ISSN (Print) 1225-9918
ISSN (Online) 2287-3406
Journal of Life Science 2015 Vol. 25. No. 1. 113~120 DOI : http://dx.doi.org/10.5352/JLS.2015.25.1.113

- Review -

Current Medical Therapies for Osteoporosis and Its Alternative Treatments Using Natural Products

Seunghoon Oh[1] and Soon-Cheol Ahn[2,3]*

[1]*Department of Physiology, College of Medicine, Dankook University, Cheonan 330-714, Korea*
[2]*Department of Microbiology and Immunology, Pusan National University School of Medicine, Yangsan 626-870, Korea*
[3]*Immunoregulatory Therapeutics Group in Brain Busan 21 Project, Pusan National University, Yangsan 626-870, Korea*

Received January 22, 2015 / Revised January 27, 2015 / Accepted January 27, 2015

Osteoporosis is a major bone disorder defined as having bone mineral density (BMD) of 2.5 standard deviations or more below the peak bone mass. Osteoporosis will increasingly be a major disorder that faces the aging mankind. It is the result of an imbalance in the bone remodeling system, where bone constantly undergoes a cycle of resorption by osteoclasts and formation by osteoblasts. Estrogen deficiency in women following menopause is identified as the predominant reason that causes disparity in this system. Current medical treatments for osteoporosis include hormone replacement therapy (HRT), biphosphonates, and teriparatide, but have various side effects that raise questions concerning their medical safety and practicality. Alternative treatments involving natural product sources are under study to find a safer therapy. Many natural sources including lactoferrin and isoflavones and numerous traditional herbal medicines exhibit anti-resorptive or anabolic effects on bone and thus show promises to provide therapeutic agents in treating osteoporosis. Unfortunately, the majority of natural product treatments are still in its preliminary stages to prove their efficacy even though the development pace of treatment for osteoporosis is astounding in the past few decades. Further progress in pre-clinical studies and the subsequent clinical studies will someday lead to a breakthrough that takes us another step forward in science.

Key words : Alternative therapy, natural product, osteoblast, osteoclast, osteoporosis

Introduction

Osteoporosis is a bone disease characterized by a decrease in bone mineral density (BMD) and thus the weakening of bone strength. It has been estimated that more than 10 million people suffer from osteoporosis in the United States alone [27]. While osteoporosis is thought to have existed throughout human history, it has only quite recently become a global health issue. Osteoporosis may occur in all of age and ethnic groups; however, osteoporosis is most common in postmenopausal women, as the decrease in estrogen is identified as the main reason for the loss of bone mineral density. Similarly, testosterone deficiency in men is also linked to osteoporosis but its effects are not as pronounced. Many factors may provoke the onset of osteoporosis, including hyperparathyroidism, hyperthyroidism, corticosteroid hormones, lack of vitamin D, with the aforementioned estrogen deficiency playing a critical role [33]. In a study done by the World Health Organization (WHO) on osteoporosis, a direct correlation between the percentage of osteoporotic population and age was reported [48] (Table 1). As new technologies emerge and developments are made in the field of medicine, life expectancy will also increase. With the ever-increasing number of people who reach the advanced age, the osteoporotic population is also expected to rise. Unfortunately, the chemically synthesized medical treatments being used today have various drawbacks that make their use somewhat problematic. Alternative methods involving natural food and plant sources are under research, in hopes of finding a safer treatment with fewer side effects.

In women, the accepted normal value for bone mineral density is within 1 standard deviation below the young adult average, or the peak bone mass. BMD between 1 and 2.5 standard deviations below the peak bone mass is categorized as low bone mass, or osteopenia, and having BMD 2.5 standard deviations or more below peak bone mass is defined as osteoporosis [48]. Osteoporosis itself does not have

***Corresponding author**
Tel : +82-51-510-8092, Fax : +82-55-382-8090
E-mail : ahnsc@pusan.ac.kr

Table 1. Percentage of 1990 US white women with osteoporosis

	Osteoporosis	
Age range (years)	Any sites (%)	Hip alone (%)
30-39	0	0
40-49	0	0
50-59	14.8	3.9
60-69	21.6	8.0
70-79	38.5	24.5
80+	70.0	47.5
≥50	30.3	16.2

*Population shows increased percentage of people with osteoporosis with advancement of age. Adapted from the World Health Organization (WHO) Report [48].

any special symptoms and is often referred to as a "silent" disease because its effects are not shown until a fracture occurs, usually in the distal forearm (wrist), proximal femur (hip) and the vertebrae (spine). A fracture caused as a result of diminished of bone strength due to osteoporosis is known as fragility fracture. This, coupled with the greater propensity to fall with advanced age, makes osteoporosis especially dangerous for the elderly. While fragility fractures are rarely lethal, they can lead to many intangible complications such as chronic pain, impaired mobility, stooped posture, and loss of independence [4]. The economic costs of treatment for osteoporosis can be difficult to measure, since not all bone fractures are caused by osteoporosis, and osteoporosis itself is not enough to directly cause a fracture.

