

A Comprehensive Review of The Existing Pharmacological and Natural Products for Osteoporosis Therapy

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ABSTRACT

Osteoporosis is a Chronic skeletal muscle disorder characterized by low bone mineral density (BMD) and deterioration of bone structure leading to an increased risk of fragility fractures. The condition is typically asymptomatic and remains undiagnosed until fractures manifest. Despite the fact both men and women are equally susceptible to osteoporosis generally women with estrogen deficiency serves as a principal etiological factor for fragility fractures. A wide range of pharmaceutical medicines are currently used to treat osteoporosis However, traditional medicines have more potential therapeutic value of has gained increasing scientific scrutiny, as synthetic treatments are frequently linked with a broad spectrum of adverse effects and limited efficacy. The current survey includes overview of medicinal plants encompassing with scientific name, parts used, phytochemical constituents and proven pharmacological actions and probable therapeutic effects in the management of osteoporosis. Natural compounds including phytoestrogens with estrogenic effects (e.g. genistein, daidzein, icariin, estrogenic isoflavones, formononetins), antioxidant and anti-inflammatory agents (e.g gingerols, shagoals, eleutherosides, ferulic acid, urosolic acid), treatments that exert their effects by multiple actions (e.g. withania somnifera, Urtica dioica, Rubia cordifolia, salvia miltiorrhiza) could offer a safer alternative to primary pharmacological approaches. This study emphasizes pharmaceutical and natural substances on their mode of action on bone remodelling, osteoclastogenesis, osteoblastogenesis, cell activity, apoptosis and oxidative stress to treat osteoporosis. To verify their effectiveness and safety as anti-osteoporotic treatments, further excellent clinical research on natural substances is necessary.

Keywords: Osteoporotic fragility fractures, Bone remodelling and apoptosis, Osteoblastogenesis, Osteoclastogenesis, Phytochemical constituents, Phytoestrogens, Antioxidants and Antiinflammatory agents.

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Introduction

Bone is a dynamic and immensely adaptive tissue, constantly undergoing rebuilding of osteoclasts and osteoblasts. This process is a biogenic for maintaining bone integrity, mineral equilibrium and responding to mechanical stresses. Disturbance in the remodelling balance can lead to bone-related disorders such as osteoporosis, fractures, and bone loss in various diseases. Recent advances have discovered the signaling pathways including the RANKL/RANK/OPG system, Wnt/ β -catenin and sclerostin in modulating bone homeostasis^{1,2} (Takayanagi, 2017; Xu et al., 2019). The bone marrow cellular environment and its key interaction with immune cells in contributing factor bone remodeling has identified the emerging research importance in new therapeutic approach³ (Zhao et al., 2020). Understanding these mechanisms plays a crucial role in treating bone-related diseases and ameliorate skeletal wellness. Osteoporosis is one of the stellar health problem that decrease both the mass and the caliber of bone, thereby accelerate the risk of fracture, mainly in the aged.

According to World Health Organization (WHO), Osteoporosis is as a skeletal disorder characterized by reduced bone strength and increases the risk of fractures. If the Bone mineral density (BMD) and the quality of the bone tissue is elevated more than 2.5 standard deviations and measured by dual-energy X-ray absorptiometry (DXA). This condition primarily affects postmenopausal women and the aged and this leads to higher frequency of fractures, especially in the hip, spine, and wrist^{4,5} (Kanis et al., 2019; Ward, 2020). Osteoporosis is often asymptomatic until a fracture happen, making early perception and organization essential for reducing its impact.

The consequences of osteoporosis are influenced by factors such as Non modifiable factors such as age, gender, ethnicity, and geographical location. The reduction of bone density in aged people particularly in postmenopausal women due to a decrease in estrogen levels. Due to hormonal changes women are at a higher risk than men especially after menopause, that speed up bone loss⁶ (Riggs & Khosla, 2016). The studies display that Caucasians and Asians have higher rates of osteoporosis and fractures compared to African Americans, with denser bones⁷ (Liu et al., 2018). Geographically, people in area with lower sunlight exposure, which alters synthesis of Vitamin D tend to have higher rates of osteoporosis⁸ (Khosla, 2018). Genetic heredity also plays a vital role in increasing the risk of osteoporosis (Hernández et al., 2021)⁹.

On the other hand, modifiable factors include sedentary lifestyle, insufficient calcium, low vitamin D intake and smoking like contributors to bone loss¹⁰ (Goh et al., 2022). Additionally, excessive alcohol consumption and usage of glucocorticoids, can also increase the risk of osteoporosis¹¹ (Huang et al., 2023).

