CHAPTER 32

Osteoporosis Treatment: Marine Algal Compounds

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Contents

Abstract

Osteoporosis is one of the most common bone diseases that occur due to imbalance during bone formation and bone resorption. About half of all women over the age of 50 will have a fracture on the hip, wrist, or vertebra. Research and treatment of osteoporosis are challenging for researchers and physicians. There are several types of treatments for osteoporosis including most famous bisphosphonates, estrogen agonists/antagonists, parathyroid hormone, estrogen therapy, hormone therapy, and recently developed RANKL inhibition. In the recent days, much attention has been paid for marine algal extracts and compounds for osteoporosis treatment. In this chapter, we extensively deal with marine algae compounds and their rich mineral constituents for osteoporosis treatment.

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I. INTRODUCTION

Bone is made up of seven hierarchical structures and consists of hydroxyapatite and collagen as major constituents (Venkatesan and Kim, 2010a,b; Venkatesan *et al*., 2011a,b; Weiner and Wagner, 1998). Defects in bone can occur due to many reasons such as motor accident, birth defect, osteoporosis, arthritis, bone gangrene, and low calcium level. Among this, osteoporosis is one of the most common bone diseases that occur due to imbalance of bone formation and bone resorption. Osteoporosis disease mainly occurs in woman rather than man at an elderly age (around 50–60) in the hip, wrist, and vertebral area. In bone, there are four kinds of cells which are playing most important function for bone remodeling. They are

Osteoblast	Bone formation
Osteoclasts	Bone resorption
Osteocytes	A mature osteoblast which no longer secretes matrix
Osteoprogenitor	Immature cells which differentiate to make osteoblasts

Osteoblast and osteoclast cells are responsible for bone formation and resorption, respectively. Calcium and phosphate are the two minerals that are essential for normal bone formation. Osteoblasts secrete a calcifiable matrix which contains minerals, collagen, and also small amount of noncollagenous proteins including osteopontin, osteonectin, bone sialoprotein, and osteocalcin (Gay *et al*., 2000). The function of osteoclast is to remove bone tissue by removal of its mineralized matrix and breaking up the organic bone (90% collagen). An increase in the number of osteoclast cells and their function normally induces bone osteoporosis, indicating that osteoclast plays a pivotal role in bone homeostasis (Miyamoto and Suda, 2003).

Cancellous bones are soft and present in the inner side of bone, whereas cartial bones are hard and found in the outer area of bone. Cancellous bone is normally found in hips, vertebral column, and wrist. Owing to an improper function of osteoclasts and osteoblasts, cancellous bones are more easily affected rather than cortical bone, which in turn results in osteoporosis (Watson, 1979).

II. TREATMENT FOR OSTEOPOROSIS

The goals of osteoporosis treatment are to control pain from the disease, reduce bone loss, and prevent bone fractures with medicines or hormone therapies. There are several types of treatments for osteoporosis including most famous bisphosphonates, estrogen agonists/antagonists, parathyroid

hormone, hormone therapy, and recently developed receptor activator of nuclear factor-κB ligand (RANKL) inhibition. Estrogen agonists/antagonists in combination with estrogen for prevention and treatment of osteoporosis have also been studied (Stovall and Pinkerton, 2008). Bazedoxifene for the prevention of postmenopausal osteoporosis (Gennari *et al.*, 2008), parathyroid hormone (Black *et al.*, 2003; Finkelstein *et al.*, 2003; Horwitz *et al.*, 2010; Neer *et al.*, 2001), estrogen therapy (Eskridge *et al.*, 2010; Genant *et al.*, 1997; Lindsay, 1987; Lindsay and Tohme, 1990), hormone therapy (Engel *et al.*, 2011; Pentti *et al.*, 2009), and recently developed RANKL inhibitory (McClung, 2006, 2007) treatment options are currently available for osteoporosis treatment.

Among this bisphosphonates are the primary drugs used to both prevent and treat osteoporosis in postmenopausal women. Bisphosphonates taken orally, once a week or once a month, include alendronate (Fosamax), ibandronate (Boniva), and risedronate (Actonel). Bisphosphonates given through a vein (intravenously) are taken less often (Gass and Dawson-Hughes, 2006; Recker *et al.*, 2009; Society, 2003). Bisphosphonates inhibit bone resorption and are therapeutically effective in diseases of increased bone turnover, such as Paget's disease and hypercalcemia of malignancy (Hughes *et al.*, 1995). In the recent years, a number of research articles have been published related to the treatment of osteoporosis (Barzel, 1988; Hodsman *et al.*, 2005; Njeh *et al.*, 1997; Pfeifer *et al.*, 2004; Prestwood *et al.*, 1995; Rubin and Bilezikian, 2003).

