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Review Article

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An updated review of single herbal drugs in the management of osteoporosis

Abstract

Osteoporosis is a bone disease characterized by a decrease in bone mass and micro–architectural alterations. This would lead to a bone with less tensile strength and significantly more susceptibility to fracture with less force. This syndrome is clinically silent but progressive, usually only noted when a fracture occurs. Though there is no direct reference of this condition in classical texts of Ayurveda, it can be correlated with the *Asthikshaya*, on the basis of pathophysiology and symptoms. For the management of this condition, various therapeutic measures are recommended in the classical texts. Among them, single herbal remedies for the management of osteoporosis are in routine clinical practice. The present review has been carried out to compile different pre–clinical and clinical research works reported on single herbal drugs for the management of osteoporosis. Analysis of results shows that, about 11 different drugs mentioned in classical texts of Ayurveda are reported for their anti–osteoporotic properties in different clinical and experimental studies. Clinically *Nigella sativa* is reported for its effect on the bone markers of postmenopausal women. Plants like *Withaniasomnifera, Cissusquadrangularis, Punicagranatum, Tinosporacordifolia,* are studied experimentally and found effective in the management of osteoporosis. The findings of present review highlight the use of these single and simple herbal remedies for the treatment of patients suffering from osteoporosis and can give a lead to further extensive research on these drugs.

Keywords: *asthikshaya*, ayurveda, herbal drugs, medicinal plants, osteoporosis

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Introduction

Osteoporosis is the most common metabolic bone disorder characterized by decreased bone strength. It is a major problem of health care delivery services, both in the developed and developing countries. According to WHO, osteoporosis is a "progressive systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[1] This is a heterogeneous cluster of abnormal processes characterized by the net loss of bone. It results in a decrease in total mineralized bone without a decrease in the ratio of bone mineral to the organic matrix.[2,3] As a result, there is a decrease in the overall amount of bone.

In Ayurvedic classical literature, there is no direct reference regarding osteoporosis and its management. Acharya Sushruta[4] has explained about *Asthikshaya* where the causative factors, signs and symptoms are similar to osteoporosis. Different Acharya like Charaka[5] and Vagbhata[6] have opined the same.

Prevalence of this disease is increasing as the population of elderly is on a rise. It is estimated that as many as 1 in 2 women and 1 in 5 men are at risk for an osteoporosis–related fracture during their lifetime.[7] Because of increase in ageing population, it is estimated that by the year 2020, the number of women affected will be double.[8] Thus, this condition has assumed major public health importance in recent years. It has been estimated that spinal compression fractures are associated with osteoporosis and 15 to 34% of all patients with hip fractures will die from complications within 6months.[9]

Though different treatment modalities like HRT, Calcium & Vit–D supplement are commonly used, there is no treatment which has satisfactory improvement without side effects. Due to some adverse effects and lacunae of synthetic drugs, there is a need of finding out better remedy for the management of osteoporosis. Therefore the present review has been made to compile the single herbal drugs reported for their beneficial effect on osteoporosis and to present them in a single place.

Material and methods

Different herbal drugs reported for their effect on management of osteoporosis were compiled from published research articles. The available data is arranged according to their Sanskrit name, English name, botanical identity and part used. The mechanism of action of reported drugs is analyzed critically and presented systematically.

Results and discussion

Analysis of data reveals that, about 11 different drugs mentioned in classical texts of Ayurveda are reported for their anti–osteoporotic properties in different clinical and experimental studies (Table 1). Clinically *Nigella sativa* is reported for its effect on the bone markers of postmenopausal women. Different parts of the plants like *Withaniasomnifera, Cissusquadrangularis, Punicagranatum, Tinosporacordifolia, Curcuma longa, Nigella sativa, Meliaazedarach, Asparagus racemosus, Moringaoleifera, Zingiberofficinale* and *Sesamumindicum*are studied experimentally and found effective in the management of osteoporosis.

