Review Article

Therapeutic Potential of Citrus Flavonoid Naringin in Management of Osteoporosis: Current Status and Future Perspectives

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ABSTRACT

Naringin is a plant based natural compound abundantly present in citrus fruits. Naringin has been reported for its vast range of therapeutic properties and it has been recognized as molecule of interest in treatment of various diseases. Naringin has been also investigated for its role in promoting bone development and maintenance. It has been found to promote bone formation and inhibit the bone resorption. It seems to be a potent candidate in treatment of osteoporosis. Osteoporosis is characterized by low bone mass and destruction of bone microstructure. Osteoporosis increases the risk of bone fracture. Naringin has been found effective in treatment of osteoporosis and improvement of bone health including bone mineral density and mechanical strength. In current review, the potential of naringin in treatment of osteoporosis has been reviewed. This article will provide important and concise information on therapeutic potential of naringin against osteoporosis.

Key words: Naringin, Osteoporosis, Alternate medicine, Bone health, Bone formation, Bone resorption.

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INTRODUCTION

Osteoporosis is a well-known disease that affects a significant volume of human population worldwide. Osteoporosis has become one of the most prevalent and costly diseases in the world.[1] Osteoporosis affects the quality of life of middle-aged and old-aged peoples. Osteoporosis significantly affects the women population over a particular age.[2] It is characterized by decreased bone strength, low bone mass and progressive destruction of bone microstructure, resulting in increased the risk of fracture.[2,3] In osteoporosis, reduction in bone mass due to an imbalance between bone formation and resorption is generally observed. Cost effective, safe and effective treatment of osteoporosis is a major concern. Plant based diets particularly flavonoids seem promising as part of safe and effective therapy in management of osteoporosis. One of the important flavonoid that have been found of immense potential in treatment and management of osteoporosis is naringin. It has shown immense potential to be used as alternate and also as part of combined therapies for osteoporosis treatment.

Dietary flavonoids have emerged as a safe and effective way of treating; controlling or managing the various diseases.[4,5] Various functional foods have proven effective and beneficial for human heath due to presence of flavonoids.[5-7] Naringin is a plant based naturally occurring flavonoid. Citrus fruits are natural source of flavonoid naringin. Naringin is well known for its therapeutic potential. It has been found effective against various diseases. Naringin has been reported for

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its antimicrobial, anti-inflammatory, anti-oxidant, anti-diabetic and anti-cancerous properties.[8] It has been found to have hepato-protective, reno-protective and cardio-protective property. Also, effect of naringin on other various diseases including osteogenesis, controlled medication discharge, bone recovery, osteoporosis, osteoblasts, metabolic condition, chromosomal damage, oxidative damage and sensory system issue have been reported so far.[5,6,9] Naringin has been elucidated to promote bone development and maintenance.[10] Recently, Yu *et al*.[11] has reviewed the potential of naringin for natural and novel orthopedic biotherapies. Naringin has been found to modulate signaling through various molecular pathways which are important and crucial to musculoskeletal development, cellular differentiation, and inflammation.[11] Naringin has been reported to improve the bone formation and supports the bone health (Figure 1). Researchers are continuously working on naringin mediated management of osteoporosis and elucidation of mechanism responsible for it. This review focuses on recent advancements regarding the role of naringin in treatment and management of osteoporosis.

Recent advances and mechanistic insights in naringin mediated management of osteoporosis

An important investigation regarding the effects of combined treatment with naringin (NG) and treadmill exercise (EX) on osteoporosis in ovariectomized (OVX) rats has been reported by Sun *et al*.[3] A total of seventy-five rats (03 months after bilateral ovariectomy,) were randomly allotted to the following treatment groups: OVX, sham-operated (SHAM), NG, EX, or NG plus EX treatment.[3] The treatments were given for 60 days.

