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Article Review: Herbs for Bone Growth Process

Annisa Rizky Afrilia[1*], Berna Elya[2], Fadilah Fadilah[3]
[1-2]Faculty of Pharmacy, University of Indonesia, Depok 16424, West Java, Indonesia
[3]Department of Medical Chemistry, Faculty of Medicine, University Indonesia, Jakarta 10430, Indonesia
**Corresponding author: annisa.rizky.afrilia@gmail.com*

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ABSTRACT

The process of bone growth occurs rapidly in childhood and stops when entering the puberty phase. Currently, stunted bone growth, known as stunting, is a health problem in the world. There is no drug that can specifically help bone growth. Likewise, the use of herbal plants for bone growth is still limited, so further research needs to be carried out to explore plants that have benefits to help increase bone growth. For this reason, the aim of writing this review article is as a basis for identifying herbal plants that can influence bone growth. So that the active compounds in related herbal plants can be developed to make new herbal medicinal products for stunted bone growth. Literature was searched using the scientific databases ScienceDirect, Pubmed, MDPI using several keywords "herbal medicine for bones" and "osteogenic activity in herbal plants". The results obtained were 18 articles that met the inclusion criteria. From these 18 articles, 11 active compounds were obtained, namely Osthole, Levistolide A, Calycosin-7-O-β-glucoside, Cistanoside A, Icariin, Naringenin, Wedelolactone, Ugonin L, Ligustroflavone, Ginsenosides, Puerarin which have the potential to help the bone growth process.

INTRODUCTION

Bones is a dynamic tissues. That continuously undergoes formation and resorption. Under physiological conditions, these processes occur in a balanced manner, allowing bone mass and anatomical structure to be maintained. Bone growth occurs rapidly during childhood and gradually slows, eventually ceasing after the pubertal growth phase.

Bone growth is primarily regulated by Growth Hormone (GH) (Sherwood, 2016). Following secretion, GH binds to the growth hormone (GHR) *(Moøller & Joørgensen, 2009)*, which subsequently stimulates gene transcription and hepatic synthesis of insulin-like growth factor-1 (IGF-1), thereby regulating circulating IGF-1 levels (Firmenich et al., 2020; Guevara-Aguirre et al., 2018). Activation of the IGF-1/IGF-1 receptor (IGF-1R) signaling pathway promotes bone formation and growth. Secreted IGF-1 binds to IGF-1R in an autocrine or paracrine manner and activates downstream signaling pathways. This interaction induces phosphorylation of glycogen synthase kinase-3β (GSK-3β) at Ser9, resulting in the release of runt-related transcription factor-2 (RUNX2), which plays a critical role in osteogenesis.

Long bone growth occurs at the epiphyseal growth plate through a tightly regulated process involving cartilage proliferation, matrix formation, and cartilage calcification, known as endochondral ossification. In this process, hyaline cartilage is gradually replaced by bone tissue, forming the majority of bones in the human skeleton (Artaria, 2008). Bone remodeling functions to maintain skeletal integrity and mineral homeostasis and involves coordinated interactions among osteoblasts, osteoclasts, and osteocytes (Yakar et al., 2018).

Cell Types Involved in Bone Growth

Chondrocytes

Chondrocytes originate from the mesoderm and synthesize an extracellular matrix rich in collagen, proteoglycans, and glycosaminoglycans. Within the growth plate, chondrocytes undergo proliferation, hypertrophy, and apoptosis, thereby regulating

longitudinal bone growth. The growth plate consists of three zones: the resting zone, proliferation zone, and hypertrophic zone. IGF-1 is predominantly produced by chondrocytes in the proliferation zone, and its activity is regulated by GH (Yakar et al., 2018).

Osteoblasts

Osteoblasts are derived from mesenchymal stem cells through sequential stages of proliferation, matrix maturation, and mineralization. Activation of IGF-1R in osteoblasts initiates signaling cascades involving the PI3K/AKT and extracellular signal-regulated kinase (ERK) pathways, leading to the expression of RUNX2. RUNX2 and its downstream target osterix (OSX) are essential for osteoblast differentiation and bone matrix formation. (Yakar et al., 2018).

Osteoclasts

Osteoclasts originate from hematopoietic monocyte–macrophage precursors. Their differentiation is regulated by macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-κB ligand (RANKL). Activation of RANK induces nuclear factor of activated T cells c1 (NFATc1), a key transcription factor involved in osteoclastogenesis (Takayanagi et al., 2002).

