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Polyphenol Antioxidants and Bone Health: A Review

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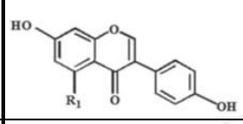
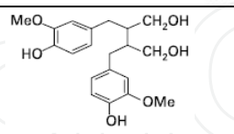
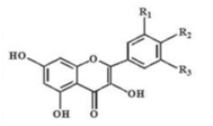
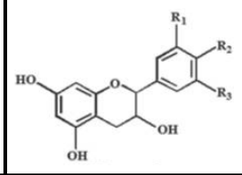
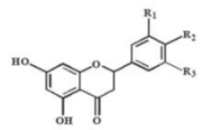
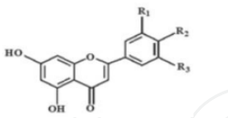
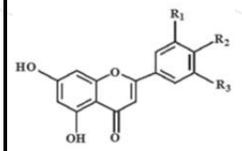
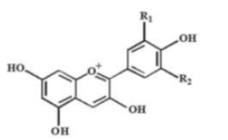
1. Introduction

Osteoporosis is a skeletal disease characterized by bone loss and structural deterioration of the bone tissue, leading to an increase in bone fragility and susceptibility to fractures, most frequently in the hip, wrist and spine (Sendur *et al.,* 2009). Bone loss is associated with such factors as age, menopause in women, smoking, alcohol excess, calcium and vitamin D deficiency, low weight and muscle mass, anticonvulsant and corticosteroid use as well as certain co-morbid conditions such as rheumatoid arthritis (Javaid *et al.,* 2008). Worldwide, it has been estimated that fractures caused by osteoporosis account for approximately one in three among women and approximately one in five among men over the age of 50. Although the mechanisms underlying osteoporosis are not fully understood, there is evidence suggesting that oxidative stress caused by reactive oxygen species (ROS) is associated with its pathogenesis (Sahnoun *et al.,* 1997; Basu *et al.,* 2001; Rao *et al.,* 2007).

Oxidative stress is a condition that can be characterized by an imbalance of pro-oxidants and antioxidants with the scale being tipped towards an excess of pro-oxidants, creating abnormally high concentrations of ROS. ROS are a family of highly reactive, oxygen-containing molecules and free radicals, including hydroxyl (OH ·–) and superoxide radicals (O2 ·–), hydrogen peroxide (H_2O_2), singlet oxygen, and lipid peroxides (Jurának and Bezek, 2005). Several recent studies reported the impact of oxidative stress on osteoclast differentiation as well as on its function resulting to an increase in bone resorption (Garrett *et al.,* 1990; Bax *et al.,* 1992; Mody *et al.,* 2001; Lean, 2003). Furthermore, recent *in vitro* studies have shown the important detrimental role of ROS on osteoblast activity (Park *et al.,* 2005; Bai *et al.,* 2004; Bai *et al.,* 2005). In addition to *in vitro* and animal models, there is also increasing clinical evidence that oxidative stress might be involved in the pathogenesis of osteoporosis (Melhus *et al.,* 1999; Sontakke & Tare., 2002; Basu *et al.,* 2001; Maggio *et al.,* 2003).

Antioxidants are known to mitigate the damaging effects of oxidative stress on cells. Epidemiological evidence has indicated a link between dietary intake of antioxidants and bone health. Fruits and vegetables are important sources of antioxidant phytochemicals that have been shown to play an important role in bone metabolism. Higher consumption of fruits and vegetables has been correlated with a reduction in the risk for the development of osteoporosis. (Arikan *et al.,* 2011; Prentice *et al.*, 2006; Macdonald *et al.,* 2004; Macdonald *et al.,* 2008; Palacios *et al.,* 2006; Tucker *et al.,* 1999; Lister *et al.,* 2007; New, 2003; Trzeciakiewicz *et al.,* 2009).

Category	Subclass	Structure	Common Flavonoid	Food Examples
Phenolic acids	Hydroxycinnamic acids		Caffeic acid	coffee beans
	Hydroxybenzoic acids		Gallic acid	gallnuts, sumac, witch hazel, tea leaves, oak bark,
Flavonoids	Anthocyanidins		Cyanidin	berries, purple cabbage, beets, grape seed extract, and red wine
	Flavanols		Catechins	white, green and black teas
			Theaflavins	black teas
			Proanthocyanidins	chocolate, fruits and vegetables, red wine, onion, apple skin
	Flavanones		Hesperidin	citrus fruits
			Narigenin	citrus fruits
			Silybin	blessed milk thistle
	Flavonols		Quercetin	red and yellow onions, tea, wine, apples, cranberries, buckwheat, beans
	Flavones		Apigenin	chamomile, celery, parsley
			Tangeritin	tangerine and other citrus peels
			Luteolin	celery, thyme, green pepers,
	Isoflavones		Genistein	soy, alfalfa sprouts, red clover, chickpeas, peanuts, other legumes.

