Open Journal of Clinical & Medical Images

www.jclinmedimages.org

Review Article

Open Access, Volume 2

Pharmacological and alternative interventions for osteoporosis

Avin Dsouza; Miriyala Amarnath; Nandhitha Madhusudhan; Jeyaparthasarathy Narayanaperumal; Ganesh Gopal*

ITC Limited - Corporate Division, Life Sciences and Technology Centre, #3, 1st Main, Peenya Industrial Area, Phase I, Bangalore 560 058, India.

***Corresponding Author: Ganesh Gopal**

ITC Limited - Corporate Division, Life Sciences and Technology Centre, #3, 1st Main, Peenya Industrial Area, Phase I, Bangalore 560 058, India.

Tel: + 91-9164205486; Email: ganesh.gopal@itc.in

Received: Oct 16, 2022

Accepted: Dec 08, 2022

Published: Dec 16, 2022

Archived: www.jclinmedimages.org

Abstract

Bone is a dynamic organ and plays crucial role in maintaining skeletal functions. The maintenance of bone is a continuous process also known as remodeling. There is a well regulated interplay between bone cells and physiological system to maintain healthy bones. This remodeling process gets disturbed because of multiple factors such as hormonal imbalance, ageing, secondary diseases, lifestyle modifications and genetic disorders. In this review, we will focus on pathophysiology of bone disorders and its therapeutic approaches. Special focus is given to the most common bone disorder namely "osteoporosis". Review also highlights available therapeutics used in pharmacological and non-pharmacological fields, in the treatment or prevention of osteoporosis.

Keywords: Bone Remodeling; Osteoporosis; Pharmacology; Alternative medicines.

Introduction

Bone is important for maintaining the skeletal system. Bone has a multifaceted role such as providing mechanical support to the body, aiding in the locomotion, maintaining mineral homeostasis, producing blood cells and protecting the organs [1]. Bone matrix is made up of cells (10%), inorganic (60%) component hydroxyapatite also represented as Ca10 $(PO_4)_6(OH)_2$ and organic (30%) components majorly collagen type 1 protein. Apart from cells, minerals and proteins bone matrix also comprises of macromolecules and blood vessels. Human body's 85% of phosphate and 99% of calcium is stored within the bone as hydroxyapatite. In a year, around 5-10% of individual's skeleton is replaced as a continuous process [1,2].

Bone cells play an important role in maintaining bone matrix. There is a balanced interplay between bone cells namely osteoblasts and osteoclasts. Osteoblasts are bone-forming cells and osteoclast are bone-resorbing cells. Upon maturation, osteoblast is trapped into bone matrix and now these cells are known as osteocytes which acts as signal transducers of mechanical stimuli. Signals from osteocytes reaches to osteoblast cells to secrete collagen and other proteins to form the bone and osteoclast to secrete proteases (to remove old or damaged bone). This interplay of cells is a physiological process known as bone remodeling. This process ensures that the amount of bone resorbed by osteoclasts equals to the amount of new bone formed by osteoblasts, which in turn leads to the maintenance of proper bone mass. Remodeling process is regulated by a number of factors such as hormones, growth factors, nutrition and lifestyle. An imbalance in these factors negatively influence bone formation and resorption, which may lead to abnormal bone remodeling thereby resulting in various bone disorders [1,3-5]. This review focuses on pathophysiology of bone and the various bone related disorders. Special emphasis is given on one of the most common bone related disorders "osteoporosis" and its multifaceted therapeutic approaches.

Pathophysiology of bone disorders

Osteoporosis

Osteoporosis is one of the most common remodeling related bone disorder which is characterized by low bone mass (osteopenia) and deterioration of bone microarchitecture. In this condition, osteoclast induced bone resorption surpasses osteoblastic bone formation. As a result, bone becomes fragile and increase the risk of fracture [1,3,8]. According to the International Osteoporotic Foundation (IFO) statistics, worldwide 1 in 3 women and 1 in 5 men whose age is over 50 years are prone to osteoporosis related fractures [8,9]. Evidences suggests globally there were 178 million cases of new fractures in 2019 and the prevalent cases of acute symptoms of fracture is 455 million. These numbers shows around 70.1% increase since 1990 [10].