Pathogenesis

To understand the pathogenesis of osteoporosis, a closer look at how the bone system works is required. Fundamentally, osteoporosis is a result of an imbalance in the bone remodeling matrix, where bone is constantly being resorbed by osteoclasts and ossified by osteoblasts. Bone remodeling, or bone metabolism, is a sequential process consisting of 5 phases: activation, resorption, reversal, formation, and quiescence [13] (Fig. 1). In the first activation phase, mononuclear pre-osteoclasts migrate to specific sites on the skeletal surface and fuse to form multinucleated osteoclasts, where it can then proceed to break down the bone matrix in the resorption phase. Apoptosis of osteoclasts occur in the reversal phase, and the resorbed bone cavity is prepared to be rebuilt. As the name suggests, the formation phase is characterized by the formation of new bone material by osteoblasts. Thus the process of bone remodeling completes, and the bone lies

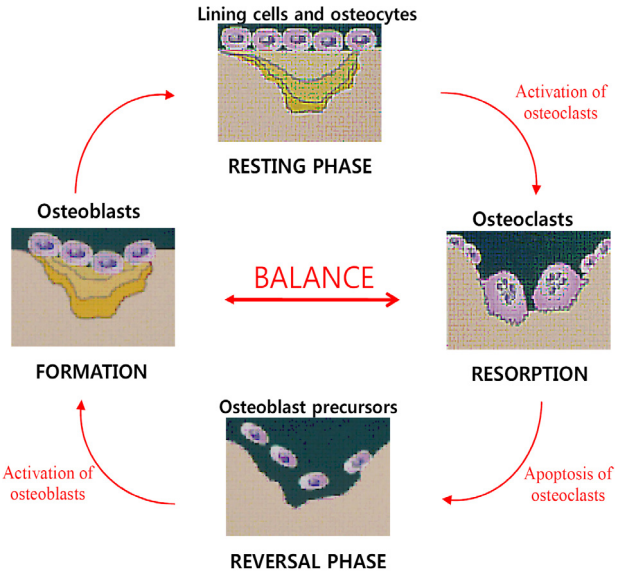

Fig. 1. Bone remodeling cycle. Bone undergoes constant turnover through various phases. These phases can largely be divided into the activation phase, resorption phase, reversal phase, formation phase, and the quiescence or resting phase. The bone remodeling cycles ensures the healthy maintenance of bone structure. Adapted from Hill [13].

dormant in its quiescence phase until the next cycle. Such constant destruction and reformation allow for the maintenance of bone mass and preservation of bone microarchitecture. For osteoporosis, the three pathogenetic mechanisms have been identified as a) failure to achieve peak bone mass during growth; b) excessive bone resorption and; c) inadequate bone formation in response to bone resorption [31].

The differentiation and activation of osteoclasts is mediated by a molecule called receptor activator for nuclear factor κ B ligand (RANKL), also known as TNF-related activation-induced cytokine (TRANCE), found on the surface of pre-osteoblasts [16]. Experiments have shown that RANKL knockout mice develop severe osteopetrosis, a condition quite contrary to osteoporosis where bones harden and become denser. RANK, the receptor for RANKL, can be in turn found on pre-osteoclasts, which ensures that the activation of osteoclasts is followed by a wave of osteoblasts. Another molecule, known as osteoprotegerin (OPG), can also bind to RANKL and block the RANK/RANKL pathway. OPG therefore acts as a "decoy" receptor that competes with RANK, and inhibits the formation of osteoclasts [43]. This OPG/RANK/RANKL system has been studied extensively in recent years, especially in its role in bone disorders includ-

Table 2. Current drugs used for bone related disorders

Drugs	Chemical Classes	Mechanisms of Action	Side Effects
Alendronate/Risedronate/ Ibandronate/Zoledronic Acid	Bisphosphonates	Osteoclast activity ↓	Gastrointestinal toxicity, weight loss, bone pain, low calcium levels
Estrogen	Sex steroid	Osteoclast development ↓	Endometrial cancer, stroke
Raloxifene	Estrogen mimic	Osteoclast development ↓	Leg cramps, hot flashes
Estren	Estrogen derivative	Osteoblast apoptosis ↓	Breast cancer
Teriaparatide	Peptide	Bone formation ↑	Pain, headache, diarrhea
Denosumab	RANKL antibody	Osteoclast development ↓	Nausea, diarrhea, cramps
Calcitonin	Peptide hormone	Osteoclasts activity ↓	Nausea, skin redness, diarrhea
Parathyroid hormone-related peptide (PTHrP)	Osteotrophin	Bone formation ↑	Nausea, weakness

*Various drugs and their side effects are summarized in this Table. Adapted from Sethi and Aggarwal [19].

ing osteoporosis.

