curr. Med. Chem.*, 23: 3754–3774.
- Goulding A., Cannan R., Williams S.M., Gold E.J., Taylor R.W., Lewis-Barne N.J. (1998). Bone mineral density in girls with forearm fractures. *J. Bone Miner. Res.*, 13: 143–148.
- Graef J.L., Rendina-Ruedy E., Crockett E.K., Ouyang P., Jarrod B., King J.B., Ciechewicz R.H., Edralin A., Lucas E.A., Smith B.J. (2018). Select polyphenolic fractions from dried plum enhance osteoblast activity through BMP-2 signaling. *J. Nutr. Biochem.*, 55: 59–67.
- Gravallese E.M., Manning C., Tsay A., Naito A., Pan C., Amento E., Goldring S.R. (2000). Synovial tissue in rheumatoid arthritis is a source of osteoclast differentiation factor. *Arthritis Rheumatism*, 43: 250–258.
- Guo C., Yang R.J., Jang K., Zhou X.L., Liu Y.Z. (2017). Protective effects of pretreatment with quercetin against lipopolysaccharide-induced apoptosis and the inhibition of osteoblast. Differentiation via the MAPK and Wnt/ β -Catenin pathways in MC3T3-E1 cells. *Cell. Physiol. Biochem.*, 43: 1547–1561.
- Haddad J.J. (2002). Antioxidant and prooxidant mechanisms in the regulation of redox (y)-sensitive transcription factors. *Cell Signal*, 14: 879–897.
- Hadjidakis D.J., Androulakis I.I. (2006). Bone remodelling. *Ann. N. Y. Acad. Sci.*, 1092: 385–396.
- Hall J.M., McDonnell D.P. (1999). The estrogen receptor beta-isoform (ERbeta) of the human estrogen receptor modulates ER alpha transcriptional activity and is a key regulator of the cellular response to estrogens and antiestrogens. *Endocrinology*, 140: 5566–5578.
- Hardcastle A.C., Aucott L., Reid D.M., MacDonald H.M. (2011). Associations between dietary flavonoid intakes and bone health in a Scottish population. *J. Bone Miner. Res.*, 26: 941–947.
- Hassan J.K., Sharrad A.K., Sheri F.H. (2018). Effect of quercetin supplement on some bone mineralization biomarkers in diabetic type 2 patients. *Adv. Pharmacol. Pharm.*, 6: 43–49.
- Heaney R.P. (2007). Bone health. *Am. J. Clin. Nutr.*, 85: 300–303.
- Hendrich A.B. (2006). Flavonoid-membrane interactions: possible consequences for biological effects of some polyphenolic compounds. *Acta Pharmacol. Sinica*, 27: 27–40.
- Henwood M.J., Binkovitz L. (2009). Update on pediatric bone health. *J. Am. Osteopath. Assoc.*, 109: 5–12.
- Hohman E.E., Weaver C.M. (2015). A grape-enriched diet increases bone calcium retention and cortical bone properties in ovariectomized rats. *J. Nutr.*, 145: 253–259.
- Honma M., Ikebuchi Y., Kariya Y., Suzuki H. (2014). Establishment of optimized in vitro assay methods for evaluating osteocyte functions. *J. Bone Miner. Metab.*, 33: 73–84.
- Hooshmand S., Kumar A., Zhang J.Y., Johnson S.A., Chaid S.C., Arjmandi B.H.

- (2015). Evidence for anti-inflammatory and antioxidative properties of dried plum polyphenols in macrophage RAW 264.7 cells. *Food Funct.*, 6: 1719–1725.
- Hooshmand S., Kern M., Metti D., Shamloufard P., Chai S.C., Johnson S.A., Payton M.E., Arjmandi B.H. (2016). The effect of two doses of dried plum on bone density and bone biomarkers in osteopenic postmenopausal women: a randomized, controlled trial. *Osteoporos. Int.*, 27: 2271–2279.
- Hussain S.A., Sulaiman A.A., Alhaddad H., Alhadidi Q. (2016). Natural polyphenols: Influence on membrane transporters. *J. Intercult. Ethnopharmacol.*, 5: 97–104.
- Ighodaro O.M., Akinloye O.A. (2018). First line defense antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defense grid. *Alexandria Med. J.*, 54: 287–293.
- Inoue J., Choi J.M., Yoshidomi T., Yashiro T., Sato R. (2010). Quercetin enhances VDR activity, leading to stimulation of its target gene expression in Caco-2 Cells. *J. Nutr. Sci. Vitaminol.*, 56: 326–330.
