

Natural Product-Derived Extracts for Longitudinal Bone Growth

Subjects: **Food Science & Technology**

Contributor: Dong Wook Lim , Changho Lee

Several herbal formulations based on traditional medicine have the potential to improve bone growth, although their effectiveness is controversial. It was confirmed that the majority of extracts containing herbal formulations were orally administered over a short period, ranging from 4 to 10 days during the experimental phase.

longitudinal bone growth

idiopathic short stature

growth plate

chondrogenesis

natural products

1. Introduction

Idiopathic short stature (ISS) is defined as an individual's height below the 3% relative to the average height for the given age without finding any specific environmental, nutritional or genetic abnormality ^[1]. Approximately 80% of children with short stature are presented as having ISS ^[2]. The treatment with recombinant human growth hormone (rhGH) for ISS was approved by the Food and Drug Administration (FDA) in the United States in July 2003, and the current FDA-approved doses for GH in ISS are up to 0.30–0.37 mg/kg per week ^[3]. rhGH treatment increases the growth rate in the first year, but its effect on final height for 5 years is controversial ^[4]. Given that it requires daily parenteral administration, and its cost remains prohibitive in many parts of the world, a new strategic approach is needed ^[5]. Recently, efforts have been made to explore therapeutic alternatives that would facilitate slower bone maturation and more prolonged spontaneous or induced growth. Treatment options, such as aromatase inhibitors, gonadotropin-releasing hormone analogues (GnRHAs), and recombinant human insulin-like growth factor-1 (rhIGF-1), have been employed to address ISS ^[6].

2. The Growth Hormone (GH)–Insulin-like Growth Factor (IGF) Axis

Although ISS does not present with any specific environmental, nutritional, or genetic abnormality, it is necessary to approach it from the perspective of genetic defects in the somatotrophic axis. The somatotrophic axis, also known as the GH–IGF axis, is composed of GH, IGFs, related carrier proteins, and receptors (**Figure 1**). It plays an important role in regulating metabolic and physiological processes, including bone growth ^[7]. Some patients with ISS show abnormalities in the somatotrophic axis, indicating GH insensitivity ^[8]. GH is primarily regulated by the interaction of two peptide hormones: GH-releasing hormone, which stimulates the secretion of growth hormone, and somatostatin, which inhibits GH secretion from the hypothalamus ^[9]. GH binds to a GH receptor (GHR), which

activates JAK2 (Janus Kinase 2) and promotes the phosphorylation of various members of the signal transducer and activator of transcription family (STAT5B). This process primarily stimulates IGF-1. IGF-1, a single-chain polypeptide, is a growth-promoting polypeptide that is essential for normal growth and development [10]. IGF-1 is closely related to the GH level and plays a crucial role in promoting the growth and development of bones, particularly in the growth plates [11]. It has been reported that children with ISS might exhibit lower IGF-1 levels compared to the average values observed in healthy children [12]. The growth plate, also known as the epiphyseal plate, is a specialized cartilaginous region at the ends of long bones where bone growth occurs during childhood and adolescence [13]. IGF-1 circulates in the bloodstream, primarily bound to IGF-binding protein-3 (IGFBP-3) and acid-labile subunit (ALS), forming a ternary complex (IGF-1/IGFBP-3/ALS) [14].

