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Age-specific bone turnover prevalence in women with post-menopausal osteoporosis: possibilities of traditional plant therapy during COVID-19 pandemic

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Abstract

Post-menopausal osteoporosis is a chronic age-related illness marked by a decrease of bone density and quality, as well as a higher risk of fragility fractures. Fragility fractures are recognized to have a major impact on individuals and society both personal and financially. In recent years, it has been a hidden epidemic impacting over 200 million people globally. It is claimed that one osteoporosis fracture happens every three seconds throughout the world. The termination of ovarian hormone production, which causes rapid bone loss, puts postmenopausal women at greater risk of developing osteoporosis. The gradual changes in structure, quality and density of the bones lead to the fracture and a rise in morbidity and death among menopausal women. Interventions that enhance a woman's well-being and quality of life by reducing the intensity and frequency of post-menopausal osteoporosis. Hormone therapy is helpful in managing menopausal symptoms; nevertheless, it has been linked to a number of potentially significant side effects, including the development of ovarian and breast cancer. As a result, there has been an increase in demand for alternative treatment options. Plant species with potential antiosteoporosis characteristics are highlighted and further discussed in order to aid future medication development for treating this illness. Many plants and there components have been demonstrated to have antiosteoporosis action based on a vast number of chemical and pharmacological studies. Plant-derived molecules have lately piqued the curiosity of researchers working on novel medicinal agents. As a result, therapeutic interventions that can delay reduce or prevent bone loss in ageing people, especially postmenopausal women, are essential to a person's well-being and quality of life. The plants included in this review are those that have been frequently used in traditional medicine and have shown clinical efficacy in the management of post-menopausal osteoporosis. While numerous plants can prevent and treat osteoporosis, only a fraction of plants have been discussed, including their origin, active components, and pharmacological activity, we evaluated the challenges and methods utilized in the therapy of postmenopausal osteoporosis during the COVID-19 pandemic.

Key words: Osteoporosis; Oestrogen; Bone Mass; COVID-19; Fragility Fracture

1. Introduction

Post-menopausal osteoporosis has regarded as a significant public health issue that affects millions of people, practically the elderly and postmenopausal women [1, 2]. Post-menopausal osteoporosis is a chronic bone metabolic disease, which decreases strength and leads to weak bones and a degradation of the bone microarchitecture, which can increase directly skeletal fragility and fracture risks [3, 4]. Bone loss quickly surge during 4-5 years in menopause, resulting in women losing their bone density by up to 25 percent. A women's postmenopausal period generally lasts one-third of her life. Around 80 percent of females in this period suffer flushes, nocturnal sweetness, osteoporosis, fatigue and irritability and 9 percent have additional symptoms which have an impact on their quality of life. According to a study,

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one in five men and one in three women, or 200 million men and women globally, may experience a fragility fracture through their lifetime [5]. Fragility fractures can have a significant impact on a person's everyday activities and quality of life and they are linked to an elevated risk of death in osteoporosis sufferers. Hip fractures are especially dangerous, as they are linked to a high prevalence of disability and death. In the United States, over 44 million men and women over the age of 50 have osteoporosis or decreased bone mass [3]. Maintaining the women's welfare and health during this era has a high priority in minimizing socioeconomical damages in order to increase life expectancy and the stability of menopausal age. A number of hormones and cytokines, regulate the activity of osteoblasts and osteoclasts. Most significantly, sex hormones are necessary for maintaining bone mass balance and a shortage of oestrogen levels linked with menopause cause an initial phase of rapid bone loss, followed by a period of gradual skeletal degeneration. In the following first 5 to 10 tears following the termination or operational removal of the ovary, this accelerated period of bone loss occurs [9]. Individuals risk factors for osteoporosis very, but they are all connected to the osteoporosis development. These factors are Non-changeable variables include age, gender, body size, ethnicity and family history; modified factors include sex hormones, calcium and vitamin D consumption, pharmaceutical uses among others. Post-menopausal osteoporosis is commonly treated and prevented through physical activity, nutritional supplements and medication. The pharmacotherapy for post-menopausal osteoporosis is aimed at adjusting the level of oestrogen or bone remodeling. However, the different biophosphonates, raloxifen, denosumab, selective oestrogen receptor modulators (SERM) as well as the bone-forming pharmacological agent teriparatide, are the most often used medicines, these drugs are linked with side effects, costly, and often have low compliance [11]. It is so essential that safe, cost effective treatment methods are vitally needed that can postpone or slow down or prevent bone loss in older people and especially postmenopausal women. Every year, several nations' health ministries spend a significant amount of money researching new antiosteoporosis medicines. Many medicinal herbs were utilized in many nations for the prevention and treatment of osteoporosis. These natural plant-based medications have less secondary effects and are more appropriate than synthetic medicines for long term usage. In this article we have summarized recent anti-osteoporotic plant studies with an emphasis on the chemical components, mechanisms of action, therapeutic uses future possibilities [12].