Pathophysiology of osteoporosis is a multifactorial in nature and are influenced by genetic, intrinsic, extrinsic and lifestyle factors [3]. Further, osteoporosis is classified into two major types namely primary and secondary. Primary has two subtypes- Type 1 and Type 2. Type 1 osteoporosis is mainly because of estrogen deficiency in postmenopausal women. Type 2 osteoporosis is due to ageing affecting both men and women. On the contrary secondary osteoporosis is mainly due to the underlying diseases or treatments to such diseases. The diseases, which are responsible for secondary osteoporosis are broadly categorised as genetic diseases (cystic fibrosis, osteogenesis imperfecta, hypophosphatasia, hemochromatosis etc.) Endocrine disorders (Central obesity, Cushing's syndrome, hyperparathyroidism, Thyrotoxicosis etc.) lifestyle change related disorders (vitamin D deficiency, low calcium intake, high salt intake, alcohol abuse, inadequate physical activity etc.), gastrointestinal disorders (malabsorption, irritable bowel syndrome etc.). Hematological disorders (hemophilia, leukemia, lymphomas etc.), neurological and musculoskeletal disorders (epilepsy, muscular dystrophy etc.), rheumatologic diseases (rheumatoid arthritis) and others (AIDS/HIV, chronic metabolic acidosis, depression, weight loss etc.). Chronic use of glucocorticoids is also one of the factors responsible for secondary osteoporosis [1,6,7,11,12]. All of these factors give rise to cascade of events, which result in improper bone mass, increase in bone loss and abnormal bone mineral homeostasis. These series of changes leads to attain lower bone density which in turn lead to bone fragility to become more fragile and increase in vulnerably of fracture.

Therapeutic approaches for osteoporosis

There are multiple approaches available for osteoporosis treatment. This multifaceted treatment options ranges from simple micronutrient supplements to various pharmacological drug interventions. Besides, various ethnic groups have their own respective alternative medicines for treatment and prevention of osteoporosis.

Pharmacological approaches for osteoporosis

The pharmacological approaches are subdivided as antiresorptive and anabolic treatments. Antiresorptive medications helps in the reduction of osteoclast mediated bone resorption whereas anabolic treatment helps in enhancing osteoblast mediated bone formation. Some of the prime antiresorptive group of medications are Bisphophonates (alendronate, risedronate, and zoledronic acid) - which binds to bone matrix with high affinity and inactivate osteoclasts thereby helping in increasing the bone mineral density. Selective estrogen receptor modulators (Raloxifene) which acts as estrogen receptor agonist and inhibits osteoclasts. Hormone replacement therapy (estrogen-progestin and calcitonin treatment) directly inhibits osteoclast and help in osteoporosis. Denosumab – is an inhibitor of receptor activator of nuclear factor kappa B ligand (RANκL). Inhibition of RANK would inactivate osteoclast mediated bone resorption. Teriparatide is used for anabolic treatment. It was the first approved parathyroid hormone analogue for treating osteoporosis. It stimulates osteoblast cells and helps in the bone formation. There are also some emerging therapies for osteoporosis such as cathepsin-K inhibitors (Odanacatib) and anti-sclerostin antibodies as anabolic treatment. Clinical studies on these medications have shown promising results in enhancing bone mineral density in osteoporotic conditions [2,3,8,13].

