OPEN ACCESS
Saudi Journal of Biomedical Research
Abbreviated Key Title: Saudi J Biomed Res
ISSN 2518-3214 (Print) |ISSN 2518-3222 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article

Bone Healing Potential of Herbal Plants as an Alternate to Conventional Therapy

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DOI: https://doi.org/10.36348/sjbr.2025.v10i03.002 | **Received:** 07.02.2025 | **Accepted:** 15.03.2025 | **Published:** 19.03.2025

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Abstract

Bone fracture is considered to be one of the common problems faced by the majority of population all over the globe. In this context the only option available with the person affected is the either the plaster or the surgery followed by the plaster. Along with this the anti-inflammatory medications as well as calcium containing drugs are being recommended for the early recovery of the patients. The problem with the medication and plaster is that the person feels a lot of discomfort. Itching, skin irritation, poor blood circulation due to tight plaster, pressure sores, infection with wetting of plaster and displacement of bones with losing of plaster might take place. Even the drugs recommended in this case like analgesic and anti-inflammatory medications might results in potential side effects. In this regard it is better to find some alternate for the same. In the recent, herbal plants are being recommended for the treatment of bone fracture. The different formulations can be designed for the delivery of the herbal constituents as the medication for fracture. In the present paper the detail description of herbal plants are being highlighted which have shown the potential of healing fracture.

Keywords: Herbal, Fracture, Potential, Bones, Side Effects.

INTRODUCTION

Bone is a dynamic biological tissue composed of metabolically active cells that are integrated into a rigid framework. The healing potential of bone, whether in a fracture or fusion model, is influenced by a variety of biochemical, cellular, hormonal, and pathological mechanisms. A continuously occurring state of bone deposition, resorption and remodeling facilitates the healing process [1]. The success of many spine operations depends on the restoration of long- term spinal stability. Whereas spinal instrumentation devices may provide temporary support, a solid osseous union must be achieved to provide permanent stability [2]. Unlike many other organs, human bones heal in response to injury or surgical treatments. Bone repair is a process that utilizes endogenous regenerative potential to restore original bone structure without increasing bone volume. It shares certain similarities with bone repair; bone regeneration is a complicated, well-orchestrated process, usually involving external elements to promote formation of new mineralized tissues, and leads to an increase in bone volume [3]. Certain bone regenerative procedures, such as bone grafting, reconstruction of large bone defects in the craniofacial region and distraction osteogenesis, sometimes fail in patients. Possible causes of such failure include, but are not limited to, impaired blood supply, damage to the periosteum, reduced number of osteoprogenitor cells as a result of age or osteoporosis, inadequate immobilization, and infection at the injury site [4]. Bone has a hierarchical structure that provides it with the strength necessary for functional loading and specific toughening mechanisms to resist fracture. At the smallest structural level, at the scale of the tropocollagen molecules and mineralized collagen fibrils, (intrinsic) toughening, i.e. plasticity, is achieved via mechanisms of molecular uncoiling and intermolecular sliding of molecules [5]. At coarser levels, at the scale of the fibril arrays, micro cracking and fibrillar sliding act as plasticity mechanisms and contribute to the intrinsic toughness. At micrometer dimensions, the breaking of sacrificial bonds at the interfaces of fibril arrays contributes to increased energy dissipation, together with crack bridging by collagen fibrils. At the larger length scales, in the range of 10s to 100s micrometers, the primary sources of toughening are extrinsic and result from extensive crack deflection and crack bridging by uncracked bone ligaments, mechanisms that are both activated by the occurrence of micro cracking [5].

The repair process can be considered to comprise of overlapping phases [6]. Phases initiated by

an immediate inflammatory response, which leads to the recruitment of mesenchymal stem cells and the subsequent differentiation into chondrocytes that produce cartilage and osteoblasts, which form bone. After cartilage matrix is produced, it is transformed from mineralized cartilage to bone. This primary bone formation is followed by remodeling, in which the initial bony callus is reshaped by resorption and then by secondary bone formation to restore the functional load-bearing anatomical structure [7]. The biological processes driving these stages are regulated by cell signaling molecules that can be categorized into three groups: (1) pro-inflammatory cytokines, (2) transforming growth factor-beta superfamily (TGF-β) members, and (3) angiogenic factors. The biological activities of these molecules trigger overlapping biological processes and coordinate interactions between differing cell populations [6].