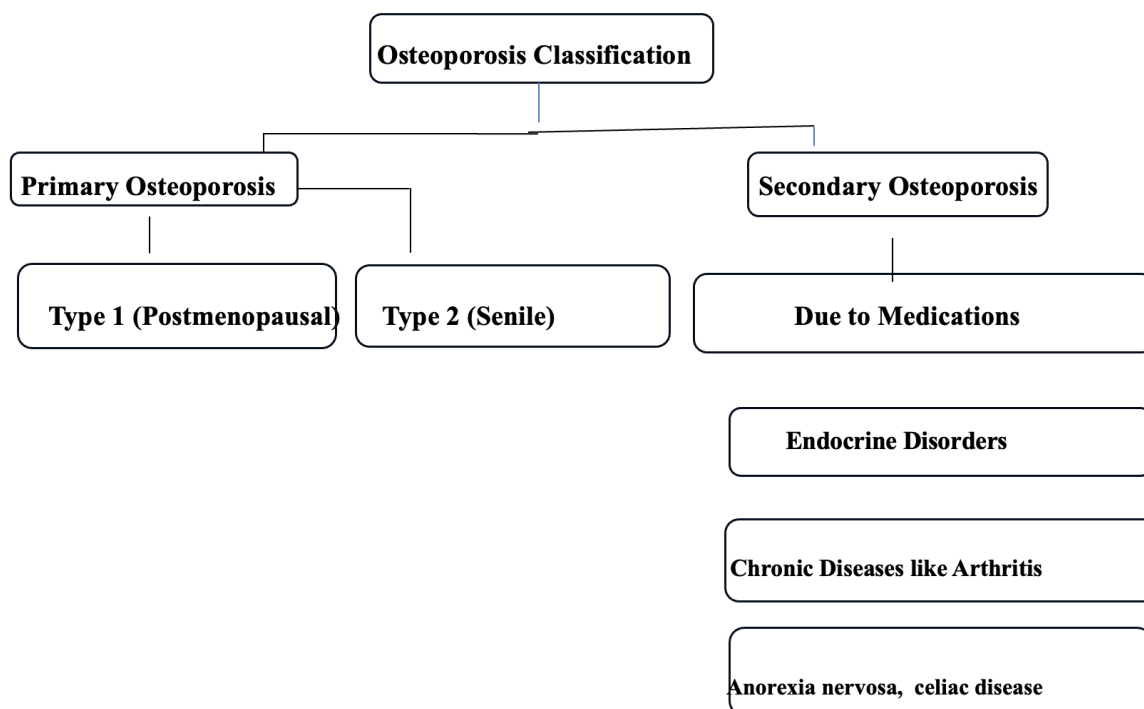


Fig .1. Classification of osteoporosis

Symptoms of Osteoporosis

Osteoporosis is often referred to as a "**Clinically silent**" until a fracture occurs.

- **Fractures:** The vital symptom of osteoporosis is fractures with minimal trauma, frequently in the spine, hip, or wrist¹² (Kanis et al., 2020).
- **Back Pain:** spine vertebrae Fractures(kyphosis) can lead to chronic back pain, height loss, or a stooped posture^{13,14,15} (Sambrook & Cooper, 2021).

Prevalence and Rank of Osteoporosis in India (2020-2024)

Prevalence and Burden:

According to a 2020 study in the *Indian Journal of Medical Research*, osteoporosis is prevalent in **approximately 30% of women over 50 years old** and about 20% of men over 60 years of age in India (Kumar et al., 2020)¹⁶.

Ranking in Disease Burden:

As per a report by the *Indian Council of Medical Research (ICMR)* in 2023, osteoporosis is one of the leading causes of morbidity in India, ranking **among the top 5 diseases** for elderly individuals. This report highlighted that osteoporosis-related fractures contribute to a significant healthcare burden, making it a primary concern, especially in aging populations ¹⁷(ICMR, 2023).

Table No1: Bacteria and Viruses Associated with Osteoporosis

Sl.no	Pathogen	Role in Osteoporosis	Mechanisms	Key Studies & References
	Bacteria			
1	<i>Helicobacter pylori</i>	Contributes to systemic inflammation, which may impact bone metabolism	Increases inflammatory cytokine production (e.g., TNF- α , IL-6), disrupting bone remodeling	18
2	<i>Escherichia coli</i>	May exacerbate bone loss via endotoxin production	Endotoxins stimulate immune responses that lead to bone resorption through osteoclast activation	19
3	<i>Streptococcus mutans</i>	Potential link between oral infections and bone health	Chronic inflammation from oral infection can lead to osteoclast activation and bone degradation	20
4	<i>Mycobacterium tuberculosis</i>	Tuberculosis infections linked to bone loss	Direct bone invasion and systemic inflammation can increase risk of osteoporosis	21
	Viruses			
6	<i>Human Immunodeficiency Virus (HIV)</i>	Increased risk of osteoporosis due to antiretroviral therapy and chronic inflammation	HIV-induced chronic inflammation and ART-induced bone mineral density (BMD) loss	22
7	<i>Herpes Simplex Virus (HSV)</i>	Inflammatory response induced by HSV can contribute to bone degradation	HSV infection leads to chronic inflammation, which accelerates osteoclast differentiation	23.
8	<i>Varicella-Zoster Virus (VZV)</i>	Zoster-induced bone pain and increased risk of osteoporosis in elderly individuals	VZV infection can induce bone loss through inflammatory cytokine release	24

9	<i>Influenza Virus</i>	Increased susceptibility to osteoporosis in post-influenza recovery phase	Influenza-induced cytokine storm leads to bone resorption and osteopenia	25
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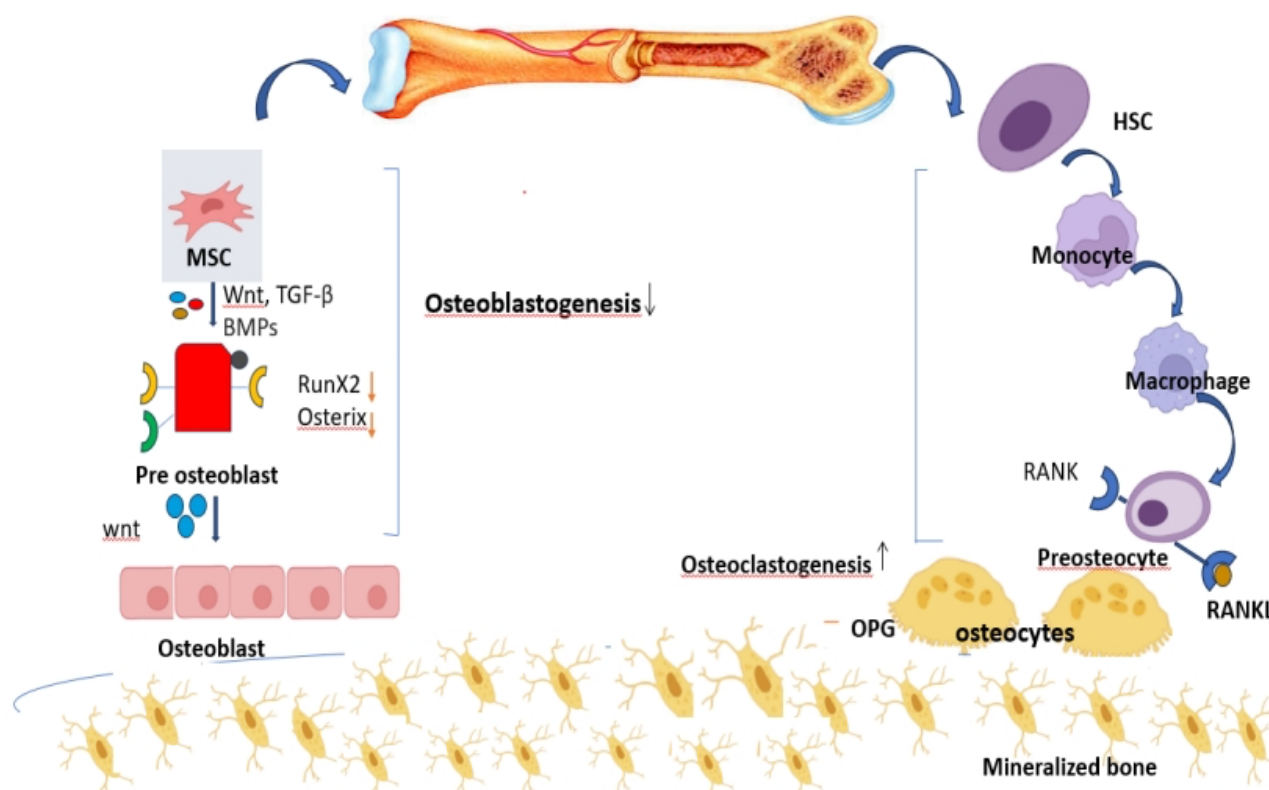