Alternative medicines for osteoporosis

Homeopathy for bone health

Homeopathy is an alternative medicine and it stimulates a self-regulatory healing response in the patients [14]. There are different forms of homeopathy especially individualized homeopathy, clinical homeopathy and isopathy. Homeopathy treats many chronic or recurrent conditions such as eczema, rheumatoid arthritis, fatigue disorders, asthma, migraine, dysmenorrhoea, irritable bowel syndrome, recurrent upper respiratory, urinary tract infections, and mood disorders [15]. Clinical study with homeopathic calcium (medium-potency calcium) showed increase in bone density in post-menopausal women [16]. Clinical studies with homeopathic formulations composed of *Rhus toxicodendron* showed positive trend towards the effectiveness on osteoarthritis patients [17]. Another clinical study reported in the homeopathy treatment showed significant improvement in fracture line, fracture edge and fracture union [18]. In addition, there were lower use of analgesics and less self-reported pain in the homeopathy treated groups [18]. Animal study also demonstrated that homeopathic formulation with *Plumbum metallicum* increased repair on surgical defect in mandibular bone, which indicate that homeopathic treatment enhanced the bone regeneration in rat model [19]. Similarly, another animal study also demonstrated that homeopathy formulation composed of Calcarea phosphorica 6CH changed from trabecular to a lamellar bone while Risedronate (allopathy medicine) increased the bone quality, however it displayed a resistance to resorption keeping trabecular bone [20]. This study clearly indicated that allopathic and homeopathic treatments led to different bone formation outcomes regarding remodeling and maturation aspects. However, currently there are very few clinical and animal studies explored for the homeopathic treatments on bone related effects. Therefore, further research is necessary to assess the mechanistic understanding in bone remodeling and other bone related diseases.

Siddha for bone health

Siddha medicine is a traditional system Indian medicine of healing and is believed to be one considered one of India's oldest systems of medicine. It is practiced in South India, Sri Lanka, Malaysia, Singapore, Mauritius and some of the South-East Asian countries. Siddha medicine plays a vital role in chronic inflammatory disease, degenerative conditions and metabolic

diseases like diabetes, hypertension, musculoskeletal disorders, psychiatric disorders and urinary problems. Despite the developments in modern medical practice, Siddha is one of the best treatment for bone setting. Most of the bone fracture patients in south India are treated successfully by cost effective Siddha treatment. Traditional medicated cloth bandages are used for the bone setting treatment. The bandages are prepared by using egg white, black gram powder, pounded rice, tamarind seeds, *Shorea robusta Gaertn* and *Senna occidentalis*. Specific medicated oils for external use such as *Kayathirumeni tailam*, *Kaya carvankat tailam* and *Vacavenney* to reduce pain, swelling and facilitate rapid union of fractured bones [21]. Similarly, internal medicines like *Varmani kulikai, Kayathirumeni tailam* and *Varma ney* are prescribed with above mentioned procedures. *Cissus quadrangularis* powder is commonly used for Siddha medicines and it is proven in rapid union of bone fractures [21]. In addition, many herbs such as *Vitex negundo, Ricinus communis, Delonix verrucusa, Cissampelos pareira, Cardiospermum halicacabum, Clerodendron phlomides, Pavetta indica, Calotropis gigantean, Piper nigram, Eclipta prostate* and *Barringtonia acutangula* are used for joint and bone health in Siddha medicine [22]. Future research is essential on Siddha herbs and their efficacy with mechanistic understanding in bone remodeling and other bone related disorders.

