Review Article

Osteoporosis and its Management – An Overview

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ABSTRACT

Osteoporosis is worldwide recognized public health problem from the last two decades there is an increase in the rate of incidence of bone fracture and there are different pharmacologically effective treatment available with herbal, synthetic and some mineral sources for osteoporosis treatment in most of the countries and around the world. Drugs under the class of Bisphosphonates(BPs) most frequently used and other drugs like calcitonin, calcium and vitamin D, hormonal replacement therapies, Growth factors, cytokines , cathepsin, strontium ranelate, anti-sclerostin antibodies, Parathyroid hormone are used in the treatment of osteoporosis and also other class of pharmacological act ion drugs also identified as antiosteoporotic drug such as Anti-hypertensive, calcium sensing receptor antagonist, Activin inhibitor, cannabinoids agonist and statins and some polymer Nano particles(NPs) . Some of the drugs under these class are under clinical trial to study the role of drugs in the treatment of osteoporosis.

Keywords: Osteoporosis, Bisphosphonates, Overiectomy induce osteoporosis, Glucocorticoids induced model, Herbal drugs.

INTRODUCTION

Bone is a mineralized connective tissue which has many functions such as giving shape to body. The skeleton bones serve as structural frame work for the body by supporting soft tissue and by providing the point of attachment for tendons of the skeletal muscle. It provide protection for most of the important internal organs such as heart, lungs, spinal cord and brain. Help in movement, blood cell production and maintains mineral homeostasis for its storage and release especially calcium, phosphorous which are most important mineral to the strength of bone. Bone is a dynamic tissue of the body, it will undergo a continuous process called as bone remodelling, this is mainly due to action of both osteoblast and osteoclast cells and these forms of cell are responsible for bone resorption and later which are involved in bone formation. The function of bone cells is growth, modelling, remodelling of bone and this are some of the reasons for development of bone disorder such as osteoporosis, osteomalacia and rheumatoid arthritis.[1] Osteoporosis is characterized by decreased bone mass and disruption of bone architecture that may result in increase in risk of fragile fracture. Osteoporosis is recognized as world-wide health problem that affects millions of people around the world, 50 % of females are affected by osteoporosis and about 30% of male above age of 65 y are affected by osteoporosis. It occurs majorly in age old people and particularly in postmenopausal women due to deficiency of estrogen level by cessation of menopause. In the present study, the expectancy of life is about 67 y in India and increases in the expectancy of life span about 71 y by the time of 2025 and at 2050 is around 77 y. In India around 10 % of population at age of 50 y are affected by osteoporosis and it may increase in a greater proportion around 34 % Indian population over the age of 50 y, which result in increased number of population are suffer from osteoporosis.[2]

Pathogenesis of Osteoporosis

Osteoporosis is mainly occurs by reducing optimal bone mass, strength, bone growth and increases bone resorption which leads to decreases in bone mass and disruption in bone micro architecture and also bone remodelling. The remodelling is the process started by the activation of hematopoietic precursor to form osteoclast cells. For formation of osteoclast which requires interaction with other cells of osteoblastic lineage leads to bone remodelling. The reversal phase of remodelling of bone become shorter period, it will result in loss of bone mass and further result in weak bone.