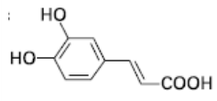
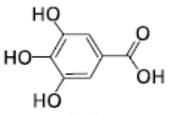
Stilbenes			Resveratrol	gapes skins, red wine
Lignans			Secoisolaiciresinol	flaxseeds

Table 1. The different categories of polyphenols, their chemical structures and sources

Of particular interest among the antioxidant phytochemicals present in fruits and vegetables are the polyphenols. Polyphenols can be sub classified as non-flavonoids and flavonoids. Ellagic acid and stilbenes are among the major non-flavonoid polyphenols. Included in the flavonoid polyphenols are the anthocyanins, catechins, flavones, flavonols and isoflavones. The different categories of polyphenols, their chemical structures and sources are shown in Table 1.

Numerous studies have shown the health-promoting properties of polyphenols, providing additional mechanisms through which they promote skeletal health by reducing resorption caused by high oxidative stress (Trzeciakiewicz *et al.,* 2009; Tucker, 2009; Hunter *et al.,* 2008). The antioxidant properties of polyphenols have been widely studied and reported in the literature (Liu *et al.*, 2005; Miyamoto *et al.*,1998; Rassi *et al.*, 2002; Viereck *et al.*, 2002; Ward *et al.*, 2001; Shen *et al.*, 2011; Rao *et al.*, 2007). They strongly support the role of polyphenols in the delayed onset or reduction in the progression of osteoporosis. The protective effects of polyphenols against diseases, including osteoporosis, have generated new expectations for improvements in health. This review will focus mainly on the role of polyphenols in osteoporosis and present results of studies undertaken in our laboratory.

2. Oxidative stress, antioxidants and osteoporosis

Oxidative stress occurs when the production of free radicals through a number of cellular events exceeds the ability of the cell's antioxidant defense to eliminate these oxidants (Baek *et al.,* 2010). These free radicals have the ability to change the integrity of, and thus, damage several biomolecules, such as DNA, proteins and lipids (Baek *et al.,* 2010). There is increasing evidence that oxidative stress is responsible for the pathophysiology of the aging process and may also be involved in the pathogenesis of atherosclerosis, neurodegenerative diseases, cancer, and diabetes. Recently, ROS were shown to be responsible for the development of osteoporosis (Sahnoun *et al.,* 1997; Basu *et al.,* 2001; Rao *et al.,* 2007; Altindag *et al.*, 2008; Becker, 2006; Feng & McDonald, 2011). Several *in vitro* and animal studies have shown that oxidative stress diminishes the level of bone formation by reducing the differentiation and survival of osteoblasts (Baek *et al.,* 2010). Furthermore, it has been reported that ROS activate osteoclasts and thus, enhance bone resorption (Baek *et al.,* 2010). The presence of ROS in osteoclasts was also demonstrated by Rao *et al.* in 2003 Recent evidences from a few clinical studies have also revealed that ROS and/or antioxidant systems might play a role in the pathogenesis of bone loss (Rao *et al.,* 2007; Mackinnon *et al.,* 2010; Abdollahi *et al.,* 2005).

A number of studies have shown that antioxidants have a fundamental role in preventing postmenopausal osteoporosis. For instance, estrogens, whose antioxidant activity is essential in protecting women of reproductive age from cardiovascular disease, stimulate osteoblastic activity through specific receptors, thus favouring bone growth (Banfi *et al.,* 2008). Antioxidant deficiency has been shown to have adverse effect on bone mass (Maggio *et al.* 2003).

Antioxidant enzymes are regarded as the markers of antioxidant defense mechanism against bone resorption. Several studies have investigated the relationship between antioxidant enzymes such as glutathione peroxidase (GP_x) and catalase (CAT) and osteoporosis (MacKinnon *et al.,* 2011; Hahn *et al.,* 2008; Maggio *et al., 2003;* Sontakke & Tare, *2002*).

Recently, many dietary antioxidant nutrients have also been reported to decrease the oxidative stress that takes part in bone-resorptive processes (Rao *et al.*, 2007; Weber, 2001; Peters & Martini, 2010; Macdonald *et al.,* 2004). In addition to the antioxidant enzymes and nutrients, studies have also been directed towards the role of antioxidant phytochemicals such as the carotenoids in osteoporosis which will not be covered here, but has previously been reviewed (Rao & Rao, 2007; Sahni *et al., 2009;* Tucker, *2009*).