Table 1 Osteoporosis risk factor, symptoms and signs, consequences of osteoporosis, diagnosis of osteoporosis and who should get a bone density testing

Osteoporosis risk factor	Symptoms and signs?	Consequences of osteoporosis?	Diagnosis of osteoporosis?	Who should get a bone density testing?	References
All postmenopausal female younger than 65	Osteoporosis symptoms do not appear until a bone fracture	Reduced quality of life and disability	Regular X-ray can detect osteoporosis	All women aged 65 and older	[13]
Inherited disorders (osteogenesis imperfecta, homocystinuria, osteoporosis-pseudoglioma syndrome)	Pain; the location ofthe pain depends on the location of the fracture	Up to 30% of hip fracture patients will need long-term nursing home care	Dual-energy X-ray absorptiometry scan (DEXA) measures the spine, hip, or total body	Postmenopausal women with fractures	[14]
Lack of calcium and vitamin D, lack of exercise, cigarette smoking,excessive alcohol consumption	Spinal fractures can result in excruciating "band-like" pain. Multiple spinal fractures may result in persistent lower back pain	Elderly people may develop pneumonia and blood clots in their leg veins that can travel to their lungs due to prolong bed rest rest	pDXA (peripheral dual-energy X-ray absorptiometry) measures the wrist or heel	Younger women with a higher-than-normal chance of fracture for their age	[15]

		following a hip fracture.			
Long-term use of heparin, antiseizure medicine such as phenytoin, phenobarbital and corticosteroids (such as prednisone)	Loss of height (getting shorter by an inch or more).	Some 20% of women with a hip fracture will die in the subsequent year	QUS (quantitative ultrasound) uses sound waves to measure density, usually at the heel	Breaking a bone in a minor accident	[16]
Malabsorption (nutrients are not properly absorbed from the gastrointestinal system)	Change in posture (stooping or bending forward)	Cardiovascular complications Bone cancer	pQCT (peripheral quantitative computed tomography) measures the wrist	Having rheumatoid arthritis	[15]
Overactive thyroid, parathyroid, or adrenal gland	Worsening of pain when standing, walking, bending or twisting	Vertebral compression fractures (VCF).	Radiography, CT scan	Drinking heavily Smoking	[13]
Chemotherapy that, because of its damaging effects on the ovaries, can results in an early menopause	Shortness of breath (smaller lung capacity due to compressed disks	Limited mobility, an increased susceptibility to various other complications	Ultrasonic measurement of bone Physical examination	Using corticosteroid drugs for three months or more	[17]

2. Bone turnover markers (BTMs) in osteoporosis:

In several metabolic bone diseases, bone BTMs give an insight into the dynamic of bone turnover. Increased bone turnover due to age and pathological conditions like osteoporosis result in degradation of bone microarchitecture and hence increases the risk of fractures irrespective of the low bone mineral density. There are two stages in bone turnover: removal of the old bone (reabsorption) and the development of the new bone (formation).