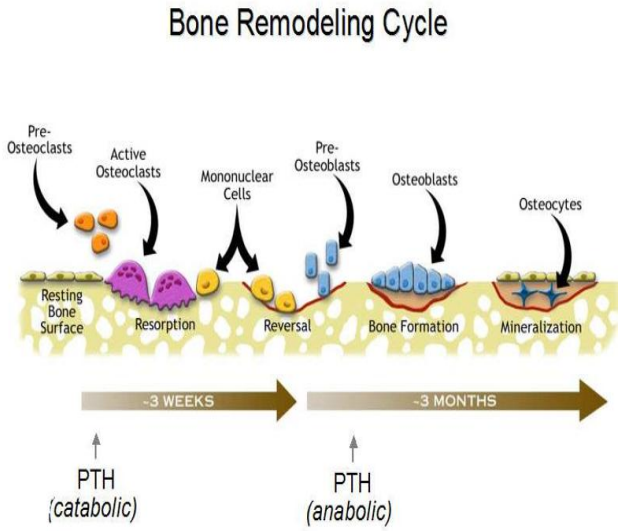

Figure 2: Bone Remodelling Cycle

Corticosteroid induced osteoporosis

Glucocorticosteroids have direct effect on osteoclast and osteoblast cells. Drugs binds to corticosteroid receptor and it inhibit the growth of osteoclast and osteoblast cell, corticosteroids depress the bone formation greatly that will result in bone remodelling which leads to great changes in histology and micro anatomy of bone. Corticosteroid reduces the calcium absorption due to disturbance in calcium regulating hormone and sex steroid hormone. Absorption of calcium in the intestine is reduced by use corticosteroid which leads to decrease in renal tubular calcium reabosrption. Initially changes are occurs due to secondary hyperparathyroidism and there is also alteration in the secretion of hypothalamic gonadotrophine releasing hormone with subsequent reduction in the level of oestradiol and testosterone. Corticosteroids produces the cellular response with in micro environment of bone by modulating the release of cytokines and other factors which act locally regulate the remodelling and those factors which include insulin-like growth factor, tumour necrosis factor and interleukin-1.

Overiectomy induced osteoporosis

The major primary type of disease is postmenopausal osteoporosis which can causes morbidity in most of the women suffering from osteoporosis, the disease is mainly due to deficiency of estrogens. It is most commonly seen in women after menopause, hence the estrogens play an important role by regulating bone remodelling and maintains bone homeostasis and in other side estrogens produces the osteoprotective action. The Receptor Activator expression of the Nuclear factor-kB Ligand is inhibited by estrogens (RANKL), hence these RANKL act as cytokine which is essential for osteoclast bone resorption and result suppression of both the differentiation and activation of cells. Estrogen can also stimulate the secretion of osteoprotegerine by stimulating osteoblast cells, hence these osteoprotegerine act as a cytokine to block the RANKL and that leads to inhibition of osteoclastogenesis, bone resorption and the increases the level of osteoclastogensis can result in the development of postmenopausal osteoporosis.[3]

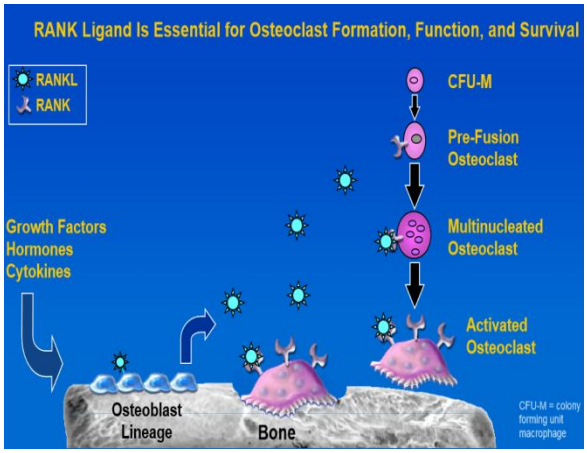

Figure 3: formation, function and survival of osteoclast cells

Immobilization induced osteoporosis

The voluntary physical activity or movements decreases in many elderly population and some are subjected to bed rest for prolonged period of time such situation can leads to bone loss. Hence the experimental model which indicates this type of diseases is limb immobilization model for development of osteoporosis in animal. Immobilization of limb effectively stimulate the bone resorption and enhances the rate of bone formation, which can leads to loss in both cortical and cancellous bone and also the bone loss is accelerated due to the increases in serum PTH.[4]

Details of traditionally used herbs for treating Osteoporosis

Table 1: List of the Herbal Plants [19-23]