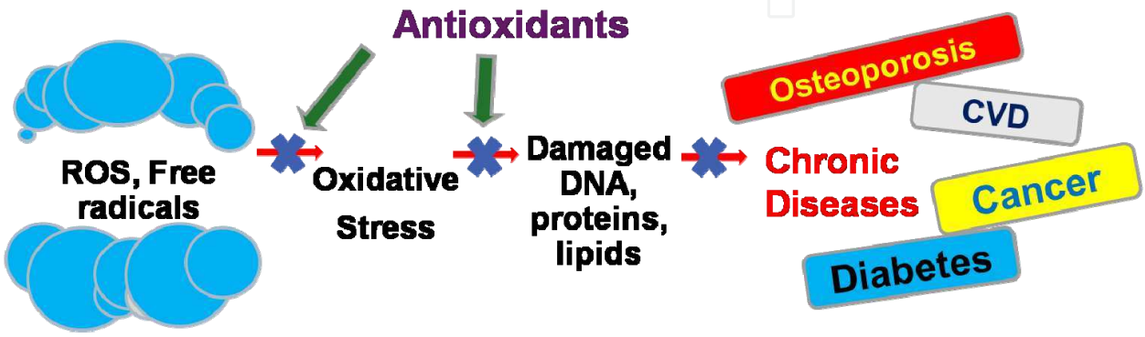


Fig. 1. The role of oxidative stress in osteoporosis and how/where antioxidants play a role in mitigating ROS

3. Natural phytochemical antioxidants

Within the last decade, there has been an increased interest on polyphenols as a result of the *in vitro* evidence demonstrating that they may have numerous benefits to human health, mainly due to their antioxidative and free radical quenching properties (Hendrich, 2006; Lotito & Frei 2006; Heinonen, 2007; Stevenson & Hurst 2007; Aron & Kennedy 2008; Lopez-Lazaro, 2009; Saura-Calixto *et al.* 2007). It is therefore hypothesized that polyphenols may aid in the prevention of aging-associated diseases, particularly cardiovascular diseases, cancers, and osteoporosis.

Polyphenolic compounds are the products of the secondary metabolism of plant and are an essential part of human diet (Goldberg, 2003; Stevenson & Hurst 2007; D'Archivio *et al.*, 2007; Saura-Calixto *et al.* 2007). To date, more than 8,000 polyphenols that have one common structural feature have been identified, a phenol, which is an aromatic ring possessing at least one hydroxyl substituent (Hendrich, 2006; Scalbert & Williamson, 2000; Harborne, 1993). The main classes of polyphenols include phenolic acids, flavonoids, stilbene, and lignans (Spencer *et al.*, 2008; D'Archivio *et al.*, 2007). Figure 1 illustrates the different groups of polyphenols, the chemical structures and food sources. Their total dietary intake can range up to 1 gram/day, which is considerably higher than that of all other classes of phytochemicals (Velioglu *et al.*, 1998). There is much evidence demonstrating that polyphenols improve the status of different oxidative stress biomarkers. However, there is uncertainty regarding both the relevance of these biomarkers as predictors of disease risk and the appropriateness of the different methods used.

Polyphenol Class	Reference	Principal polyphenol	Model	Main findings
Phenolic Acids	Papoutsi et al., (2008)	Ellagic acid (10-100nM)	KS483	↑ nodule formation
	Ayoub et al., (2009)	3-methoxyellagic acid (25ug/ml)	HOS58 & SaOS-2	↑ mineralization of bone cell
Flavonoids	Zhang et al. (2009)	Naringin	bone mesenchymal stem cells (BMSCs)	Dose-specific (1–100 μg/ml) of the naringin solution may enhance the proliferation and osteogenic differentiation of human BMSCs
	Choi (2007)	Apigenin	MC3T3-E1 cells	Apigenin (0.01 mM) increased the growth of MC3T3-E1 cells and caused a significant elevation of alkaline phosphatase (ALP) activity and collagen content in the cells
	Kim et al. (2011)	Luteolin	Bone marrow cells were prepared by removing from the femora and tibiae of ICR mice	luteolin decreased differentiation of both bone marrow mononuclear cells and Raw264.7 cells into osteoclasts, inhibited the bone resorptive activity of differentiated osteoclasts.
	Choi (2011)	Kaempferol	MC3T3-E1 cells	induced the activation of PI3K (phosphoinositide 3-kinase), Akt (protein kinase B), and CREB (cAMP-response element-binding protein). This may prevent or reduce degerneration of osteoblasts
	Wattel et al. (2004)	Quercetin	RAW 264.7 cells, peripheral blood monocytic cells (PBMC)	Quercetin (0.1–10 mM) decreased osteoclastogenesis in a dose dependent manner in both models with significant effects observed at low concentrations, from 1 to 5 mM
Isoflavones	Sugimoto & Yamaguchi (2000)	Daidzein	MC3T3-E1 cells	increase alkaline phosphatase activity
	Rassi et al. (2002)	Daidzein	osteoclasts from young female piglets	inhibits development of osteoclasts from cultures of porcine bone marrow and reduces bone resorption
	Viereck et al. (2002)	Genistein	mature human osteoblasts (hOB)	up-regulated OPG production 2–6-fold in a time- and dose-dependent manner, neutralizing RANKL
Lignans	Hasegawa et al. (2010)	Honokiol	bone marrow cells of 6wk old mice	Inhibits osteoclast differentiation by suppressing the activation of MAPKs (p38 MAPK, ERK and JNK)
Stilbenes	Chang et al. (2006)	Piceatannol	immortalized fetal osteoblasts (hFOB), and osteosarcoma cells (MG-63)	piceatannol increased BMP-2 synthesis, induced osteoblasts maturation and differentiation
	Kupisiewicz et al. (2010)	Modified resveratrol analogues	Myeloma cell lines U266 and OPM-2	Resveratrol analogues showed an up to 5,000-fold increased potency to inhibit osteoclast differentiation and promoted osteoblast maturation compared to resveratrol.