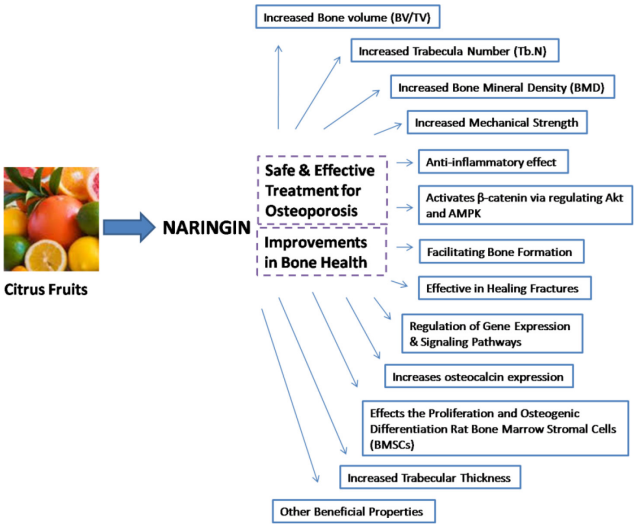

Figure 1: General presentation showing beneficial effects of naringin on bone health and naringin as promising therapeutic candidate for safe and effective treatment of osteoporosis.

Authors evaluated the bone metabolism, trabecular bone parameters, bone mineral density, immune-histochemistry, and also the bone strength. As compared to the OVX groups, all treatments increased the bone volume (BV/TV), trabecula number (Tb.N), trabecula thickness (Tb.Th), bone mineral density (BMD), and mechanical strength. The naringin combined with treadmill exercise (NG + EX) showed the strongest effects on BV/TV, Tb.Th, and biomechanical strength. In addition, decreased C-terminal telopeptides of type I collagen (CTX-1) and enhanced osteocalcin (OCN) expression were observed in the combined (naringin combined with treadmill exercise; NG + EX) group. The study revealed that naringin combined with treadmill exercise (NG + EX) may have a therapeutic advantage over each monotherapy for the treatment of osteoporosis.[3]

The effect of naringin on osteoblastic cell differentiation and proliferation has been reported.[2] Authors assessed therapeutic effects of naringin on a rat osteoporosis model. The proliferation, differentiation, and function of rat bone marrow stromal cells (BMSCs) were investigated after treatment with different concentrations of naringin. Ovariectomy (OVX)-induced osteoporotic rats were administered orally with naringin daily at specific low, medium, and high dosages. A control group was treated with PBS for 2 months. Authors used femoral X-ray images and micro-CT scans for bone mineral density (BMD) and BV/TV (bone volume/total volume) analyses. Changes in trabecular thickness (Tb.Th) and trabecular space (Tb.Sp) in the groups were also assessed. In results, naringin was found effective at enhancing the proliferation and osteogenic differentiation of BMSCs.[2] Naringin at a concentration of 10 (μg/ml) resulted in highest levels of osteocalcin expression among the *in vitro* study groups. A delayed response pattern of BMSCs appeared to the naringin treatment. Further, naringin also effectively reversed OVX induced bone loss via increasing BMD, bone volume, and trabecular thickness. The study suggested that naringin administration may represent an effective treatment for osteoporosis.[2]

Positive and beneficial role of naringin has been reported in various reports related to the bone health. Suvarna *et al*.[12] has reviewed the important properties of naringin on bone health. The covered studies include several conditions related to the bones. It has been found that naringin enhances the BMP-2 expression and osteogenic response mediated through Akt, PI3K, c-Fos/c-Jun, and AP-1.[12,13] Further it was found to increase ALP activity, OPN synthesis, cell proliferation, and OCN level. BMP-2 transcriptional regulation was