Botanical name	Family	Part used	Chemical constituents
Asparagus racemosusWilld.	*Asparagaceae*	Tuberous root	Steroids and flavonoids
Achyranthes bidentata Bl.	*Amaranthaceae*	*Root*	*Achyranthesbidentata,* leanolic acid glycosides, saponins, ecdysterone, ketosteroids, and flavonoids
Cissusquadrangularis L.	*Vitaceae*	Aerial parts	Vitamin C and Betacarotene
Cimicifugaracemosa	*Ranunculaceae*		Flavonoids, triterpine glycoside and aromatic acids
CurculigoorchioidesGaertn	*Hypoxidaceae*	Rhizome	flavonoids, lignans, saponins and iridoid glycosides
Cistanche salsa G. Beck	Orobanchaceae	Stem	Phenylethanoid glycosides , Echinacoside,
Cuscuta chinensis Lam.	Convolvulaceae	Seed	flavonoids, polysaccharides, alkaloids, steroids, volatile oils, lignans
Cimicifugafoetida	*Ranunculaceae*		Cimicifoetisides A and B, triterpenoides
Cissusquadrangularis)	*Vitaceae*	Stems	Steroids, alkaloids, calcium
Curcuma longa L.	*Zingiberaceae*	Rhizome	Curcumin

Carthamustinctorius L.	*Asteraceae*	Flower	Flavonoids, Kinobean A, fixed oil etc.
Camellia sinensis	*Theaceae*	Leaves	Polyphenols and flavonoids
Dendrobiumofficinale orchid	Orchidaceae	Stem	Polysaccharides, stillnodes, alkaloids, amino acids,
Epimediumbrevicornium	*Berberidaceae*	Herb	Icarin,flavonoids,sterols, fatty acids
Eupatorium lindleyanum DC.	*Compositae*	Root	Ginkgolides, bilobilides
Lepidiummeyenii	*Brassicaceae*	Stem	Alkaloids, steroids, glucosinolates, macamides
LigustrumlucidumAit	*Oleaceae*	Rhizome	Oleanolic acid, lupeol, betulin, fatty acids etc
Nigella sativa L.	*Ranunculaceae*	Seeds	
Onobrychisebenoides	*Leguminosae*	Leaves	Arylobenzofuransandisoflavonoid
Pleurotuseryngii	*Pleurotaceae*	Aerial parts	Polysaccharides, volvatoxin, ganoderic acid, etc.
Psoraleacorylifolia	*Fabaceae*	Rhizome	Furano-coumarins, Flavonoids, terpenoids
Punicagranatum L.	*Lythraceae*	Fruit	Ellagic acid, Gallic acid, Chlorgenic acid Coumaric acid
Rumexcrispus L.	*Polygonaceae*	Root	
Rehmanniaglutinosa	*Scrophulariaceae*	root tubers o	Steroids, norcarotenoids, remophilanetrioletc
Sophora japonica	*Leguminosae*	Seed	Isoflavonoids
Sambucuswilliamsii	*Leguminosae*	Branches and Stems	Steroids, triterpenoids, phenolic acid etc.
Saracaindica,	*Caesalpinaceaceae*	Barak	Beta stosterols,qercetine, kaempferol,epgenine,flavonods
Trifoliumpratense	*Fabaceae*	Aerial parts	Isoflavonoids like biochanin A and genistein
Tinosporacordifolia (Thunb.) Miers	*Menispermaceae*	Stem	Terpenoids, alkaloids, steroids
Verbascumblattaria L.	*Scrophulariaceae*	Aerial parts	E-harpagoside, laterioside, kaempferol 3-O-β-D-glucopyranoside, bis(2-ethylhexyl)phthalate, and (2S)-liquiritigenin
Withaniasomnifera (L.) Dunal	*Solanaceae*	Root	Withaferin,withanolides,withanone and withasomidienone
Wedeliacalendulaceae	*Solanaceae*	Perennial herb	Isoflavonoids, wedelolactone
Zingiberofficinale Roscoe	*Zingiberaceae*	Seeds	α-pinene, Camphene, Heptanol