Osteocytes

Osteocytes are terminally differentiated osteoblasts embedded within the bone matrix and play a crucial role in mechanotransduction and mineral metabolism (Z. Liu et al., 2016). Mechanical stimulation activates Wnt/β-catenin signaling in osteocytes and increases IGF-1 expression, thereby contributing to bone remodeling (Yakar et al., 2018). Impaired bone growth, commonly manifested as stunting, remains a global public health concern. Suboptimal growth during childhood may adversely affect physical capacity and health outcomes in adulthood. Infectious diseases and inadequate nutrition are major contributing factors, and current management strategies primarily focus on infection control and nutritional improvement. To date, no pharmacological agents specifically target bone growth enhancement.

However, traditional medical practices in China and India have long utilized herbal plants for the management of bone-related disorders. For example, *Drynaria* species have been traditionally used to support bone health. Experimental studies have demonstrated that administration of *Drynaria* extracts increases bone mass in ovariectomized mice through enhanced endochondral ossification (Lee et al., 2014). In addition, naringin, an active compound derived from *Drynaria*, has been reported to stimulate osteogenesis by promoting the proliferation and differentiation of bone marrow stromal cells (Lee et al., 2014).

Therefore, this review aims to identify and synthesize research findings on herbal plants and their active compounds that may be associated with bone growth-related processes. Particular emphasis is placed on evaluating the potential of herbal-derived bioactive compounds to support bone growth.

METHODS

This study employed a narrative review design with a structured literature search. Secondary data were obtained from previously published scientific articles retrieved from the ScienceDirect, Pubmed, MDPI databases. Literature searches were conducted using the keywords “herbal medicine for bones” and “osteogenic activity in herbal plants.” A total of 939 articles were initially identified. Screening based on predefined inclusion and exclusion criteria resulted in 18 eligible studies. Inclusion criteria comprised original research articles published between 2014 and 2024 that investigated herbal plants and their bioactive compounds in relation to bone growth or osteogenic activity. Exclusion criteria included articles not relevant to the research topic and studies that did not identify specific herbal plants or active compounds associated with bone-related processes. Selected articles were summarized in a table describing plant species, active compounds, proposed mechanisms of action, and references (Table 1). The literature selection process is illustrated in Figure 1. Data were analyzed descriptively and synthesized narratively.

RESULT

Bone growth is regulated through GH-mediated signaling pathways (Sherwood, 2016). Following GH binding to GHR, downstream signaling influences multiple factors involved in bone formation (Moøller & Joørgensen, 2009).

Analysis of the selected literature identified several herbal-derived bioactive compounds reported to modulate these pathways and influence bone-related outcomes. The identified compounds and their proposed mechanisms are summarized in Table 1.

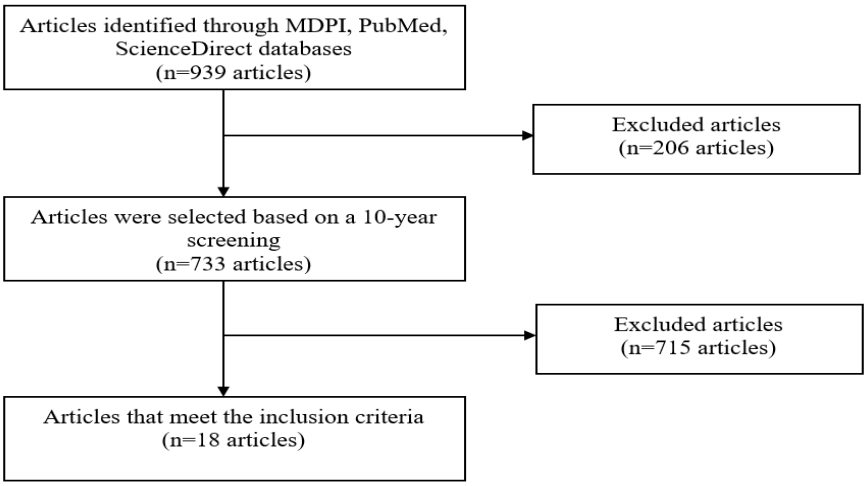

Figure 1. Article Search Flow Diagram

Table 1. Results of Review of Scientific Articles on Herbal Plants for Bone Growth