mediated through Akt phosphorylation and c-Jun and c-Fos activator protein (AP-1) components. Naringin was found to stimulate binding of c-Jun and c-Fos to the AP-1 protein associated with BMP-2 promoter.[13] Moreover, *in vitro* studies using osteoclasts revealed that naringin enhanced apoptosis of osteoclasts. In addition, naringin was also found to suppress expression of key marker genes of osteoclast in turn leading to inhibition of RANKL induced NF-kb activation through suppression of RANKL mediated IkB-a degradation. Also, naringin inhibit RANKL induced ERK phosphorylation.[12,14,15] Authors reviewed that naringin significantly decrease bone resorption area and enhance the apoptosis of osteoclast. These investigations revealed that naringin has beneficial role in the prevention and treatment of osteoporosis through inhibition of osteoclast formation and bone resorption.[12,16] A study to investigate the antiosteoarthritic and anti-inflammatory effect of naringin in MIA- induced Osteoarthritis (OA) rat model revealed that naringin promoted the recovery of hindlimb weight-bearing, reduced the generation or production of inflammatory mediator and proinflammatory cytokines, and protected the tissue from the damage. The outcomes revealed naringin as an effective therapeutic molecule for the treatment of the OA and OA-related symptoms.[12,17] Naringin was found to attenuate TNF-a-mediated inflammation and catabolism in chondrocytes. The study involving surgically induced OA mice models showed that oral administration of naringin improved degradation of cartilage matrix and offered protection against OA development. Moreover the protective effect of naringin in cartilage and chondrocyte was attributed to suppression of NF-kB signaling pathway.[18]

Effect of naringin on bone development has been investigated by Wang *et al*.[10] Authors studied biological roles of naringin *in vitro* using osteoblast-like UMR-106 cells and *in vivo* by performing ovariectomy to mimic osteoporosis in female mice.[10] The effect of naringin on Wnt/β-catenin signaling was also studied because the Wnt/β-catenin signaling play significant role in osteoblastogenesis. In this study, naringin enhanced the expression of mRNA and protein of β-catenin due to improved phosphorylation of Ser552 on β-catenin in UMR-106 cells, which further activated the lymphoid enhancer factor (LEF)/ T-cell factor (TCF) transcription factors. Authors also found that the employment of protein kinase B (Akt) inhibitor (Akti-1/2) and AMP-activated protein kinase (AMPK) inhibitor (Dorsomorphin) reduced the influence of naringin on β-catenin phosphorylation. These findings suggested that naringin activates β-catenin via regulating Akt and AMPK. The ovariectomized (OVX) mice treated with naringin exhibited improved bone strength while involvement of AMPK and Akt inhibitors partly reversed this effect, which further proved the involvements of Akt and AMPK in the action of naringin *in vivo*. Authors reported a novel finding on the mechanism of naringin in facilitating bone formation via Akt and AMPK signaling.[10]

Anti-osteoporosis activity of naringin has been reported in the retinoic acid-induced osteoporosis model of rat *in vitro* by Wei *et al*.[19] The osteoporosis was induced in the rats by giving a 14-day supplement of retinoic acid. Then the SD rats were treated with naringin. After the blood test, it has been observed that the naringin-treated rats showed significantly lower activity of serum alkaline phosphatase and higher femur bone mineral density as compared to the untreated rats. It has also been recorded that the specified dosages of naringin improved the decrease in bone weight coefficient, the length and the diameter of the bone, the content of bone ash, calcium, and phosphorus content induced by retinoic acid. These findings suggested the promising role of naringin in the management of osteoporosis.[19]

Various research groups are working on the exploration of natural compound naringin as safer and suitable osteoinductive agent.[20] Various preclinical studies demonstrated the immense potential of naringin for bone diseases or instructing stem cell osteogenic differentiation.[20] In addition, naringin has also been reported as a promising molecule for applications in skeletal disorders for which efficient strategies are lacking in current pharmaceutics.[20] The studies related to loading and controlled release of naringin are emerging and their outcome may improve the future biomedical applications.[20] Naringin is also found effective in healing fractures and strengthening the bones.[21] Femoral head disease (FH) is one of the refractory diseases. Clinically, it can be divided into invasive and non-invasive categories. The invasive is mainly due to skeletal trauma that may include femoral neck fracture or hip dislocation. The non-invasive is generally caused by the application of corticosteroids and heavy consumption of alcohol in long-term.[21-23] It has also been reported that naringin play protective role against the steroid-induced avascular necrosis of the femoral head (SANFH) through up regulation of PPARγ and activation of the Notch signaling pathway.[21] Authors found that naringin treated SANFH rabbit showed protection against the steroid-induced decrease in serum osteocalcin levels, and also the rate of osteonecrosis. Additionally, treatment with naringin resulted in decreased level of total cholesterol and low density lipoprotein/high density lipoprotein ratio