Fig 2. Osteocytes as regulators of bone remodeling.

The origination of osteoporosis is due to the imbalance in bone building blocks i.e. osteoclasts (bone resorbing cells) and osteoblasts (bone forming cells). In general, osteoclasts differentiate from hematopoietic stem cells through monocyte/macrophage lineage upon stimulation of macrophage colony stimulating factor (M-CSF) it binds to its receptor c-Fms and cause excitation of receptor activator of nuclear factor κB (RANK) by its ligand (RANKL) M-CSF promotes the production and survival of preosteoclast via the stimulation of several kinases, Including Src and Akt. RANKL, expressed by osteoblasts, osteocytes, and stromal cells, fixes to RANK on osteoclast ancestor cells. The RANKL/RANK interaction subsequently activates nuclear factor κB (NF-κB), mitogen-activated protein kinases (MAPKs) and helps the expression of other osteoclastogenic factors such as nuclear factor of activated T-cells 1 (NFATc1). On the other hand, osteo protegrin (OPG), which is also produced by cells in the osteoblast lineage, that prevents binding of RANKL to RANK. Thus, the RANKL/RANK/OPG system is a key mediator of osteoclastogenesis. Osteoblasts differentiate from mesenchymal stem cells (MSCs) in which Runt-related transcription factor 2 (Runx2) Osterix (Osx) and Sp7 are crucial transcription factor for bone formation. Runx2 are the key regulators in production of bone building proteins such as osteocalcin (OC), bone sialoprotein (BSP), and collagen type I (COL1A1) (15) and regulated by signalling molecules like bone morphogenetic proteins (BMPs) and Wnt proteins. BMPs particularly BMP2 & BMP4 bind to the bone cell receptors and leads to signal transducer proteins SMAD1/5/8 with the transforming growth factor-β (TGF-β) a multifunctional cytokine. activates Wnt/β-catenin signalling, the Wnt proteins like Wnt3a and Wnt1 bind to Frizzled (FZD) receptors and lipoprotein receptor-related protein (LRP5/6) complexes, which results in the stabilization and translocation of β-catenin into the nucleus. β-catenin is an important transcriptional co-activator that regulates transcription of target genes including Runx2 target genes leads osteoblastogenesis^{26,27}

PHARMACOLOGICAL AGENTS FOR TREATMENT OF OSTEOPOROSIS

The Current and Viable Therapies in Osteoporosis is a significant challenge in treating fractures especially in elderly and menopause women hence focused on supportive the estrogen level. The mechanisms involves mainly stimulating parathyroid hormone (PTH) synthesis, encouraging the expression of OPG, declining interleukin (IL)-1, 4, 6 and M-CSF, increasing estrogens or like-estrogens supplementing calcium, phosphate in bones, to achieve the goal of inhibit the proliferation of osteoclasts and inducing apoptosis and to enhance the proliferation and differentiation of osteoblasts. A wide range of pharmacological products used for the treatment of osteoporosis in the clinical practice. The most used drugs include anti-resorptive agents and anabolic agents. The anti-resorptive agents decrease bone resorption through inhibiting the osteoclasts activity examples are bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid), selective estrogen receptor modulators (SERMs; raloxifene), hormone therapy (HT; estrogen), calcitonin, denosumab calcium and vitamin D supplementation, while anabolic agents results in enhanced bone formation through stimulating the osteoblasts function examples are teriparatide (parathyroid hormone), strontium ranelate, romosozumab. Bisphosphonates are considered as a frontline therapy for treating osteoporosis. The nitrogen containing bisphosphonates inhibits the mevalonate pathway and further inhibits the GTPase which is the key role for the osteoclast survival. The non nitrogen complex of bisphosphonates forms cytotoxic metabolites in osteoclasts, which further interferes with mitochondrial function and cause osteoclasts to die. Denosumab acts as a monoclonal antibody that binds with RANKL, blocking the RANK/RANKL signaling, thus preventing differentiation, activation and survival of osteoclast formation and promotes a raise in bone mass. Estrogen therapy involves blockage of new osteoclast cells formation by regulating the balance between RANKL (receptor activator of nuclear factor- κ B ligand) and OPG (osteoprotegerin) and enhances OPG manufacture in maintaining bone density by inhibiting bone resorption process.^{26,29,30,31} Selective estrogen receptor modulators (SERMs) act through stimulating osteoblast activity (bone formation) by selectively binding to estrogen receptors in bone tissue while concurrently inhibiting osteoclast activity (bone resorption), leading to increased bone mineral density and reduced bone loss; basically, mimicking the useful effects of estrogen on bone. SERMs representing dual agonistic and antagonistic properties in estrogenic pathways. According to FDA a combination of conjugated estrogens and bazedoxifene was a safer option in treatment of osteoporosis for postmenopausal women but associated with a small increase in the risk of venous thromboembolism and stroke^{28,32} Calcitonin a synthetic polypeptide hormone works to treat osteoporosis in postmenopausal women who have the condition more than five years and not able to access other alternative treatments. Because it develops resistance to calcitonin over time, it is measured as effective short-term treatment due to Calcitonin primarily binds to the osteoclast receptors and triggers a signalling cascade causing inhibition of bone resorption, increase in bone mineral density and lowers blood calcium levels. The calcitonin-salmon nasal spray has some adverse effects includes including rhinitis, nasal irritation, back pain, nosebleed, and headache^{28,33}