Current Medical Treatments

Many treatments for osteoporosis have been used over the years, but no permanent cure has been found to date. Present day medical treatments for osteoporosis largely fall under one of two categories: inhibitors of bone resorption, or bone anabolic agents aimed at rebuilding resorbed bone. All major medications for osteoporosis in use today such as biphosphonates, estrogen or estrogen analogues, and teriparatide are included in these categories (Table 2). Intake of nutritional factors such as calcium, phosphate, and vitamin D were shown to have beneficial results as well [5]. Weight-bearing exercises can also be used, similar to how astronauts regularly perform exercises during space flight to maintain skeletal mass. Following an 11 month-long weight-bearing exercise schedule, it was shown that the BMD of test subjects (postmenopausal women) were significantly increased, specifically in the lumbar spine and the proximal femur [18]. Furthermore, weight-bearing exercise was shown to have an additive effect when used in conjunction with hormone replacement therapy (HRT).

As previously mentioned, the lack of estrogen, which determines the rate of bone resorption, plays a key role in the development of osteoporosis. Hormone replacement therapy, which involves artificially boosting hormone production using a group of medication to alleviate the symptoms of menopause, has improved the conditions of female osteoporotic patients. Although experiments have shown that total body BMD except for wrist was significantly increased in response to HRT, prolonged use of HRT have side effects such as the increased risk of uterine cancer [18]. Also, there has been 20% to 50% increase in the risk of breast cancer, and rarer side effects include thromboembolic disease, which HRT increases the risk by three-fold [32].

Biphosphonates, named for its two phosphonate groups, are currently very popular and used as first line drugs in treating osteoporosis. Once taken, biphosphates block essential protein synthesis pathways and therefore inactivates and eventually leads to apoptosis of osteoclasts. Decrease in the number of osteoclasts leads to an increase in BMD and biphosphates have suppressed bone fractures by up to 50% [32]. However, certain side effects are noted. Oral intake of biphosphate has caused inflammation of esophagus and sometimes, osteonecrosis of the jaw [47]. Recent researches indicate that intake of biphosphonate may lead to atrial fibrillation [2]. Also, unlike other medications, biphosphates are not fully metabolized or ejaculated out of the body system. Although their long term effects have yet to be discovered, it has been shown that biphosphates are accumulated in bone with use [28].

Teriparatide is a type of parathyroid hormone and therefore the primary regulator of calcium and phosphate metabolism. Teriparatide has shown to increase BMD in lumbar spine and hip [34]. Although teriparatide shows promising results, it has also shown certain side effects. Teriparatide is known to increase the risk of osteosarcoma in rats and National Institute of Health recommends that teriparatide should not be used to prevent or treat mild osteoporosis [42]. However, studies have not yet confirmed causual relationship between teriparatide and human osteosarcoma.

Natural Product Treatments

Despite their success in treating osteoporosis, present day medications have numerous side effects that make their use somewhat limiting [37] (Table 2). Alternatively, treatments using natural products are being researched in hopes of finding safer and inexpensive ways of treating osteoporosis (Table 3). Historically, many cultures, most notably those in Eastern Asia, have been using natural remedies to cure illnesses for many centuries. These "Oriental" medicines, while not founded on modern chemistry or pharmacology, have nonetheless proven their use through years of development. There is no doubt that many of these medicines do have a positive effect on the illnesses they are claimed to cure. However, it is unclear as to which ingredients, or chemical compounds are the ones primarily involved in the mechanisms that heal the patient. Recent studies have re-evaluated traditional herbal medicines and identified a few compounds that show potential as anti-resorptive, or bone anabolic agents. Once fully developed, these herbal medicines can provide a cost-effective alternative to chemically synthesized medicines.

With the advent of the Internet age, a growing trend of seeking self-medication or simple dietary changes to improve one's health has also contributed to the increased popularity of natural remedies. However, because unsubstantiated or unreliable claims are made on many of the websites providing natural treatments for osteoporosis [43, 46], more studies need to be conducted in order to establish a firm foundation supported by scientific evidences. The beneficial effects of calcium and vitamin D on bone are well publicized, but little is known of other food derivatives and their effects on bone physiology. Some common food sources have been examined for their effects on bone disorders [30], of which lactoferrin purified from milk and isoflavones from soy beans (*Glycine max)* are two of the best studied.