PHYSIOLOGY OF BONE HEALING

Bone healing is a complex, multi-stage process that involves the regeneration of bone tissue. This process can be broadly categorized into two distinct mechanisms: primary bone healing, which occurs directly, and secondary bone healing, which occurs indirectly [8]. Primary bone healing, also known as direct healing, takes place when fractured bone fragments are stabilized under compression, allowing for direct union without the formation of a callus. This process is facilitated by the coordinated action of osteoclasts and osteoblasts, which enable the bony ends to join and heal [9]. In contrast, indirect healing, also known as secondary bone healing, is a more common process that involves both endochondral and intramembranous ossification. Notably, indirect healing can occur even in the absence of precise anatomical reduction and stable conditions [10]. Indirect bone healing typically occurs in scenarios where there is some degree of movement or instability at the fracture site. This can happen in the following situations:

- Non-surgical treatment of fractures
- Surgical treatments where some motion is present, such as:
- Intramedullary nailing
- External fixation
- Internal fixation of complex or fragmented fractures [10]

The acute inflammatory response is a crucial stage in the healing process, peaking within 24 hours and resolving within 7 days. Immediately after injury, a hematoma forms comprising cells from peripheral and intramedullary blood, as well as bone marrow cells. The inflammatory response triggers coagulation of the hematoma around the fracture ends and within the medulla, laying the groundwork for callus formation [10]. Bone remodeling is a secondary, restorative stage that follows the formation of a hard callus. Although the hard callus provides stability, it lacks the properties of normal bone. During remodeling, the hard callus is transformed into a lamellar bone structure with a central medullary cavity, restoring the bone's original strength and function [10]. Direct fracture healing requires precise reduction of the fracture ends, eliminating any gaps, and stable fixation. This type of healing typically occurs after open reduction and internal fixation surgery, rather than naturally. Direct bone healing involves the remodeling of lamellar bone, haversian canals, and blood vessels, a process that can take months to years to complete [10].

Primary fracture healing occurs through two distinct mechanisms: contact healing and gap healing. Both processes aim to restore the original lamellar bone structure. However, primary healing can only take place under specific conditions, where the fracture ends are in direct contact and compressed together, and rigid fixation is used to minimize movement and strain between the fragments [8]. Contact healing occurs when the fracture gap is extremely small, less than 0.01 mm, and the interfragmentary strain is minimal, below 2%. Under these conditions, the healing process involves the formation of cutting cones at the ends of the osteons near the fracture site. The cutting cones, tipped with osteoclasts, traverse the fracture line and create longitudinal cavities, facilitating the reunion of the bone [10].

Gap healing is a distinct process where bony union and Haversian remodeling occur sequentially, rather than simultaneously. For gap healing to take place, the fracture gap must be relatively small, measuring less than 800 μm to 1 mm. During this process, the fracture site is initially filled with lamellar bone that forms perpendicular to the long axis of the bone. However, this primary bone structure is not strong and requires secondary osteonal reconstruction. Over time, longitudinal revascularized osteons form, carrying osteoprogenitor cells that differentiate into osteoblasts. These osteoblasts then produce new lamellar bone on either side of the gap. This initial phase of gap healing typically takes between 3 to 8 weeks [10].

BONE REGENERATION

Bone possesses the intrinsic capacity for regeneration as part of the repair process in response to injury, as well as during skeletal development or continuous remodeling throughout adult life [11, 12]. Clinically number of treatment methods available in the surgeon’s armamentarium, which can be used either alone or in combination for the enhancement of these complex clinical situation, which can often be recalcitrant to treatment, representing a medical and socioeconomic challenge. Standard approaches used in clinical practice to stimulate or augment bone regeneration include distraction osteogenesis and bone transport [13, 14], and the use of a number of bone grafting methods, such as autologous bone grafts, allografts, bone graft substitutes or growth factors [15, 16]. Second method is gene therapy which involves the