Ayurveda for bone health

It is a traditional medicine native to India. Evidences suggests that plants and their respective extracts (leaves, roots, stem etc.) are used in bone healing process. Some of the potential plants or extracts are namely, *Bambusa arundinacea, Coelogyne cristata Lin., Symphytum officinale, Salvia miltiorrhiza*, *Terminalia arjuna*, *Ehretia cymosa, Griffonia simplicifolia*, *Cicuta maculate, Curcuma domestica, Cedrus deodara, Mesua ferrea, Commiphora weightu* and *Piper longum.* These herbals possess very good anti-inflammatory efficacy, some also have natural calcium content and others are efficacious in bone formation. Because of these potentials, the above mentioned herbals are believed to be useful in bone fracture healing, joint healing and pain reduction [23,24]. Furthermore, ayurvedic herbals like *Ficus religiosa, Withania somnifera, Cissus Quadrangularis, Tinospora Cordifolia, Chenopodium ambrosioides and Dalbergia sissoo* are widely used for its bone healing properties. Herbals have different mechanisms to protect the bone or enhance the bone healing. Bioactives may target catabolic or anabolic pathways such as estrogen signaling, mitogen-activated protein kinase (MAPK) signaling, wingless-related integration site)/β-catenin signaling (Wnt/β-catenin), transforming growth factor-beta /bone morphogenic protein (TGF-β/BMP) signaling and calcium signaling. *Cissus quadrangularis* acts through regulation of genes responsible for osteoblastogenesis (bone formation) and osteoclastogenis that is Wnt/β-catenin signaling and MAPK signaling respectively. Some studies also suggests that *Cissus quadrangularis* helps in the stimulation of osteoblasts through upregulation of genes like runt-related transcription factor 2 (Runx2) , collagen type I alpha 1 chain (COL1A1), bone gamma-carboxyglutamate protein (BGLP2) and activity of alkaline phosphatase (ALP) which are integral part of bone formation process [25]. In addition, downregulation of osteoclastic gene tartrate-resistant acid phosphatase-5b (TRAP) which is important for bone resorption. *Withania somnifera* acts through inhibition of osteoclasts by downregulating nuclear factor kappa B (NFκB) thereby increasing Runx2 levels. However, in the case of *Tinospora cordifolia* research shows that because of pharma like activity, shows inhibition of osteoclasts and helps in up-regulation of bone formation related genes [25,26]. Future research on these herbals are warranted to understand the details of mechanisms in bone remodeling and other bone related disorders.

Unani (Greek-o-Arabic) for bone health

According to the Unani system, osteoporosis can be prevented by living in ventilated space, eating healthy diet containing vitamins and minerals in adequate quantitates and taking Unani based calcium preparations [27]. Unani system also has some preparations for osteoarthritis condition. Some of the herbs that are used to treat this condition are *Boswellia serrata, Curcuma longa linn*, *Withania somnifera*, *Zingiber officinale*, *Terminalia chebula*, *Terminalia belerica*, *Emblica myroblan*, *Commiphora wightii* and *Asparagus racemose* [28]. This beneficial effect could be due to reduction of pro-inflammatory levels of the causal markers. Future research and clinical studies are necessary to evaluate the mechanisms involved in Unani medications for bone health benefits.

Chinese traditional (herbal) medicines for bone health

Chinese traditional medicines are used in the treatment of osteoporosis and studied extensively for their bone formation and improving bone mineral density. Some of them are *Gynochthodes officinalis*, *Morinda officinalis*, *Curculigo orchioides Gaertn*, *Psoralea corylifolia*, *Medik Eucommia ulmoides Oliv*, *Dipsacus inermis Wall*. *Cibotium barometz, Cistanche deserticola Ma, Cuscuta chinensis Lam., Cnidium monnieri, Cusson, Epimedium brevicornum Maxim, Pueraria montana Merr.* and *Salvia miltiorrhiza Bunge* [29]. *Gynochthodes officinalis* and *Morinda officinalis* are few of the famous Chinese medicine which contains many bioactive molecules like oligosaccharides, iridoid glycosides and bajijiasu. Study of these root extracts showed to enhance the bone mineral density of tibia bone in ovariectomized rats [30-32]. *Fructus Ligustri Lucidi* is another Chinese herbal medicine that increased bone mineral density and bone mineral content at both tibial and femoral diaphysis and lumbar vertebra in ovariectomized rats with induced bone loss [33]. *Curculigo orchioides Gaertn* (CO) is another Chinese herbal medicine used to treat the postmenopausal osteoporosis in vivo [34]. CO when administered, was able to prevent trabecular bone loss in tibia of ovariectomized rats through inhibition of bone resorption and increasing the levels of serum phosphorus and calcium [34]. CO is also used to treat limb weakness and knee joint arthritis [35]. In similar ways, all the above mentioned herbal Chinese medicines have been reported to decrease the osteoporosis acting through various pathways of biological system. Some of the mechanisms are increasing ALP activity, upregulation of bone specific matrix proteins like collagen, improving the osteocalcin levels and thereby improving bone strength, preventing trabecular microstructural damages and upregulating the bone formation markers in many animal studies [29].