Milk is a highly nutritional fluid drunk primarily in the infantile stages of mammals, when rapid skeletal development is required. So it may come as no surprise that lactoferrin, a component in human, as well as bovine milk, can have positive effects on bone health. Lactoferrin is an iron-binding glycoprotein and is known to have antibacterial properties in addition to transferring iron. The skeletal effects of lactoferrin have been studied both *in vitro* and *in vivo*, which has powerful anabolic, differentiating, and anti-apoptotic effects on osteoblasts and inhibits osteoclastogenesis [8].

Soy beans have long been thought to be beneficial to the bone in East Asian cultures. Although they are native to East Asia, soy bean and its derivative tofu are increasingly being studied for their health effects in the west since its role in disease prevention received widespread attention in the scientific community in the 1990s [24]. Soy and its bean (Fabaceae) family are the almost exclusive producers of isoflavones, with soybeans being a particularly high producer of one type of isoflavone, daidzein [11]. Because daidzein and other isoflavones can bind to estrogen receptors, they act as phytoestrogens (literally, plant estrogens). Despite the initial expectations, studies of isoflavones and their effects on bone health have yielded mixed results, with some papers reporting increased BMD in test subjects [9], while others maintain that they are merely suggestions and not conclusive evidence that isoflavones are beneficial [3, 6]. The variance in study results may be explained by another isoflavone called equol. Equol is metabolized from daidzein, however only 30 to 50% of the human population can biotransform daidzein into equol [12]. There are indications that the prevalence of equol-producing phenotype may be greater in the Asian subpopulation than the Caucasian subpopulation [40]. Equol attracts and binds to estrogen receptors better than daidzein. Setchell *et al.* proposed that the clinical effectiveness of soy on various health issues including bone health may be a function of the ability to produce equol, and therefore the failure to distinguish subjects as an "equol producer" or "non-equol producer" in prior studies could explain the variance in results [36]

The seeds of *Carthamus tinctorius* L., more commonly known as safflower, have long been used in traditional Korean medicine. It is known as Honghwa in Korea and believed to be effective in treating bone-related injuries, such as fractures, as well as postmenopausal osteoporosis. Trials on ovariectomized rats suggest that safflower seeds can indeed stimulate osteoblastic differentiation [17]. Experiments showed that safflower seeds combined with human placenta in a medicinal recipe called Gami-honghwain enhanced the activity of alkaline phosphatase (ALP), the biochemical marker of osteoblastic activity, in a dose-dependent manner [17]. The rhizome ("root") of the fern *Drynaria fortune* (known as Golsebo in Korean and Gusuibu in Chinese) is another herbal medicine traditionally used to strengthen bone, in addition to promoting blood circulation and kidney health. In 1996, it was found that *Drynaria* rhizome injection promoted

Table 3. Natural products for treatment of bone related disorders

Natural Products	Sources	Mechanisms of Action	References
BNO 1055	*Cimicifugae* sp.	Bone formation ↑ (similar to estrogen)	49
Camphor, thymol	Herbs rich in essential oils	Bone resorption pits ↓	25
Catechin	Green teas	Osteogenesis ↑ Bone resorption pits ↓	7
Curcumin	*Curcuma longa*	Osteoclastogenesis ↓	1, 14
Daidzein	Soy beans and peas	Bone strength ↑	3
DT56a	Soy beans	Skeletal tissues ↑ Bone mineral density ↑	39
Echinacoside	*Cistanche tubulosa*	Bone regeneration ↑	21
Epigallocatechin	Green teas	Apoptosis of osteoclasts ↑	26
Equol	Soy beans (metabolized daidzein)	Similar to daidzen	36
Fructo-oligosaccharides	Yacon roots, chicory roots, leeks	Restored bone mineral density and microarchitecture	10
γ-L-glutamyl-propenyl-L-cysteine sulfoxide	*Allium cepa* (Onion)	Osteoclasts activity ↓ Bone resorption ↓ Tartrate-resistant acid phosphatase ↓	45
Genistein	Soy beans	Bone protection Osteoblasts differentiation ↑	29
Icariin	*Herba epimedii*	Osteoblasts proliferation, differentiation and mineralization ↑	41
Isotaxiresinol	*Taxus yunnanensis*	Bone mineral density ↑ Bone resorption ↓	51
Lactoferrin	Milks	Anti-apoptosis of osteroblasts ↑ Osteoclastogenesis ↓	9
Naringin	Citrus peels	Osteoblasts differentiation ↑ Osteoclasts apoptosis ↑ Osteoclastogenesis ↓ Bone resorption ↓	20, 23
Oleuropein	Olives	Osteoblastogenesis ↑	35
Puerarin	Radix *Puerariae*	Osteoblasts differentiation ↑ Bone formation ↑	44
Resveratrol	Grapes	Osteoblastogenesis and bone formation ↑	52
Triterpenoids	*Cimicifugae rhizome*	Bone mineral density protecttion Osteoclasts formation and bone resoption ↓	22
Ursolic acid	Apples, bilberries, cranberries, elderflower, peppermint, rosemary, lavender, thyme	Osteoblasts differentiation ↑ New bone formation ↑	19
Extract	*Carthamus tinctorius* (Safflower)	Osteoblasts differentiation ↑ Alkaline phosphatase activity ↑	17
Extract	*Drynariae fortune* (Glosebo in Korean)	Bone formation ↑ Alkaline phosphatase activity ↑ Osteoblasts proliferation and differentiation ↑	15
Extract	*Angelica sinensis* (Danggwi in Korean)	Alkaline phosphatase activity ↑ Osteoprecursor cells ↑	50