New therapies emerged for treating bone resorption

osteoclast releases the primary enzyme called Cathepsin k that helps to break down collagen in bones. It further causes stunt growth of osteoclast without affecting the normal bone remodelling and helps in promoting the production of osteoblast. Odanacatib is a selective cathepsin k inhibitor which has been ceased due to it possess high risk of Stroke³⁴. The third-generation SERM is Lasofoxifene. A clinical trial showed that the group receiving 0.5 mg of Lasofoxifene daily showed 42% reduction of lower risk of vertebral fractures and a 24% reduction of lower risk of non-vertebral fractures. There is research evidence stating that Lasofoxifene drugs lowers the stroke incidence, coronary heart disease and breast cancer. According to FDA this drug is recommended for treatment of estrogen receptor-positive, HER2-negative metastatic breast cancer in women.³⁵

Anabolic compounds:

PTH and Parathyroid Hormone-Related Protein (PTHrP) Analogues

Both PTH and Parathyroid Hormone-Related Protein (PTHrP) binds to osteoblast and stimulate RANKL receptor which is a key factor in promoting the differentiation of osteoclasts, the cells responsible for bone resorption from precursor cells ultimately leading to bone breakdown. This gland Secretes low blood calcium levels in order to maintain the equilibrium of serum calcium and phosphate levels

Teriparatide, a recombinant human PTH (1–34) analogue, was the first anabolic therapy for osteoporosis. It shows catabolic effect on Continuous administration and an anabolic effect on intermittent consumption. Low doses of teriparatide promotes osteoblastic activity through the stimulation of Wnt signaling, inhibition of DKK-1, and production of interleukin-11A which significantly increased bone mineral density. However, at 18 and 36 months, teriparatide medication was associated

with noticeably few new vertebral fractures than alendronate treatment. However, teriparatide's use is limited because of its risk for osteosarcoma³⁶.

In 2017, FDA confirmed that Abaloparatide (PTHrP1-34), the second recombinant human PTH analogue is expected to produce more anabolic impact of decrease the incidence of new vertebral fractures by 86% and non-vertebral fractures by 43% when compared to its teriparatide over the duration of 18 months in three clinical trials phase. This medication is used only for 2 years of treatment. In addition to this abaloparatide is more economical than teriparatide³⁷.

Strontium shows biphasic effect in increasing bone formation and inhibits bone resorption. It promotes differentiation of preosteoblast into osteoblast and further causes osteoblast to secrete OPG, which can obstruct osteoclast differentiation of a RANKL decoy receptor functioning. Its use is limited in severe osteoporosis because of elevated risk of cardiac issues³⁸.

An Importance of Sequential and combinational therapy in managing osteoporosis

In treatment of osteoporosis combinational therapy used several treatment strategies to improve bone density and lower fracture risk more successfully than monotherapy treatment many research investigations have been done in combination of anabolic and antiresorptive drugs from last decade. Wei et al 2021 studied the beneficial effects of the parathyroid hormone teriparatide in conjunction with the bisphosphonate zoledronic acid for the treatment of osteoporosis in postmenopausal women among ninety-six patients. One group received treatment with parathyroid hormone 1-34 only, whereas the other group received treatment with zoledronic acid in addition to parathyroid hormone 1-34. Treatment with both medications was done in six months reported noticeable higher bone mineral density and noticeably lower levels of bone resorption³⁹.

Shimizu et al 2021, examined the effects of introducing and discontinuing of from vitamin D or bisphosphonates to either Denosumab, a RANKL antibody, or romosozumab, a monoclonal sclerostin antibody among 154 postmenopausal and osteoporotic women. The study's findings demonstrated that romosozumab treatment outperformed denosumab in terms of BMD increase during a 12-month period⁴⁰. They drew to the conclusion that more research is required for forecasting romosozumab's effectiveness.

Shane et al. (NCT02049866) conducted a clinical trial phase II in the US to evaluate the potency of Denosumab in minimizing post-teriparatide bone loss in postmenopausal women⁴¹.

Shoback et al, San Francisco VA Medical Center performed phase IV clinical trial on combining multiple medicines to treat osteoporosis in males (NCT03994172). One therapy option is combination of teriparatide with calcio mimetic, that stimulates calcium receptors in osteoblasts and promotes bone growth. And compared the results to those of teriparatide alone. This combination was tested on mice and found to enhance bone mineral density and structure after six weeks⁴².

Besides to human trials, preclinical studies have been used to test alternative medication combinations One combination is zoledronic acid with propranolol, a beta blocker. Alendronate and alfacalcidol, a vitamin D active metabolite, were also evaluated. Combining anabolic medicines like teriparatide with bisphosphonates like alendronate or zoledronate has been found to improve bone mineral density (BMD) New biomolecules and biomaterials are being presented to treat osteoporotic patients with vertebral fractures and critical size bone defects. New invented techniques that use biomolecules and nanomaterials to target critical size bone defects and vertebral fractures that have already occurred^{43,44,45}.