transfer of genetic material into the genome of the target cell. Gene transfer can be performed using a viral (transfection) or non -viral (transduction) vector, and either by in vivo method or ex vivo gene transfer strategy [17, 18]. Third method is mechanical stability and the role of mechanical stimulation which involves stabilization and use of fixation devices is also an important element for optimal bone repair [19]. Systemic enhancement is an another alternative to local augmentation of the bone-regeneration process, the use of systemic agents, including growth hormone (GH) [20], and parathyroid hormone (PTH) [21], is also under extensive research. Current evidence suggests a positive role for growth hormone in fracture healing, when systemically administered to enhance bone repair [20]. There are also numerous animal studies and clinical trials showing that intermittent parathyroid hormone administration induces both cancellous and cortical bone regeneration, enhances bone mass, and increases mechanical bone strength and bone-mineral density, with a relatively satisfactory safety profile [21, 22].

Medicinal Plants are used in Bone Healing

Herbal medicines have great history of the healing and curing of the disease. The repair of bone defects can be significantly enhanced by medicinal plants that help modulate inflammation, stimulate new blood vessel formation, and accelerate the process of bone regeneration [23, 24]. In fracture repair, a wide variety of plants are utilized by indigenous and underprivileged communities, some of which have been scientifically proven to be effective in promoting bone healing but stilled due to the limited controlled studies are presented their validation are scarce [23-26]. The primary goal of fracture treatment is to facilitate swift bone union. To achieve this, a range of advanced techniques have been developed, including mechanical stimulation, electrical and electromagnetic devices, low-intensity ultrasound, bone morphogenetic protein implantation, and grafting. These grafts may be autogenous, allogeneic, synthetic, or other newly developed therapeutic approaches [27, 28]. Despite their beneficial effects on bone healing, their clinical applications remain limited due to high costs, complex instrumentation, significant morbidity, various restrictions, and the inconsistency of results [29, 30]. Therefore, the use of medicinal plants as an alternative therapy holds great potential in bone regeneration, as they offer biocompatibility, ease of application and storage, and have demonstrated the ability to support osteogenesis [31]. Table 1 presents a list of medicinal plants that have demonstrated potential in facilitating bone healing and treating bone fractures, as evidenced by various research studies.

Table 1: Herbal Plants with Bone healing Potential

Sr no.	Plant Name	Biological Name	Family	Picture
1	Bamboo	*Bambusa arundinacea*	Poaceae	
2	Aloe vera	*Aloe barbadensis*	Liliaceae.	
3	Turmeric	*Curcuma longa*	Zingiberaceae	

4	Pipal tree	*Ficus religiosa*	Moraceae	
5	Cannabis	*Cannabis sativa*	Cannabaceae	
6	Himalayan elm	*Ulmus wallichiana*	Ulmaceae	
7	Arjuna tree	*Terminalia arjuna*	Combretaceae	

Bambusa Arundinacea

Bambusa arundinacea is an important spice of the bamboo that belongs to *Poaceae (Gramineae*) family. In different regions, *Bambusa arundinacea* is known by various names, such as Bnah in Assamese, Spanish bamboo in English, Wans in Gujarati, Kanta Bans in Hindi, Bansa in Urdu, Vansa in Sanskrit, and Bilawar in Kashmir [32]. *Bambusa arundinacea* is an arboreal grass that has been known to humanity for centuries and has been traditionally utilized by indigenous communities as both a food source and a material for shelter [33, 34]. There are various studies on *Bambusa arundinacea* which have been documented to exhibit various pharmacological properties, including anti-inflammatory, antidiabetic, antioxidant, antimicrobial, insecticidal, anthelmintic, anticancer, protective effects, and anti-arthritic activities [35-43]. In joint and bone related problems *Bambusa arundinacea* was used from the decades by the indigenous peoples for example The Kani tribal community utilizes the seeds of *Bambusa arundinacea* in the form of a paste as a traditional remedy for rheumatism [44], in Kanyakumari, traditional healers prepare a paste using the whole *Bambusa arundinacea* plant, turmeric, and Areca catechu, which is applied to treat bruises and reduce swelling [45]. Various parts of *Bambusa arundinacea* contain a diverse array of phytochemicals, including resins, silica, cyanogenic glycosides, betaine, oxalic acid, reducing sugars, benzoic acid, albuminoids, waxes, and a range of amino acids such as arginine, cysteine, histidine, isoleucine, phenylalanine, leucine, threonine, methionine, lysine, valine, riboflavin, tyrosine, niacin, thiamine, glutelin, protein, choline, betaine, proteolytic enzymes, urease, and nuclease [46].