calcification of chick embryo bone primordium and increased ALP activity. A more recent investigation on cell cultures confirmed the increase in ALP activity, indicating that *Drynaria* rhizome directly stimulates proliferation and differentiation of osteoblasts [15]. Similarly, aqueous extracts of *Angelica sinensis*, an herb with a ginseng-like appearance known as Danggwi in Korean and Dongquai in Chinese, was found to stimulate ALP activity, protein secretion and type I collagen synthesis of osteoprecursor cells [50].

In 2005, Shishodia *et al.* reviewed the various health effects of the Indian spice turmeric, which is derived from the rhizome of the plant *Curcuma longa* [38]. The key active ingredient in turmeric is identified as curcumin, which gives turmeric its distinctive orange-yellow color. Curcumin is used in Ayurveda and Chinese medicine to treat inflammation. More specifically, it was reported by Bharti *et al.* that curcumin inhibits osteoclastogenesis by suppressing RANKL signaling [1]. Tumeric has traditionally been used in many South Asian and Middle Eastern cuisine. Phase I clinical trials of curcumin indicate that humans can take doses of up to 3,600-8,000 mg daily for 4 months without side effects, other than mild nausea and diarrhea [14].

Conclusion

It is clear that osteoporosis is and will increasingly be a major disorder that faces the aging mankind. In this field, much still remain unknown and a cure, elusive. As many controversies surround the medical safety of current treatments for osteoporosis, a greater urgency is placed on the discovery of a treatment from a natural source that is proven to be safe and effective. Unfortunately, the majority of natural product treatments is still in its preliminary stages, and has yet to prove their efficacy in clinical trials. Nonetheless, the pace of developments regarding osteoporosis treatment in the past few decades is astounding. Further progress in pre-clinical studies and the subsequent clinical studies will someday lead to a breakthrough that takes us another step forward in science.

Acknowledgement

This study was supported by Basic Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0004620).