Drugs (Anabolic Agents and Anti-Resorptive Agents)	Targets	References
Bisphosphonates (anti-resorptive agents) Alendronate and risedronate (short-term doses). Ibandronate and risedronate (long-term doses)	Bisphosphonates reduce osteoclast endurance in two ways with nitrogen compounds blocks the GTPase activity and mevalonate pathway. whereas with non-nitrogen compounds impair osteoclast mitochondrial activity	46

Denosumab (anti-resorptive effects)	Denosumab, a monoclonal antibody, increasing bone mass that blocks RANKL & blocks RANK/RANKL signaling, inhibiting osteoclast development, activation, and survival	47
Estrogen Therapy	Estrogen regulates bone remodeling and density by inhibiting osteoclast formation by balancing RANKL and OPG and increasing OPG production to maintain bone density.	48
Selective estrogen receptor modulators (SERMs)	SERMs mimic estrogens action on bone by inhibiting osteoclast activity and stimulating osteoblast activity, further increasing bone density	49
Calcitonin	A Synthetic hormone, short lived due to building tolerance binds to osteoclast receptors, inhibiting bone resorption, increasing bone density and lowering blood calcium levels.	33
Cathepsin K	Is an enzyme that inhibits osteoclasts by breaking down collagen in bones supporting osteoblast production.	50
Lasofloxifene	In a clinical study reveals that lowers the risk of vertebral fractures by 42% and non-vertebral fractures by 24% in those taking 0.5 mg daily	35
<u>Anabolic compounds</u> Both PTH and PTHrP	This gland secretes PTH to regulate blood calcium and phosphate by binding to osteoblasts, stimulating RANKL, which promotes osteoclast differentiation and bone resorption.	36
Teriparatide	A recombinant human PTH analogue, has a catabolic effect with continuous use and an anabolic effect with intermittent use. Low doses enhance osteoblastic activity, boosting bone mineral density.	36
Abaloparatide (PTHrP1-34)	second recombinant human PTH analogue, activates cAMP signaling in osteoblasts, activity increases bone remodeling and is expected to reduce new vertebral fractures by 86% and nonvertebral fractures by 43% compared to teriparatide after 18 months in clinical trials.	37
Strontium	It promotes preosteoblast differentiation into osteoblasts and secretes OPG, improving bone formation and inhibiting bone resorption by inhibiting RANKL.	38

An overview of medicinal plants on osteoporosis

From the earliest days of civilization medicinal plants play a vital resource for human and other organisms' survival for food, energy, clothing, and all of them came exclusively from plants. 80% of pharmaceuticals are used as medicinal plants in the field of herbal medicine. For example, Aspirin from willow bark, nabilone from Cannabis sativa L., and pseudoephedrine from Ephedra sinica Staph. Before, there was no standard method for using plants safely on contrary people depended only on their senses—smell, sight, and touch^{51,52,53,54}.

Scientific Name	Part Used	Chemical Constituents	Effect On Bone
<i>Allium cepa</i>	Bulbous/ Juice	flavonoids, anthocyanins, vitamins and minerals	Low ALP, Low free radicals, Increase TEAC, Increase BMD ⁵⁵
<i>Zingiberofficinale</i>	Rhizomes	Paradol, di-acetyl derivatives of gingerol, zingiberene, phellandrene, and methyl ether derivatives	Promotes osteoblast differentiation, increasing bone mineral density (BMD) inhibit osteoclastogenesis by modulating key signaling pathways, including the NF- κ B pathway
<i>Acanthopanax senticosus</i> (Rupr. & Maxim. Harms)	Dried leaf extract	Both syringin and elutide E	Improve BMD (bone mineral density) by reducing osteoclast formation with inhibition of NF- κ B and MAPK blockage
<i>Actaea racemosa</i> L.	Dried Rhizome	Isopropanol and rhizomes	Increase in BALP and no effect on osteoclast enzymes.
<i>Asparagus racemosus</i>	Root / capsule	Carbohydrates, flavonoids, steroids, organic acids, and saponin glycosides.	femur biomechanical parameters decreased in osteoporosis.
<i>Camellia sinensis</i> L.	leaves	Polyphenols, Tannins, flavonoids and theanine catechins	No effect on BMD
<i>Cissus quadrangularis</i> L.	leaves	Flavonoids, Triterpenoids and Steroids, Phenolic Acids, Vitamins and Minerals	Decrease in Procollagen Type 1 Terminal Propertied
<i>Cronus mas</i> L.	Fruits	Flavonoids (quercetin), and kaempferol	Enhances osteoblastic bone growth genes like RUNX2 and ALP and blocks the expression of genes bone resorption, including Ctsk, Acp5, and Nfatc1.
<i>Dioscorea Lata</i>	Root tubers	dioscorin, saponins and dioscin	Dispo85E promotes mesenchymal cell adaptation into osteogenic lineage
<i>Erythrina variegata</i>	leaves	Alkaloids, flavonoids, triterpenes, steroids, lecithin	It is considered as alternate for Hormonal replacement Therapy
<i>Ficus carica</i>	leaves	alkaloids, tannins, glycosides, flavonoids, saponins, coumarins, sterols, terpenes, carbohydrates, anti phenols and proteins	It serves as a alternative therapy for estrogen replacement therapy with fewer effects.
<i>Emblica officinalis</i>	Fruits and leaves	Tannins, alkaloids, vitamin C, Emblicanin A, E	improved Ovariectomy induced bone damage

Glycine max (L.) Merr.	seeds	Isoflavones genistein and daidzein,	Decrease lumbar spine BMD
Cicerarietinum	seeds	Amino acids, methionine, glycine, aldehydes, hydrocarbons, terpenoids, esters, ketones and few phytoestrogen compounds like daidzein and genistein	Enhances OPG by reducing RANKL expression.
Lepidiummeyerii	Roots	Maca alkaloids, steroids, glucosinolates, isothiocyanates and moctamides	Improved bone mass, trabecular system in lumbar vertebrae in Ovariectomized rats
Punicagranatum	peel extract	Genistein, daidzein alkaloids such as isopelletierine, pseudopelletierine, N-methylisopelletierine, anthocyanidins, ellagitannins, gallic acid and ellagic acid	Showed anti-inflammatory & antioxidant property by modulating bone cell differentiation.
Trifoliumpratense	Flowers	Estrogenic isoflavones	Competitively bond to estrogen receptors such as ER alpha and ER beta receptors
Salvia miltirrhiza	Leaves	Rosmarinic Acid , Ursolic Acid , Baidaric acid, Stigmasterol and some lipophilic compounds isolated are tanshinone I , IIA, calcitriol, IIB, V, VI, salviol , miltirone	Showed defensive mechanism against estrogen induced bone loss
Moringaoleifera	Fruit extract	Glucosinolates , Flavonoids, Phenolic Compounds, Moringine , Vanillin , Beta-Sitosterol, Ascorbic Acid, Moringine , , Niazimicinniazirin	Prompted elevated collagen content and bone mineral production
Rubiocordifolia	Leaves and Flowers	Glycosides, Naphthoquinones , Glycosides , Terpenes , Bicyclic Hexapeptides, Iridoids	There was a increased in biomechanical strength, high osteoblastic activity and minimal osteoclastic activity accounted for the bone formation
Withaniasomnifera	Roots and leaves	Withanine , Withanone , Sitoindosides X , Withanolide, Withaniasomnifera Withaferin (steroidal lactone) and Withanone	An increase in the biomechanical strength of the tibia in the ovariectomized animals
Urticadioica	Leaves and seeds	Phytosterols, saponins, tannins, sterols, carotenoids, fatty acids	It rectified the lower serum calcium and phosphorous levels