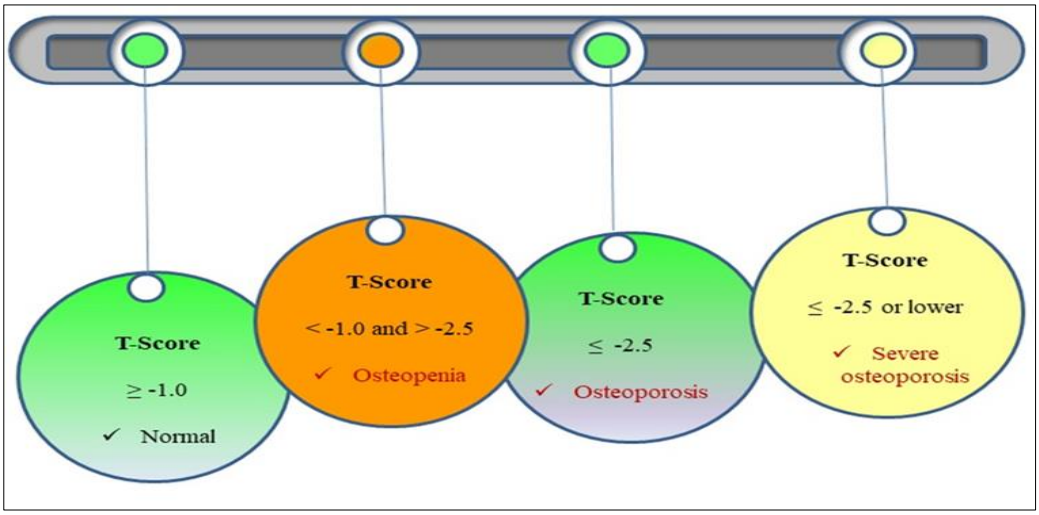

Figure 1 Osteoporosis diagnostic criteria based on T-score

Bone formation and resorption indicators include the N-terminal propeptide of type I procollagen (PINP) and the C-telopeptide of type I collagen (CTX-I). These indicators, however, are susceptible to a variety of factors, including nutrients (reabsorption reduces) and recent fractures (all markers increases for several months) [18].

3. Why is osteoporosis a major public health concern?

Its estimated that 50 million Indians have low bone mass or are have osteoporotic (T-score less than 2.5). According to a studies conducted among women in India, 46 million of the 230 million Indians anticipated to be over the age of 50 years have osteoporosis. In the US, there are 44 million people with low bone mass (10 million have osteoporosis and 34 million have osteopenia). Over 20 percent of individuals who suffers a hip fracture will die within a year of the injury. Within a year following a hip fracture, one-third of patients are released to their nursing homes. Only one third of individuals with hip fracture returns to their prefracture level of function. Only one-third of hip-fracture patients regain their pre-fracture level of function [19].

4. Therapeutic perspectives of medicinal plants in the management of postmenopausal osteoporosis

4.1. Dried plum: its therapeutic effects in postmenopausal osteoporosis

Dried plums are high in nutritional bioactive components including dietary fiber, vitamin K, boron, copper, magnesium and more, many to known to have a beneficial effect on bone. Ovariectomy resulted in a substantial decreases in femoral bone mineral density (BMD) compared to operated (Sham) rats. Overiectomized rats administered 25 percent of diet in form of dried plum for 45 days did not loss bone but rat given 5 percent of their diet as dried plum lost bone, despite this, dried plum was shown to raise circular insulin-like growth factor –I (IGF-I) levels in a dose dependent manner while having no effect on tartrate-resistant acid phosphatase-5b (TRAP-5B) levels. TRAP-5B considered to be a biomarker of bone resorption. Finally, the dried plum's nutrients reduced bone loss in by boosting the rate of bone formation but not by blocking bone reabsorption according to the findings [20].

