ijlpr 2023; doi 10.22376/ijlpr.2023.13.6.L312-L324

International Journal of Life science and Pharma Research

ISSN 2250-0480

Review Article

Herbal Bone Grafts

Check for updates

Revolutionizing Bone Regeneration: A Comprehensive Review On Bone Grafts

Sayali Raut[1*], Dr. Priyanka Paul Madhu[2] and Dr. Amit Reche[3]

[1] Intern, Department of Public Health Dentistry, Sharad Pawar Dental College & Hospital, Datta Meghe Institute of Higher Education & Research, Sawangi (Meghe) Wardha 442001, Maharashtra, India.

[2] Assistant Professor, Department of Public Health Dentistry, Sharad Pawar Dental College & Hospital, Datta Meghe Institute of Higher Education & Research, Sawangi (Meghe) Wardha 442001, Maharashtra, India.

[3] Head of Department, Department of Public Health Dentistry, Sharad Pawar Dental College & Hospital, Datta Meghe Institute of Higher Education & Research, Sawangi (Meghe) Wardha 442001, Maharashtra, India.

Abstract: Herbal medicines are plant-based medicines and have been documented 4000 years back. Great results have been extracted from several studies with a minimum amount of side effects. These medicines help osteogenesis as the bone grafts obtained from such are utilized as a filler and scaffold. Such grafts are bioresorbable and do not possess any reaction like antigen antibodies. The aim is to have a comprehensive review study on bone grafts. This review article covers a combination of all aspects regarding bone grafts and their different forms of availability. The Objectives of this review are to explore various bone grafts and to summarize them so that the reader can have enough information just by reading this article. The article gives thorough information about bone grafts and mainly focuses on several ethnopharmacological studies collected using databases such as Pubmed, Medline, Scopus, and Google Scholar. Regarding their osteogenic, angiogenic, anti-inflammatory, and remodeling effects, acting on bone receptors, promoting bone metabolism, increasing mineral uptake, and supporting free radical oxidation, Chenopodium ambrosioides, Piper sarmentosum, Quadrangularis Cissus, Ricinus communis, and Radix salviae miltiorrhizae plants were the most extensively studied in several works of literature. This article concludes that using herbal bone grafts on the site of a defect holds promise for bone regeneration and offers an alternative to conventional therapies when they are impractical. Very few studies have been conducted to date and this has raised interest in using herbal bone grafts.

Keywords: Herbal medicine plants, osteogenic, filler, scaffold, ethnopharmacological, regeneration.

***Corresponding Author**

Sayali Raut , Intern, Department of Public Health Dentistry, Sharad Pawar Dental College & Hospital, Datta Meghe Institute of Higher Education & Research, Sawangi (Meghe) Wardha 442001, Maharashtra, India.

Received On **19 April, 2023**
Revised On **3 August, 2023**
Accepted On **16 August, 2023**
Published On **1 November, 2023**

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Sayali Raut, Dr. Priyanka Paul Madhu and Dr. Amit Reche , Revolutionizing Bone Regeneration: A Comprehensive Review On Bone Grafts.(2023).Int. J. Life Sci. Pharma Res.13(6), L312-L324 http://dx.doi.org/10.22376/ijlpr.2023.13.6.L312-L324