Table 2. Polyphenols- *In vitro* studies

4. Polyphenols and osteoporosis

There has been an increase interest in the field of bone health and nutrients, and within the last decade, it has been well recognized that some polyphenols, whether ingested as supplements or with food, do in fact improve bone health status. Currently, most of the research on polyphenols and their effects has emerged from *in vitro* and *in vivo* studies with only a few clinical studies available. Compounds present in fruits and vegetables influence bone health as shown with *in vitro* osteoblast cell culture. On the other hand, epidemiologic studies tend to have mixed results with regards to the protective effects of polyphenol consumption against osteoporosis. Tables 2, 3, and 4 illustrate some of the recent *in vitro, in vivo* and clinical studies that have been reported in the literature, respectively.

Polyphenol Class	Reference	Substance given	Principal polyphenol	Model	Dose per day	Main findings
Phenolic Acids	Chen (2010)	Blueberries	Phenolic acid mixture	Sprague-Dawley rats		Increase serum osteoblast progenitors, increased osteoblast differentiation, reduced osteoclastogenesis, increase bone mass
	Zych et al. (2010)		Ferulic,caffeic, *p*-coumaric, chlorogenic, clohexanecarboxylic acid	Wistar Cmd:(WI)WU rats	10 mg/kg p.o.	caffeic acid worsened bone mechanical properties
	Folwarczna et al. (2010)		Curcumin	Wistar Cmd:(WI)WU rats	10 mg/kg, po	no sig. improvement of bone mineralizasation or mechanical properties
	Folwarczna et al. (2009)		Caffeic, *p*-coumaric, chlorogenic acid	Wistar Cmd:(WI)WU rats	10 mg/kg p.o.	caffeic acid ↓ bone mass, p-coumaric acid ↑ bone mass/body mass ratio and bone mineral mass/body mass ratio in long bones
Flavonoids	Devareddy et al. (2008)	Blueberries	Variety of phenolic acids and flavonols	OVX rat	5% w/w	Ovx resulted in loss of whole-body, tibial, femoral, and 4th lumbar BMD by approximately 6%. Blueberry treatment was able to prevent the loss of whole-body BMD and had an intermediary effect on prevention of tibial and femoral BMD
	Arjmandi et al. (2010)	(1) 2% Fructooligosaccharides (FOS); 5% FOS+7.5% DP; 2% FOS+5% DP; 2% FOS+2% DP	Variety	OVX rat		diet of 5% FOS + 7.5% dried plum was most effective in reversing both right femur and fourth lumbar BMD and fourth lumbar