- Jagger C.J., Lean J.M., Davies J.T., Chambers T.J. (2005). Tumor necrosis factor- α mediates osteopenia caused by depletion of antioxidants. *Endocrinology*, 146: 113–118.
- Jaksevic M., Aaby K., Borge G.I., Jeppsson B., Ahrne S., Molin G. (2011). Antioxidative protection of dietary bilberry, chokeberry and *Lactobacillus plantarum* HEAL 19 in mice subjected to intestinal oxidative stress by ischemia-reperfusion. *BMC Complement. Altern. Med.*, 11: 8–20.
- Karlsen A., Retterstøl L., Laake P., Paur I., Bøhn S.K., Sandvik L., Blomhoff R. (2007). Anthocyanins inhibit nuclear factor-kappa B activation in monocytes and reduce plasma concentrations of pro-inflammatory mediators in healthy adults. *J. Nutr.*, 137: 1951–1954.
- Khalid I., Khoshhal K.I. (2011). Childhood osteoporosis. *J. Taibah Univ. Med. Sci.*, 6: 61–76.
- Khosla S. (2001). Minireview: the OPG/RANKL/RANK system. *Endocrinology*, 142: 5050–5055.
- Ko C.H., Lau K.M., Choy W.Y., Leung P.C. (2009). Effects of tea catechins, epigallocatechin, gallic acid, and gallic acid gallate, on bone metabolism. *J. Agric. Food Chem.*, 57: 7293–7297.
- Křížová L., Dadáková K., Kašparovská J., Kašparovský T. (2019). Isoflavones. *Molecules*, 24: 1076–1104.
- Lambert M.N.T., Hu L.M., Jeppesen P.B.A. (2017 a). A systematic review and meta-analysis of the effects of isoflavone formulations against estrogen-deficient bone resorption in peri- and postmenopausal women. *Am. J. Clin. Nutr.*, 106: 801–811.
- Lambert M.N.T., Thybo C.B., Lykkeboe S., Rasmussen L.M., Frette X., Christensen L.P., Jeppesen P.B. (2017 b). Combined bioavailable isoflavones and probiotics improve bone status and estrogen metabolism in postmenopausal osteopenic women: A randomized controlled trial. *Am. J. Clin. Nutr.*, 106: 909–920.
- Lampropoulos C.E., Papaioannou I., D'Cruz D.P. (2012). Osteoporosis – A risk factor for cardiovascular disease? *Nat. Rev. Rheumatol.*, 8: 87–98.
- Langie S.A.S., Kowalczyk P., Tomaszewski B., Vasilaki A., Maas L.M., Mooney E.J., Palagani A., Godschalk R.W.L., Tudek B., van Schootend F.J., Berghe W.V., Zabielski R., Mathers J.C. (2014). Redox and epigenetic regulation of the APE1 gene in the hippocampus of piglets: The effect of early life exposures. *DNA Repair*, 18: 52–62.
- Langsetmo L., Hanley D.A., Prior J.C., Barr S.I., Anastassiades T., Towheed T., Goltzman D., Morin S., Poliquin S., Kreiger N. (2011). Dietary patterns and incident low-trauma fractures in postmenopausal women and men aged ≥ 50 y: A population-based cohort study. *Am. J. Clin. Nutr.*, 93: 192–199.
- Law Y.Y., Chiu H.F., Lee H.H., Shen Y.C., Venkatakrishnan K., Wang C.K. (2016). Consumption of onion juice modulates oxidative stress and attenuates the risk of bone disorders in middle-aged and post-menopausal healthy subjects. *Food Funct.*, 7: 902–912.
- Lean J.M., Davies J.T., Fuller K., Jagger C.J., Kirstein B., Partington G.A., Urry Z., Chambers T.J. (2003). A crucial role for thiol antioxidants in estrogen deficiency bone loss. *J. Clin. Invest.*, 112: 915–923.
- Leelarungrayub D., Sallepan M., Charoenwattana S. (2011). Effects of acute caffeinated coffee consumption on energy utilization related to glucose and lipid oxidation from short submaximal treadmill exercise in sedentary men. *Nutr. Metab. Insights*, 4: 65–72.

- Lipiński K., Mazur M., Antoszkiewicz Z., Purwin C. (2017). Polyphenols in monogastric nutrition – a review. *Ann Anim Sci.*, 17: 41–58.