African traditional (herbal) medicines for bone health

The African traditional medicine believed to be the holistic approach, which includes use of herbs in combination with spiritualism and divination [36]. Many parts across Africa known to use their local herbarium for treatments of ailments out of which the southern Ghana region was found to be having many such herbal medicines. Out of 28 plant families of Ghana known for providing cure for various ailments, *Sapindaceae* is one such family having bone repair effect [37]. Currently very few clinical

and animal studies are available in African traditional medicine for its benefits on bone health. Hence, it's important that future studies focuses on details of molecular mechanisms which involves bone remodeling.

Non-pharmacological approaches for osteoporosis

Micronutrients for bone health

Adequate nutrition plays an important role in the prevention and treatment of bone related disorders. Enough evidences suggest micronutrients such as calcium and vitamin D are beneficial for bone health at all ages [38] and recommended for postmenopausal women to reduce the risk of bone fracture [39]. Studies have revealed that there is an increasing trend in dietary vitamin D and calcium deficiencies in modern society [40]. Many clinical studies have reported that Vitamin D is important for bone mineral density and bone turnover. Supplementation of vitamin D decreases bone turnover and increases bone mineral density and combination of vitamin D along with calcium showed a significant decrease in bone fracture incidence [41]. There is enough scientific evidences, to prove that calcium supplementation reduces bone loss and prevent risk of fracture [42]. Moreover, it is important to be aware that dietary magnesium, silicon, vitamin K, boron, vitamin C, copper, zinc and manganese are also essential nutrients for bone health [40]. Clinical study on women with osteoporosis reported that magnesium supplementation significantly increased the bone mineral density [43]. Silicon is another vital contributor for bone health. Electron probe microanalysis study clearly revealed that silicon plays a role in the initiation of the mineralization process [44]. Vitamin K is another lesser-known micronutrient that has vital role on bone health. Supplementation of vitamin K has the regulation on carboxylation of osteocalcin, thereby reducing osteopenia, bone fracture and improves bone strength [45]. Boron supplementation improved calcium and magnesium retention in post-menopausal women and increased bone strength [46,47].

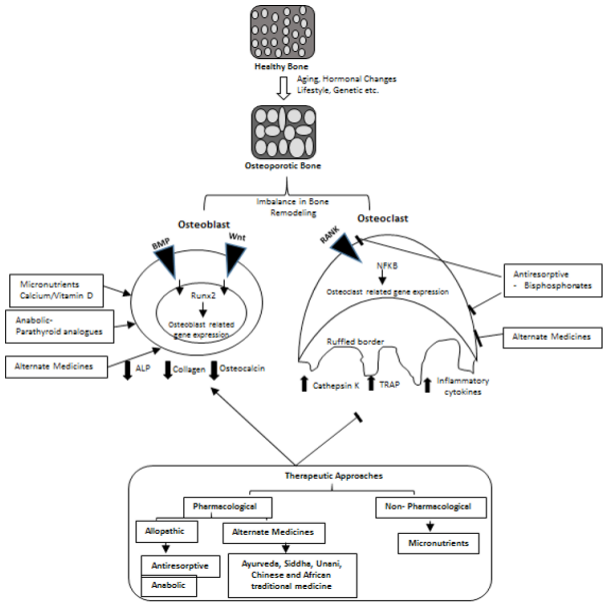

Figure 1: Schematic Representation of Pharmacological and Non-pharmacological Mechanisms Intervening in Osteoporosis.

In addition, other essential micronutrients vitamin C, L-arginine and inositol were found to be beneficial for their role in enhancing bone mineral density and improved bone strength. Supplementation of micronutrients are important for bone health and it is to be noted that excessive supplementation may be harmful [48-50]. Interestingly, we have studied the effect of herbal with micronutrient combination in bone formation, which showed positive effects towards improving bone turnover markers [51].

