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A REVIEW ON ROLE OF NUTRACEUTICALS IN BONE HEALTH

RANE M*, PARMAR U, AHUJA R AND PARADIA P

SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Gate No.1 Mithibai College Campus, V.M. Road, Navpada, Suvarna Nagar, Vile Parle (West), Mumbai-400056, Maharashtra

Running title: Nutraceuticals for bone health

***Corresponding Author: E Mail: Dr. Meenal M Rane: meenalrane12@gmail.com**

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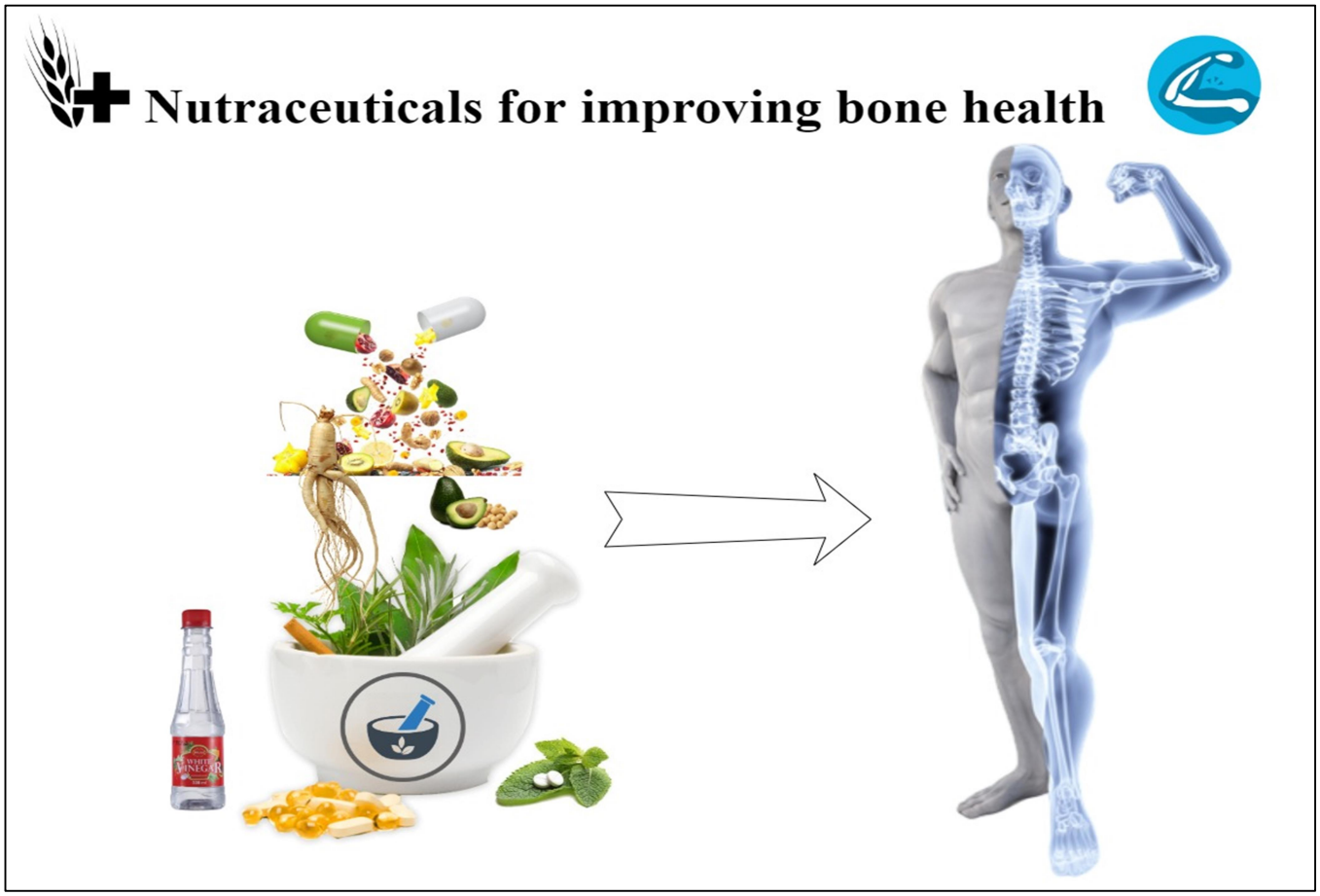
ABSTRACT

Advancements in medical technology has led to a new category of products with medicinal value is developed which involves the use of nutraceuticals. A nutraceutical is any substance that is a food or part of food that provides health benefits, including prevention or treatment of diseases. Nutraceuticals are pharmaceutical alternatives that claim physiological benefits however, they differ from a typical pharmaceutical product wherein they aren't stringently sanctioned under the law. This article aims to postulate promising nutraceutical alternatives to medicines that can be potentially developed into marketed preparations to improve bone health. Thus, combatting bone disorders such as osteoporosis, osteoarthritis, or faster recovery from fracture improving bone strength in normal humans. The newer nutraceutical alternatives for improving bone health is promising. We conclude on our fair understanding and judgment that in due course, these alternative approaches may completely replace the traditional methods.