- Maetani M., Maskarinec G., Franke A., Cooney R. (2009). Association of leptin, 25-hydroxyvitamin D, and parathyroid hormone in women. *Nutr. Cancer.*, 61: 225–231.
- Mane C., Loonis M., Juhel C., Dufour C., Malien-Aubert C. (2011). Food grade lingonberry extract: Polyphenolic composition and in vivo protective effect against oxidative stress. *J. Agric. Food Chem.*, 59: 3330–3339.
- Manolagas S.C., Jilka R.L. (1995). Bone marrow, cytokines, and bone remodeling. Emerging insights into the pathophysiology of osteoporosis. *N. Engl. J. Med.*, 332: 305–311.
- Marchionatti A.M., Pacciaroni A., de Talamoni N.T. (2013). Effects of quercetin and menadione on intestinal calcium absorption and the underlying mechanisms. *Comp. Biochem. Physiol., A*, 164: 215–220.
- Marwan A.L.I., Saleh A.A.S. (2012). Comparative study of quercetin or/and urate oxidase against gentamicin-induced nephrotoxicity and oxidative stress in rat kidneys. *Am. J. Sci.*, 8: 600–607.
- McKane W.R., Khosla S., Burritt M.F., Kao P.C., Wilson D.M., Ory S.J., Riggs B.L. (1995). Mechanism of renal calcium conservation with estrogen replacement therapy in women in early postmenopause – a clinical research center study. *J. Clin. Endocrinol. Metab.*, 80: 3458–3464.
- McLean R.R. (2009). Proinflammatory cytokines and osteoporosis. *Current Osteoporosis Reports*, 7: 134–139.
- McTiernan A., Wactawski-Wende J., Wu L., Rodabough R.J., Watts N.B., Ty-lavsky F., Freeman R., Hendrix S., Jackson R. (2009). Low-fat, increased fruit, vegetable, and grain dietary pattern, fractures, and bone mineral density: The women's health initiative dietary modification trial. *Am. J. Clin. Nutr.*, 89: 1864–1876.
- Memon S.S., Kamboh A.A., Leghar I.H., Leghari R.A. (2019). Effect of *in ovo* and post-hatch administration of honey on the immunity and intestinal microflora of growing chickens. *J. Anim. Feed Sci.*, 28: 346–353.
- Mody N., Parhami F., Sarafian T.A., Demer L.L. (2001). Oxidative stress modulates osteoblastic differentiation of vascular and bone cells. *Free Radic. Biol. Med.*, 31: 509–519.
- Mølgaard C., Thomsen B.L., Michaelsen K.F. (1999). Whole body bone mineral accretion in healthy children and adolescents. *Arch. Dis. Child*, 81: 10–15.
- Muthusami S., Ramachandran I., Muthusamy B., Vasudevan G., Prabhu V., Subramaniam V., Jagadeesan A., Narasimhan S. (2005). Ovariectomy induces oxidative stress and impairs bone antioxidant system in adult rats. *Clin. Chim. Acta*, 360: 81–86.
- Nakashima T., Takayanagi H. (2009). Osteoimmunology: crosstalk between the immune and bone systems. *J. Clin. Immunol.*, 29: 555–567.
- Neveu V., Perez-Jiménez J., Vos F., Crespy V., du Chaffaut L., Mennen L., Knox C., Eisner R., Cruz J., Wishart D., Scalbert A. (2010). Phenol-Explorer: an online comprehensive database on polyphenol contents in foods. *Database*, 2010, article ID: bap024, doi:10.1093/database/.
- New S.A., Robins S.P., Campbell M.K., Martin J.C., Garton M.J., Bolton-Smith C., Grubb D.A., Lee S.J., Reid D.M. (2000). Dietary influences on bone mass and bone metabolism: Further evidence of a positive link between fruit and vegetable consumption and bone health? *Am. J. Clin. Nutr.*, 71: 142–151.
- Nijveldt R.J., van Nood E., van Hoorn D.E., Boelens P.G., van Norren K., van Leeuwen P.A. (2001). Flavonoids: a review of probable mechanisms of action and potential applications. *Am. J. Clin. Nutr.*, 74: 418–425.
- Nojiri H., Saita Y., Morikawa D., Kobayashi K., Tsuda C., Miyazaki T., Saito M., Marumo K., Yonezawa I., Kaneko K., Shirasawa T., Shimizu T. (2011). Cytoplasmic superoxide causes bone fragility owing to low-turnover osteoporosis and impaired collagen cross-linking. *J. Bone Miner. Res.*, 26: 2682–2694.