Conclusions and future directions

Bone related disorders especially osteoporosis poses global burden because of increased prevalence of fracture. Osteoporotic conditions negatively influences the bone formation and resorption. Currently there are many therapeutic approaches available for the treatment of osteoporosis. Allopathic approaches are relatively well studied, clinically proven and have specific mechanism of action. On the contrary, its benefits comes with several side effects. Therefore, it is imperative to identify alternative medicines that are safe, efficacious and cost effective. Worldwide, many alternative medicinal plants have been used in different traditions/cultures such as Ayurveda, Siddha, Unani, Chinese and African. Some of the plants such as *Withania somnifera* and *Cissus Quadrangularis* etc. have proven very effective in treating osteoporosis. It is also vital to note that some of the bioactives from these plants are clinically proven and there is a clear understating of their mode of action. In addition, the non-pharmacological approaches like micronutrients such as calcium, vitamin D, vitamin k etc. are also gaining importance because of their role in enhancing bone mineral density. Despite its effectiveness in bone healing, many of the potential medicinal plant's mechanism of action is not clearly understood. Hence more work on molecular mechanisms and supporting clinical studies to substantiate these effects of the bioactives are warranted. We have conducted a clinical study to evaluate the effect of polyherbal formulation on improving low bone mass in elderly subjects. The outcome was promising and showed a significant improvement in bone mineral density and other bone turnover markers [52]. We also believe that medicinal plants in conjunction with micronutrients may prove to be better alternative therapy for bone related disorders especially in osteoporosis. Furthermore, to evaluate the mechanistic understanding of traditional medicines we suggest using 3D scaffold models which mimic bone microenvironment. It is to be noted that bone diseases unlike others, goes unnoticed until and unless there is a clinical manifestations. In this regard, development of a predictive method, which serves as a cue for bone health would prove very useful. For instance, studying the nail components, which may serve as predictive tool for measuring bone health. In addition, Cathepsin Z mRNA as a biomarker to detect osteoporosis aiding in prevention of fragility fracture can also be explored [53].

Declarations

Acknowledgements: We acknowledge our chief scientist Dr. Suresh Ramamurthi for his encouragement/support for the manuscript.

Conflicts of interest: The authors declare no competing financial interest and declare no conflict of interest.