4.2. Black cohosh: its therapeutic effects in postmenopausal osteoporosis

Black cohosh, a plant belonging to the Ranunculaceae family, has long been used in Native American medicine to treat a variety of illnesses, including dysmenorrhea and the symptoms of menopause. Triterpene glycosides, resin, salycilates, isoferulic acid and alkaloids are just a few of the black cohosh's potentially bioactive constituents. Black cohosh does not appear to alter the hormonal pattern associated with menopausal. The trabecular bone mineral density of the proximal metaphysis of the tibia significantly increase as a result of improved differentiation and boost in the OPG-to- RANKLE ratio of normal human osteoblast. In cells, deoxyacten triggers significant rise in cell proliferation, alkaline phosphate activity, and mineralization. Deoxyacten also reduces the formation of reactive oxygen species (ROS) and osteoclast differentiation-inducing factor such as TNF-α, IL-6. Extract of black cohosh attenuated bone loss at tibial metaphysis after 3 months in an orchidectomized rat model of osteoporosis. In a rat model with ovariectomies, the effect of black cohosh on bone loss and serum levels of osteocalcin showed only modest protective effects on bone loss and a decrease in osteocalcin levels. Sixteen randomized controlled trials found a reduction I daily hot flush frequency and menopausal atherosclerosis in 2027 postmenopausal women who administered 40 mg/day of monoformulation of black cohosh for a mean of 23 weeks [21].

4.3. Hop (*Humulus lupulus* L.) and its therapeutic effects in postmenopausal osteoporosis

Hop (*Humulus lupulus* L.) is a source of several biological active chemicals such as sesquiterpenoids, phytoestrogens and the flavonoid xanthohumol in addition to being a significant ingredient in beer brewing. 8-prenylnaringenin (8-PN), a noteworthy chemical, gas been demonstrated to be a prominent phytorstroen (mimicking the action of estrogenic hormones, due to their ability to interact with estrogenic receptors). The ability of 8-PN to reduce bone reabsorption was tested in 24 postmenopausal women who were 8-PN orally. Furthermore, the ability of 8-PN to inhibit bone loss has been investigated. 8-PN prevent the production of osteoclasts and induced apoptosis in rabbit bone marrow cells to a greater than niringenin and showed the importance of the phenyl group in bone protecting properties. The effect of hope on preventing bone reabsorption and evaluating the estrogen mechanism of action in initiating proliferation in the endometrium were investigated in vivo in ovariectomized rats that were given orally a standardized hop extract for 8 weeks [22].

4.4. Lavender (*Lavandula angustifolia*) Aromatherapy and its therapeutic effects in postmenopausal symptoms

Lavender oil is an essential oil extracted from the lavender flower. During a 12 week double-blind cross-over scientific experiment, 100 menopause women (45 to 55) were exposed to the scent of lavender two times daily for 20 minutes

each time demonstrated that inhaling lavender alleviated the symptoms of early menopause. Inhaling lavender reduced anxiety, depression and vasomotor symptoms; this reduction may be related to a decrease in stress hormone and Beta-endorphins release. Taavoni *et al.,* claim that massage the belly with lavender for 30 minutes twice a week for four weeks reduces menopause symptoms. Women in both the aromatherapy and placebo massage groups had lower menopausal score than the control group (P0.001), according to post hoc analysis. When the aromatherapy message and placebo massage groups were compared, the aromatherapy massage group scored considerably lower (P0.001) than the placebo group. Menopausal symptoms are said to be reduced after drinking 200 cc of lavender, according to Bradely *et al*. [23].

4.5. Genistein as potential therapeutic candidate for post-menopausal osteoporosis

Genistein is an isoflavone generated from soy-rich foods that makes up around 60 percent of all isoflavones found in soybeans. Several biological effects of genistein have been described including anti-tumor activity, improved glucose metabolism, reduction of postmenopausal hot flashes, osteoporosis and antioxidant modulation. Genistein is an estrogenic isoflavone with selectivity for the oestrogen receptor that is twenty times greater than that oestrogen [11]. Genistein works by interacting with a variety of enzymes, including topoisomerase I and II. During clinical trials, a randomized double-blind in menopausal women found that taking 30 mg of genistein for 12 weeks reduced hot flashes by 51 percent whereas the placebo group only saw a 27 percent drop. In ovariectomized rats, the natural isoflavone phytoestrogen genistein was found to increase osteoblastic bone resorption, and prevent bone loss [13].