- Okamoto F., Okabe K., Kajiya H. (2001). Genistein, a soybean isoflavone, inhibits inward rectifier K(+) channels in rat osteoclasts. *Jpn. J. Physiol.*, 51: 501–509.
- Oteiza P.I., Erlejtman A.G., Verstraeten S.V., Keen C.L., Fraga C.G. (2005). Flavonoid-membrane interactions: A protective role of flavonoids at the membrane surface? *Clin. Dev. Immunol.*, 12: 19–25.

- Paszkiewicz M., Budzyńska A., Różalska B., Sadowska B. (2012). The immunomodulatory role of plant polyphenols. *Postępy Hig. Med. Dosw.*, 66: 637–646.
- Petti S., Scully C. (2009). Polyphenols, oral health and disease: A review. *J. Dent.*, 37: 413–423.
- Pieszka M., Gogol P., Pietras M., Pieszka M. (2015). Valuable components of dried pomaces of chokeberry, black currant, strawberry, apple and carrot as a source of natural antioxidants and nutraceuticals in the animal diet. *Ann. Anim. Sci.*, 15: 475–491.
- Pino A.M., Ríos S., Astudillo P., Fernández M., Figueroa P., Seitz G., Rodríguez J.P. (2010). Concentration of adipogenic and proinflammatory cytokines in the bone marrow supernatant fluid of osteoporotic women. *J. Bone Miner. Res.*, 25: 492–498.
- Prouillet C., Mazière J.C., Mazière C., Wattel A., Brazier M., Kamel S. (2004). Stimulatory effect of naturally occurring flavonols quercetin and kaempferol on alkaline phosphatase activity in MG-63 human osteoblasts through ERK and estrogen receptor pathway. *Biochem. Pharmacol.*, 67: 1307–1313.
- Raggatt L.J., Partridge N.C. (2010). Cellular and molecular mechanisms of bone remodelling. *J. Biol. Chem.*, 285: 25103–25108.
- Rahman I. (2000). Regulation of nuclear factor-[kappa] B, activator protein-1, and glutathione levels by tumor necrosis factor-[alpha] and dexamethasone in alveolar epithelial cells. *Biochem. Pharmacol.*, 60: 1041–1049.
- Rao L.G., Rao A.V. (2012). Oxidative stress and antioxidants in the risk of osteoporosis – role of the antioxidants lycopene and polyphenols. Open access peer-reviewed chapter. DOI: 10.5772/54703.
- Ray P.D., Huang B.W., Tsuiji Y. (2012). Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. *Cell Signal.*, 24: 981–990.
- Reid I.R. (2008). Menopause. *J. Bone Miner. Res.*, 7: 95–97.
- Rendina E., Hembree K.D., Davis M.R., Marlow D., Clarke S.L., Halloran B.P., Lucas E.A., Smith B.J. (2013). Dried plum's unique capacity to reverse bone loss and alter bone metabolism in postmenopausal osteoporosis model. *Plos One*, 8: e60569.
- Resende F.A., de Oliveira A.P.S., de Camargo M.S., Vilegas W., Varanda E.A. (2013). Evaluation of estrogenic potential of flavonoids using a recombinant yeast strain and MCF7/BUS cell proliferation assay. *Plos One*, 8(10): e74881.
- Riggs B.L., Parfitt A.M. (2005). Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. *J. Bone Miner. Res.*, 20: 177–184.
- Ritchlin C.T., Haas-Smith S.A., Li P., Hicks D.G., Schwarz E.M. (2003). Mechanisms of TNF- α - and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J. Clin. Invest.*, 222: 821–831.
- Rizzoli R., Bianchi M.L., Garabédian M., McKay H.A., Moreno L.A. (2011). Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. *Bone*, 46: 294–305.
- Ruiz-Larrea M.B., Martín C., Martínez R., Navarro R., Lacort M., Miller N.J. (2000). Antioxidant activities of estrogens against aqueous and lipophilic radicals; differences between phenol and catechol estrogens. *Chem. Phys. Lipids*, 105: 179–188.
- Sadowska B., Różalska B. (2010). Imbalance of defense reactions as a risk factor for the development of wound infections (in Polish). *Sepsis*, 3: 87–92.
- Seferos N., Petrokokkinos L., Kotsiou A., Rallis G., Tesseromatis C. (2016). Hypericum perforatum L. treatment restored bone mass changes in swimming stressed rats. *Stomatologija, Baltic Dent. Maxillofac. J.*, 18: 9–13.