References

1. Bharti, A. C., Takada, Y. and Aggarwa, B. B. 2004. Curcumin (diferulolylmethane) inhibits receptor activator of NF-κB ligand-induced NF-κB activation in osteoclast precursors and suppresses osteoclastogenesis. *J. Immunol.* **172**, 5940-5947.
2. Black, D. M., Delmas, P. D., Eastell, R., Reid, I. R., Boonen, S., Cauley, J. A., Cosman, F., Lakatos, P., Leung, P. C., Man, Z., Mautalen, C., Mesenbrink, P., Hu, H., Caminis, J., Tong, K., Rosario-Jansen, T., Krasnow, J., Hue, T. F., Sellmeyer, D., Eriksen, E. F. and Cummings, S. R. 2007. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N. Engl. J. Med.* **356**, 1809-1822.
3. Branca, F. 2003. Dietary phyto-oestrogens and bone health. *Proc. Nutr. Soc.* **62**, 877-887.
4. Brenneman, S. K., Barrett-Connor, E. S., Sajjan, L. E., Markson and Siris, E. S. 2006. Impact of recent fracture on health-related quality of life in postmenopausal women. *J. Bone Miner. Res.* **21**, 809-816.
5. Brouns, F. and Vermeer, C. 2000. Functional food ingredients for reducing the risks of osteoporosis. *Trends Food Sci. Technol.* **11**, 22-33.
6. Cassidy, A., Albertazzi, P., Nielsen, I. L., Hall, W., Williamson, G., Tetens, I., Atkins, S., Cross, H., Manios, Y., Wolk, A., Steiner, C. and Branca, F. 2006. Critical review of health effects of soyabean phyto-oestrogens in post-menopausal women. *Proc. Nutr. Soc.* **65**, 76-92.
7. Chen, C. H., Ho, M. L., Chang, J. K., Hung, S. H. and Wang, G. J. 2005. Green tea catechin enhances osteogenesis in a bone marrow mesenchymal stem cell line. *Osteoporos Int.* **16**, 2039-2045.
8. Cornish, J., Callon, K. E., Naot, D., Palmano, K. P., Banovic, T., Bava, U., Watson, M., Lin, J., Tong, P. C., Chen, Q., Chan, V. A ., Haggarty, N. W., Grey, A. B. and Reid, I. R. 2004. Lactoferrin is a potent regulator of bone cell activity and increases bone formation *in vivo*. *Endocrinology* **145**, 4366-4374.
9. Cotter, A. and Cashman, K. D. 2003. Genistein appears to prevent early postmenopausal bone loss as effectively as hormone replacement therapy. *Nutr. Rev.* **61**, 346-351.
10. Devareddy, L., Khalil, D. A., Korlagunta, K., Hooshmand, S., Bellmer, D. D. and Arjmandi, B. H. 2006. The effects of fructooligosaccharides in combination with soy protein on bone in osteopenic ovariectomized rats. *Menopause* **13**, 692-699.
11. Fonseca, D. and Ward, W. E. 2004. Daidzein together with high calcium preserve bone mass and biomechanical strength at multiple sites in ovariectomized mice. *Bone* **35**, 489-497.
12. Frankenfeld, C. L., Atkinson, C., Thomas, W. K., Gonzalez, A., Jokela, T., Wahala, K., Schwartz, S. M., Li, S. S. and Lampe, J. W. 2005. High concordance of daidzein-metabolizing phenotypes in individuals measured 1 to 3 years apart. *Br. J. Nutr.* **94**, 873-876.
13. Hill, P. A. 1998. Bone Remodeling. *Br. J. Orthod.* **25**, 101-107.
14. Hsu, C. H. and Cheng, A. L. 2007. Clinical studies with