Ashwagandha–withaniasomnifera (L.) wunal

Effect of *Withaniasomnifera* root ethanolic extract has been evaluated for anti–osteoporotic activity in ovariectomized Sprague–Dawley rats. Extract at the dose of 65 mg/kg for 16 weeks has shown a significant increase in serum alkaline phosphatase levels and urinary calcium and phosphorus excretion. Histological findings has revealed narrowed, and disappearance of trabeculae with widened medullary spaces in the ovariectomized group.[10]

Table 1 Single herbal drugs reported for their effect on osteoporosis

S No	Sanskrit name	English name	Botanical identity	Part used
	Ashwagandha	Winter cherry, Indian Ginseng	*Withaniasomnifera* (L.) Dunal (Solanaceae)	Root
	Asthishrinkhala	Edible stemmed wine	*Cissusquadrangularis* L. (Vitaceae)	Aerial parts
	Dadima	Pomegranate	*Punicagranatum* L. (Lythraceae)	Fruit
	Guduchi	Gulbel, Indian Tinospora	*Tinosporacordifolia* (Thunb.) Miers (Menispermaceae)	Stem
	Haridra	Turmeric	*Curcuma longa* L. (Zingiberaceae)	Rhizome
	Krishna jiraka	Black cumin	*Nigella sativa* L. (Ranunculaceae)	Seeds
	Nimba	Neem	*Meliaazedarach* L. (Meliaceae)	Bark
	Shatavari	Wild Asparagus, Sparrow grass	*Asparagus racemosus* Willd. (Asparagaceae)	Tuberous root
	Shigru	Moringa, drumstick tree	*Moringaoleifera* Lam. (Moringaceae)	Aerial parts
	Shunthi	Ginger	*Zingiberofficinale* Roscoe (Zingiberaceae)	Rhizome
	Tila	Sesam	*Sesamumindicum* L. (Pedaliaceae)	Seeds

Asthishrunkala– cissusquadrangularis l.

The phytoestrogen–rich fraction (IND–HE) from aerial parts of *C. quadrangularis* has shown presence of phytoestrogen–rich fraction. Treatment with IND–HE (75 and 100mg/kg) showed statistically significant increase in bone thickness, bone density and bone hardness in ovariectomised in rats. IND–HE and estrogen treatment significantly increased serum estradiol, serum vitamin D3 and serum calcium compared to control. Alkaline phosphatase was significantly reduced. Results of Histopathology studies indicated that IND–HE (75 and 100mg/kg) prevented bone loss.[11] In another experimental study, ethanol extract of *Cissusquadrangularis* at two different dose levels of 500 and 750mg/kg per day showed a definite antiosteoporotic effect.[12] The petroleum–ether extract at the dose of 500mg/kg, for 3 months reduced bone loss, as evidenced by the weight gain in femur, and also reduced the osteoclastic activity there by facilitating bone formation in experimental animals.[13] Asthishrunkhala contains anabolic and phytogenic steroids like Ketosteroids, sitosterol, alpha amayrin, alpha ampyrone and tetracyclic triterpenoids.[14] These anabolic and steroidal components showed a marked influence on fracture–healing. Ketosteroid acts as antagonists to the glucocorticoid receptor and promotes good bone health. It mobilizes fibroblast and chondroblasts to an injured tissue and enhances regeneration. The anabolic steroidal component of Asthishrunkhala showed a marked influence in the rate of fracture healing by influencing early regeneration of all connective tissues of mesenchyme origin, namely the fibroblasts, the chondroblasts and osteoblasts involved in the healing and quicker mineralization of the callus.[15]

Dadima – punicagranatum l.