Keywords: Bone Health, Bone Remodeling, Nutraceuticals, Osteoporosis, Osteoarthritis

Graphical abstract



1. INTRODUCTION

"Let food be thy medicine and medicine be thy food", quoted by Hippocrates around 2,500 years ago is definitely the tenet of today. Nutraceuticals are the emerging class of natural products that makes the line between food and drugs to fade. The nutraceuticals of both plant and animal origin have great opportunities for the food industries to innovate novel food products in the future.

The term "nutraceutical" was coined from "nutrition" and "pharmaceutical" by Stephen De Felice, founder, and chairman of the Foundation for Innovation in Medicine (FIM). According to De Felice, nutraceutical can be defined as, "a food or a part of food that provides medical or health benefits, including the prevention and or treatment of a disease". On the other hand, Health Canada defines nutraceutical as "a product prepared from

foods but sold in the form of pills, or powder (potions) or other medicinal forms, not usually associated with foods." It ranges from dietary supplements to genetically engineered such as beverages.

Nutraceuticals cover most of the therapeutic areas such as anti-arthritic, cold, cough, sleeping disorders, digestion and prevention of certain cancers, osteoporosis, blood pressure, cholesterol control, pain killers, depression, and diabetes. This review attempts to elucidate the novel nutraceuticals that can be used in improving bone health **[1]**. This article discusses the bone ameliorating effects of nutraceuticals. To understand the mechanisms of action of the said nutraceuticals, let us start with the basic principles of bone remodeling mechanisms.

2. Bone Remodeling

Bones are highly organized living tissues. They consist of two types of osseous tissues – 1. Cortical bones present in shaft of long bones which are built up of overlapping of the unit known as reversion system **[2]**. Cancellous bones which are also called spongy bones are present on the terminal end of long bones and flat bones of the hip. They are also present in the vertebral bodies which comprise of the trabecular meshwork. There are two types of cells in bones which include osteoclasts and osteoblasts. Osteoclasts are the cells that are capable of breaking bone down or bone resorption. Osteoblasts in contrast are known bone-building cells. The extracellular matrix is further divided into inorganic and organic components. The bone comprises 40% of inorganic components (hydroxyapatite-$Ca_3(PO_4)_2]3Ca(OH)_2$.), 25% of water, and 35% organic component (proteins). Out of which the almost 90% of the organic component constitutes collagen type I, proteoglycans and 10% non-collagenous proteins such as osteopontin, vitronectin, bone sialo protein and dentin matrix protein-1 (as shown in **Figure 1**) The inter-digitated assembly gives great strength, rigidity and also maintains elasticity **[2]**.

The bone linings are found on the surface of the quiescent bone. The formation is coupled for maintaining high strength, mechanical integrity, regulation of calcium (Ca), phosphorus (P) release and restoration of damages. This plays an important part in fulfilling the body's metabolic needs. Bone remodeling consists of 4 important processes - Activation, Resorption, Formation and Resting.