curcumin. *Adv. Exp. Med. Biol.* **595**, 471-480.
15. Jeong, J. C., Lee, J. W., Yoon, C. H., Lee, Y. C., Chung, K. H., Kim, M. G. and Kim, C. H. 2005. Stimulative effects of *Drynaria*e Rhizoma extracts on the proliferation and differentiation of osteoblastic MC3T3-E1 cells. *J. Ethnopharmacol.* **96**, 489-495.37.
16. Khosla, S. 2001. Minireview: The OPG/RANKL/RANK system. *Endocrinology* **142**, 5050-5055.
17. Kim, K. W., Suh, S. J., Lee, T. K., Ha, K. T., Kim, J. K., Kim, K. H., Kim, D. I., Jeon, J. H., Moon, T. C. and Kim, C. H. 2008. Effect of safflower seeds supplementation on stimulation of the proliferation, differentiation and mineralization osteoblastic MC3T3-E1 cells. *J. Ethnopharmacol.* **115**, 42-49.
18. Kohrt, W. M., Snead, D. B., Slatopolsky, E. and Birge, S. J. 1995. Additive effects of weight-bearing exercise and estrogen on bone mineral density in older women. *J. Bone Miner. Res.* **10**, 1303-1311.
19. Lee, S. U., Park, S. J., Kwak, H. B., Oh, J., Min, Y. K. and Kim, S. H. 2008. Anabolic activity of ursolic acid in bone: stimulating osteoblast differentiation *in vitro* and inducing new bone formation *in vivo*. *Pharmacol. Res.* **58**, 290-296.
20. Li, F., Sun, X., Ma, J., Ma, X., Zhao, B., Zhang, Y., Tian, P., Li, Y. and Han, Z. 2014. Naringin prevents ovariectomy-induced osteoporosis and promotes osteoclasts apoptosis through the mitochondria-mediated apoptosis pathway. *Biochem. Biophys. Res. Commun.* **452**, 629-635.
21. Li, F., Yang, Y., Zhu, P., Chen, W., Qi, D., Shi, X., Zhang, C., Yang, Z. and Li, P. 2012. Echinacoside promotes bone regeneration by increasing OPG/RANKL ratio in MC3T3-E1 cells. *Fitoterapia* **83**, 1443-1450.
22. Li, J. X., Liu, J., He, C. C., Yu, Z. Y., Du, Y., Kadota, S. and Seto, H. 2007. Triterpenoids from *Cimicifugae rhizoma*, a novel class of inhibitors on bone resorption and ovariectomy-induced bone loss. *Maturitas* **58**, 59-69.
23. Li, N., Jiang, Y., Wooley, P. H., Xu, Z. and Yang, S. Y. 2013. Naringin promotes osteoblast differentiation and effectively reverses ovariectomy-associated osteoporosis. *J. Orthop. Sci.* **18**, 478-485.
24. Messina, M. 2010. A brief historical overview of the past two decades of soy and isoflavone research. *J. Nutr.* **140**, 1350-1354.
25. Muhlbauer, R. C., Lozano, A., Palacio, S., Reinli, A. and Felix, R. 2003. Common herbs, essential oils, and monoterpenes potently modulate bone metabolism. *Bone* **32**, 372-380.
26. Nakagawa, H., Wachi, M., Woo, J. T., Kato, M., Kasai, S., Takahashi, F., Lee, I. S. and Nagai, K. 2002. Fenton reaction is primarily involved in a mechanism of (-)-epigallocatechin-3-gallate to induce osteoclastic cell death. *Biochem. Biophys. Res. Commun.* **292**, 94-101
27. National Osteoporosis Foundation. 2010. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC. *National Osteoporosis Foundation.*
28. Ott, S. M. 2005. Long-term safety of biphosphonates. *J. Clin. Endocrinol. Metab.* **90**, 1897-1899.
29. Pan, W., Quarles, L. D., Song, L. H., Yu, Y. H., Jiao, C., Tang, H. B., Jiang, C. H., Deng, H. W., Li, Y. J., Zhou, H. H. and Xiao, Z. S. 2005. Genistein stimulates the osteoblastic differentiation via NO/cGMP in bone marrow culture. *J. Cell Biochem.* **94**, 307-316.
30. Putnam, S. E., Scutt, A. M., Bicknell, K., Priestley, C. M. and Williamson, E. M. 2007. Natural products as alternative treatments for metabolic bone disorders and for maintenance of bone health. *Phytother. Res.* **21**, 99-112.
31. Raisz, L. G. 2005. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *J. Clin. Invest.* **115**, 3318-3325.
32. Rodan, G. A. and Martin, T. J. 2000. Therapeutic approaches to bone diseases. *Science* **289,** 1508-1514.
33. Rodan, G. A., Raisz, L. G. and Bilezikian, J. P. 2002. Pathophysiology of osteoporosis. *Principles of Bone Biology* San Diego: Academic Press.
34. Saag, K. G., Shane, E., Boonen, S., Marin, F., Dongley, D. W., Taylor, K. A., Dalsky, G. P. and Marcus, R. 2007. Teriparatideor alendronate in glucocorticoid-induced osteoporosis. *N. Engl. J. Med.* **357**, 2028-2039
35. Santiago-Mora, R., Casado-Díaz, A., De Castro, M. D. and Quesada-Gómez, J. M. 2011. Oleuropein enhances osteoblastogenesis and inhibits adipogenesis: the effect on differentiation in stem cells derived from bone marrow. *Osteoporos Int.* **22**, 675-684.
36. Setchell, K. D. R., Brown, N. M. and Lydeking-Olsen, E. 2002. The clinical importance of the metabolite equol - a clue to the effectiveness of soy and its isoflavones. *J. Nutr.* **132**, 3577-3684.
37. Sethi, G. and Aggarwal, B. B. 2007. Mending the bones with natural products. *Chem. Biol.* **14**, 738-740.
38. Shishodia, S., Sethi, G. and Aggarwal, B. B. 2005. Curcumin: getting back to the roots. *Ann N Y Acad Sci* **1056**, 206-217.
39. Somjen, D. and Yoles, I. 2003. DT56a (Tofupill/Femarelle) selectively stimulates creatine kinase specific activity in skeletal tissues of rats but not in the uterus. *J. Steroid Biochem. Mol. Biol.* **86**, 93-98.
40. Song, K. B., Atkinson, C., Frankenfeld, C. L., Jokela, T., Wahala, K., Thomas, W. K. and Lampe, J. W. 2006. Prevalence of daidzein-metabolizing phenotypes differs between Caucasian and Korean American women and girls. *J. Nutr.* **136**, 1347-1351.
41. Song, L., Zhao, J., Zhang, X., Li, H. and Zhou, Y. 2013. Icariin induces osteoblast proliferation, differentiation and mineralization through estrogen receptor-mediated ERK and JNK signal activation. *Eur. J. Pharmacol.* **714**, 15-22.
42. Subbiah, V., Madsen, V. S., Raymond, A. K., Benjamin, R. S. and Ludwig, J. A. 2010. Of mice and men: divergent risks of teriparatide-induced osteosarcoma. *Osteoporos Int.* **21**, 1041- 1045.
43. Teitelbaum, S. L. 2000. Bone resorption by osteoclasts. *Science* **289**, 1504-1508.
44. Wang, P. P., Zhu, X. F., Yang, L., Liang, H., Feng, S. W. and Zhang, R. H. 2012. Puerarin stimulates osteoblasts differentiation and bone formation through estrogen receptor, p38 MAPK, and Wnt/β-catenin pathways. *J. Asian Nat.*