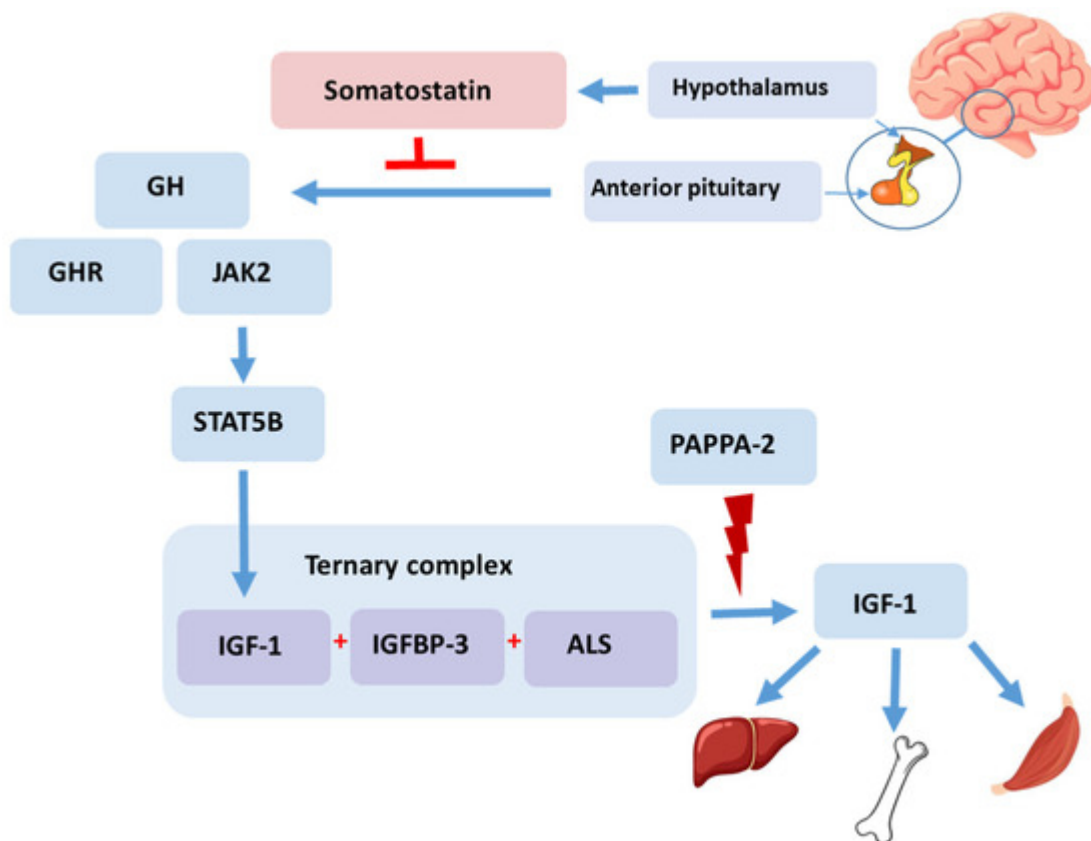


Figure 1. Growth hormone–insulin-like growth factor-1 axis. GH binds to a GHR, which activates JAK2 and promotes the phosphorylation of various members of the STAT5B protein family. This process primarily stimulates the production of IGF-1. IGF-1 circulates in the bloodstream, primarily bound to IGFBP-3 and ALS, forming a ternary complex. PAPP-A-2 proteolyzes IGFBP-3, increasing the bioavailability of IGF-1. As the ternary complex reaches the growth plate, it interacts with specific IGF-1 receptors located on the surface of chondrocytes, which are responsible for bone growth. GH: growth hormone, GHR: growth hormone receptor, JAK2: Janus kinase 2, STAT5B: signal transducer and activator of transcription 5B, IGF-1: insulin-like-growth factor 1, IGFBP-3: IGF-binding protein-3, ALS: acid-labile subunit, PAPP-A-2: Pregnancy-associated plasma protein-2.

3. Regulator of Growth Plate Chondrogenesis

The growth plate, comprising the resting zone (RZ), proliferative zone (PZ), and hypertrophic zone (HZ), is a crucial structure involved in bone development [15]. According to previous reports on the mechanistic pathways of human height growth [16], chondrocytes in the RZ are irregularly distributed within the cartilage matrix layer, while those in the PZ and HZ align in columns parallel to the bone's long axis. The RZ acts as a reservoir of precursor cells that support growth plate maintenance and contribute to bone growth. The PZ plays a crucial role in endochondral bone formation as it hosts active cell replication. Similarly, the HZ consists of chondrocytes derived from the terminal differentiation of PZ chondrocytes located the farthest from the epiphysis. These hypertrophic chondrocytes cease dividing and undergo significant enlargement, making substantial contributions to the overall growth process (Figure 2).