Synthetic Drugs Used in Treatment of Osteoporosis

Bisphosphonates (BPs)

Bisphosphonates are the first line therapy for treatment of osteoporosis and this drug act by inactivating osteoclastic bone resorption and enhances apoptosis of osteoclast cells. BPs increases bone mineral disease and decreases bone fracture risk. Residronate, Ibandronate, Minodronate, Pamidronate, Clodronate, Aledronate, Etidronate, Zoledronate, Tiludronate. All these drugs are different in structure, affinity and potency on bone. Among these drugs Zoledronate and Alendronate are two common drugs used frequently in treatment of osteoporosis because of high affinity towards bone and affects shows for longer period of time.[5]

Calcitonin

Calcitonin used as second line therapy for treatment of osteoporosis, it act as endogenous inhibitor by decreasing osteoclast formation result in inhibition of bone resorption. Calcitonin is secreted from the C-cells of the thyroid. Calcitonin available in two forms of formulation such as nasal sprays and injectable forms (example Salmon calcitonin and Salmon calcitoninare) 40 times more potent than naturally occurring calcitonin human body.[6]

Denosumab

It is a human monoclonal RANKL antibody used in treatment of osteoporosis by inactivation of osteoclast cells, osteoclast apoptosis and by reduction in osteoclast cells differentiation by blocking the binding of RANKL to RANK. Denosumab is not a first line therapy (FLT) for treatment of osteoporosis but it can be choice for FLT, if patient who receiving oral BPs shows intolerance and renal failure. Patients at high fracture risk its beneficial effects were shown in older men under androgen deprivation therapy for prostate cancer, and women who receive adjuvant aromatase inhibitor for breast cancer. Generally, it is not recommended to be used in premenopausal women or children and for prevention of osteoporosis. Its combination with other pharmacological agents for osteoporosis is not suggested. Similar to BPs, hypocalcaemia and vitamin D deficiency should be

managed before starting treatment, and adequate Ca and vitamin D should be administered during treatment with Denosumab.[7]

Calcium and vitamin D

Both the supplements can be used as base line therapy for treatment of osteoporosis and also used as preventive measure for diseases in elderly patient. Only vitamin D cannot reduce the bone fracture hence it is used in combination with calcium. The recommended daily intake of vitamin D and calcium in postmenopausal osteoporotic women is 800 international units (IU) and 1200 mg total by diet and supplements respectively and daily intake can also changed to 600 IU and 1000 mg respectively in both osteoporotic women and men.[6]

Estrogen Replacement Therapy (ERT)

This therapy is recommended when deficiency of estrogens in menopausal women. Estrogens Replacement Therapy (ERT) or Estrogen Progestin Replacement Therapy (HRT) alone can suggest for treatment of osteoporosis in postmenopausal women. This therapy is acts by inhibiting bone resorption and also provides anabolic effect. The Women's Health Initiative (WHI) and the Postmenopausal Estrogen Progestin Intervention (PEPI) trial showed beneficial effects of either ERT or HRT at all skeletal sites concomitant with some adverse effects in long term usage. Therapy includes Tibolone, it is a synthetic steroids having androgenic, estrogenic and gesagenic properties by binding to estrogen receptor.[5]

Selective Estrogen Replacement (SER) Therapy

SERs acts by blocking the conformational changes in estrogen receptors. Raloxifene is the example for (SERs). When postmenopausal treated with Raloxifene shows 30 % reduction in vertebral fracture and drugs shows other pharmacological action such significant reduction (72%) breast cancer and decreases incidence of cardiovascular events in women.[8]

Parathyroid hormone

Parathyroid hormone is a single-chain peptide consisting of 84 amino acids and that have anabolic effects on bone mass and skeletal architecture by intermittent administration. The physiological function of parathyroid hormone is to maintain extracellular calcium levels. It acts either directly on target cells or indirectly through the synthesis of 1, 25-dihydroxyvitamin D3. Evidence suggests that parathyroid hormone has a dual action on bone, with both osteoblasts and osteoclasts being responsive to parathyroid hormone.[6]