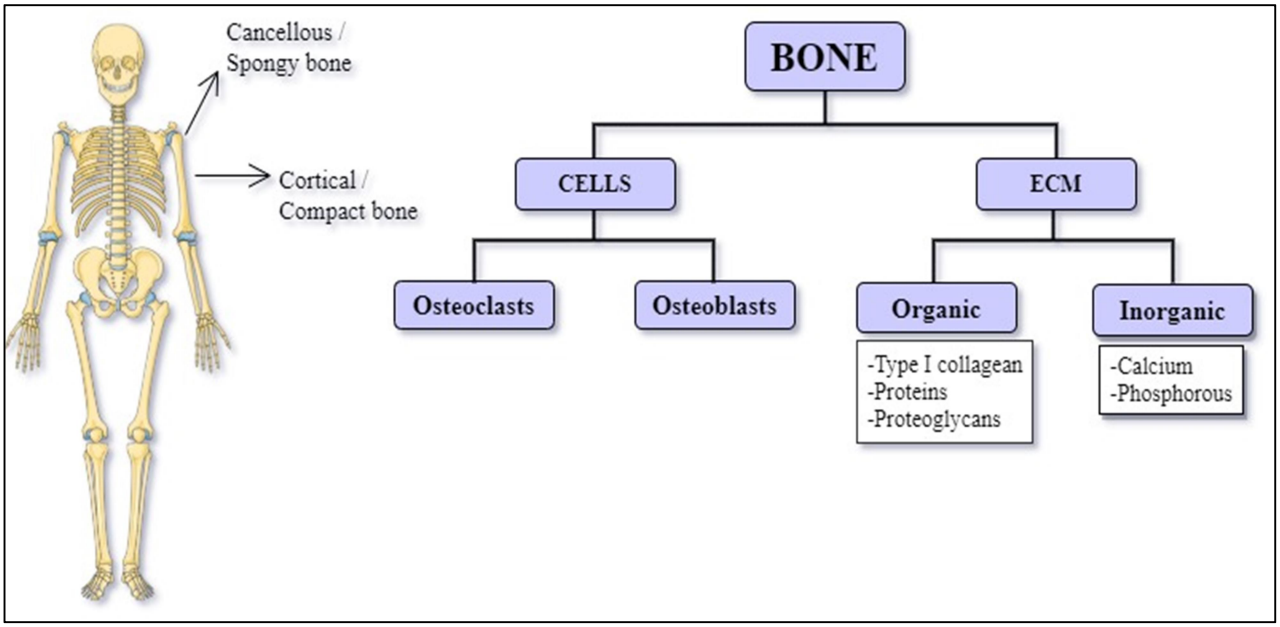


Figure 1: Differentiation of bone components

3. Signaling pathways

Studies suggest that nutraceuticals have can induce osteogenesis by modulation of signaling pathways which are an integral part of bone metabolism. Below listed are the various signaling pathway affecting bone

3.1. RANKL and NF-κB signaling

Osteoclasts are obtained from the hematopoietic precursor cells which are found in the macrophage lineage granulocytes. These cells are capable of breaking down mineralized bone and desire two hits for activation. The clonal expansion in the number of macrophages is initiated by M-CSF. The precursor displays RANK or receptor activate of nuclear factor Kappa B (NF-κb). The precursor cells can be activated by marrow stromal cells and osteoblasts which can differentiate by binding to its RANK-ligand (noted here as RANKL). The release of RANKL initiates the process of osteoclastogenesis which is stimulated by vitamin D, parathyroid hormone, interleukin 1 and prostaglandins. Under the influence of factors such as estrogen, stromal cells secrete a decoy receptor for RANK-Ligand known as osteoprotegerin or OPG that prevents its conversion to osteoclast. The activated osteoclast fuses to form mature bone-resorbing cells and gets recruited to the activated surface. An isolated lacuna is known as 'Howship's lacunae' is created by the tight attachment of osteoclast to the matrix. The acidic environment thus created dissolves the inorganic matrix called board resolution. The bone is catabolized by a protease enzyme

called Cathepsin K which is secreted by osteoclasts in the acidic resorptive pit. The resorption phase completes within 3 to 4 weeks as the calcium and phosphorus are released from the matrix in the blood. Osteoclast disappears from the resorption pits. The bone-building osteoblasts are formed by the differentiation of multipotent mesenchymal stem cells. Further, the osteoblasts synthesize a new organic matrix which includes Collagen type I and Alkaline phosphatase. It is known that a high alkaline phosphatase level is a sign of cholestatic disease or increased bone turnover. The step of formation requires enough amount of calcium and phosphorus and a period of 3 to 4 months (Diagrammatic representation shown in **Figure 2**). The surface of the bone remains dormant until the next cycle is about to begin. Osteoblast gets trapped in the matrix and form mechano-receptors called osteocytes. These osteocytes are connected. They respond to damages by releasing substances that impact bone remodeling. Sclerostin stops osteoblast formation which is the main target for osteoporosis treatment. Osteocytes have great influence on bone turnover that repairs any microscopic damage which ensures maintenance of new strong bones **[3-6]**.

3.2. Macrophage-colony stimulating factor

The macrophage-colony stimulating factor (M-CSF), are useful in the proliferation, differentiation of hematopoietic cells. M-CSF looks after the regulation of changes in cytoskeletal bones. The studies prove that M-CSF is required for osteoclasts differentiation. M-CSF binds to receptor C-FMS which activates downstream signaling pathways. M-CSF revives the osteoclasts precursors by activating survival protein Bcl-xL **[7]**.

3.3. Src

Src is a non-receptor tyrosine kinase (NRTK). The Src shows a major effect on the bone-resorption activity of fully formed osteoclasts and not on its formation. Src acts by promoting the reshuffling of the podosomes in the osteoclasts. Src is essential for bone resorption. Wedelolactone, and fisetin are capable of inhibiting Src thereby preventing bone loss **[8]**.

3.4. TGF-βSmad signaling

TGF functions by binding type I and II having serine/ threonine kinases. The Smad proteins function by transmitting signals from the receptor to the nucleus. Bone morphogenetic protein (BMPs) a type of TGF protein is important in the process of osteogenesis as it mediates various activities in skeleton tissues which promotes bone formation Eg. BMP-2. These pathways can be Smad-dependent as well as independent. The BMPs are also

responsible for regulating genes that are necessary for the differentiation of osteoblasts **[9]**. The BMP-2 regulates the p38 in the osteoblasts. MAPKS induces by the BMP-2 regulates the osteocalcin expression. Inhibiting NF-κb signaling is beneficial for the inhibition of bone loss.