No.	Plant	Active compound	Mechanism	Reference
1	*Angelica pubescens Maxim.f.*	Osthole	Promotes osteogenesis in osteoblasts by increasing alkaline phosphatase (ALP) activity and mineralization	(Zhang et al., 2017)
2	*Angelica sinensis*	Levistolide A	Promotes proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells	(Han et al., 2024)
3	*Astragalus membranaceus*	calycosin-7-O-β-glucoside (Caly)	Increases expression and enzymatic activity of ALP and formation of mineralized nodules during MSC osteogenesis	(Park et al., 2021)
4	*Cistanche deserticola*	Cistanoside A	Promotes bone regeneration	(X. Xu et al., 2023)
5	*Cnidium monnieri (L.) Cusson*	Osthole	Promotes osteogenesis in osteoblasts by increasing alkaline phosphatase (ALP) activity and mineralization	(ZR Zhang et al., 2017)
6	*Curculigo orchioides Gaertn*	Icariin	Promotes cell proliferation and osteogenic differentiation	(Ren et al., 2023)
7	*Drynaria Fortunei*	Naringenin	Enhances bone regeneration through the TGF-β signaling pathway.	(Y. Zhao et al., 2024)
8	*Drynariae fortunei*	Naringin	Enhances osteogenic differentiation and bone regeneration by activating the BMP/Smad/Runx2 signaling pathway, increasing proliferation of human bone marrow mesenchymal stem cells, and upregulating estrogen receptor alpha (ERα) expression	(Lei et al., 2024; Zhao et al., 2024)
9	*Eclipta prostrata*	Wedelolactone	Increased osteoblastogenesis	(Tian et al., 2023)
10	*Epimedii*	Icariin	Enhances proliferation, differentiation and mineralization in BMSCs and also upregulates the	(Lei et al., 2024)

No.	Plant	Active compound	Mechanism	Reference
			expression of key genes in the BMP/Smad/Runx2 pathway.	
11	*Epimedii*	Icariin	Promotes cell proliferation and osteogenic differentiation	(Ren et al., 2023)
12	*plants of the genus Epimedium*	Icariin	Increases osteogenic differentiation	(M. Chen et al., 2019)
13	*Helminthostachys zeylanica*	Ugonin L	Reduces osteoclastogenesis receptor activator	(CL Liu et al., 2023a)
14	*Ligustri Lucidi*	Ligustroflavone	Distinct osteogenic activity by increasing proliferation, differentiation and mineralization of osteoblastic cells	(Jiao et al., 2024)
15	*Panax ginseng*	Ginsenosides	Anti-inflammatory and anti-apoptotic activities, further highlighting its therapeutic potential	(Jiang et al., 2024)
16	*Pueraria lobata*	Puerarin	Improves bone microstructure and bone mineral density	(Song et al., 2024)
17	*Platycodon*	Puerarin	Improves bone microstructure and bone mineral density	(Song et al., 2024)

DISCUSSION

Based on the summarized findings in Tabel 1, several herbal-derived bioactive compounds have been reported to be associated with bone growth-related processes, primarily in experimental models.

Osthole

Osthole or Osthol with the molecular formula $C_{15}H_{16}O_3$, is a chemical compound derived from coumarin (Z. R. Zhang et al., 2015). Osthole is found in various plants including Cnidium monnieri, Angelica Archangelica and Angelica pubescens (Yu et al., 2020).

In a study of osthole on fracture repair in mice, carried out by Z. Zhang et al. (2016), mice that had femoral fractures received 20 mg/kg osthole orally, and after 1 week post-surgery, the results in the treatment group were a two-fold increase in the rate of bone formation compared to the control group. Osthole increased the expression of alkaline phosphatase and collagen type In conclusion in the process of bone growth or repair, osthole promotes endochondral ossification through upregulation of maturation osteogenic marker genes in chondrocytes and then accelerates fracture repair and bone fusion (Zhang et al., 2016).

Levistolide A

Levistolide A is included in the phtalide group, specifically in the phtalide subgroup known as butenolide. Thus, Levistolide A is one of the constituents of the phtalide group. This is a compound found in several plants, especially in Ligusticum chuanxiong. Previous studies have shown that levistolide A has pharmacological activities that are potentially beneficial to human health (Qu et al., Mohammadzadeh et al., 2024).

Levistolide A, is a compound in *Angelica sinensis* which has the potential to treat bone damage because of its angiogenic ability. *In vitro* research shows that Levistolide A can increase the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells. In addition, Levistolide A can also indirectly promote the proliferation and recruitment of endothelial cells (Han et al., 2024).

Calycosin-7-O-β-glucoside

Calycosin-7-O-β-glucoside is a compound belonging to the isoflavonoid glycosides. The isoflavone-calycosin-7-O-β-d-glucopyranoside is the main constituent of *Astragalus gallinaceus*, which in vitro has benefits in inhibiting osteoclast development and in vivo inhibits bone loss (Jian et al., 2015).

Cistanoside A

Cystanoside A, is an active phenylethanoid glycoside isolated from *Cistanche deserticola* which from previous research results is known to have a role in the treatment of osteoporosis.