Mechanism of Action

Bambusa arundinacea contains bioactive compounds such as benzoic acid, traces of cyanogenic glycosides, and silicon. These substances are believed to aid in fracture healing. Additionally, the plant is rich in essential minerals like calcium, phosphorus, and zinc, which are vital for bone health [47]. It also has the anti-inflammatory action that is the crucial for the healing of the bone fractures [47]. Research studies have been conducted over the bamboo stem in 2021 the show elevation in the osteogenic differentiation [48], and in another study conducted in 2003 on rabbits show that the alcoholic extract of the bamboo show enhanced bone fracture healing [49].

Aloe Barbadensis

The *Aloe barbadensis Mill* is commonly known as aloe vera is the a perennial succulents or xerophytes that belongs from the family *Liliaceae*. The Aloevera plant has been used in folk medicine for over 2000 years, and Aloe vera has remained an important component in the traditional medicine of many contemporary cultures, such as China, India, the West Indies, and Japan. Over the years, aloe vera plant have been used for the treatment of many conditions such as frostbites, burns, ulcer, psoriasis and also it was reported that it have the anti arthritic and ant rheumatic property which have a good effect on the bone health [50]. Aloe vera has the various bioactive compounds that are responsible for its medicinal therapeutic properties. These compounds includes vitamin A, C, and E, which are potent antioxidants, as well as vitamins such as B1 (thiamine), B2 (riboflavin), B3 (niacin), B6, choline, B12, and folic acid, calcium, chromium, copper, iron, magnesium, manganese, potassium, phosphorus, sodium, and zinc, polysaccharides such as glucosamanna, acemannan, enzymes such as amylase lipases, fatty acids and amino acids [51-53].

Mechanism of Action

Aloe vera promotes bone healing primarily through its active component, acemannan. Acemannan stimulates bone marrow stem cells to multiply and transform into osteoblasts, the cells responsible for bone formation. It also increases the production of essential proteins like bone sialoprotein and osteopontin, which are crucial for bone strength and structure. Additionally, acemannan enhances blood vessel formation by boosting vascular endothelial growth factor (VEGF) levels, ensuring that the developing bone tissue receives adequate nutrients and oxygen. These combined actions facilitate effective bone regeneration [54, 55]. The presence of inorganic compounds such as calcium, chlorine, chromium, copper, iron, magnesium, manganese, potassium, phosphorus, sodium, and zinc facilitates the mineralization of new bone, athroquinoneslaloin and emodin exhibit the antioxidant and anti-inflammatory action that help in the bone healing process [56].

In 2012 research study done on bone marrow stromal cells show that the acemannan extract from the aloe vera show rapid healing for the bone by enhanced BMSC proliferation, increased the production of vascular endothelial growth factor (VEGF) and bone morphogenetic protein-2 (BMP-2), elevated alkaline phosphatase activity, and promoted the expression of bone sialoprotein and osteopontin [57]. In another study in 2019 on incorporated Aloe vera gel extract into hydroxyapatite-coated titanium implants show enhanced osteoblast cell viability *in vitro* and improved new bone formation *in vivo*. The controlled release of acemannan from the implant coatings contributed to better osseointegration, indicating its potential for load-bearing orthopedic applications [58].

Curcuma Longa

Curcuma longa is the tropical plant that belongs to the *Zingiberaceae* family. It is the native plant to the south east tropical Asia and have great history of use in the eastern society. In Hindu religion it have great importance, it is used in the Hindu ceremony in one or another form. It is used as spice in the food stuffs [59]. It is used in the tradition ayurveda for various beneficial actions such as actions such analgesic, disinfectant, anti-inflammatory, and analgesic therapeutic action. Various scientific studies in past have been reported that the turmeric have the wide spectrum of therapeutic action such as anti inflammatory, anti ulcer, anti cancer, antidepressant, antimicrobial, antioxidant, anti arthritic property. *Curcuma longa* rhizomes have curcumin as the main chemical constituent which is responsible for the yellow pigmentation of it also have the demethoxycurcumin and bisdemethoxycurcumin which are responsible for its antioxidant action, volatile oil and curcumin that is responsible for the anti-inflammatory, antibacterial, antifungal, anti protozoan, antiviral, antitumor and antioxidant action [60].