in the SANFH rabbit. It has been found that naringin markedly inhibit the caspase-3 activity while increased the mRNA expression of runt-related transcription factor 2 and transcription factor sp7.[21] Authors also reported that naringin has positive affect on alkaline phosphatase activity and upregulated collagen I, peroxisome proliferator-activated receptor (PPAR) γ2, neurogenic locus notch homolog protein (Notch), β-catenin and phosphorylated-Rac-α serine/threonine protein kinase protein expression in the SANFH rabbit.[21] These findings concluded that naringin protects against SANFH and can be used for the treatment of femoral head diseases.[21]

The effect of naringin on bone disuse osteoporosis has been investigated by Ma *et al*.[24] Authors examined whether naringin can prevent disuse osteoporosis induced by unilateral sciatic neurectomy (USN). They also studied the involvement of the Semaphorin 3A-induced Wnt/β-catenin signalling pathway in the osteoprotective effect of naringin (Ma *et al*., 2016). In dose-dependent manner, naringin checked the deterioration of bone mineral density (BMD), trabecular structure and biomechanical strength in femur due to USN. Further it was found that naringin increased the bone formation but inhibited resorption phenomenon. Semaphorin 3A (Sema3A) and active β-catenin protein was found to decrease after USN and could be restored by naringin to the levels of the sham-operated rats. Naringin also promoted the differentiation of osteoblasts and inhibited the osteoclastic differentiation *in vitro*. These findings suggested that the down-regulation of Sema3A and the subsequent inactivation of Wnt/β-catenin signalling may be some of the mechanisms involved in USN-induced osteoporosis. Naringin could increase the expression of Sema3A and the activation of Wnt/β-catenin signalling to prevent disuse osteoporosis induced by denervation. Authors finally concluded that naringin play significant role in bone maintenance and it may be a promising therapeutic molecule in prevention of disuse osteoporosis.[24]

Osteoporosis decreases bone strength and increases the risk of bone fracture. Li *et al*.[2] has reported that naringin promotes osteoblast differentiation and effectively reverses ovariectomy-associated osteoporosis. In this study, authors determined the proliferation, differentiation, and function of rat bone marrow stromal cells (BMSCs) following treatment with various concentrations of naringin.[2] Ovariectomy (OVX)-induced osteoporotic rats were orally administered naringin daily at low, medium, and high dosages, while a control group received PBS for 2 months. Femoral X-ray images and microCT scans were used for bone mineral density (BMD) and BV/TV (bone volume/total volume) analyses, and histological assessments of left tibiae were employed to check for changes in trabecular thickness (Tb.Th) and trabecular space (Tb.Sp) in the groups. Naringin was found effective at enhancing the proliferation and osteogenic differentiation of BMSCs. Naringin treatment effectively reversed the OVX-induced bone loss via increasing BMD, bone volume, and trabecular thickness. The medium dose (300 mg/kg) appeared to be the optimal dosage for delivering satisfactory therapeutic effects. Naringin promotes the proliferation and differentiation of BMSCs, increases osteocalcin expression and effectively reverses ovariectomy-induced osteoporosis in rats. The study suggests that administration of naringin may represent an effective treatment for osteoporosis.[2]

Postmenopausal osteoporosis is the most common type of osteoporosis.[25,26] At menopause, estrogen withdrawal accelerates bone remodeling with a net increase in bone resorption, which leads to bone loss and even osteoporosis.[26-28] Recently, Zhu *et al*.[26] have investigated the therapeutic effect of naringin on postmenopausal osteoporosis in ovariectomized (OVX) rats. Authors reported that bone mineral density (BMD) significantly increased after naringin treatment. However, there was no significant increase in BMD after estrogen treatment in comparison with naringin. Trabecular bone volume (BV/TV) and trabecular thickness (Tb.) significantly increased after naringin treatment. Authors found naringin as promising molecules which inhibit bone loss in OVX rat models and exhibit antiosteoporotic pharmacological activity.[15,26]