Natural agentsthat cause osteoblasts to differentiate via reducing TGF-β-Smad pathways arequercetin, celastrol, andrographolide, silymarin **[10]**.

3.5. ***Fibroblast Growth Factor Signaling (FGF)***

FGFare polypeptides that bind to the FGF tyrosine kinase receptors (FGFRs) for the regulation of events such as endochondral and intramembranous ossification. The Runx2 is activated by FGF viaMAPK pathways and helps in regulatingthe formation of bone **[11]**.

Nutraceuticals such as curcumin, apigenin, genistein, oleanolic acid, berberine emodin, quercetin, resveratrol, silymarin, withanolide are capable in activating the transcription factor Runx2 via MAPK pathway and thereby contributes in bone formation **[12]**.

3.6 Wnt/β -catenin signaling

Wnt/β -catenin signaling suppresses CCAAT/enhancer-binding protein alpha(C/EBPα) and peroxisome proliferator-activated receptor-gamma (PPARγ) which leads to activation of transcription factors for osteoblastogenesis **[13, 14]**. Inhibition of C/ebpa or PPARγ expression in ST2 cells causes a reduction in adipogenicity and leads to generation of osteoblasts. A study confirmed that β -catenin is essential forpostpartum bone homeostasis.Wnt signaling pathways are modulated by nutraceuticals such as curcumin, wedelolactone, celastrol, andrographolide, and berberine **[15]**.

3.7 Ephrin Signaling

Two directional signaling is done by Ephrins which is regulated by EphrinB2 ligand and EphrinB4 in osteoclasts and osteoblasts respectively **[10]**. Ephrin signaling is considered to be one of the important signaling pathways for bone homeostasis. Curcumin, quercetin, Resveratrol, celastrol, fisetin, emodin, genistein, and berberine are capable of inducing differentiation of osteoblasts.Thus, preventing the decaying of bones **[16]**.

3.8 Hedgehog Signaling

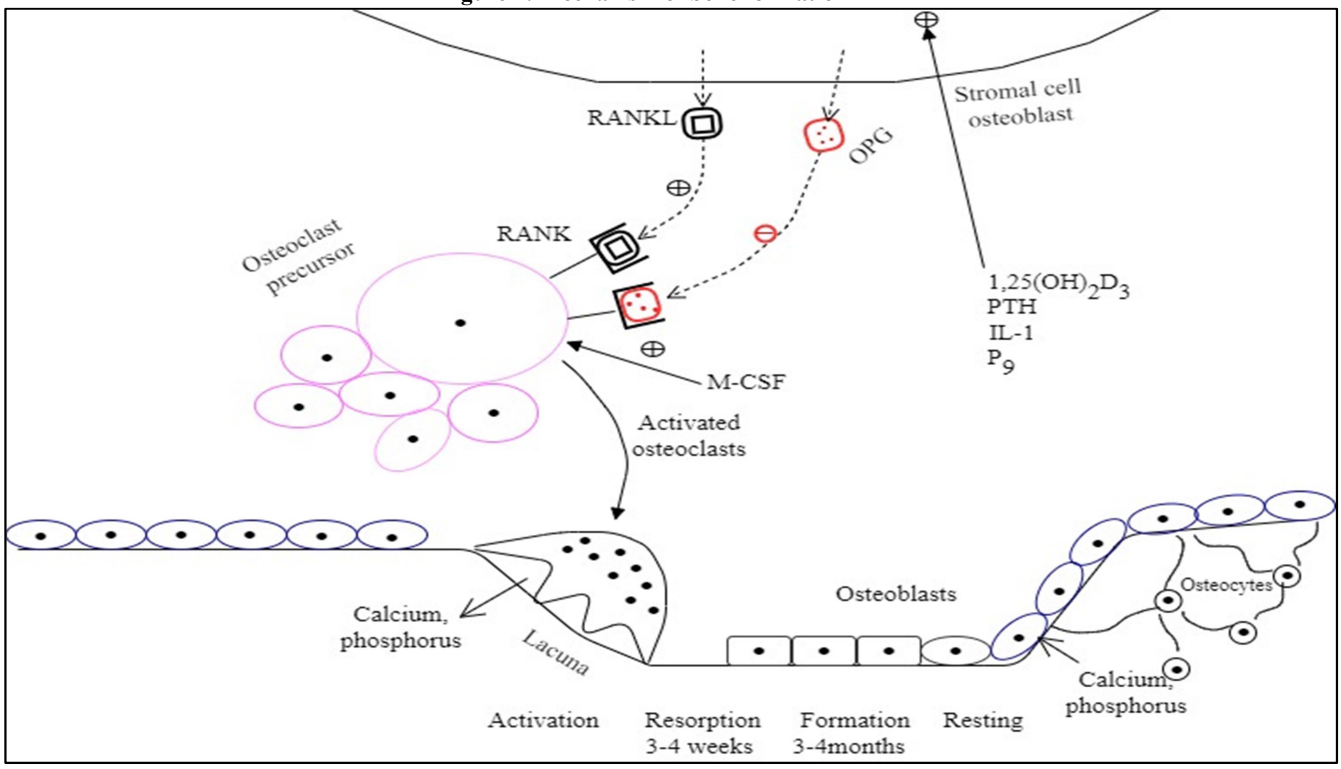
The Hedgehog Signaling (Hh) pathway has a role in the skeleton mutation which causes brachydactyly type A1 and gorlin syndrome.(17)Deregulation of chondrocyte homeostasis is a result of homozygous mutation of the Hh pathway **[18]**. Recent studies confirm that osteogenic differentiation can be induced by resveratrol by the inhibition