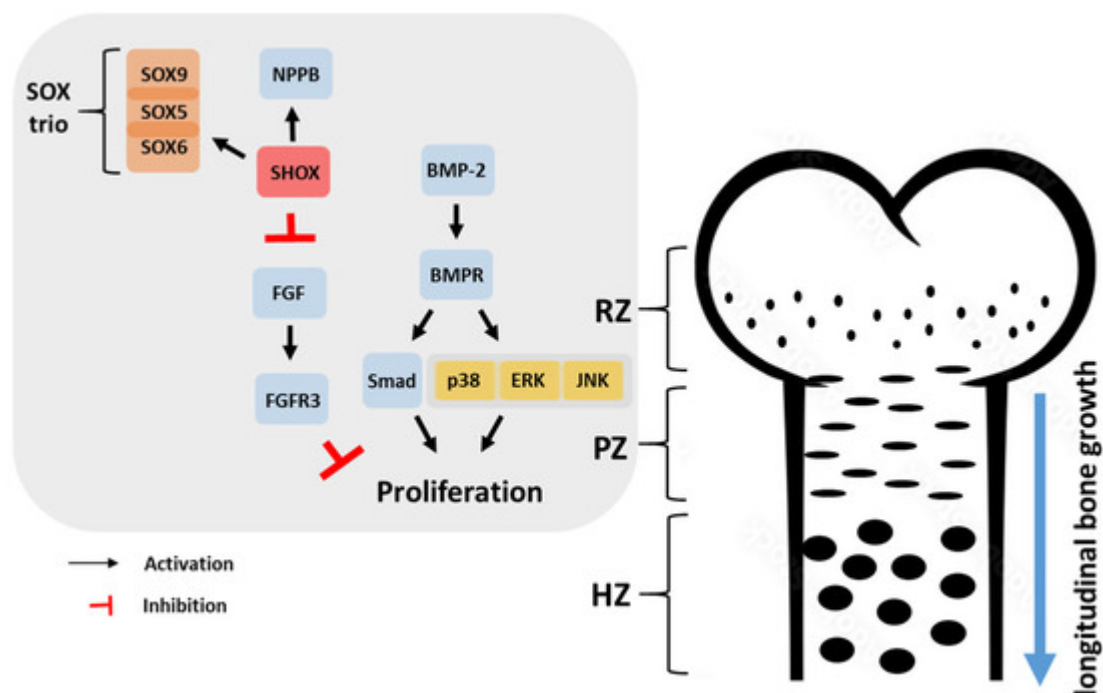


Figure 2. Bone growth and mechanism of FGF and SHOX on growth plate chondrogenesis. The RZ stores the precursor cells supporting growth plate maintenance and bone growth. The PZ is crucial for active cell replication in endochondral bone formation. The HZ contains large, non-dividing chondrocytes contributing significantly to overall growth. SHOX stimulates chondrocyte proliferation and differentiation by activating NPPB, inhibiting FGFR3 expression, and interacting with the SOX trio (SOX9, SOX5, and SOX6) for cartilage matrix production. FGFR3 negatively impacts growth plate chondrogenesis. RZ: Resting zone, PZ: Proliferative zone, HZ: Hypertrophic zone, BMP-2: Bone morphogenetic protein-2, BMPR: Bone morphogenetic protein receptor, p38: p38 MAP kinase, ERK: extracellular signal-regulated kinase, JNK: c-Jun NH2-terminal kinase, NPPB: Natriuretic peptide precursor B gene, SHOX: Short stature homeobox, FGF: Fibroblast growth factor, FGFR3: Fibroblast growth factor receptor 3.

4. Animal Models for Studying the Effect of Longitudinal Bone Growth

Hypophysectomy was performed in rats to establish an animal model of growth hormone deficiency [17]. Evidence from animal models shows that hypophysectomy in rats significantly decreased body weight, tail length, and bone lengths, as well as bone mineral density. These results improved to normal levels with the treatment of growth hormone through daily injections of 0.25 mg/kg of rhGH [18]. However, hypophysectomy also renders the animals deficient in other growth-regulating hormone systems. Therefore, GH deficiency produced by hypophysectomy may not be the ideal model to study the growth effects of hormone replacement strategies [19].