Osteoprotegerin is a cytokine receptor which plays an important role in osteoblast differentiation and bone formation.[1] Hence, activators and ligands of osteoprotegerin are promising drug targets for the development of therapeutics against osteoporosis. It has been found that naringin could synergistically enhance the action of 1α, 25-dihydroxyvitamin D3 in promoting the secretion of osteoprotegerin by osteoblasts *in vitro*.[1] In addition, naringin can also influence the generation of osteoclasts and subsequently bone loss during organ culture.[1] These findings suggested that the natural compounds such as naringin have immense potential to be used as alternative medicines for the prevention and treatment of osteolysis.[1]

The osteoclast bone resorption is critical in aseptic loosening after joint replacement.[29] The balance between activator of nuclear factor kappa B ligand (RANKL) and osteoprotegerin (OPG) is considered to play a central role in osteoclast maturation (Yang *et al*., 2020). Fibroblasts from the periprosthetic membrane express

RANKL and promote osteoclast formation. Naringin have been reported to inhibit osteoclastogenesis and wear particle induced osteolysis. Authors investigated the naringin-induced OPG/RANKL effects and its underlying mechanism in fibroblasts from periprosthetic membrane.[29] The fibroblasts were isolated from the periprosthetic membrane during hip arthroplasty for revision due to aseptic loosening. Fibroblasts were cultured and treated with or without naringin and DKK-1 (the classical inhibitor of Wnt/β-catenin signaling pathway). OPG and RANKL mRNA and protein levels, gene expression of β-catenin, and cyclin D1, which participate in the Wnt signaling pathway, were examined by real-time polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA). The mRNA and protein levels of OPG were enhanced by naringin in a dose-dependent manner in comparison to the non-treated control. In contrast, naringin did not affect the expression of RANKL. Importantly, DKK-1 attenuated OPG expression in fibroblasts under naringin treatment. Moreover, naringin stimulated the gene expression of β-catenin and cyclin D1 in fibroblasts, and the effect could be inhibited by DKK-1 (Yang *et al*., 2020). The results indicated that naringin enhanced OPG expression through Wnt/β-catenin signaling pathway in fibroblasts from periprosthetic membrane. This may be useful to inhibit periprosthetic osteolysis during aseptic loosening after total joint arthroplasty.[29]

The efficacy of naringin therapy in reducing the osteolysis, characteristic of common musculoskeletal pathologies such as osteoporosis, degenerative joint disease, and osteomyelitis, as well as inflammatory conditions affecting bone such as diabetes mellitus, has been extensively demonstrated *in vitro* and in animal models.[11] Naringin thus represents a naturally abundant, cost-efficient agent whose potential for use in novel musculoskeletal biotherapies warrants revisiting and further exploration through human studies. Here, we review the cellular mechanisms of action that have been elucidated regarding the action of naringin on bone resident cells and the bone microenvironment, *in vivo* evidence of osteostimulative and chondroprotective properties of naringin in the setting of osteolytic bone disease, and current limitations in the development of naringin-containing translational therapies for common musculoskeletal conditions.[11]

Conclusion and Future Perspectives

Osteoporosis is a common pathological condition that influences a significantly large population world wide. Osteoporosis decreases bone strength and increases the risk of bone fracture. Researchers are working on finding the safe, effective and natural compound based remedy for this diseases. Naringin is well known for its broad range therapeutic potential. Naringin has also been investigated for its beneficial role in treatment of osteoporosis. Naringin has been found to improve the bone health and mechanical strength. Various research reports also suggests the molecular mechanisms involved in naringin mediated treatment of osteoporosis. Further studies and clinical evidences are required to establish the naringin based therapy for a effective, safe and natural compound based treatment of osteoporosis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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