of hedgehog signaling **[19]**. Studies are required for confirming whether the natural agents are capable of inducing bone formation by modulation of the hedgehog signaling pathway.

3.9 Parathyroid hormone Signaling

Parathyroid hormone Signaling is generally for building bone. Parathyroid hormone (PTH) can show a catabolic or anabolic effect. Parathyroid hormone-related protein (PTHrP), and the PTH/PTHrP receptor have an important function in bone metabolism. Studies confirm that phytoestrogen is capable of inhibiting osteoporosis in the menopausal group.

Figure 2: Mechanism of bone formation



4. Nutraceuticals for Bone Health

Several nutraceuticals such as ginseng, resveratrol, curcumin, quercetin, ursolic acid, glycine max, modulate NF-κb signaling pathways and inhibits bone loss. Isoflavone induces osteoblast differentiation by upregulation of PPARγ, BMP2, Wnt/β-catenin, Smad5, Runx2, oestrogen and oestrogen receptors. It inhibits osteoclastogenesis by inhibition of transcription factors, which are important for bone loss such as, NF-κb, AP-1, or cytokines such as IGF-1 and TGF-β.

Following are some of the nutraceuticals that help to prevent osteopenia (bone loss) thereby maintaining the integrity of the bone.

4.1 Ginseng

Ginseng is a short, slow-growing plant with fleshy roots consisting of 11 species. It belongs to the family Araliaceae and genus Panax. The pharmacological actions of 5 have been examined. Panax ginseng is the most commonly used species. It is claimed that ginsenosides, chemical components found in ginseng, are responsible for the clinical effect of the herb **[9, 10]**.

A study was conducted by Zhou W, *et al*., in which species 229 of Paecilomyces bainier was isolated and maintained by periodical transfers on potato dextrose agar slant. Biotransformation of ginsenoside Rb1 was done to produce compound K (C-K) was identified as Rb1→Rd→F2→C-K.(20) Wnt/b-catenin pathway controls osteoblast differentiation and bone formation. Results showed upregulation in the expression of Wnt/b-catenin genes (2.2 and 6.5 times respectively in case of Wnt10 and Wnt11, critical in bone formation) and differentiation markers [ALP (3 times), Runx2 and Colla1] **[12]**.

4.2 Avocado-Soyabean Unsaponifiables (ASU)

They are botanical extracts of residual fractions of avocado and soybean oils that can no longer be made into soap after saponification and are present in the ratio 1:2 respectively. ASU has been known to relieve pain in Osteoarthritis (OA) and other bone-related disorders. It possesses chondroprotective, anabolic, and anticatabolic properties **[22, 23]**.

ASU exhibits disease-modifying properties rather than structure-modifying effects. A.S.A. Al-Afify *et al*. Conducted a study in 40 mono-iodoacetate-induced knee-arthritis (MIA) rats (Sprague-Dawley). The study concluded that ASU significantly reduced the oxidative stress and inflammation in the cartilage and subchondral bone. It also marked a decrease in the pro-matrix metalloproteinase 13 (MMP-13) and thus was observed combating cartilage destruction.

Despite the proven potential benefits of ASU in improving the bone structure and its prominent disease-modifying action in OA, it is yet to be clinically proven that ASU can be marketed to treat OA or other bone disorders. Current strategies to combat OA include using ASU as a combination therapy **[24]**.

4.3 Chondroitin Sulphate and Glucosamine sulfate

Chondroitin sulfate and glucosamine are required for the biosynthesis of proteoglycans