	polyphenol (equivalent to 7.5% DP powder); (5) 2% FOS+7.5% DP juice; (6) 2% FOS+7.5% DP puree; (7) 2% FOS+7.5% DP pulp skins; (8) 2% FOS+7.5% raisin; (9) 2% FOS+7.5% fig; (10) 2% FOS+7.5% date; (11) 2% FOS+7.5% blueberry; (12) 2% FOS+0.25% HMB; and (13) 0.25% HMB.				calcium loss while significantly decreasing trabecular separation. No significant effects of treatment on serum or urine measures of bone turnover.
Shen et al. (2008)	Green tea polyphenols (GTP)	(-)Epigallocatechin gallate	OVX rat	0.1% or 0.5% concentration of GTP in drinking water	GTP supplementation increased urinary epigallocatechin and epicatechin concentrations, femur BMD, decreased urinary 8-hydroxy-2′-deoxyguanosine and urinary calcium levels; no effect on serum estradiol
Shen et al. (2010)	Green tea polyphenols (GTP)	(-)Epigallocatechin gallate	40 female CD rats	0.5% concentration of GTP in drinking water	GTP supplementation increased urinary epigallocatechin and epicatechin concentrations and showed higher values for femur BMC, BMD and serum OC, but lower values for serum TRAP, urinary 8-OHdG and spleen mRNA expression of TNF-α and COX-2 levels.
Shen et al. (2011)	Green tea polyphenols (GTP)	(-)Epigallocatechin gallate	50 OVX	0.5% concentration of GTP in drinking water	GTP supplementation resulted in increased serum osteocalcin concentrations, bone mineral density, and trabecular volume, number, and strength of femur; increased trabecular volume and thickness and bone formation in both the proximal tibia and periosteal tibial shaft
Das et al. (2005)	Black tea extract	Theaflavin	Bilaterally oophorecto	2.5% aqueous	BTE increase serum estradiol level

				mized rats	BTE at a single dose of 1 ml /100 g body weight	
	Chiba et al. (2003)	hesperidin & α-glucosylhesperidin	Hesperidin & α-glucosylhesperidin	OVX mice	0.5 g/100 g hesperidin, 0.7 g/100 g α-glucosylhesperidin	hesperidin or α-glucosylhesperidin restored BMD caused by OVX, α-glucosylhesperidin significantly prevented loss of trabecular bone volume and trabecular thickness in the femoral distal metaphysis
	Park et al. (2008)	apigenin	Apigenin	OVX rats	10 mg/kg	apigenin increased the mineral content and density of the trabecular bone at the neck of the left femur, decreased body weight and dietary consumption
	Kim et al. (2011)	luteolin	Luteolin	OVX mice	5 and 20 mg/kg	luteolin increased bone mineral density and bone mineral content of trabecular and cortical bones in the femur as compared to those of OVX controls
	Do et al. (2008)	Rubus coreanus	Anthocyanin	OVX rats	100 & 200 mg/kg	RCM increased femur trabecular bone area in a dose-dependent manner in ovariectomized rats, increased osteoblast differentiation and osteoclast apoptosis.
	Horcajada-Molteni et al. (2000)	Rutin	Rutin	OVX rats	2.5 g/kg	Rutin prevented decrease in both total and distal metaphyseal femoral mineral density by slowing down resorption and increasing osteoblastic activity caused by OVX,
Isoflavones	Arjmandi et al. (1998)	Soy protein	Genistein	72 OVX rats	1462 mg/kg genistein, 25.1 mg/kg daidzin, 11.3 mg/kg daidzein	no effect on BMC
	Lee et al. (2004)	Soybean	Glycitein	24 OVX rats	6.25 g/kg	soybean isoflavone appear to prevent bone loss in femur and lumber vertebrae via a

						different mechanism of estrogen
	Miyamoto et al (1998)	8-isopentenylnaringenin	8-isopentenylnaringenin	OVX rats	30 mg/day	8-isopentenyl naringenin prevented decrease in BMD and bone turnover markers
Lignans	Xiao et al. (2011)	Sambucus williamsii HANCE (SWH)	Lignans	56 OVX/6J specific-pathogen-free (SPF) female mice	17b-oestradiol (3·2 mg/kg), SWH (60% ethanol crude extract; 1·0 g/kg), SWA (water eluate; 0·570 g/kg), SWB (30% ethanol eluate; 0·128 g/kg) or SWC (50 and 95% ethanol eluates; 0·189 g/kg)	SWC significantly restored bone mineral density and improved bone size and bone content in femur and tibia
	El-Shitany et al. (2010)	Silymarin	Silymarin	OVX rats	50 mg/kg	protected trabecula thickness, decreased serum levels of ALP and increased serum levels of both calcium and phosphorus
	Ward et al. (2001)	Flaxseed	Secoisolariciresinol diglucoside	20 Sprague-Dawley male rats	293 µmol SDG/kg	exposure to a diet with flaxseed during lactation through to early adolescence can reduce bone strength, but lignan does is not the mediator, no sig. change in BMD and BMC those fed flaxseed
Stilbenes	Pearson et al. (2008)	Resveratrol	Resveratrol	Male C57BL/6NIA mice	100 mg/kg or 400 mg/kg	Both diets improved distal trabecular tissue mineral density (TMD) and bone volume to total volume ratio over the entire femur compared to control
	Liu et al. (2005)	*trans-Resveratrol*	Resveratrol	OVX rat	0.7 mg/kg	epiphysis BMD and bone calcium content was significantly greater with resveratrol treatment than that in the OVX group, no differences in femoral midpoint BMD