- Seibel M.J. (2003). Biochemical markers of bone remodeling. *Endocrinol. Metab. Clin. N. Am.*, 32: 83–113.
- Shahnazari M., Turner R.T., Iwaniec U.T., Wronski T.J., Li M., Ferruzzi M.G., Nissenson R.A., Halloran B.P. (2016). Dietary dried plum increases bone mass, suppresses proinflammatory cytokines and promotes attainment of peak bone mass in male mice. *J. Nutr. Biochem.*, 34: 73–82.
- Shen C.L., von Bergen V., Chyu M.C., Jenkins M.R., Mo H., Chen C.H., Kwun I.S. (2012). Fruits and dietary phytochemicals in bone protection. *Nutr. Res.*, 32: 897–910.
- Shewaita S.A., Al Samghan A.S., Khoshhal O.K. (2019). Osteoporosis in children: Possible risk factors and role of antioxidants. *J. Musculoskelet. Surg. Res.*, 3: 319–325.

- Singla K.R., Dubey A.K., Garg A., Sharma R.K., Fiorino M., Ameen S.M., Hadad M.A., Al-Hiary M. (2019). Natural polyphenols: Chemical classification, definition of classes, subcategories, and structures. *J. AOAC Int.*, 102: 1397–1400.
- Sirota R., Gorelik S., Harris R., Kohen R., Kanner J. (2013). Coffee polyphenols protect human plasma from postprandial carbonyl modifications. *Mol. Nutr. Food Res.*, 57: 916–919.
- Smith B.J., Bu S.Y., Wang Y., Rendina E., Lim Y.F., Marlow D., Clarke S.L., Cullen D.M., Lucas E.A. (2014). A comparative study of the bone metabolic response to dried plum supplementation and PTH treatment in adult, osteopenic ovariectomized rat. *Bone*, 58: 151–159.
- Song L., Zhao J., Zhang X., Li H., Zhou Y. (2013). Icaritin induces osteoblast proliferation, differentiation and mineralization through estrogen receptor-mediated ERK and JNK signal activation. *Eur. J. Pharmacol.*, 714: 15–22.
- Sözen T., Özişik L., Başaran N.C. (2017). An overview and management of osteoporosis. *Eur. J. Rheumatol.*, 4: 46–56.
- Stein B., Yang M.X. (1995). Repression of the interleukin-6 promoter by estrogen receptor is mediated by NF-kappa B and C/EBP beta. *Mol. Cell Biol.*, 15: 4971–4979.
- Streicher C., Heyny A., Andrukhova O., Hofbauer L.C., Paul J., Kostenuik P.J., Erben R.G. (2017). Estrogen regulates bone turnover by targeting RANKL expression in bone lining cells. *Sci. Rep.*, 7: 6460.
- Tanck E., Homminga J., van Lenthe G.H., Huiskes R. (2001). Increase in bone volume fraction precedes architectural adaptation in growing bone. *Bone*, 28: 650–654.
- Tang J., Diao P., Shu X., Li L., Xiong L. (2019). Quercetin and quercitrin attenuates the inflammatory response and oxidative stress in LPS-induced RAW264.7 cells: In vitro assessment and a theoretical model. *Biomed Res. Int.*, article ID 7039802, 8 pp.
- Teitelbaum S.L. (2000). Bone resorption by osteoclasts. *Science*, 289: 1504–1508.
- Tortelli F., Pujic N., Liu Y., Laroche N., Vico L., Cancedda R. (2009). Osteoblast and osteoclast differentiation in an in vitro three-dimensional model of bone. *Tissue Eng. - A*, 15: 2373–2383.
- Turner C.H. (2004). Mechanical loading and bone formation. *Int. Bone Min. Soc. Knowledge Environ.*, 1: 15–23.
- Ullah M.F., Khan M.W. (2008). Food as medicine: potential therapeutic tendencies of plant derived polyphenolic compounds. *Asian Pac. J. Cancer Prev.*, 9: 187–196.
- Valko M., Rhodes C.J., Moncol J., Izakovic M., Mazur M. (2006). Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem. Biol. Interact.*, 160: 1–40.
- Valko M., Leibfritz D., Moncol J., Cronin M.T., Mazur M., Telser J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *Int. J. Biochem. Cell Biol.*, 39: 44–84.
- Van Dyke T.E., Serhan C.N. (2003). Resolution of inflammation: a new paradigm for the pathogenesis of periodontal diseases. *J. Dent. Res.*, 82: 82–90.