in the human body which are vital for maintaining the integrity of the cartilage. The use of the combination may serve as a non-invasive means to protect the cartilage joint and delay the progression **[25]**. Both are available as over the counter (OTC) medicines and dietary supplements **[26]**. The use of the combination may serve as a non-invasive means to protect the cartilage joint and delay the progression **[27]**. CS possesses anti-inflammatory activity. It aids in osteoarthritis by providing homeostasis maintaining structural integrity, slows breakdown and shows a reduction in the sore muscle. Often intermix with glucosamine for the treatment of osteoarthritis **[28]**. ESCEO (European Society for the clinical and economic aspect of osteoporosis and osteoarthritis) recommends chronic Symptomatic slow-acting drugs for osteoarthritis (SYSDOA'S) including glucosamine and chondroitin sulfate as the first-line therapy for knee arthritis **[29]**. The amount generally administered are Glucosamine 1500 mg and chondroitin sulfate as 1200 mg daily. The amount of chondroitin sulfate can be 1200 mg as a single dose or 400 mg three times a day both have an equivalent effect. The study shows that the prescription form of the patented crystalline glucosamine (PCGs) demonstrates high efficacy over glucosamine sulfate and glucosamine hydrochloride formulation which also shows high bioavailability and plasma concentration **[26]**. But both glucosamine and chondroitin sulfate as single or in combined form does not effectively cause a reduction in pain in the overall group of patients suffering from osteoarthritis of the knee but analysis suggests that the combination may be effective in a subgroup of the patient with moderate to severe knee pain. However, a recent study suggests that the combination has comparable efficacy to celecoxib in reducing stiffness, pain, joint swelling/effusion, functional limitation after 6 months in patient with painful knee Arthritis **[28]**. Another meta-analysis suggests that it helps in knee osteoarthritis but robust evidence is required for it to be used as a dietary supplement **[27]**. It is accredited in the US as the dietary supplement for osteoarthritis while it is used as SYSDOA in Europe **[30]**. It shows a long term safety profile but hepatotoxicity can occur in a patient with chronic liver disease. There is a long term reduction in additional pain analgesia and NSAIDS with the PCGS with over 50% reduction in the cost of medication and other expenses over 12 month period **[29]**. The synergistic combination of this world widely preferred nutraceuticals is a step forward in the management of the osteoarthritis.

4.4 Troxerutin

It is a trihydroxy ethylated derivative of rutin (commonly known as bioflavonoid) used as a nutraceutical that helps reduce pain. It is also used as a vasoprotective agent. This drug has anti-oxidant properties and is good for venous health (strengthens capillary walls and prevents leakage). In females, postmenopausal osteoporosis is caused due to an imbalance between osteoclasts and osteoblasts. Formulations such as Troxerutin 500mg + Calcium dobesilate 500mg are available in the market.It is used in ovariectomy (OVX) induced osteoporosis as it shows its effect on regulation of osteoclast and osteoblasts.

Female mice were used for in vivo experiment. They were injected intraperitoneally with TRX (150 mg/kg) or with saline and TRX (50 mg/kg). The mice were then sacrificed and used for techniques such as micro-computed tomographical analysis and biochemical analysis. Osteoclasts derived from RAW264.7 and osteoblasts derived from MC3T3-E1 were treated in vitro with various concentrations of Troxerutin to test its effect on osteoclastogenesis and bone resorption, osteogenesis and mineralization. From the study, it was demonstrated that Troxerutin prevented the loss of cortical bone and trabecular bone in ovariectomized mice. This is due to a reduction in osteoclastogenesis. It also promotes in vivo osteogenesis. While the activity of RAW264.7 derived osteoclasts was inhibited, Troxerutin also inhibits its formation in vitro. Inhibition of the expression of activated T-cell's nuclear factor was observed. Mineralization of MC3T3-E1 was improved, it was due to improving the expression of osterix, transcription factor 2 and also collagen type1 alpha1. Osteogenesis was improved. This data demonstrated and showed the results that Troxerutin prevents osteoporosis induced by OVX. Thus, can be used in as a Novel Drug Delivery System (NDDS) in treatment for postmenopausal osteoporosis **[31]**. The research on this compound has been very less likely to be focused, further research might bring up new facts and uses of the compound.

4.5 Curcumin

Curcumin is obtained from rhizomes of turmeric (C.longa) belonging to the Zingiberaceae family. Curcumin is the main active component of turmeric which is a prime spice in India. It is an ancient herb of Ayurveda and well known for the treatment of many diseases including inflammatory diseases, cancer, various skin diseases. Many studies demonstrate that the curcumin is capable of downregulating the activation of pathways responsible for bone loss i.e NF-κb, Wnt/β-catenin, RANKL and TNF-α **[32]**.

Curcumin is capable of inhibiting osteoclastogenesis by inhibition of HMGB1 in p38-MAPK mechanism **[33]**. Curcumin has been proven potential for inhibition of bone loss due to various reasons such as ovariectomy, breast cancer etc. Curcumin controls bone metabolism by inhibition of adipose-derived MSCsuch as Wnt/β-cateninsignaling **[34]**.

4.6 Resveratrol

Resveratrol is obtained from various plants such as blueberries (Vaccinium spp.), blackberries (Morus spp.), and peanuts (Arachis hypogaea). Resveratrol is known for suppressing NF-κb activation which is an important signaling pathway for bone loss. Resveratrol regulate Runx2 by inducing SIRT1, which causes differentiation of osteoblast. It has been proven potential against MTX-induced bone loss **[35, 36]**.