Prod. Res. **14**, 897-905.
45. Wetli, H. A., Brenneisen, R., Tschudi, I., Langos, M., Bigler, P., Sprang, T., Schürch, S. and Mühlauer, R. C. 2005. A gamma-glutamyl peptide isolated from onion (*Allium cepa* L.) by bioassay guided fractionation inhibits resorption activity of osteoclasts. *J. Agric. Food Chem.* **53**, 3408-3414
46. Whelan, A. M., Jurgen, T. M., Bowles, S. K. and Doyle, H. 2009. Efficacy of natural health products in treating osteoporosis: what is the quality of internet patient advice?. *Ann. Pharmacother.* **43**, 899-907.
47. Woo, S., Hellstein, J. and Kalmar, J. 2006. Narrative review: biphosphates and osteonecrosis of the jaws. *Ann. Intern. Med.* **144,** 753-761.
48. World Health Organization (WHO). 1994. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organ Tech Rep Ser* **843**, 1-129.
49. Wuttke, W., Seidlova-Wuttke, D. and Gorkow, C. 2003. The *Cimicifuga* preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. *Maturitas* **44**, S67-S77.
50. Yang, Q., Populo, S. M., Zhang, J., Yang, G. and Kodama, H. 2002. Effect of *Angelica sinensis* on the proliferation of human bone cells. *Clinica Chimica Acta* **324**, 89-97.
51. Yin, J., Tezuka, Y., Subehan, Shi, L., Nobukawa, M., Nobukawa, T. and Kadota, S. 2006. *In vivo* anti-osteoporotic activity of isotaxiresinol, a lignan from wood of *Taxus yunnanensis*. *Phytomedicine* **13**, 37-42.
52. Zhang, Y., Leung, P. C., Che, C. T., Chow, H. K., Wu, C. F. and Wong, M. S. 2008. Improvement of bone properties and enhancement of mineralization by ethanol extract of fructus *Ligustri lucidi*. *Br. J. Nutr.* **99**, 494-502.

초록 : 골다공증 치료법과 천연물을 이용한 대체요법

오승훈[1] · 안순철[2,3]*

([1]단국대학교 의과대학 생리학교실, [2]부산대학교 의학전문대학원 미생물학 및 면역학교실, [3]부산대학교 Brain Busan 21 면역조절치료소재연구인력양성사업단)

골다공증은 골밀도(bone mineral density, BMD)가 평균 성인 정점에서 2.5 이상의 표준편차가 감소되는 뼈의 질환으로서 나이가 들어가면서 점차 증가하고 있다. 골다공증은 뼈를 흡수하는 파골세포와 뼈를 형성하는 조골세포로 이루어진 bone remodeling system의 불균형 때문에 발생한다. 이 불균형의 가장 큰 원인은 여성 폐경기 후에 따르는 에스트로겐 결핍 때문이다. 현재 골다공증의 치료에 사용되는 약들로는 호르몬 대체요법(hormone replacement therapy, HRT), biphosphonate, teriparatide 등이 있지만, 여러 가지 부작용 때문에 그들의 안정성과 실용성엔 의문의 여지가 있다. 더 안전한 대안을 찾기 위해 현재 천연물을 사용한 여러 가지 치료법이 연구되고 있다. Lactoferrin, isoflavone 등과 한약재를 이용한 많은 전통 치료법들이 있으며, 이는 뼈 흡수를 막거나, 뼈 동화를 일으킴으로써 골다공증 치료제로서의 가능성을 보여주고 있다. 그러나 대부분의 천연물 치료법은 지난 10여 년간 괄목할만한 발전에도 불구하고 그 효능을 증명하기 위한 임상 예비단계에 머물고 있다. 따라서 천연물의 전임상 연구와 후속 임상 연구를 통해 새로운 골다공증 치료법으로 소개될 것이다.