The evaluation of outcomes following 12 weeks of Cystanoside A administration in ovariectomized mice demonstrated a significant anti-osteoporotic effect, as indicated by enhanced bone strength, increased bone mineral density, and improved trabecular bone microarchitecture. Meanwhile, the activity of bone resorption markers, including tartrate-resistant acid phosphatase (TRAP), deoxypyridinoline (DPD) and cathepsin K, decreased and the bioactivity of the bone formation marker alkaline phosphatase (ALP) increased. So it can be concluded, Cystanoside A can encourage bone formation and prevent bone resorption (X. Xu et al., 2017).

Icariin

Icaarin is an active compound from Epimedium. Icaarin is included in the flavonoid glycoside group of compounds. Icariin's pharmacological properties are diverse, such as anti-inflammatory, antioxidant, and osteogenic effects. Icariin is known to stimulate bone formation, by encouraging the transformation of mesenchymal stromal cells into osteoblasts and increasing the subsequent mineralization process. Several studies have demonstrated the osteogenic effects of icariin, which may be attributed to its hormone-like function (Mohammadzadeh et al., 2024).

Naringenin

Naringenin is a biologically active flavanone compound, produced from the breakdown of naringin glycosides. This process allows naringenin to be more easily absorbed by the body and facilitates a variety of beneficial health effects. Previous studies showed that naringin can promote osteogenic differentiation, inhibit osteoclast formation, and show protective effects against osteoporosis in vivo and in vitro (Gan et al., 2023).

Wedelolactone

Wedelolactone is a natural compound that belongs to the coumarin group and more specifically as furanocoumarin. Coumarins are a group of organic compounds that have the basic structure of benzopyran, while furanocoumarins are a subclass of coumarins that have a furan ring fused with a coumarin ring.

Wedelolactone is a compound isolated from Ecliptae herba and is known to have a role in increasing bone formation by encouraging osteoblastogenesis and inhibiting osteoclastogenesis (Y. Q. Liu et al., 2016).

Ugonin L

Ugonin M is a unique flavonoid found in Helminthotachys zeylanica (L.) Hook., a plant used in traditional Chinese medicine (K. C. Wu et al., 2017). Ugonin L inhibits osteoclast formation and promotes osteoclast apoptosis by targeting the MAPK and NF-κB2 pathways (C. L. Liu et al., 2023b).

Ligustroflavone

Ligustroflavon is one of the main compounds contained in the active fraction of Fructus Ligustri Lucidi (Ligustrum lucidum fruit), which can regulate levels of parathyroid hormone (PTH), which is very important for maintaining calcium homeostasis in the body.

Ligustroflavone interacts with Calcium-Sensing Receptor (CaSR) Antagonist in regulating calcium balance. By acting as a Calcium-Sensing Receptor (CaSR) antagonist, ligustroflavon can temporarily increase parathyroid hormone (PTH) levels and regulate calcium metabolism which plays a role in the bone formation process (R. Feng et al., 2019).

Ginsenosides

Ginsenosides are pharmacologically active compounds found in plants of the genus Panax, commonly known as ginseng. In the bone remodeling process, Ginsenosides play a role in increasing bone formation, inhibiting bone resorption, and providing anti-inflammatory effects (Yang et al., 2020).

Puerarin

Puerarin is a natural compound found in Radix Puerariae, a traditional Chinese herb. Puerarin increased the OPG/RANKL ratio, upregulated the protein expression and transcriptional activity of FoxO1, and suppressed the differentiation of RAW264.7 cells into osteoclasts. FoxO1 is an important target of puerarin to exert anti-osteoporosis effects (Y. Feng & Tang, 2024).

Key mechanisms reported across studies include stimulation of osteoblast differentiation, inhibition of osteoclastogenesis, enhancement of bone matrix mineralization, and modulation of signaling pathways related to GH/IGF-1, Wnt/β-catenin, MAPK, and NF-κB. Nevertheless, the majority of evidence is derived from in vitro and animal models, which limits direct translation to clinical settings.

CONCLUSIONS

Based on the findings of this narrative review, herbal plants containing active compounds such as Osthole, Levistolide A, Calycosin-7-O-β-glucoside, Cistanoside A, Icariin, Naringenin, Wedelolactone, Ugonin L, Ligustroflavone, Ginsenosides, Puerarin have been reported to be associated with bone growth-related processes, predominantly in preclinical studies. While these findings suggest potential osteogenic roles of herbal-derived compounds, further well-designed experimental and clinical studies are required to confirm their efficacy and safety. Future research may support the development of herbal-based therapeutic strategies to assist bone growth.

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AUTHORS' CONTRIBUTIONS

All authors contributed substantially to the conception and design of the study, data collection, analysis and interpretation of data, manuscript preparation, and approval of the final manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ETHICAL CONSIDERATION

Not applicable. This study did not involve human participants or animals.

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