4.7 Quercetin

Quercetin is a flavonoid obtained from onion and other fruits and vegetables. This flavonoid is capable of regulating bone metabolism by activating osteoblast and inhibiting osteoclasts. Quercetin activates Smadand p38 MAPKand inhibits Wnt/β-cateninpathways. It helps to inhibit osteoclastogenesis induced by RANKL by inhibiting NF-κb **[37]**. It inhibits bone loss in the animal model having underwent ovariectomy **[8]**.

4.8 Glycine max

Glycine max is obtained from soybean belonging to the Fabaceae family. Genistein isoflavone obtained from genesta tinctoria. Isoflavone induces osteoblast differentiation by upregulation of PPARγ, BMP2, Wnt/β-catenin, Smad5, Runx2, oestrogen, and oestrogen receptors. It inhibits osteoclastogenesis by inhibition of transcription factors, which are important for bone loss such as NF-κb, AP-1 or cytokines associated with bone loss such as IGF-1 and TGF-β **[8]**.

Mechanisms for improvement of bone health of various nutraceuticals are shown in **Table 1**.

Table 1: Overview of nutraceuticals for bone health [1]

Sr. no	Nutraceuticals	Natural source	Mechanism		References
			Facilitates	Inhibits	
1	Withanolide	*Acnistus arborescens*	Runx2	RANKL, Smurf2, NF-κb	
2	Silibinin	*Silybum marianum* (milk thistle)	BMP-2, p-AKT	p38,NFATc1, NF-κb,cathepsin-K, AP-1,	(38)
3	Rosmarinicacid	*Rosmarinus officinalis*	-	NFATc1, MMP-9,cathepsin-K, NF-κb	(39)
4	Lupeol	*Senegalia visco*	-	NFATc1, NF-κb	(40)
5	Syringetin	*Lysimachia*	-	AKT, RANKL	(7)

		congestiflora			
6	**Oleanolicacid**	***Phytolacca Americana,* oliveoil**	**osteocalcin,Runx2**	**-**	**(41)**
7	**Indole-3-carbinol**	**Cruciferous vegetables**	**-**	**IL-6,NF- κb,TNF-α, IL-1,PGE2**	**(42)**
8	**Gambogic acid**	***Garcinia***	**-**	**NF-κb, IL-6, NFATc1, p-Akt, Erk1/2**	
9	**Harpagoside**	***Hanburyi* (false mangosteen)**	**-**	**NFATc1**	**(43)**
10	**Wedelolactone**	***Harpagophytum m procumbens* (tweed spider) *Eclipta alba***	**β- catenin, Runx2**	**NF-κb, NFATc1, GSK3B activity, c-Src**	**(44)**
11	**Celastrol**	**Tripterygium (false daisy)**	**-**	**β-catenin, Runx2, BMP-2, osteocalcin**	**(45)**
12	**Theallavin-3,3 digallate**	**Camellia sinensis**		**C-Fos, NF-κb, RANKL**	**(46)**
13	**Zerumbone**	***Zingiber zerumbet* (bitter Ginger)**	**-**	**NF-κb,**	**(47)**
14	**Ursolic acid**	***Ocimum Sanctum* (Holy Basil)**	**-**	**NFATc1, NF- κb,JNK,**	**(48)**
15	**Gingerol**	***Zingiber officinale* (Ginger)**	**Collagen typeI, ALPactivity**	**IL-6, NF- κb,**	**(49)**
16	**Piperine**	***Piper nigrum***	**-**	**p38, NFATc1**	**(50)**
17	**Embelin**	***Ardisiajaponica***	**-**	**NF-κb**	**(51)**
18	**Andrographolide**	***Andrographis paniculata*(King ofBitters)**	**ALP, Runx2**	**Calcitonin receptors, Cathepsin- K, NF-κb, NFATc1**	**(52)**
19	**Butein**	**Toxicodendron Vernicifluum (Chinese lacquer)**	**-**	**RANKL,NF-κb,PGE2**	**(53)**
20	**Sulforaphane**	**Cruciferous vegetables**	**STAT1**	**NF-κb, NDATc1, cathepsin-K**	**(54)**
21	**Silymarin**	***Silybum marianum* (milk thistle)**	**collagen secretion,osteocalcin, BMP,SMAD, Runx2,**	**NF-κb, JNK, p38, ERK, NFATc1, OSCAR,**	**(55)**
22	**Plumbagin**	***Drosera and Nepenthes* (pitcher plants)**	**-**	**NF-κb, MAPK, RANKL**	**(56)**
23	**Honokiol**	***Magnolia grandiflora* (bull bay)**	**BMP-2, Smad**	**p-p38 MAPK,ERK, JNK, NFATc1,IL-6, RANKL, TNFα, NF-κb,**	**(57)**
24	**Fisetin**	***Acacia greggiil, Acacia berlandieri,* (Cat claw)**	**MKP-1, Runx-1**	**p38 MAPK, c-Fos,NFATc1, cathepsin-K, NF-κb, c-Src-2, osteocalcin,**	**(58)**
25	**Ellagic acid**	***Juglans regia* (Walnut)**	**-**	**p38 MAPK**	**(59)**
26	**Betulinic acid**	***Betula pubescens* (downy birch)**	**-**	**MMP-2,MMP-9, cathepsin-K**	**(60)**
27	**Emodin Rheum**	***Emodi* (Himalayan rhubarb)**	**Runx2, osterix, osteocalcin, ALP**	**RANKL, PPARγ,C/ebpα,**	**(61)**
28	**Caffeic acid**	***Eucalyptus globulus* (blue gum)**	**Runx2**	**p38, NFATc1, TRAP, cathepsin-K,c-Src,**	**(62)**
29	**Apigenin**	***Petroselinum crispum* (parsley)**	**BMP-6, Osteopontin, Runx2, p-JNK,p-p38**	**IL-6,MCP-1, MCP-3, MCP-1, RANKL,**	**(63)**