The adverse side effects of bisphosphonates are renal toxicity, acute-phase reactions, gastrointestinal toxicity, hypocalcemia, ocular complications, asthma erythema, phlebitis, altered taste, and central nervous system side effects. The osteonecrosis of the jaw is the emerging one (Diel *et al.*, 2007; Tanvetyanon and Stiff, 2006). To overcome this kind of problem, researchers are now turning toward nature-based drugs.

III. MARINE ALGAE

Marine algae are generally known as sea weeds; they contain abundant active compounds. There are commonly found in seashore area in all shapes and classified into three different kinds which are red, green, and brown algae as protists, chromists, and plantae, respectively (Hedgpeth, 1957).

In the recent years, significant development has been paid in the isolation of active compounds from marine algae for various disease treatments such as anticancer (Kim *et al.*, 2010), anti-inflammation (Kim *et al.*, 2009; Zhang *et al.*, 2010), antioxidant (Li *et al.*, 2009a), α-glycosidase and α-amylase inhibitory activities (Lee *et al.*, 2009), matrix metalloproteinase (Li *et al.*, 2009b; Ryu *et al.*, 2009b), and inhibitory effect of ROS generation (Kang *et al.*, 2004).

IV. MARINE COMPOUND FOR OSTEOPOROSIS

A. Bone mineral density

Bone mineral density (BMD) level of people living in arctic and subarctic regions is lower than that of Europeans and American Whites; this has been linked to high meat diets, as a protein-rich diet may cause calcium loss (Lynnerup and Von Wowern, 1997). The BMD can alter based upon age (Maugeri *et al*., 2001). The habitual dietary pattern of a population has major influence on the prevalence and incidence of arteriosclerotic vascular disease (Brown, 1990). The insufficient dietary calcium is associated with a number of common and chronic diseases worldwide including osteoporosis, osteoarthritis, cardiovascular disease (hypertension and stroke), diabetes, obesity, and cancer (Kim and Mendis, 2006).

B. Rich mineral extracts of marine algae

Marine alga not only consists of organic active compounds, but it is also an abundant source of rich minerals such as calcium, magnesium, and other bone-supporting elements (Adluri *et al*., 2010; Kim *et al*., 2006). Mineral-rich extracts have been isolated from red marine algae *Lithothamnion calcareum* and checked as a dietary supplement for prevention of bone mineral loss. Female mice on the high-fat Western-style diet had reduced bone mineralization and reduced bone strength relative to female mice on the low-fat chow diet. The bone defects developed in the female mice fed on the high-fat Western-style diet could be reversed in the presence of the mineral-rich algal extract supplement (Aslam *et al*., 2010). The effect of water-soluble extract of *Sargassum horneri* has been shown to have an anabolic effect on bone components due to stimulating bone formation and inhibiting bone resorption in rat femoral tissues *in vitro* and *in vivo* (Matsumoto *et al*., 2008).

The effect of various algae such as *Undaria pinnatifida*, *S. horneri*, *Eisenia bicyclis*, *Cryptonemia scmitziana*, *Gelidium amasii*, and *Ulva pertusa Kjellman* on bone calcification in the femoral-metaphyseal tissues of rats have been studied. As a result, bone calcium content was significantly increased (Yamaguchi *et al*., 2001).

C. Osteoblast differentiation

Marine collagen peptides (MCP) derived from Chum Salmon (*Oncorhynchus keta*) skin were investigated for the development of femurs in growing rats of both sexes (Xu *et al*., 2010).

The modification of chromatin structure thereby regulating gene transcription through histone deacetylases (HDACs) plays important roles in

osteogenesis and is considered to be a promising potential therapeutic target for bone diseases. Largazole (Fig. 32.1A) exhibited *in vitro* and *in vivo* osteogenic activity by HDAC inhibition and significantly induced the expression of alkaline phosphatases, osteopontin expression, and increased expression of Runx2 and BMPs. Largazole showed *in vivo* bone-forming efficacy in the mouse calvarial bone formation assay and the rabbit calvarial bone fracture healing model (Lee *et al.*, 2011).