New agents used in treatment of osteoporosis

Growth factors, cytokines, cathepsin, strontium ranelate, anti-sclerostin and antibodies.[9]

Other Class of Drugs Used in Treatment of Osteoporosis

Statins

Statins are cholesterol lowering drugs. But these drugs also identified enhancer for the bone formation and bone morphogenetic protein-2-gene expresser in vivo. Statins increases the osteoblast number and promotes osteoblasts differentiation. Statins are in clinical studies to study the beneficial effect on bone formation. The particular dose required for bone formation is much higher than hypolipidemic action.[6]

Activin inhibitor

Activin is a protein for membrane growth and differentiation. It involves in the regulation of bone mass that stimulates bone resorption and inhibits bone formation.[6]

Cannabinoids agonist

The receptors of cannabinoids and endocannabiniods are involved in the bone regulation and osteoblast differentiation. Hence the drugs agonist and antagonist of cannabiniods receptor suppress function of ostoblast cells and number of cells. The drugs are under clinical study to investigate the role of cannabinoids in treatment of osteoporosis.[6]

Calcium sensing receptor antagonist (Calcilytics)

These are orally administered new class of drugs to stimulate endogenous PTH release and have bone forming action. Still drugs are under clinical trial to study the role of drugs for treatment of osteoporosis.[10]

Anti-hypertensive drugs as Antiosteoporotic drugs

The class of drugs used in treatment of CVS disorder can also be used in treatment of osteoporosis particularly Anti-hypertensive drugs, in both positive and negative manner. Commonly prescribed antihypertensive medications, including Thiazide and Non-thiazide Diuretics, Beta-blockers, Calcium channel blockers, Renin–angiotensin–aldosterone system agents, and Nitrates.[10]

Different Types of Nano Particles (Nps) Used to Treat Osteoporosis

Chitosan NPs

Chitosan is one of the most commonly used polymer to target bone for drug delivery, because of its properties such as non toxic, biocompatibility and biodegradability with environmental safety. It is obtained from chitin by deacetylation , copolymer of β-(1-4) linked 2 acetamido-2deoxy- β-D-glucopyranose and 2-amino-2-deoxy- β-D-glucopyranose. Chitosan protonated at low pH and soluble in water due to presence of amino group and in other hand chitosan permits deprotonation due to increases in pH over 6 and it become insoluble. Nano particles of chitosan is prepared by gelation process and during this process the interaction between the positive

amino group of chitosan and negative charge to tripolyphosphate leads to formation of NPs. Hence, BPs was loaded into NPs and used as target bone for treatment of osteoporosis. Chitosan NPs are act as novel kind of drug target.[11]

Poly (lactic-co-glycolic acid)

It is one of the synthetic biodegradable polymer and it is extensively used polymer for synthesis of NP due to its excellent biocompatibility, non toxic in nature and also have tuneable degradation, it is a copolymer of PEG-PLGA and intermixed with ALN (Aluminium Nitride) functionalized PLGA to produce surface of modified NPs.[11] These polymer achieve different drug release profile through the modification of particle size, molecular weight, the copolymer action ratio, the porosity and the manufacturing condition. Hence the accumulation of drug in the nanoparticles was more and permits higher concentration of drug to reach the target bone site and even the developed NPs of PEG-PLGA copolymer have good binding capacity of to apatite and BPs loaded in the copolymer has bone targeting action.[12]

Hydroxyapatite NPs

It is important mineral content present in the bone. HA possess biocompatibility, bioactivity and excellent osteoconductive properties with the respect to the bone cells and tissue. HA nanoparticles have effective osteoblast bioactivity and increases bone regeneration hence this polymer used for growth of bones and tissue and also increases the deposition of mineral content in the bone. Hence in the current research the formulation developed with hydroxyapatite have better and excellent effective in biomedical application especially bone target disease produces minerals related to bones.[13] HA, surface grain properties, pore size and wettability controls protein interaction and modulate the enhancement of osteoblast adhesion and long functionality.[11]