30	**Luteolin**	**Found in many cruciferous vegetables, fruits and herbs**	**Hsp90b1**	**p38 MAPK, NFATc1,TNF-α, CTX,**	**(64)**
31	**Genistein**	***Genista tinctoria* (dyer's broom)**	**ALP,TGF-β1,Estrogen Receptor, Runx2, SMAD5, BMP2**	**TNF-α, PPARγ, adipsin,NF-κb,**	**(65)**
32	**Lycopene**	***Solanum lycopersicum* (tomato)**	**-**	**ALP, IL-6**	**(66)**

5. CONCLUSION

Bone loss treatment requires a life-long regimen of drugs which causes an unnecessary impact on the quality of a patient's life. The allopathic pharmacotherapies available in the market are facing the advent of side effects such as atrial fibrillation, hypersensitivity reactions, hot flashes, leg cramps, atypical subtrochanteric fracture, nausea, constipation, etc. Nutraceuticals offer a promising alternative to traditional pharmacotherapy due to their property of modulating cell signaling pathways and thereby reversing or slowing down the process of osteopenia and osteoporosis. They are economical and relatively new category of products with medicinal value that are neither pharmaceuticals nor dietary products, which lie in a category between these two possessing both their properties. With the emergence of the concept of nutraceuticals, exhaustive research has begun to exploit their benefits which propose a low-risk factor. In this article, we have attempted to highlight the bone ameliorating properties of nutraceuticals. We would strongly emphasize that the use of nutraceuticals might be fruitful for the treatment of bone loss. Further, we postulate the possibility of formulating nutraceuticals into pharmaceutical preparations as alternatives or adjuncts to existing allopathic treatment approaches for improving overall quality of life of the patients.

6. Conflict of interest

The authors declare no conflicts of interest.

7. Funding

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Abbreviations: RANKL - Receptor Activator Of Nuclear Factor Kappa-B Ligand (RANKL); NF-Kb - Nuclear Factor Kappa B; M-CSF - Macrophage-Colony Stimulating Factor; OPG – Osteoprotegerin; NRTK - Non-Receptor Tyrosine Kinase; Bmps - Bone Morphogenetic Protein; Bcl-Xl - B-Cell Lymphoma-Extra Large; Pparγ - Eroxisome Proliferator-Activated Receptor-Gamma; Pcgs - Patented Crystalline Glucosamine; ESCEO - (European Society For The Clinical And

Economic Aspect Of Osteoporosis And Osteoarthritis); SYSDOA'S - Symptomatic Slow-Acting Drugs For Osteoarthritis; TRX – Troxerutin; TNF-A – Tumor; Necrosis Factor Alpha; HMGB1 - High Mobility Group Box 1 Protein; P38-MAPK - P38 Mitogen-Activated Protein Kinases (Mapks); MTX – Methotrexate; Runx2 - Runt-Related Transcription Factor 2; IGF-1 - Insulin-Like Growth Factor 1; TGF-B - Transforming Growth Factor Beta; Nfatc1 - Nuclear Factor Of Activated T-Cells, Cytoplasmic 1; AP-1 - Activator Protein 1; MMP-9 - Matrix Metallopeptidase 9 ; IL-6 – Interleukin; PGE2 - Prostaglandin E2; Erk1/2 - Extracellular Signal-Regulated Kinase 2; GSK3B - Glycogen Synthase Kinase 3 Beta; JNK - Jun N-Terminal Kinase; OSCAR – Osteoclast Associated Receptor ; Pparγ - Peroxisome Proliferator-Activated Receptor Gamma; C/Ebpα - CCAAT-Enhancer-Binding Proteins; TRAP - Tartrate Resistant Acid Phosphatase; MCP-1 Monocyte Chemotactic Protein-1; CTX - C- Terminal Cross Link Telopeptide; ALP - Alkaline Phosphatase

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