Norzoanthamine (Fig. 32.1B) is a nontoxic marine alkaloid and its collagen protective activity indicates that it provides significant therapeutic benefits. Norzoanthamine accelerates the formation of a collagen–hydroxyapatite composite and enhances collagen release from an immobilized matrix vesicle model. Norzoanthamine recognizes a peptide chain nonspecifically and stabilizes its secondary structure, and collagen has polyvalent binding sites for norzoanthamine. Collagen–norzoanthamine supramolecular association is considered to be one of the most significant modes of action for enhancement of bone formation. Norzoanthamine suppressed the proteolysis not only of collagen but also of elastin and bovine serum albumin, so it apparently has a universal

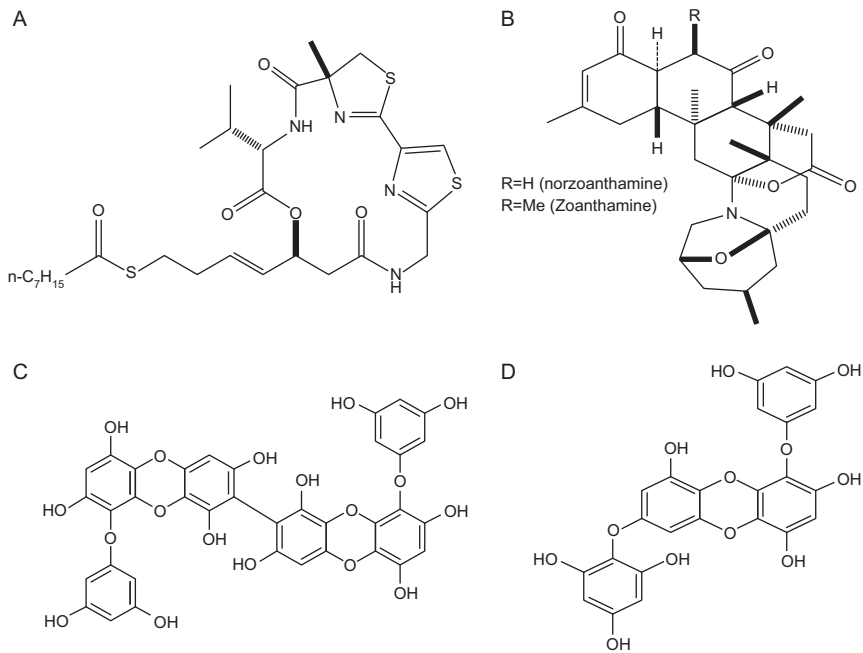

FIGURE 32.1 (A) Largazole, (B) norzoanthamine, (C) dieckol, and (D) 1-(3′,5′-dihydroxyphenoxy)-7-(2″,4″,6″-trihydroxyphenoxy) 2,4,9-trihydroxydibenzo-1,4,-dioxin.

protective effect of guarding extracellular matrix (ECM) proteins from degradation (Hikage *et al*., 1998; Kinugawa *et al*., 2009).

Norzoanthamine has also been isolated from zoanthid *Zoanthus* sp. which suppresses the decrease in bone weight and strength in ovariectomized mice, indicating that it could be a good candidate as an osteoporotic drug (Kuramoto *et al*., 1998).

Arthritis is one of the most prevalent chronic inflammatory diseases, and it is characterized by structural and biochemical changes in major tissues of the joint, including degradation of the cartilage matrix, insufficient synthesis of ECM. *Ecklonia cava* (EC) is a member of the family of Laminariaceae, which is an edible marine brown alga with various bioactivities. The methanol extracts of brown alga EC, the dieckol (Fig. 32.1C) and 1-(3′,5′-dihydroxyphenoxy)-7-(2″,4″,6″-trihydroxyphenoxy) 2,4,9-trihydroxydibenzo-1,4,-dioxin (Fig. 32.1D) have been used for arthritis treatment at *in vitro* level (Ryu *et al*., 2009a).

The effect of the fractionated extracts obtained from *S. horneri* on bone calcium content and osteoclast-like cell formation *in vitro* has also been investigated. The effects of *S. horneri* on bone components in the femoral diaphyseal and metaphyseal tissues of young and aged rats were studied. The oral intake of the water-solubilized *S. horneri* extract significantly altered the bone components of young rats *in vivo* (Uchiyama and Yamaguchi, 2002; Uchiyama *et al*., 2004).

D. Osteoclast differentiation in osteoporosis

An inhibitor of osteoclast differentiation and/or function is expected to be useful for treatment of bone lytic diseases such as osteoporosis, rheumatoid arthritis, and tumor metastasis into bone. Paenol inhibits RANKL-induced osteoclastogenesis by inhibiting ERK, p38, and NF-κB pathway (Tsai *et al*., 2008). Symbioimine (Fig. 32.2A) from the symbiotic marine dinoflagellate *Symbiodinium* sp. exhibits inhibitory effect on osteoclast differentiation (Kita *et al*., 2004).