Liposome's

Liposome are the lipid vesicles used as first carrier system to deliver drug to the target site and this lipid vesicles are formed by the addition of lipid to aqueous solution. Preparation of liposome can be done by using different methods like film method. The application intended is dependence on the size, composition of phospholipids and surface characteristics.[14] Liposome can be widely used for different hormone such as growth hormone, parathyroid hormone and enzymes like Elastase, Beta glucoridase etc and also therapeutic agent such as paclitaxel, Doxorubicin etc for treat different kind of diseases because of its low toxicity profile, biocompatibility and biodegradability.[15] There are different types of liposome such cationic and neutral and anionic, in that the cationic have more lower toxicity profile, longer circulation, longer half life and less interaction with protein. The designed liposome with Chloesteryl-trisoxyethylenebisphosphonic acid can act as derivative for bone target and these kind of liposome can be used in treatment of bone disorders.[14]

Metal Nanoparticles

Different metals can be used in treatment of osteoporosis like Iron (II, III) and Gold Nano particles through thermotherapy. These metals have capable of generating cell death by causing the disruption of cell membrane and by denaturing intracellular protein. These Iron metal can be used as NPs because of its properties such as nontoxic, chemically stable and cost efficient and they can also be used in the low temperature because of its higher magnetic field. In such way that iron NPs are used in order to treat osteoporosis by destroying the osteoclast cells and by decreasing osteoclast regulation through thermolysis mechanism and finally causes osteoclast cell death. Gold NPs are another metal have been studied for osteoporosis disease. Hence, in recent study proved that Gold NPs for treatment of osteoporosis. The mechanism involved is by promoting osteoblast differention and inhibition of osteoclast differentiation.[11]

Marine Environment as a Source of Natural Products

Earth surface covers with 70% ocean and contains diversified marine source because of the ocean extreme condition and complex habitats of marine organism varieties of biologically active secondary metabolites. These metabolites are unique in their structure and functions. The ocean contains rich source of novel compounds with enormous prospective Pharmaceuticals, Neutraceuticals, Cosmetics, Agrochemicals, and Enzymes). Marine plants, algae, microorganisms and invertebrates such as sponges, tunicates, bryozoans, molluscs, and fishes are possible sources of bioactive compounds. MNP's such as steroids, Terpenoids, isoprenoids, nonisoprenoids, quinones, brominated compounds, nitrogen heterocyclics, and nitrogen sulfurheterocyclics have potential to be bioactive compounds. These compounds are being used for treating several diseases like Cancer, Tuberculosis, Malaria, Osteoporosis, Alzheimer's disease, Neurological disorders, Inflammatory diseases, and HIV from past decade, beyond 13,000 molecules have already been described out of which 5,000 exhibited good bioactive properties. *Marine Cyanobacteria, Marine Dinoflagellates, Marine Fungi, Marine Algae, Marine Sponges, Marine Soft Corals, Marine Molluscs, Marine Fishes and Marine Mangroves are Marine derived compounds* in clinical trial. [16]

Supplements Used to Improve Bone Mineral Density

1. Calcium- it is one of the most important supplements to take during osteoporosis, women under age of 51 and older should take 1200 mg of Ca per day not more than 2000 mg. Calcium rich food are vinegar, apple, figs, milk etc
2. Vitamin- it present naturally in many food, among all vitamin D is important to prevent from osteoporosis

by enhancing the body- calcium absorption and utility helping the body to build strong bones