- Van Leeuwen J., Koes B.W., Paulis W.D., van Middelkoop M. (2017). Differences in bone mineral density between normal-weight children and children with overweight and obesity: a systematic review and meta-analysis. *Obesity Rev.*, 18: 526–46.
- Villarreal A., Stoecker B.J., Garcia C., Garcia K., Rios R., Gonzales C., Mandadi K., Faraji B., Patil B.S., Deyhim F. (2007). Cranberry juice improved antioxidant status without affecting bone quality in orchidectomized male rats. *Phytomedicine*, 14: 815–820.
- Wallace R.J., Oleszek W., Franz C., Hahn I., Baser K.H.C., Mathe A., Teichmann K. (2010). Dietary plant bioactives for poultry health and productivity. *Brit. Poultry Sci.*, 51: 461–487.
- Wang C.H., Lai Y.H., Lin Y.L., Kuo C.H., Syu R.J., Chen M.C., Hsu B.G. (2020). Increased serum leptin level predicts bone mineral density in hemodialysis patients. *Int. J. Endocrinol.*, Article ID 8451751.
- Weaver C.M., Gordon C.M., Janz K.F., Kalkwarf H.J., Lappe J.M., Lewis R., O’Karma M., Wallace T.C., Zemel B.S. (2016). The National Osteoporosis Foundation’s position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporos. Int.*, 27: 1281–1386.
- Weitzmann M.N., Pacifici R. (2005). The role of T lymphocytes in bone metabolism. *Immunol. Rev.*, 208: 154–168.

- Weitzmann M.N., Pacifici R. (2006). Estrogen deficiency and bone loss: an inflammatory tale. *J. Clin. Invest.*, 116: 1186–1194.
- Welch A., MacGregor A., Jennings A., Fairweather-Tait S., Spector T., Cassidy A. (2012). Habitual flavonoid intakes are positively associated with bone mineral density in women. *J. Bone Miner. Res.*, 27: 1872–1878.
- Xing L.Z., Ni H.J., Wang Y.L. (2017). Quercitrin attenuates osteoporosis in ovariectomized rats by regulating mitogen-activated protein kinase (MAPK) signaling pathways. *Biomed. Pharmacother.*, 89: 1136–1141.
- Yamaguchi M., Weitzmann M.N. (2009). The estrogen 17 β -estradiol and phytoestrogen genistein mediate differential effects on osteoblastic NF- κ B activity. *Int. J. Mol. Med.*, 23: 297–301.
- Yamaguchi Y., Park J.H., Inouye M. (2011). Quercetin, a potent suppressor of NF- κ B and Smad activation in osteoblasts. *Int. J. Mol. Med.*, 28: 521–525.
- Yanbaeva D.G., Dentener M.A., Creutzberg E.C., Wesseling G., Wouters E.F.M. (2007). Systemic effects of smoking. *Chest*, 131: 1557–1566.
- Yesilbag D., Eren M., Agel H., Kovanlikaya A., Balci F. (2011). Effects of dietary rosemary, rosemary volatile oil and vitamin E on broiler performance, meat quality and serum SOD activity. *Brit. Poultry Sci.*, 52: 472–482.
- Zhang J., Lazarenko O.P., Blackburn M.L., Shankar K., Badger T.M., Ronis M.J.J., Chen J.R. (2011 a). Feeding blueberry diets in early life prevent senescence of osteoblasts and bone loss in ovariectomized adult female rats. *Plos One*, 6(9): e24486.
- Zhang X., Zhao L., Cao F., Ahmad H., Wang G., Wang T. (2013). Effects of feeding fermented Ginkgo biloba leaves on small intestinal morphology, absorption, and immunomodulation of early lipopolysaccharide-challenged chicks. *Poultry Sci.*, 92: 119–130.
- Zhang Y.B., Zhong Z.M., Hou G., Jiang H., Chen J.T. (2011 b). Involvement of oxidative stress in age-related bone loss. *J. Surg. Res.*, 169: e37–e42.
- Zhang Y.J., Gan R.Y., Li S., Zhou Y., Li A.N., Xu D.P., Li H.B. (2015). Antioxidant phytochemicals for the prevention and treatment of chronic diseases. *Molecules*, 20: 21138–21156.
- Żary-Sikorska E., Juśkiewicz J., Jundziłł A., Rybka J. (2016). Effect of diets varying in the type of dietary fibre and its combination with polyphenols on gut function, microbial activity and antioxidant status in rats. *J. Anim. Feed Sci.*, 25: 250–258.

Received: 12 II 2021

Accepted: 24 V 2021