Table 3. Polyphenols- *In vivo* Studies

Polyphenol Class	Reference	Substance given	Principal polyphenol	Model	Dose per day	Main findings
Flavonoids	Hardcastle et al. (2011)	None	Catechin	perimenopausal Scottish women		flavanones were negatively associated with bone-resorption markers, association between energy-adjusted total flavonoid intakes and BMD at the femoreal neck and lumbar spine, annual percent change in BMD was associated with intakes of procyanidins and catechins
Isoflavones	Chen et al. (2004)	Soy isoflavone	Daizein	203 postmenopausal women	placebo: 0 mg isoflavones + 500 mg calcium, mid-dose:40 mg isoflavones+ 500 mg calcium, high-dose:80 mg isoflavones + 500 mg calcium	no effect on BMD in all groups, effect of soy isoflavones on BMC at the total hip and trochanter was less strong in women in early menopause or in those with higher body weight, nonsignificantin BMC in those with a high level of dietary calcium intake
	Arjmandi et al. (2005)	Soy protein	Daizein	87 postmenopausal women	25 g protein and 60 mg isoflavones	Whole body and lumbar BMD and BMC significantly decreased, and BSAP and osteocalcin increasedin control and soy groups
	Kenny et al. (2009)	Soy protein + isoflavone tablets	Isoflavones	131 postmenopausal women >65 years old	18 g soy protein and 105 mg isoflavone tablets	no differences in BMD
Lignans	Cornish et al. (2009)	Flaxseed	Secoisolariciresinol diglucoside	50 men, 50 postmenopausal women		no effect on BMD
	Dodin et al. (2005)	Flaxseed	Secoisolariciresinol diglucoside	199 menopausal women		no sig. change in BMD

Table 4. Polyphenols - Clinical Studies

There have been several results suggesting that the combination of polyphenolic compounds found naturally in fruits and vegetables may reduce the risk of osteoporosis via increasing bone mineral density (Wu *et al.*, 2002; Morton *et al.*, 2001; Melhus *et al.*, 1999; Leveille *et al.*, 1997; Singh, 1992). In 1992, Singh was able to show that polyphenols afford protection against oxidative stress-induced bone damage during strenuous exercise. Similarly, Melhus was able to show its counteractive effect of polyphenols among smokers (Melhus *et al.*, 1999).

5. Research results on the role of polyphenols in osteoporosis from the author's laboratory

Previous *in vitro* results from our laboratory have shown that a supplement rich in a variety of polyphenols commercially known as greens+*TM*, is more effective in stimulating

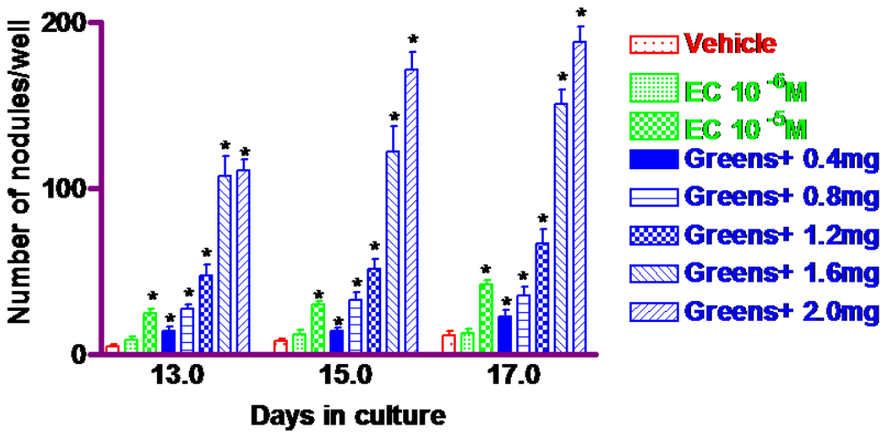


Fig. 2. Dose dependent effect of greens+*TM* (g+) and epicatechin (EC) compared to vehicle. ($p<0.05$)