5. Natural Products-Derived Extracts, including Herbal Formulations, for Short Stature

Multiple studies have demonstrated that changes in bone growth-related biomarkers, such as IGF-1, BMP-2, and IGFBP-3, contribute significantly to the development of longitudinal bone growth. Therefore, targeting these markers through the regulation of growth hormone has been proposed as a therapeutic strategy for the treatment of ISS [20]. Many natural products, including herbal formulations, have been found to exert enhancing effects on longitudinal bone growth in animal models by increasing IGF-1, BMP-2, and IGFBP-3 levels in both the serum and tissue-sectioned growth plates. These studies suggest that natural products may enhance longitudinal bone growth by regulating IGF-1. **Figure 3** present a summary of the natural products that have been found to possess the potential to alleviate longitudinal bone growth.

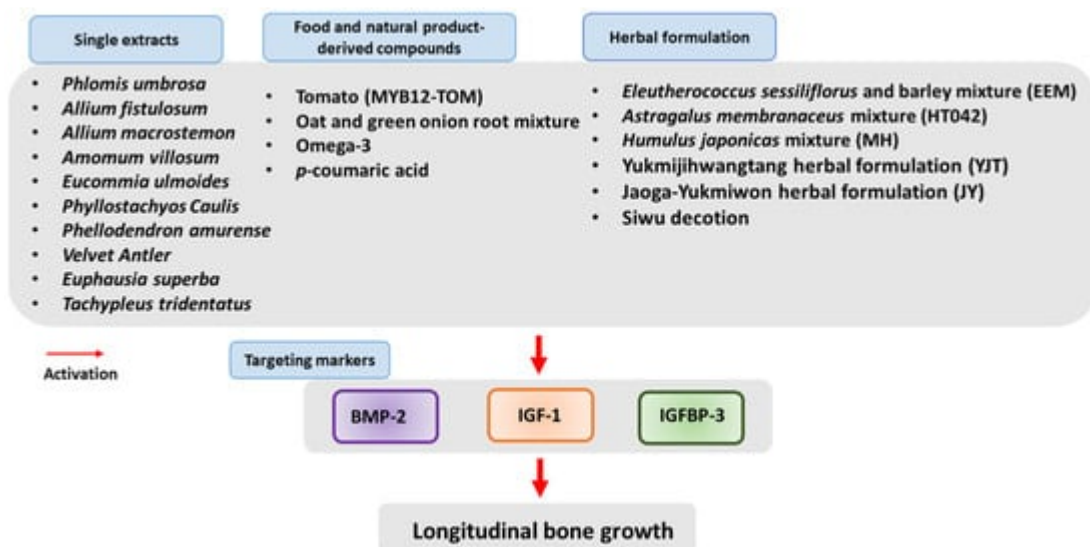


Figure 3. Effect of natural products, including of herbal formulations, on longitudinal bone growth by the activation of growth hormone-mediated biomarkers in animal models. Natural products may enhance longitudinal bone growth by regulating BMP-2, IGF-1, and IGFBP-3. IGF-1: Insulin-like-growth factor 1, IGFBP-3: IGF-binding protein-3, BMP-2: Bone morphogenetic protein-2.

5.1. *Eleutherococcus sessiliflorus* and Barley Mixture (EEM)

E. sessiliflorus is a medicinal herb with a range of biological effects, including anti-inflammatory, anti-cancer, antioxidant, and anti-obesity properties [21]. Barley (*Hordeum vulgare*) stands out as one of the most crucial crops

globally. Barley has been demonstrated to effectively remove superoxide anion radicals [22]. In vivo experiments have confirmed that EEM, a standardized mixture of these two components, *E. sessiliflorus* and barley, promotes bone length growth in rats [23].