Materials and Methods

The computerized data bases such as PUBMED, SCOPUS and google scholar were extensively used. Hint words such as osteoporosis postmenopausal osteoporosis, medicinal plants, ovariectomized rat, medicinal plants, herbs and plant medicine was used while searching the titles. The paper satisfies a) studies on anti-osteoporotic activity conducted in animals and or cell lines, b) extractions from plants or compounds isolated from them.

Allium cepa, or onion

Allium cepa (onion) is a bulbous perennial plant of the Amaryllidaceae family and the *Allium* genus, containing over 3700 species. It can be grown easily in India and other subtropical regions. *Allium cepa*, frequently referred to as onion, is a versatile food plant known for its health and nutrition advantages. Onions are abundant in organo-sulphur compounds (diallyl sulfide, di-propyl trisulfide, S-methyl-L-cysteine sulfoxide, and alkyl sulfoxides), flavonoids (quercetin and its conjugates), phenols, anthocyanins, vitamins and minerals and is rich in sulphur amino acids (Marrelli, Amodeo, Statti, & Conforti, 2019) rutin, phytoestrogens such as komestrol, zeranol, isoflavones and humulone, and vitamins K and C, through maintaining calcium in the bones, stimulating the secretion of IL-3 and IL-4 and decreasing the secretion of IL-6 and TNF- α , protects bones. It is used as an anti-bacterial agent (Bakht, Khan, & Shafi, n.d.) anti-diabetic, anti-cancer, cardio-protective, anti-parasitic, antimicrobial, antihyperlipidemic, antispasmodic (R. K. Upadhyay, 2016). Tsang et al. antiplatelet reported that high onion rich diets were able to decrease ovariectomy induced osteoporosis and declining of the biomechanical strength (T. Huang et al., 2008) eight weeks reduced the levels of ALP and increased total antioxidant capacity (TEAC) and BMD.^{56,57}

Zingiberofficinale– Ginger

Often referred as ginger, belonging to *Zingiber officinale* and is native to Asia's warm tropical regions. Hawaii, Mexico, Jamaica, India, and Africa (Zadeh & Kor, 2014). According to Pesset.al (2015) the chemical components of ginger includes, gingerols, paradols, di-acetyl derivatives of gingerols, zingiberene, phellandrene, and methyl ether derivatives^{58,59}. It has beneficial effects on the gastrointestinal tract, antimicrobial properties (Sebiomo, Awofodu, Awosanya, Awotona, & Ajayi, 2011), cardiovascular activity (Nabeel, Hassan, Afridi, & Houghton, 2005), antioxidant properties (Stoilova, Krastanov, & Stoyanova, 2007), hypoglycaemic activity (Communication, 2010), anti-inflammatory properties (Ojewole, 2006), anticancer action (Taylor et al., 2011), and platelet aggregation (Liao, Leu, Chan, Kuo, & Wu, 2012). According to Mohamed et al. due to potent antioxidant property, ginger enhanced the osteoporotic effect of bilateral ovariectomy in cadmium chloride induced is toxicity (Mustafa, Mahmoud, & Hussein, 2013)^{60,61}.

Acanthopanax senticosus (Siberian Ginseng)

Usually known as Siberian ginseng, is a deciduous shrub belonging to the Araliaceae family. This plant is native to Eastern Asia, including regions of China, Korea, and Russia, and is widely cultivated for its medicinal properties. The most important chemical constituents of *Acanthopanax senticosus* include eleuthero sides, saponins, flavonoids, phenolic acids, polysaccharides, triterpenoids, and essential oils^{62,63}. These compounds work together to enhance its therapeutic effects include Adaptogenic Effects (Wayne et al., 2005), Antioxidant Properties (Zhou et al., 2010), Anti-inflammatory Effects (Kim et al., 2012), Neuroprotective and Cardioprotective Properties (Kim et al., 2014). Studies suggest that *Acanthopanax senticosus* can help improve bone mineral density (BMD) in animals, particularly by promoting the activity of osteoblasts (bone-forming cells) and inhibiting osteoclasts (bone-resorbing cells) stimulate the proliferation and differentiation of osteoblasts, (Zhao et al., 2017) & Zhou, S. et al. (2012) suggesting its role in enhancing osteogenesis Inhibition of Bone Resorption inhibit osteoclastogenesis (Nakamura et al., 2016)^{64,65}.

Actaea racemosa (Black Cohosh)

is a perennial herb, commonly known as Black Cohosh, belongs to the Ranunculaceae family. It endemic to North America, particularly in regions such as the United States and Canada. The Chief Chemical Constituents include Triterpene Glycosides, Flavonoids, Phenolic acids, Isoflavones which exhibits a variety of medicinal activities like Menopausal Symptom Relief^{66,67} (Lupattelli et al., 2014), Anti-inflammatory Effects (Sharma et al., 2015) Antioxidant Properties (Fugh-Berman, 2001), Neuroprotective Effects (Teschke et al., 2011). It showed the potential benefits on maintaining bone mineral density (Crouch et al., 2009), improve BMD in women with osteoporosis, providing a natural alternative to hormone replacement therapy (HRT) (Ernst, 2002)⁶⁸

Asparagus racemosus Willd

known as Shatawari, belongs to the family Asparagaceae and is indigenous to Sri Lanka, India, and the Himalayas. The primary active phytochemicals are steroidal saponins, oligospirostanoside, and isoflavones⁷¹. In Ayurvedic medicine, dried roots are widely used in the treatment of gastric ulcers, neurological disorders and lactation, extend life, female reproductive tonic. *A. racemosus* has incontestable several pharmacological properties such as antiulcer, antioxidant, antidiarrheal, antidiabetic, and immunomodulatory activities⁶⁹. Due to its phytoestrogen content, it is foreseen to be effective in menopausal osteoporosis. Postmenopausal women who received 1000 mg of Shata Vari daily experienced an improvement in muscle function and contractility in a 6-week randomized, double-blind study. osteoblast activity plasma indicators of bone turnover such as beta-CTX, and Procollagen Type I Intact N-terminal Propertied (PINP), were unaffected⁷⁰.