3. Boron – it is one of trace element present in body and it helps in make effectively use of calcium during osteoporosis by activating minerals and vitamins for bone formation
4. Vitamin k- helps calcium to bind with the bones and improves its strength
5. Silicon- the trace element of silicon can enhance the bones strength, ligaments and tendons.[17]
6. Magnesium- magnesium is one of the second most important mineral in the body that plays an important role in metabolic process, including building bone formation, bones strength, enhances bone calcium absorption and adenosine triphosphate production.
7. Isoflavones –many research suggest that soya isoflavones can prevent the risk of development of osteoporosis. Diets that are rich in Isoflavones can decreases bone resorption in postmenopausal. The semi synthetic flavones were found to be ineffective in restoring bone density in rats.[18]
8. Exercise is another therapy that can fight against osteoporosis by forcing bones to carry lots of pressure against an opposing force, helping the body to produces more bone cells leading to increases in body mass and making bones stronger. Exercise can be either jogging, dancing, weight bearing or aerobics.[17]

Non pharmacological treatment for prevention of postmenopausal osteoporosis and osteoporotic fracture

There are some of non pharmacological approaches for prevention of osteoporosis they are;

- Life style changes
- Intake of adequate dietary foods
- Advice patient to stop smoking
- Advice patient to drink alcohol at safe level
- To do suitable weight bearing and muscle strengthening exercise
- Reduce dosage or avoid drugs with sedative
- Identify and treat sensory deficits that can contribute to osteoporosis
- To treat neurological and rheumatologic condition that can lead to osteoporosis
- Providing gait and balance training if it is necessary
- For elderly women, provide occupational therapy by giving household items such as non skid mats, anchor rugs and also advice to do some home modification such as improvements in lighting and handrails.[24]

CONCLUSION

Osteoporosis is the condition were bone become fragile and weak and leads to bone fracture. Osteoporosis is multifunctional disease; hence its prevention and treatment are very important. There are different types of drugs such as herbal. Synthetic, mineral and hormone therapy, other pharmacological action drugs such anti-hypertensive, calcium sensing receptor antagonist, activin inhibitor, cannabinoids agonist, statins and polymer Nano particles are acts as anti-osteoporotic drugs by regulating bone growth through increases in bone mineral density, bone formation and gives bone protective action.

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REFERENCES

1. Shivakumar K, Mukund H, Rabin P, Evaluation of antiosteoporotic activity of Root extract of Rubia Cordifolia in Ovariectomized Rats,Int J Drug Dev Res, 4(3), 2012 Jul, 163-72.
2. Khadilkar AV, Mandlik RM, Epidemiology and treatment of osteoporosis in women, an Indian perspective, International Journal of Women's Health, 7, 2015, 841, DOI: 10.2147/IJWH.S54623; PMCID: PMC4621228.
3. Mazanec DJ, Grisanti J, Drug-induced osteoporosis, Cleveland Clinic journal of medicine, 1, 56(3), 1989 May, 297-303.
4. Jee WS, Yao W, Overview: animal models of osteopenia and osteoporosis, J Musculoskelet Neuronal Interact, 1(3), 2001 Mar, 193-207, PMID: 15758493.
5. Tabatabaei-Malazy O, Salari P, Khashayar P, Larijani B, New horizons in treatment of osteoporosis, DARU Journal of Pharmaceutical Sciences, 25(1), 2017 Dec, DOI: 10.1186/s40199-017-0167-z.
6. Åkesson K, New approaches to pharmacological treatment of osteoporosis, Bulletin of the World Health Organization, 2003, 81:657-63, PMCID: PMC2572533. PMID: 14710507.
7. Schneider A, Shane E, Osteoporosis secondary to illnesses and medications, In Osteoporosis 2001 Jan 1 (pp. 303-326), Academic Press.
8. Shirwaikar A, Khan S, Medicinal plants for the management of post menopausal osteoporosis: A review, The Open Bone Journal, 2, 2010, 1-3.
9. Jalil A, Azri M, Shuid AN, Muhammad N, Role of medicinal plants and natural products on osteoporotic fracture healing, Evidence-Based Complementary and Alternative Medicine, 2012, 2012, PMCID: PMC3438813. PMID: 22973405.
10. Ghosh, M, and Majumdar, S.R, Antihypertensive medications, bone mineral density, and fractures, a review of old cardiac drugs that provides new insights into

osteoporosis, Endocrine, 46(3), 2014, pp.397-405, PMID: 24504763.