Biselyngbyaside (Fig. 32.2B) has been isolated from marine cyanobacterium *Lyngbya* sp. and subjected to osteoclast differentiation study. Biselyngbyaside inhibited RANKL-induced osteoclastogenesis in mouse monocytic RAW264 cells and primary bone marrow-derived macrophages at a low concentration (Yonezawa *et al*., 2011). Effects of *Spirulina* algae on bone metabolism in ovariectomized estrogen-deficient rats and hindlimb-unloaded mice have also been examined (Ishimi *et al*., 2006).

The BMD of the whole femur and tibia of ovariectomized rats in any of the *Spirulina*-treated groups was not significantly different from that of the ovariectomized group, although BMD of the distal femur and proximal tibia was significantly lower in the *Spirulina*-treated groups than in the ovariectomized group after a 6-week experimental period (Ishimi *et al*., 2006).

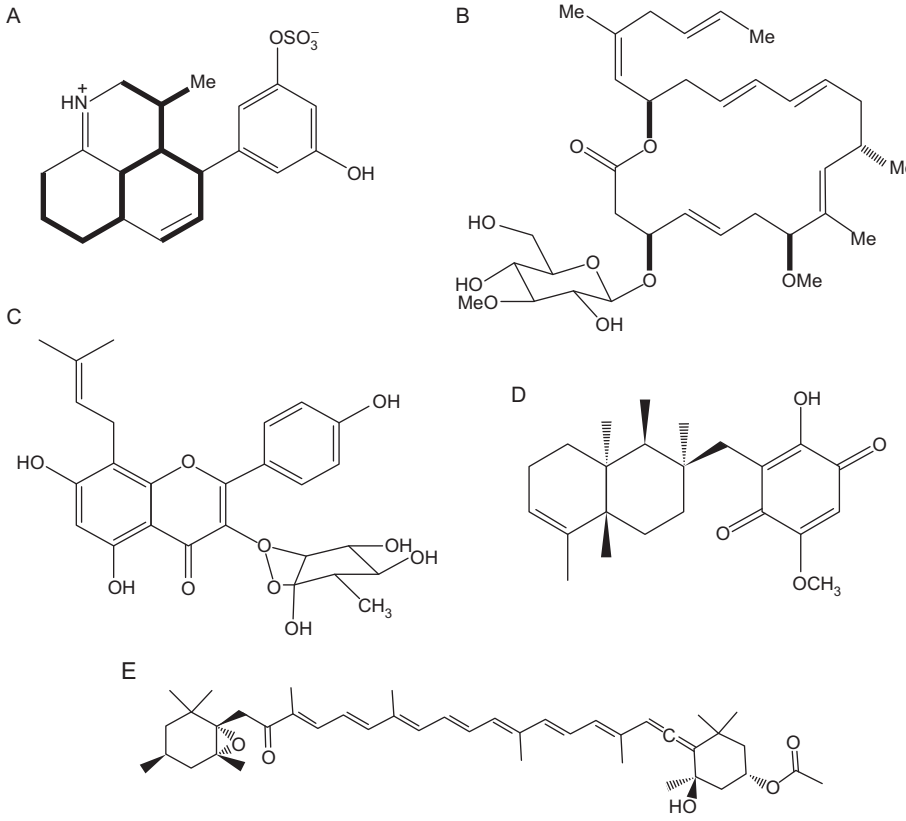

FIGURE 32.2 (A) Symbioimine, (B) biselyngbyaside, (C) ikarisoside A, (D) bolinaquinone, and (E) fucoxanthin.

Inhibition of osteoclastogenic differentiation by ikarisoside A (Fig. 32.2C) in RAW 264.7 cells via JNK and NF-κB signaling pathways have been recently reported (Choi *et al.*, 2010). Lucas *et al.* (2003) studied the modulatory effect of bolinaquinone (Fig. 32.2D), a marine sesquiterpenoid, on acute and chronic inflammatory processes. Fucoxanthin (Fig. 32.2E) that induces apoptosis also induced osteoclast differentiation in a study conducted by Das *et al.* (2010).

V. CONCLUSION

Very few marine compounds have been studied and reported for osteoporosis treatment. Still much research work is needed for further implications. Although synthetic bisphosphonates compounds are more promising for osteoporosis treatment, marine algal extracts and their

compounds are excellent in the biocompatibility without side effects at *in vitro* and *in vivo* condition. Further clinical trials for marine active compounds are considered necessary for their further commercialized implications.

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