Camellia sinensis

Commonly referred as the tea plant, is a member of the family Theaceae. It is a tiny, evergreen shrub indigenous to East Asia, especially Southeast Asia, China, and India. The bioactive compounds seen in *Camellia sinensis* are Catechins epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), and epigallocatechin gallate (EGCG), (Cabrera et al., 2006) Caffeine, theaflavins, amino Acids like L-theanine, (Juneja et al., 1999). Vitamins and Minerals, vitamin C, vitamin B2, vitamin B3, Saponins. Due to the presence of antioxidant property (Rice-Evans et al., 1996) it showed a wide therapeutic activity done for Anti-inflammatory Effects (Babu et al., 2006), Anti-cancer effects (Yang et al., 2009), Cardioprotective activity (Dong et al., 2012). Anti-bacterial and Antiviral Properties (Prakash et al., 2011), Anti diabetic activity (Jiang et al., 2011). The poly phenols in green tea, particularly epigallocatechin gallate (EGCG), have shown a promising potential in advance bone health by reducing osteoclast activity and increasing osteoblast activity (Cheng et al., 2003) by regulating several bone-related signaling pathways including the Wnt/ β -catenin pathway (Kang et al., 2010)^{72,73,74}.

Cissusquadrangularis

commonly identified as headhood, pirandai, nalleru in different languages, this perennial plant belongs to family Vitaceae (Siddiqua & Mittapally, 2017). Widely found in India, Sri Lanka and Bangladesh. The plant is abundant in constituents like flavonoids, triterpenoids, vitamin c, stilbene derivatives, α - sitosterol, α - amyrin and α -anyone (Mehta, Kaur, & Bhutani, 2001). The phytochemicals exhibits anti-oxidant and free radical scavenging activity (Prabhavathi, Prasad, & Jayaram, 2016), anti-microbial and anti-bacterial activity (Basker, Yassir, & Kottamparambath, 2013), anti-ulcer activity (Mag, Jainu, Vijai Mohan, & Kannan, 2010), anti-helminthic activity (“A review on *Cissus quadrangularis* and evaluation of its in- vitro anthelmintic activity,” 2014), and bone healing activity (Mishra, Srivastava, & Nagore, 2010). According to Jameela et al *Cissusquadrangularis* can reduce Ovariectomy induced bone loss with more effects on the cancellous bone of femur followed by tibia. The presence of flavonoids (Banu et al., 2012) down regulates proinflammatory cytokines that are often increased after ovariectomy^{75,76,77}.

Dioscorea Lata– purple yam

usually known as purple yam belonging to the family of Dioscorea is well cultivated in all the ecological zones of the country especially Sri Lanka (Foods, Nutrition, Publishers, Science, & Lanka, 1994). The bio active components found in purple yam are dioscorin, saponins and disoing (⁸⁰Nabawiyati et al., n.d.). It is reported for its various pharmacological activities like for its anti-inflammatory activity⁸¹ (Dey, Chowdhuri, & Sarkar, 2016), anti-hypertensive (Liu et al., 2014), anti-carcinogenic, anti-thrombotic, anti-mutagenic and immunomodulatory activities (Nikawati et al., n.d.). According to Kang et al Dispo85E a active compound regulated the mesenchymal stem cells differentiation into an osteogenic lineage rather than an adaptogenic lineage and ameliorates osteoporosis in the mouse models (Peng, Horng, Sung, Huang, & Wu, 2011)^{78,79}

Salvia miltirrhiza– (red sage)

A Chinese medicinal herb called Dan's hen. sometimes described as simply the red sage. It is mostly available along the slopes and the stream banks in the west and southwest province in China and Japan. Seventy compounds have been isolated from *Salvia miltirrhiza* and have been separated as hydrophilic and lipophilic compounds. Some of the hydrophilic compounds isolated are rosmarinic acid, ursolic acid, baicalin, stigmaterol and some lipophilic compounds isolated are tanghinin I, IIA, IIB, V, VI, salviol, miltirrhizone (B. Wang, 2010). The pharmacological activities of these plant reported for its anticancer activity, anti-inflammatory⁸², antimicrobial, Cardio-protectivity⁸³ antiviral and antioxidant (B. Wang,

2010). Bong Kyun Park et al reported that SML(Combination of ethanolic extract of *S.miltiorrhiza* and liquefied calcium) had protective mechanism against estrogen deficient bone loss through blocking of the RANKL signaling pathway .this also inhibit expression of TRAF6 and NFTAcl as well as the unregulated cathepsin K and calcitonin receptor to support osteoclast differentiation(Park et al., 2017)⁸⁴

Lepidiummeyerii

commonly known as maca belonging to the family of Brassicaceae native to Peruvian central Andes (Gonzales, 2012) (Lee, Kim, & Lee, 2017). maca contains a variety of primary and secondary isolated chemical constituents like alkaloids, sterols, glucosinolates and their derivatives, Macrene and moctamides (Y. Wang, Wang, McNeil, & Harvey, 2007) and rich in antioxidants⁸⁶. Traditionally it is used to enhance fertility and sexual function⁸⁵ (Yongzheng Zhang, Yu, Ao, & Jin, 2006) (Oshima, Gu, & Tsukada, 2003) It was noted for its antifatigue property (Jieying Li et al., 2017), ability to improve memory and learning enhancer (Rubio et al., 2011). According to Yongzheng et al stated that *Lepidiummeyerii* improved bone mass, re-established trabecular system in the lumbar vertebrae in Ovariectomised rats which suggests potential benefits for postmenopausal osteoporosis (Yongzheng Zhang et al., 2006)⁸⁷