5.2. Astragalus membranaceus Mixture (HT042)

HT042 is a mixed herbal formulation comprising the dried roots of *Phlomis umbrosa*, the roots of *Astragalus membranaceus*, and the stem barks of *Eleutherococcus senticosus* [24]. The group treated with HT042 at a dosage of 100 mg/kg for four days showed a significant increase in the proximal tibia growth plate of female SD rats. Additionally, the number of 5-bromodeoxyuridine (BrdU)-positive cells in the HT042 group was significantly higher compared to that of the control group in the tibia growth plate. Moreover, the expression levels of BMP-2 and IGF-1 were notably elevated in the PZ and HZ of growth plate in the HT042-treated group. The randomized controlled trial demonstrated that supplementation with HT042 for 23 weeks increased height growth in children who had not yet reached skeletal maturation [25]. This effect was attributed to elevated levels of serum IGF-1 and IGF-binding protein-3 [26].

5.3. Humulus japonicus Mixture (MH)

H. japonicus, commonly known as Japanese hops, is used for the treatment of inflammatory diseases [27]. In an in vivo study, it was observed that nose–tail length gain, body weight gain, and femur and tibia length significantly increased in the group treated with *H. japonicus* water extracts combined with garlic and watermelon powder (MH) at dosages of 100 and 300 mg/kg for 5 weeks in adolescent female SD rats.

5.4. Yukmijihwang-Tang (YJT) Herbal Formulation

Yukmijihwang-tang (YJT) contains six medicinal herbs, such as *Rehmannia glutinosa*, *Cornus officinalis*, *Dioscorea batatas*, *Alisma orientale*, *Poria cocos*, and *Paeonia suffruticosa*, in traditional Korean medicine (TKM) [28]. YJT is widely used in TKM to treat age-related disorders, such as Alzheimer's disease [29]. An in vivo study showed that YJT, at a dosage of 300 mg/kg in the treated group, significantly increased the length of the proximal tibia in the growth plate of female SD rats.

5.5. Jaoga-Yukmiwon (JY) Herbal Formulation

Jaoga-Yukmiwon (JY) consists of the alcohol extracts of seven medicinal herbs: *Acanthopanax senticosus*, *Rehmannia glutinosa*, *Poria cocos*, *Dioscorea japonica*, *Cornus officinalis*, *Cervus Nippon*, and *Panax ginseng*. JY is an herbal formulation from TKM used for the treatment of growth disorders [30]. The administration of JY at a dosage of 100 mg/kg showed a significant increase in the tibial length and the induction of BMP-2 in the tibial growth plates in adolescent male SD rats [31].

5.6. Siwu Decoction

Siwu decoction, consisting of *Angelica sinensis*, *Cnidium officinale*, *Paeonia lactiflora*, and steam-prepared root of *Rehmannia glutinosa*, has traditional uses for pain relief, anemia improvement, and blood circulation. The main ingredients responsible for these effects are quercetin, kaempferol, cytoglucide, apigenin, and stigmasterol [32]. Administered as water extracts to 33-day-old SD rats twice daily for 4 days, it promoted cartilage cell proliferation and new bone formation in the growth plate.

5.7. *Phlomis umbrosa*

The *P. umbrosa* root has been used in traditional Chinese medicine to enhance muscular and skeletal strength and to address fractures. In previous reports, *P. umbrosa* was found to possess various properties, including anti-allergic, anti-inflammatory, and anti-nociceptive effects [33]. These effects are likely attributed to the presence of various active compounds, such as sesamoside, shanzhiside methyl ester, chlorogenic acid, and barlerin [34]. When administered orally at doses of 100 and 300 mg/kg for 10 consecutive days, *P. umbrosa* root 70% ethanol extracts markedly increased longitudinal bone growth within the proximal tibial growth plate in adolescent SD female rats (5-weeks-old), consistent with findings showing a significant increase in the number of BrdU-labeled chondrocytes in the *P. umbrosa* groups at doses of 100 and 300 mg/kg.

5.8. *Allium fistulosum*

A. fistulosum is a perennial plant species that grows globally and belongs to the Liliaceae family. Previous studies reported the effects of *A. fistulosum* on antioxidant activity [35]. Administering 450 mg/kg of *A. fistulosum* water extracts significantly increased the length of the proximal tibial growth plate and bone mineral density in C57BL/6 mice (4-weeks-old) that were fed a diet deficient in vitamin D and calcium for 5 weeks.