Anti–osteoporotic activity of ethanolic extract of *Punicagranatum* in ovariectomized rat model of osteoporosis at 100, 300 and 500 mg/kg is reported experimentally. There was significant increase in femur length, weight and density, increase in serum calcium, phosphorus and reduction in alkaline phosphatase, tartrate resistant acid phosphatase, osteocalcin whereas urine calcium, creatinine and phosphorous levels were significantly decreased. Histology of femur exhibits restorative progress with increased ossification, mineralization and increased osteoclastic activity.[16] Polar fraction of *Punicagranatum* (L) peel extract at the doses of 50, 100, and 200 mg/kg significantly prevented bone loss in ovariectomized rats. These effects were described in increased mineral content of calcium. On histology data shown that fraction could increase osteoblast number.[17] Consumption of pomegranate peel extract was able to significantly prevent the decrease in bone mineral density and bone micro–architecture impairment in ovariectomized mice.[18] The alcoholic extract of fruit peel at the dose of 500mg/kg and 750mg/kg, daily for 90 days showed significant increase in uterine weight, femur BMD and femur hardness. In addition, increased levels of calcium and phosphorus in serum and significant decrease in urine were observed.[19] Exposure of different concentrations (10–100µg/ml) of the ethanolic extract on osteoblastic cells showed characteristic morphological changes and increment in cell number. A significant growth in cell proliferation, ALP activity, collagen contents and matrix mineralization of osteoblasts in a dose dependent manner suggested that extract has a stimulatory effect on osteoblastic bone formation or potential activity against osteoporosis.[20]

Guduchi–tinosporacordifolia (thunb.) miers

Effects of alcoholic extract of *Tinosporacordifolia* on the proliferation, differentiation and mineralization of bone like matrix was studied on human osteoblast–like cells MG–63 and primary osteoblast cells isolated from femur of rats. The extract at a dosage of 25µg/ml stimulated the growth of osteoblasts, increased the differentiation of cells into osteoblastic lineage and increased the mineralization of bone like matrix on both the osteoblast model systems used in the study. Cell morphology studies clearly indicated the increase in cell numbers and absence of adverse change in the cell morphology on treatment with the extract.[21] Aqueous and alcoholic extracts were evaluated for osteogenic effect using a widely employed in vitro model system for human osteoblasts (human osteoblast like cells SAOS–2). It was observed that ethanolic extract stimulated proliferation of osteoblasts at a dosage of 25µg/ml but, the aqueous extract showed no influence on cell proliferation. The extract also elicited pro–stimulatory effects on osteoblasts.[22] Probably with this insight, the fermented form of medication is recommended for therapeutic purposes in Ayurveda.

Haridr –curcuma longa l.

Curcumin is considered as a potential treatment in numerous diseases, including osteoporosis. Curcumin has been reported to affect osteoclastogenesis and osteoblast proliferation and activity in vitro.[23] Extracts prepared from *Curcuma longa* L., containing bioactive phenolic curcuminoids was evaluated for bone–protective effects in a hypogonadal rat model of postmenopausal osteoporosis. The curcuminoid–enriched turmeric prevented up to 50% of ovariectomized induced loss of trabecular bone and also preserved the number and connectedness of the strut–like trabeculae.[24] Treatment with curcumin was able to reverse all the ovariectomy–induced deteriorations. The high dose of curcumin treatment was not only able to reduce the osteoclast number but also increase the osteoblast count.[25] Curcumin administration ameliorates oxidative stress–induced apoptosis in osteoblasts by preserving mitochondrial functions and activation of Akt–GSK3β signalling. These data provide experimental evidence supporting the clinical use of curcumin for prevention or treatment of osteoporosis.[26]

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Krishna jeeraka –nigella sativa linn.

In an experimental study, ovariectomized rats showed significant decrease in plasma Ca^{+2}, accompanied by a significant increase in plasma ALP, amino terminal collagen type 1 telopeptide, MDA, nitrates, TNF–α and IL–6. These changes were reversed by supplementation of test drug.[27] *Nigella sativa* seed oil improved the micro architecture and biomechanical properties of the femur in male diabetic rats to a level equivalent to that achieved with parathyroid hormone treatment.[28,29] In a clinical study, effects of *Nigella sativa* supplements was evaluated on the bone markers of postmenopausal women. The test drug failed to cause any significant changes in the bone markers levels, when supplemented for the duration of 3 months to these postmenopausal women.[30] The sample size of the study was only 15 and the duration of study was not longer to obtain the readings of bone markers at several time points and any changes in the bone mineral density. So, a long term study with larger sample size may give more convincing results.