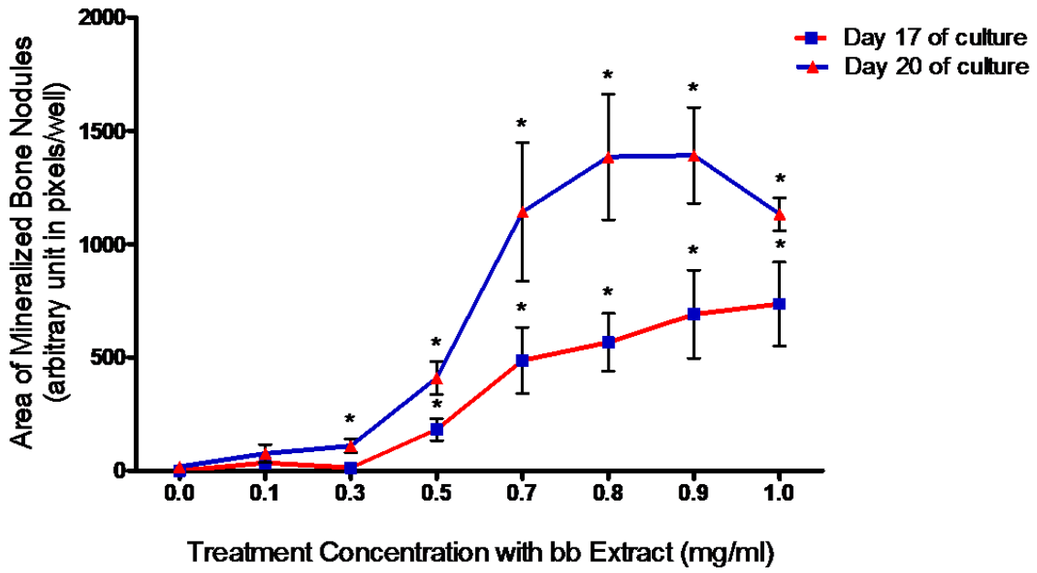


Fig. 3. Time and dose-dependent effects of bone builder*TM* on mineralized bone nodule area in Sa0S-2 cells ($p< 0.05$).

osteoblasts to form more bone nhodules in a dose-dependant manner than epicatechin, the main polyphenol found in green tea (Fig. 2). Our laboratory also studied the effects of a second supplement, bone builder*TM*, which is rich in minerals, vitamins and nutrients. Similarly to the greens+*TM*, the water-soluble bone-builder extract had a significant dose-dependent stimulatory effect on bone nodules formation (Fig. 3). Figure 4 shows that when the two supplements, greens+*TM* and bone builder*TM*, were tested as combination, the effects were six times more effective than either one alone. This led us to believe that synergistic effects of greens+*TM* and bone builder*TM* may have a beneficial effect on osteoporosis. We then conducted a clinical evaluation of this nutritional supplement greens+ bone builder*TM* Results have shown that there was an increase in total antioxidant capacity after 8 weeks of treatment compared to placebo (Fig 4). as well as a decrease in both lipid and protein oxidation over a 4 and 8-weeks of intervention with greens+ bone builder*TM* compared to placebo (Fig. 6 & 7). This suggests that the nutritional supplement may have a beneficial effect on bone health by mitigating the effects of oxidative stress.

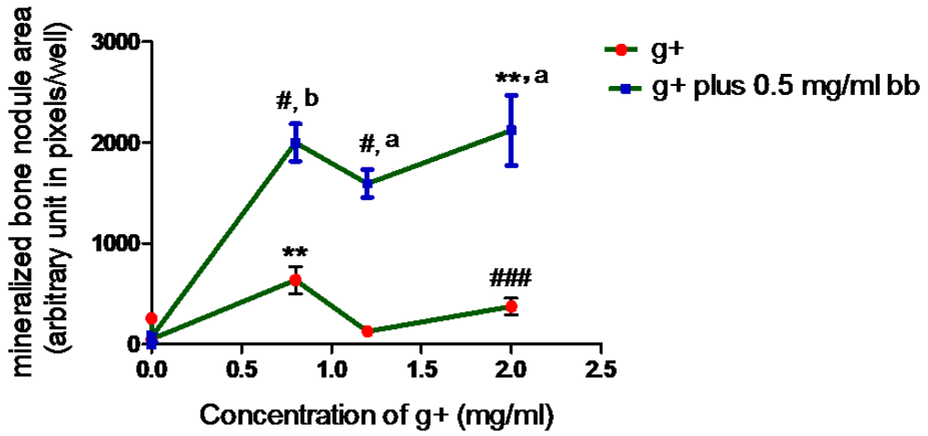


Fig. 4. Dose Dependent Effect of greens + (g+) with and without 0.5 mg/ml of bone builder (bb) on the area of mineralized bone nodules in osteoblasts Sa0S-2 Cells. * p<0.0005, **p<0.005; ***p<0.05; # p<0.0001; ## p<0.001; ### p<0.01; significance differences were found when treatment with g+ plus 0.5 mg/ml bb was compared to treatment with g+ alone as follows: $^{a\backslash b}$< 0.0001; ^{b}p< 0.005