5.9. *Allium macrostemon*

A. macrostemon, as an important medicinal and edible herb, has been used to treat some diseases for thousands of years in China [36]. Steroidal saponins, a class of oligoglycosides, are the major active compounds in *A. macrostemon*, and they have biological activities, including hypoglycemic, antithrombotic, and anti-inflammatory effects [37]. The administration of *A. macrostemon* 30% ethanol extracts at a dosage of 100 mg/kg for 10 days significantly increased the proximal tibial length of female SD rats.

5.10. *Amomum villosum*

A. villosum has been traditionally used to improve gastrointestinal motility in traditional medicine [38]. When administered at a dosage of 500 mg/kg for 5 days, *A. villosum* extracts significantly increased the length of the proximal tibial growth plate in female SD rats [39]. BrdU-labeled cells were also significantly observed in the chondrocytes treated with *A. villosum* extracts.

5.11. *Eucommia ulmoides*

E. ulmoides is well-known as a tonic medicinal herb for the treatment of bone diseases in traditional Chinese medicine [40]. Geniposidic acid, geniposide, and aucubin from *E. ulmoides* have been shown to increase bone metabolism [41]. In the group treated with *E. ulmoides* 70% ethanol extracts at a dose of 100 mg/kg for 4 days, there was a significant enhancement in the length of the proximal tibial growth plate due to the promotion of chondrogenesis in the growth plate, along with increased levels of BMP-2 and IGF-1 in adolescent female SD rats [42].

5.12. *Phyllostachyos caulis*

P. caulis, well-known as the stem of giant timber bamboo, is used for the treatment of hypertension and cardiovascular diseases in traditional Chinese medicine [43]. It has various biological effects, such as those related to inflammatory diseases [44]. When administered at a concentration of 200 mg/kg of bamboo extract for 10 days to female SD rats, there was a significant increase in the total tibial length, which was attributed to the heights of the proliferative and hypertrophic zones in the tibia.

5.13. *Phellodendron amurense*

P. amurense is one of the major plants in traditional Chinese medicine. It has been used traditionally in folk medicine for hepatitis, dysentery, and gynaecological inflammation [45]. *P. amurense* contains mainly isoquinoline alkaloids, such as berberine chloride [46]. When administered at dosages of 100 and 300 mg/kg for 41 days, *P. amurense* extracts significantly increased the length of the proximal tibial growth plate in female SD rats without changes in food intake or body weights. The levels of IGF-1 and BMP-2 in the proliferative zones of the tibial growth plate significantly increased in the *P. amurense* extract-treated groups.

5.14. Velvet Antler

Velvet antler (VA), sourced from young male deer antlers, has a long history of use in Asian countries for its immune-boosting, stamina-enhancing, and bone health benefits. In a study on male SD rats (3-week-old), a 100 mg/kg dose of VA for 5 days significantly increased bone density, growth plate height, and BMP-2 expression. When applied to MG-63 cells, VA also stimulated cell proliferation, ALP activity, collagen synthesis, calcium deposition, and increased mRNA levels of collagen, ALP, and osteocalcin [47].

6. Conclusions

The effectiveness of the long-term administration of therapeutic agents used for idiopathic short stature (ISS), such as recombinant human growth hormone (rhGH), aromatase inhibitors, metformin, and insulin-like growth factor-1 (IGF-1), remains a topic of controversy. Consequently, there is an expectation of positive outcomes from easily accessible traditional herbal medicine complexes or health supplements. However, there is a lack of scientific evidence regarding the clear mechanisms of their effects or their potential toxicity. In Korea, only the *Astragalus* extract mixture HT042 has been approved by the Korea Food and Drug Administration (KFDA) to promote height growth in children. Several herbal formulations based on traditional medicine have the potential to improve bone

growth, although their effectiveness is controversial. Ongoing research efforts are actively working to uncover a clear mechanism, emphasizing the importance of a scientific approach.

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