Mechanism of Action

Over the period various studies have been conducted that shows*curcuma longa* have suggestive that it have been effective for the bone healing [61]. Curcumin the active constituent of the *curcuma longa* cause the Dkk1, RANKL/OPG ratio and RANKL gene expression down regulation by which it promote bone healing and inhibition of the oesteogenesis [62]. It also causes the inhibition of the osteocyte apoptosis which is responsible for the bone diminished osteocytes. Curcumin reduces inflammation by silencing inflammatory genes IL-1b and TNF-a via the JAK-STAT pathway. It also combats oxidative stress-induced apoptosis in osteoblasts by activating the Akt/GSK3β pathway, which inhibits caspase3 and cytochrome C release. Lastly, curcumin prevents osteoblasts from apoptosis through ERK pathway activation, boosting pro-apoptotic Bax expression and reducing anti-apoptotic Bcl2.Curcumin exhibits the capability to mitigate NF-kB activity help to reduce the differentiation

of the osteoclast and help in maintaining the bone health [63].

Ficus Religiosa

*Ficus religiosa*has been used in Ayurvedic culture to treat fractured bones. The young bark of this plant, belonging to the *Moraceae* family, has been utilized for this purpose. The leaf extract of *Ficus religiosa*contains significant amounts of tannins, phenols, triterpenoids, glucosides, and sterols. These compounds have been shown to possess analgesic and anti-inflammatory properties. Research has indicated that excessive nitric oxide release can lead to tissue damage and inflammation. However, tannic acid and polyphenols have been found to inhibit nitric oxide synthetase activity and generation. As a result, the plant's ability to reduce swelling and alleviate pain can be attributed to its high tannin content [64, 65].

Mechanism of Action

Ficus religiosa extracts have been shown to inhibit the production of pro-inflammatory mediators like TNF-α, IL-1β, and IL-6 [66]. The plant's antioxidants, such as flavonoids and phenolic acids, scavenge free radicals, reducing oxidative stress and inflammation [67]. *Ficus religiosa* extracts have been found to inhibit the activation of pain pathways, including the inhibition of COX-2 and LOX enzymes [68]. The plant's compounds may modulate neurotransmitters like serotonin and dopamine, which play a role in pain perception [66]. *Ficus religiosa* extracts have been shown to inhibit the destruction of joint tissues, including cartilage and bone [67]. The plant's compounds may modulate the immune response, reducing inflammation and joint damage [66]. *Ficus religiosa* extracts have been found to enhance collagen synthesis, promoting wound healing [68]. The plant's compounds exhibit antimicrobial activity, reducing the risk of infection and promoting wound healing [67].

Cannabis Sativa

Cannabis Sativa (Bhang, family *Cannabaceae)* – A nonpsychotopic compound of cannabinoid cannabidiol (CBD) can help in healing of bone fracture and speed up the process. As per the study done on the rat at Israel, they found that CBD alone makes bone stronger. Researchers had previously discovered cannabinoid receptors within human bodies stimulated bone formation and inhibited bone loss. According to Gabet, the human body is equipped with a cannabinoid system that is involved with the regulating both vital and non-vital system. This is why the psychogenic compound in marijuana tetrahydrocannabinol (THC) has an effect on the human brain. They tested CBD alone as well as CBD with THC on group of rats with fractured femora [69].