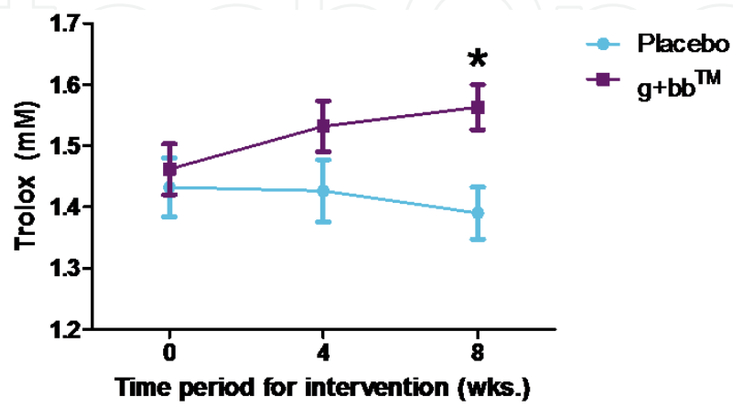


Fig. 5. The effect of nutritional intervention with g+bb™ compared to placebo on serum total antioxidant capacity (p<0.05).

Fig. 6. Change in TBARS over 4 and 8-weeks of nutritional intervention with g+bb™ compared to placebo ($p<0.001$).

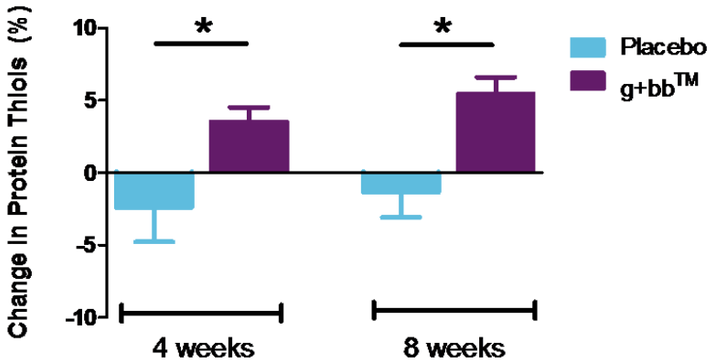


Fig. 7. Change in protein oxidation over 4 and 8-weeks of nutritional intervention with g+bb™ compared to placebo ($p<0.05$).

6. Conclusions

Although epidemiologic studies are practical for the evaluation of human health effects on the physiologic concentrations of polyphenols, reliable data on polyphenol contents of foods are limited. This review has shown that polyphenols or polyphenol-rich diets can provide significant protection or treatment for the development and progression of osteoporosis. Keeping in mind that many nutrients are co-dependent, and they may interact among themselves and others. The complexity of these interactions may possibly be the reason why many studies show controversial or inconsistent results regarding the effects of a single nutrient or groups of nutrients in bone health. Based on current knowledge, polyphenols offer a platform for the prevention of many human chronic diseases involved with oxidative stress, including osteoporosis.

To value the actual significance of food phenolics, it is necessary to investigate not only their bioavailability, but also their mechanisms of action and their possible synergism with other constituents either in the diet or within the human body, as well as the polyphenolic content and composition of foods. We have attained this goal by studying the nutritional supplement greens+*TM*, which is rich in polyphenols and their interactions with minerals, vitamins and nutrients that were present in the nutritional supplement bone builder*TM*.

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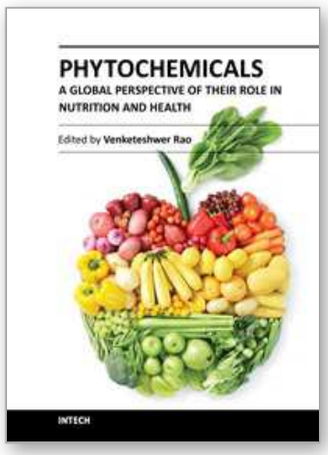

Phytochemicals - A Global Perspective of Their Role in Nutrition and Health

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Phytochemicals are biologically active compounds present in plants used for food and medicine. A great deal of interest has been generated recently in the isolation, characterization and biological activity of these phytochemicals. This book is in response to the need for more current and global scope of phytochemicals. It contains chapters written by internationally recognized authors. The topics covered in the book range from their occurrence, chemical and physical characteristics, analytical procedures, biological activity, safety and industrial applications. The book has been planned to meet the needs of the researchers, health professionals, government regulatory agencies and industries. This book will serve as a standard reference book in this important and fast growing area of phytochemicals, human nutrition and health.

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