4.6. Effect of caffeine ((1,3,7-trimethylxanthine) on ovariectomy-induced osteoporosis in rats

The most typical source of caffeine in natural are the cacao, tea and coffee plants. Caffeine intake for people with osteoporosis or low bone density should be kept to less than 300 mg per day. Caffeine should be used with caution by older women who have an inherited disorder that affects the utilization of vitamin D. together with calcium, vitamin D helps to build bones.

The pharmacological impact of long-term caffeine administration on postmenopausal osteoporosis induced by ovariectomy in female rats was examined by Huanhuan Xu *et al.* low, medium and high doses of caffeine (9.6, 19.2 and 38.4 mg/kg of body weight\day, respectively) were given to the ovariectomized (OVX) rats. Caffeine therapy effectively improved the lipid profile and raised the calcium concentration in the serum of OVX rats, according to in-vivo studies. Caffeine treatment at a medium or high dose significantly reduced the alkaline and acid phosphatese activities in OVX rats. These findings need more research because they are still debatable. Notably, moderate doses of caffeine (20mg/kg per day for 4 weeks) have been shown to benefit the OVX rats' skeletal systems [14].

4.7. The Anti-Inflammatory, Phytoestrogenic, and Antioxidative Role of Labisia pumila in prevention of post-menopausal osteoporosis

Labisia pumila is a flowering plant in the family Primulaceae. It is a small, 20 cm long, woody, and leafy plant that thrives in the shade of tropical forest floors. Labisia pumila exhibits a wide range of biological activities in-vitro and in-vivo, including phytoestrogenic, anti-inflammatory, antooxident and anti-microbial properties.

Proinflammatory cytokines like IL-1, IL-6,IL-7 and TNF-α can be reduced by oestrogen. Studies have demonstrated that lowering oestrogen levels can promote localized bone inflammation. Positive effects on bone without causing side effects were produced by 17.5 mg/kg/day of water extract from *Labisia pumils*, which is known to exert this effect. Hence, preventing the synthesis of TNF-α, which results in a decrease in receptor activator of nuclear factor kappa-B ligand (RANKAL) expression, a reduction in osteoclast activity and subsequently a reduction in bone loss. By inhibiting ROS, oestrogen can stop osteoblast cell death and RANKL stinulation. A crucial step in the ROS-mediated stimulation of bone loss via TNF-α signaling pathway is oestrogen deficiency [24, 25].

5. Discussion

Although oestrogens, bisphosphates, and calcitonin are the mainstays in the treatment of osteoporosis and controlling fracture, they have numerous side effects and do the little to change the course of complications from bone fractures. Plants are always a prime source for many of the drugs that are currently on the market. The possibility of the obtaining natural products to recover from osteoporosis and its complications has been demonstrated by clinical practice and common experience. Numerous herbs, which are all made of natural ingredients, are believed to treat osteoporosis primarily by strengthening the kidney and enhancing bone quality. Therefore, active lead compound from natural medicinal plants should be screened and obtained using biological, chemical and pharmacological methods in order to treat osteoporosis and its complications.

For the treatment of osteoporosis, there are primarily two categories of medicines. One is anabolic agents, which primarily build bone and the other is antiresorptive agents which inhibits bone resorption. The majority of the medications work as inhibitors of the bone resorption, including bisphosphonates, oestrogen, selective oestrogen receptor modulators and calcitonin all of which can lessen bone loss, stabilise the microarchitecture of the bone and slow down bone turnover.

6. Conclusion

Although it is clear that many plants have the ability to both prevent and treat osteoporosis, only a small number of these plants have received through research.to systematically assess the anti-osteoporotic efficacy of plant extract, to identify the bioactive compound responsible for the manifestation of bone protection and to elucidate anti-osteoporotic mechanisms, it is imperative to develop more effective and reliable bioassays.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interests.

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