Punicagranatum

Commonly known as pomegranate belonging to the family of Punicaceae and is cultivated Cyprus, Egypt, Morocco, Spain, Tunisia and Turkey (Maurya & Asthana, 2018). The bioactive compounds comprise of flavonoids like genistein, daidzein alkaloids such as isopelletierine, pseudopelletierine, N-methylisopelletierine, anthocyanidins, ellagitannins, gallic acid and ellagic acid⁸⁸(Reza, Arastoo, & Nasser, 2012). It is extensively studied for its therapeutic activity on Alzheimer's disease(Hartman et al., 2006) , obesity(Lei et al., 2007), erectile dysfunction(Azadzi, Schulman, Aviram, & Siroky, 2005) , male infertility(Aydin, Yu, & Gu, 2008) , bacterial infections(Machado et al., 2002) , diabetes(T. H. Huang et al., 2006) , hypertension⁹⁰(Stowe, 2011) and atherosclerosis(Ignarro, Byrns, Sumi, Nigris, & Napoli, 2006).A study by Melanie et al stated that Pomegranate peel extract metabolites precisely regulates bone cell differentiation with antiinflammatory ⁸⁹and anti-oxidative effects in the bone microenvironment. These findings suggest that pomegranate consumption could be a promising replacement and additive therapeutic agent for the prevention of osteoporosis (Spilmont et al., 2015)⁹¹.

Withania somnifera– ashwagandha

commonly known as ashwagandha, belongs to the family Solanaceae and is indigenous to India , Srilanka , Afghanistan , Baluchistan and Sind(Uddin, Samiulla, Singh, & Jamil, 2012).The plant has various chemical constituents like Withanine , Withanone , Sitoindosides X , Withanolide , Withaferin (steroidal lactone) and Withanone (Mir, Khazir, Mir, Hasan, & Koul, 2012)(Africa, 1993).It is reported for its therapeutic benefits on neuroprotective activity⁹² anti-oxidant , anti-stress , hepatoprotective, anti-tumor , immunomodulatory , anti-convulsant, antiproliferative, antidiabetic⁹³ and anti-diuretic activity(Ahlawat, Khajuria, Bhagwat, & college ,2012) .Prabhakara et al studied that the treatment with *Withania somnifera* in ovariectomized animals restored the metaphyseal bone loss in femur and exhibited an increase in the biomechanical strength of the tibia (Nagareddy& Lakshmana, 2006)^{94,95}

Discussion:

Bisphosphonates, estrogen therapy and calcitonin are considered as primary therapy in the treatment of osteoporosis but they are associated with many side effects and they often fail to fulfil the fracture complications. Plant sources have significantly played an important role in replacing conventional medications. Both Clinical practice and traditional medicine have imparted the possibility of using natural products in managing osteoporosis and its symptoms. Numerous medicinal plants have the ability to regulate bone metabolism in order to reduce the bone loss. By applying Biological, chemical and pharmacological methods to obtain the active compounds from plant extracts developed a potential for the treatment of osteoporosis and its related complications.

Antiresorptive drugs and anabolic drugs are the two primary pharmacological classification in treatment of osteoporosis. Anti-resorptive drugs suppress the bone resorption and anabolic drugs promotes in build up the new bone. Drugs like bisphosphonates, estrogen therapy aim to slow down the bone resorption while calcitonin stabilizes bone matrix and slow down bone loss and finally decreasing the bone turnover. On the contrary the anabolic drugs rarely help in development of bone proliferation and improve bone health. FDA has approved Teriparatide, a synthetic

parathyroid hormone the only anabolic in treatment of osteoporosis. The plant-based medications enhance osteoblast proliferation activity and improve bone formation. The physicians prescribe either antiresorptive therapy or anabolic therapy or their combination for the treatment of osteoporosis depending on patients need. Bone health can be enhanced by adequate nutrition and lifestyle practices. However, there is no proper treatment for osteoporosis or any bone related illness. The administered drugs for treatment have severe side effects. Certain considerations are required to note before taking medicinal plants a).Compatibility's chemical compounds of the plant should be safe and must be clear).Selection: The drug action must be specified that specifically bind to the targeted drug surface for promoting drug action's).Therapeutic index: The new invented drug should be optimized to increase efficacy and decrease side effects from other drugs and finally d).convenience :The drug should be easily taken orally rather than other parenteral routes. Numerous plants undoubtedly possess both preventive and curative of osteoporosis. The primary hindrance is only small portion of plants are surveyed so far hence commonly used plants need to evaluate for their pharmacological and therapeutic effects in osteoporosis patients. Clinical trials are still to be conducted and medicinal products from plants are regarded as a preventive instead of curative. If research is supported more natural pharmaceuticals could be soon accessible to the general public.

Conclusion:

The impact of osteoporosis and fragility fractures on morbidity, mortality, and socioeconomic expenses result in serious concerns for health. Anti-resorptive drugs (e.g., bisphosphonates, hormone therapy, calcitonin) are frequently used for osteoporosis patients whereas anabolic medications (such as teriparatide and strontium ranelate) are modern choice based upon clinical trials. It was recently tested to improve bone mass and reduce resorption by combining anabolic and anti-resorptive drugs. Novel treatments including gene therapies, antibody agents, stem cells are made more accessible in advancements of bioengineering and molecular bone metabolism. Phytochemicals that have antioxidant or estrogen-like properties Bone loss was caused by ursolic acid, rosmarinic acid, SML (a combination of baicalin, stigmasterol saponins, coumarins, stilbene derivatives, and β -sitosterol), and it by controlling osteoblast and osteoclast activity, β -amyrin and β -anyone has demonstrated the ability to support bone health. Daidzein and genistein have a direct impact on bone cells by altering important signalling pathways. Even though natural therapies have great potential, further study is required to fully comprehend their workings and determine their safety and effectiveness in treating osteoporosis.

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