References

1. Feng Xu, McDonald JM. Disorders of Bone Remodeling. Annu Rev Pathol. 2011; 6: 121-145.
2. Chindamo G, Sapino S, Peira E , Chirio D, Gonzalez MC, et al. Bone Diseases: Current Approach and Future Perspectives in Drug Delivery Systems for Bone Targeted Therapeutics. Nanomaterials. 2020; 10: 875.
3. Föger-Samwald U, Dovjak P, Azizi-Semrad U, Kerschan-Schind K, Pietschmann P. Osteoporosis: pathophysiology and therapeutic options. EXCLI Journal. 2020; 19:1017-1037.
4. Raubenheimer EJ, Noffke CE, Hendrik HD. Recent Developments in Metabolic Bone Diseases: a Gnathic Perspective. Head and Neck Pathol. 2014; 8: 475-481.
5. El Demellawy D, Davila J, Shaw A, Nasr Y. Brief Review on Metabolic Bone Disease. Acad Forensic Pathol. 2018; 8: 611-640.
6. Bacon S, Crowley R. Developments in rare bone diseases and mineral disorders. Ther Adv Chronic Dis. 2018; 2018; 9: 51-60.
7. Dhanwal DK. Thyroid disorders and bone mineral metabolism. Indian Journal of Endocrinology and Metabolism. 2011; 15 Supplement 2: S107-S112.
8. Curtis EM, Moon RJ, Dennison EM, Harvey NC, Cooper C. Recent advances in the pathogenesis and treatment of osteoporosis. Clin Med (Lond). 2015; 15 Suppl 6: s92-6.
9. International Osteoporosis Foundation.
10. GBD 2019 Fracture Collaborators. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease. Lancet Healthy Longev. 2021; 2: 9 e580–92.
11. Sözen T, Özışık L, Başaran NC. An overview and management of osteoporosis. J Rheumatol. 2017; 4: 46-56.
12. Salari N, Ghasemi H, Mohammadi L, Behzadi M, Rabieenia E, Shohaimi S et al. The global prevalence of osteoporosis in the world: a comprehensive systematic review and meta-analysis. J Orthop Surg Res. 2021; 16: 609.
13. Tu KN, Lie JD, Wan CKV, Cameron M, Austel AG, Nguyen JK et al. Osteoporosis: A Review of Treatment Options. P T. 2018; 43: 92-104.
14. Mathie RT, Ramparsad N, Legg LA, Clausen J, Moss S, Davidson JR et al. Randomised, double-blind, placebo-controlled trials of non-individualised homeopathic treatment: systematic review and meta-analysis. Syst Rev. 2017; 6: 63.
15. Vickers A, Zollman C. ABC of complementary medicine. Homoeopathy. 1999; 319: 1115-1118.
16. Harkin C. Effect of Homeopathic Calcium on Bone Density. Homeopathic Links. 2008; 21: 44-49.
17. Long L, Ernst E. Homeopathic remedies for the treatment of osteoarthritis: a systematic review. British Homoeopathic Journal. 2001; 90: 37-43.
18. Sharma S, Sharma N, Sharma R. OA15.04. Accelerating the healing of bone fracture using homeopathy: a prospective, randomized double-blind controlled study. BMC Complement Altern Med. 2012; 12(Suppl 1): O61.
19. Almeida JD, Arisawa EA, Balducci I, da Rocha RF, Carvalho YR. Homeopathic treatment for bone regeneration: experimental study. Homeopathy. 2009; 98: 92-96.
20. Werkman C, Senra GS, da Rocha RF, Brandão AA. Comparative therapeutic use of Risedronate and Calcarea phosphorica--allopathy versus homeopathy--in bone repair in castrated rats. Braz Oral Res. 2006; 20: 196-201.
21. Siddha system of medicine: The science of holistic health. Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH), Government of India 2019.
22. Murugesamuthaliyar KS. Siddha Materia Medica (Plant division). Chennai, India: Indian Maruthueam, Homeopathy thurai. 2013.
23. Singh V. Medicinal plants and bone healing. Natl J Maxillofac Surg. 2017; 8:4-11.
24. Sharma S, Sharma S, Singh M. Fracture management principles in ayurveda with current interpretation: A review. Int J Res. Ayurveda Pharm. 2016; 7.
25. Jalil M, Shuid A and Muhammad N. Role of Medicinal Plants and Natural Products on Osteoporotic Fracture Healing. Evid Based Complement Alternat Med. 2012; 714512: 7.
26. Singh P, Gupta A, Qayoom I, Singh S and Kumar A. Orthobiologics with phytobioactive cues: A paradigm in bone regeneration. Biomed Pharmacother. 2020; 130:110754.
27. Aijaz A and Ansari A. The Etiology and Prevention of Osteoporosis in Greek-O-Arabic (Unani) Medicine. Global Journal of Medical research Orthopedic and Musculoskeletal System. 2013; 13.
28. Nisa A, Hameed A, Hassan R and Atiqa. Osteoarthritis and unani treatment-a review. Int J Adv Res. 2018; 6: 991-999.
29. He J, Li X, Wang Z, Bennett S, Chen K, Xiao Z, et al. Therapeutic Anabolic and Anticatabolic Benefits of Natural Chinese Medicines for the Treatment of Osteoporosis. Front Pharmacol. 2019; 10: 1344.
30. Chen DL, Li N, Lin L, Long HM, Lin H, Chen J, et al. Confocal mirco-Raman spectroscopic analysis of the antioxidant protection mechanism of the oligosaccharides extracted from Morinda officinalis on human sperm DNA. J Ethnopharmacol. 2014; 153: 119-124.
31. Wu ZQ, Chen DL, Lin FH, Lin L, Shuai O, et al. Effect of bajijiasu isolated from Morinda officinalis F. C. how on sexual function in male mice and its antioxidant protection of human sperm. J Ethnopharmacol. 2015; 164: 283-292.
32. Li C, Dong J, Tian J, Deng Z, Song X. LC/MS/MS determination and pharmacokinetic study of iridoid glycosides monotropein and deacetylasperulosidic acid isomers in rat plasma after oral administration of Morinda officinalis extract. Biomed Chromatogr. 2016; 30: 163-168.
33. Zhang Y, Leung P, Che C, Chow H, Wu C, et al. Improvement of bone properties and enhancement of mineralization by ethanol extract of Fructus Ligustri Lucidi. British Journal of Nutrition. 2008; 99: 494-502.
34. Cao DP, Zheng YN, Qin LP, Han T, Zhang H, et al. Curculigo orchioides, a traditional Chinese medicinal plant, prevents bone loss in ovariectomized rats. Maturitas. Epub. 2008; 59: 373-380.
35. Tan S, Xu J, Lai A, Cui R, Bai R, Li S, et al. Curculigoside exerts significant antiarthritic effects in vivo and in vitro via regulation of the JAK/ STAT/NFkappaB signaling pathway. Mol Med Rep. 2019; 19: 2057-2064.
36. Ozioma E J, Chinwe OAN. Herbal Medicines in African Traditional Medicine in P.F. Builders (ed.), Herbal Medicine. IntechOpen, London 10.5772/intechopen. 2019; 80348.
37. Boadu AA, Asase A. Documentation of Herbal Medicines Used for the Treatment and Management of Human Diseases by Some Communities in Southern Ghana. Evid Based Complement