11. Mora Raimundo P, Manzano García M, Vallet Regí M, Nanoparticles for the tratment of osteoporosis, AIMS Bioengineering, 4(2), 2017 Mar 27, 259-74, DOI: 10.1007/s11914-016-0324-1.
12. Low SA, Kopeček J, Targeting polymer therapeutics to bone, Advanced Drug Delivery Reviews, 1, 64(12), 2012 Sep , 1189-204, DOI: 10.1016/j.addr.2012.01. 012.
13. Ferraz MP, Monteiro FJ, Manuel CM, Hydroxyapatite nanoparticles, a review of preparation methodologies, Journal of Applied Biomaterials and Biomechanics, 2(2), 2004 May, 74-80, PMID: 20803440.
14. Monteiro N, Martins A, Reis RL, Neves NM, Nanoparticle-based bioactive agent release systems for bone and cartilage tissue engineering, Regenerative Therapy, 1, 1, 2015 Jun,109-18.
15. Baki M, Keskin D, Uçkan D, Tezcaner A, bone marrow-targeted liposomal drug delivery systems: pp-058, Regenerative Medicine, 6(6), 2011 Jan 1, 241.
16. Chaugule SR, Indap MM, Chiplunkar SV. Marine Natural Products: New Avenue in Treatment of Osteoporosis. Frontiers in Marine Science. 2017 Nov 29, 4, 384, https://doi.org/10.3389/fmars.2017.00384.
17. Whelan AM, Jurgens TM, Bowles SK, Doyle H. Efficacy of natural health products in treating osteoporosis, what is the quality of internet patient advice, Annals of Pharmacotherapy, 43(5), 2009 May, 899-907.
18. Ulbricht C, Kamhi E, Kronenberg F, Low Dog T, Crawford AM, Sollars D, Roundtable discussion, Women's health menopause and related conditions, Alternative and Complementary Therapies, 16(5), 2010 Oct 1, 265-71.
19. Abdallah HM, Al-Abd AM, Asaad GF, Abdel-Naim AB, El-Halawany AM. Isolation of antiosteoporotic compounds from seeds of Sophora japonica. PLoS One, 9(6), 2014 Jun 3, e98559, DOI: 10.1371/journal.pone.0098559.
20. Rajagopal PL, Amrutha C, Premaletha K, Premkumar N, Medicinal plants in osteoporosis-A review, Int J Adv Pharm Biol Chem, 2(4), 2013, 605-8.
21. Spilmont M, Léotoing L, Davicco MJ, Lebecque P, Miot-Noirault E, Pilet P, Rios L, Wittrant Y, Coxam V, Pomegranate peel extract prevents bone loss in a preclinical model of osteoporosis and stimulates osteoblastic differentiation in vitro, Nutrients, 7(11), 2015 Nov; 9265-84, PMCID: PMC4663593. PMID: 26569295.
22. Whelan AM, Jurgens TM, Bowles SK, Doyle H, Efficacy of natural health products in treating osteoporosis, what is the quality of internet patient advice, Annals of Pharmacotherapy, 43(5), 2009 May, 899-907, DOI:10.1.1.882.8093
23. Wu X, Xie CQ, Zhu QQ, Wang MY, Sun B, Huang YP, Shen C, An MF, Zhao YL, Wang XJ, Sheng J, Green tea (Camellia sinensis) aqueous extract alleviates postmenopausal osteoporosis in ovariectomized rats and prevents RANKL-induced osteoclastogenesis in vitro. Food & Nutrition Research, 62, 2018, DOI:10.29219/fnr.v62.1478, PMCID:PMC6190732.
24. Ji MX, Yu Q, Primary osteoporosis in postmenopausal women, Chronic Diseases and Translational Medicine, 1(1), 2015 Mar, 9, DOI : 10.1016/j.ddtm.2015.02.006, PMCID: PMC5642776.

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