Mechanism of Action

*Cannabis Sativa*mechanism of action involves the interaction of its active compounds, such as THC and CBD, with the body's endocannabinoid system (ECS). The ECS consists of two primary receptors: CB1 and CB2. THC, the primary psychoactive compound, binds to CB1 receptors, altering neurotransmitter release and influencing pain perception, mood, and cognition [70]. THC also activates dopamine release, contributing to its euphoric and rewarding effects. On the other hand, CBD, a non-psychoactive compound, interacts with CB2 receptors, reducing inflammation and immune response [71]. CBD also inhibits fatty acid amide hydrolase (FAAH), increasing anandamide levels and contributing to its therapeutic effects [72]. Furthermore, CBD exhibits antioxidant properties, reducing oxidative stress and inflammation. The synergistic effects of THC and CBD, along with other compounds in *Cannabis Sativa*, such as terpenes and flavonoids, contribute to its therapeutic benefits.

Ulmus Wallichiana

Ulmus wallichiana, also known as the Himalayan elm, is a deciduous tree belonging to the family Ulmaceae and kingdom Plantae [73]. This species has been used in traditional medicine for centuries, particularly in treating various ailments such as fever, rheumatism, and skin conditions [74]. The plant's bark, leaves, and roots are used in traditional medicine, and its phytochemicals, including flavonoids, alkaloids, and glycosides, contribute to its medicinal properties [73]. Research has shown that *Ulmus wallichiana* exhibits anti-inflammatory, antioxidant, and antimicrobial properties, and may also enhance bone fracture healing [74].

Mechanism of Action

Ulmus wallichiana flavonoids, such as quercetin and kaempferol, inhibit the production of pro-inflammatory cytokines, thereby reducing inflammation [74]. The plant's antioxidant compounds, including flavonoids and phenolic acids, scavenge free radicals, thereby protecting against oxidative stress and cell damage [75]. *Ulmus wallichiana* glycosides, such as ulmoside and ulmofurano side, stimulate osteoblast activity, leading to enhanced bone formation and fracture healing [74]. The plant's alkaloids, such as ulmaceae alkaloids, modulate the immune response, thereby preventing excessive inflammation and promoting tissue repair [76].

Terminalia Arjuna

Terminalia arjuna (TA), a deciduous tree of the Combretaceae family, is widely distributed throughout India and recognized in Ayurveda for its therapeutic values. The bark of TA is used as a cardio protective agent and to treat fractured bones [77]. The bark paste of TA is used to treat fractured bones in animals and humans, promoting faster bone regeneration. The decoction of the bark is used to relieve pain and inflammation [78]. Bone damages or traumatic events can lead to critical size defects, necessitating bone substitutes to aid regeneration. Calcium phosphate

ceramics, such as biphasic-calcium phosphate (BCP), are used as bone substitutes due to their bioactivity, biodegradability, and biocompatibility. *In vitro* studies have shown that bioactive materials can form bone apatite on their surface when placed in simulated body fluids (SBFs). BCP is gaining interest due to its flexibility in changing resorbability [79, 80]. To impart osteoinductivity to bone substitutes, growth factors like bone morphogenetic protein (BMP) are used. These growth factors promote bone formation and regeneration [81].

Mechanism of Action

Terminalia Arjuna flavonoids, such as arjunolic acid, and glycosides, such as arjunin, exhibit antioxidant and anti-inflammatory activities, protecting the heart from oxidative stress and inflammation [77]. The flavonoids and glycosides cause vasodilation, improving blood flow and reducing blood pressure [78]. *Terminalia Arjuna* flavonoids and glycosides inhibit the production of pro-inflammatory cytokines, reducing inflammation and oxidative stress [79]. *Terminalia arjuna*flavonoids and glycosides scavenge free radicals, protecting against oxidative stress and cell damage [77]. The glycosides, such as arjunin, stimulate osteoblast activity, promoting bone formation and regeneration [80].

CONCLUSION

In the context of the present scenario the bone fracturing is a very come problem occurring on consistent basis. The present option available for the treatment and repair of the fractured bones are associated with one or the other side effect. Though, this is the only option available to the patients in case of emergency. However, the alternate needed to be look upon for the conventional therapies. On the wider view the herbal plants can be one of the best alternate for the treatment and management in case of fracture. These substances contain many ingredients and constituents with bone regeneration, anti-inflammatory, antioxidant and antimicrobial properties which is the requirement of the treatment. Although in future the different formulation and drug delivery systems needed to be developed with economical values.

Conflict of Interest: The authors declare no conflict of interest in this work

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