Alternat Med. 2017; 2017: 3043061.

38. Nieves JW. Osteoporosis: the role of micronutrients. Am J Clin Nutr. 2005; 81: 1232S-1239S.

39. Gehrig L, Lane J, O'Connor MI. Osteoporosis: management and treatment strategies for orthopaedic surgeons. J Bone Joint Surg Am. 2008; 90: 1362-1374.

40. Price CT, Langford JR, Liporace FA. Essential Nutrients for Bone Health and a Review of their Availability in the Average North American Diet. Open Orthop J. 2012; 6: 143-149.

41. Lips P, van Schoor NM. The effect of vitamin D on bone and osteoporosis. Best Pract Res Clin Endocrinol Metab. 2011; 25: 585-591.

42. Zhu K, Prince RL. Calcium and bone. Clin Biochem. 2012; 45: 936-942.

43. Stendig-Lindberg G, Tepper R, Leichter I. Trabecular bone density in a two year controlled trial of peroral magnesium in osteoporosis. Magnes Res. 1993; 6: 155-163.

44. Carlisle EM. Silicon: a possible factor in bone calcification. Science. 1970; 167: 279-280.

45. Bügel S. Vitamin K and bone health in adult humans. Vitam Horm. 2008; 78: 393-416.

46. Nielsen FH. Studies on the relationship between boron and magnesium which possibly affects the formation and maintenance of bones. Magnes Trace Elem. 1990; 9: 61-69.

47. Armstrong TA, Spears JW, Crenshaw TD, Nielsen FH. Boron supplementation of a semipurified diet for weanling pigs improves feed efficiency and bone strength characteristics and alters plasma lipid metabolites. J Nutr. 2000; 130: 2575-2581.

48. Hall S, Greendale GA. The relation of dietary vitamin C intake to bone mineral density results from the PEPI study. Calcif Tissue Int. 1998; 63:183-189.

49. Sahin K, Onderci M, Sahin N, Balci TA, Gursu MF, et al. Dietary arginine silicate inositol complex improves bone mineralization in quail. Poult Sci. 2006; 85: 486-492.

50. Küçükbay F, Yazlak H, Sahin N, Akdemir F, Orhan C, et al. Effects of dietary arginine silicate inositol complex on mineral status in rainbow trout (Oncorhynchus mykiss) Aquac Nutr. 2008; 14: 257-262.

51. D'souza A, Narayanaperumal J, Miriyala A, Gopal G. A composition comprising phycocyanin, and at least one mineral and uses thereof". Indian Patent No: 380437; 2021.

52. Clinical Trials Registry - India (CTRI).

53. Dera AA, Ranganath L, Barraclough R, Vinjamuri S, Hamill S, et al. Cathepsin Z as a novel potential biomarker for osteoporosis. Sci Rep. 2019; 9: 9752.