Nimba –meliaazadirech linn.

In an in vitro study, it has been reported that, the root extracts of *M. azedarach*, could be used as medicines for osteoporosis. The extract s inhibited osteoclast proliferation and induced apoptosis by up–regulation of caspase activity and increase of mitochondrial pro–apoptotic proteins expression. Furthermore, the extracts enhanced differentiation, but did not affect proliferation of both osteoblasts and chondrocytes. The osteo–inducible effect was also observed in cultured primary bone marrow cells.[31]

Shatavari– asparagus racemosus willd.

Methanolic and aqueous extract obtained from *Asparagus racemosus* root has shown significant effect on mineralization, ossification and osteoclastic activity suppression were observed in histopathological examination. Significant increase in total ash weight, ash percent and ash calcium content were obtained. The extract significantly reduced serum alkaline phosphatase activity, serum calcium and also inhibited the ovariectomized induced excessive loss of calcium in urine. It also improved biomechanical parameters including hardness of 4th lumbar vertebra, femoral length and its weight. Phytosterols and other active constituents present in the root of *Asparagus racemosus* may effect on estrogen receptor similar to estrogen and produce antiosteoporotic effect.[32]

Shigru– moringaoleifera lam.

In an in–vivo study, methanolic extracts of *Moringaoleifera* components showed a positive effect on osteoblast cell line SaOS2. Flower and fruit were found to have significant osteoblast stimulating property. Flower extract was found to be increasing the number of osteoblastic cells; while the fruit extract was having more elaborative effect as it increased ALP activity, induced bone formation, increased hydroxyproline content and bone mineral formation.[33] Regenerative effect of *Moringaoleifera* extract on haematological parameters and bone marrow of adult Wistar rat is reported.[34] Ethanolic extract at the dose of 600 mg/kg, significantly reduced urinary calcium excretion and significantly increased calcium content of bones in ovariectomised rats. The osteoprotective effect was comparable with estradiol.[35] Ethanolic extract of leaves at the dose of 100, 200, and 300ng/ml enhanced osteogenic differentiation capacity of porcine bone marrow derived mesenchymal stem cells as demonstrated by increased alkaline phosphatase staining and alkaline phosphatase activity.[36]

Shunti– zingiberofficinale roscoe

The osteo–protective effects of structurally–related polyphenols (gingerols) isolated from the rhizomes of *Z. officiale* was reported in experimental studies. All the extracts were found bone protective in streptococcal cell wall induced arthritis, preventing bone mineral density loss as determined by dual energy absorptiometry.[37] Treatment with 6–gingerol stimulated osteoblast differentiation in normal and inflammatory settings. This compound induced the differentiation of osteoblast like cells with increased transcription levels of osteogenic markers, upregulated ALP enzyme activity, and enhanced mineralized nodule formation. It also reduced the degree of inflammation in TNF–a–treated MG–63 cells.[38] Oil extract of garlic possibly has a positive role in suppressing ovariectomy induced bone resorption. Garlic oil extract supplementation prevented ovariectomy–induced significant alteration of serum alkaline phosphatase activity, serum tartrate resistant acid phosphatase activity, urinary excretion of calcium, phosphate, hydroxyproline and urinary calcium to creatinine ratio.[39]

Tila– sesamumindicum linn.

In an experimental study, feeding of 10% sesame oil reduced the significantly altered alkaline phosphatase activity and tartrate resistant acid phosphatase activity in ovariectomized rats. The test drug also reduced disruptive, lytic bone trabeculae and improved bone microarchitecture.[40]

Conclusion

Osteoporosis is the most common metabolic bone disorder characterized by reduced bone mass and osteoporotic fracture. This condition seriously hampers the quality life of individual and needs an effective treatment measure without any adverse effect. Different single herbal drugs mentioned in Ayurveda showed significant results in improvement of osteoporotic changes. All these drugs are easily available, simple for administration and devoid of any adverse reactions. Further clinical studies can be planned to establish their role in the effective management of osteoporosis in clinical practice.

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Conflicts of interest

The authors declared that there are no conflicts of interest.

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