1. INTRODUCTION

Herbal medicines are a healthier choice. Surgery, trauma, infection, or congenital malformations can all lead to ridge defects. To improve bone and soft tissue healing, osseous replacement aims to maintain contour, eliminate dead space, and decrease postoperative infection. When a tooth is lost, rapid resorption of alveolar bone is seen, for instance, in the pneumatization of the maxillary sinus after the tooth is compromised. Bone grafting is a surgical process where the missing bone is replaced with the patient's bone, artificial, synthetic, or natural bone replacements. When growing natural bone entirely replaces the graft material, a fully integrated area of new bone is created[1]. Numerous factors, such as tissue viability, defect dimension, graft shape, dimension, volume, biomechanical qualities, graft handling, cost, ethical issues, biological characteristics, and associated consequences, might affect the selection of the best bone graft[2]. Autografts, allografts, and xenografts are three major materials utilized in bone grafting. Other alternatives include tissue-engineered biomaterials with synthetic or biological foundations and mixtures of these biomaterials[3]. Each of these choices offers benefits and drawbacks. Allografts and xenografts lack the osteogenic qualities of autografts but have osteoinductive and osteoconductive features[2-4]. Autografts have significant osteogenic qualities that are important for bone healing, modeling, and remodeling and are known to be "the golden standard" for rebuilding tiny bone lesions[5]. Discomfort, donor site complications, and extra risks, including significant artery or visceral injury during harvest, are among the disadvantages of autografts[6]. These factors have led to introducing and testing various alternative choices[7,8]. Allografts are a different option, although they have significant drawbacks such as rejection, disease transmission, and expense[9,10]. Allografts have less integrating qualities with the host's recovering tissues than autografts.
Moreover, the drawbacks of allografts are that xenografts risk spreading zoonotic illnesses, and graft refusal is more common and severe[10,11]. The last ten years have seen the introduction of tissue engineering in response to these issues. The methodology of tissue development includes the use of appropriate scaffolds, the addition of appropriate growth stimulants and cells, and, in recent times, the use of appropriate stem cells. To lessen the limitations of traditional grafts and improve graft acceptance, osteogenicity, osteoconductivity, and osteoinductivity, innovative scaffolds and tissue grafts can be made utilizing tissue engineering techniques[10].

2. BIOLOGY OF BONE STRUCTURE

Before knowing about bone grafts, it is essential to know the biological configuration of bone. The bone, a hard organ in the body, may protect and support a variety of organs while also facilitating mobility[12]. The amazing hierarchical architecture, which comprises the brittle apatite mineral and the supple collagen protein, is largely responsible for this characteristic[13]. Regardless of understanding that the gross structures of bones of numerous kinds and species differ and the organizations of the protein collagen and minerals remain unresolved, the mineralized fibrils, which are bonded together by collagen peptides and mineralized by apatite crystals throughout the development of the bone, continue to function as the bone's common fundamental building block[14, 15, 16]. The stiffness of bone tissue, which is influenced by the natural mineral content of the collagen/mineral composite, is connected to bone tissue's functioning in the human body. For instance, the ear vibrates to transmit sound with great quality since it contains over 80% minerals, yet it cannot resorb energy[12]. Deer antlers, conversely, are not load-bearing but can distort while absorbing energy due to less dense mineral composition[17]. Because the long bone's mineral concentration is over 20%, it can absorb energy and maintain its lightweight for movement[18]. Once produced, the bone is actively maintained by two distinct processes, modeling and remodeling, which are also part of bone fracture healing[19]. While bone remodeling involves the production of new bone after bone resorption, bone modeling involves the formation of new bone beforehand. During growth, there is active bone modeling that changes the size and form of the bone. By improving one's capacity to withstand bending and adjust to functional difficulties, it persists throughout adulthood[20, 21]. Bone remodeling is a continual process that starts before fetal development and is responsible for preserving bone function by consistently replacing the worn-out bone with new bone[22]. According to reports, 3% of cortical and 25% of trabecular bone are eliminated and replaced annually[23]. Except for emerging loads beyond bone potency or progressively accumulating damage under cyclic loading, the dynamic equilibrium of the bone effectively avoids bone fracture[24, 25]. It has been demonstrated that, in contrast to other tissues, bone healing recapitulates the ontological processes that occur all through the embryonic growth of the skeleton, enabling the wounded organ to be entirely recovered to its pre-injury formulation, structure, and function[26]. The amount of tissue loss is one of the mending parameters that may be used to categorize bone healing[27].

3. PROPERTIES OF BONE GRAFTS

Knowledge of each graft's biological characteristics is required to choose which is best for a certain ailment. The features of a good bone graft material are osteogenesis, osteoinductivity, osteoconductivity, and osseointegration[28, 29]. Osteogenesis is the ability of osteoblasts to differentiate osteoprogenitor cells from either the receiver's bone or generate new bone. In contrast to allografts and xenografts, which have minimal survivability following implantation of their cellular structures, autogenous grafts primarily possess this feature[30, 31]. By differentiating multipotent mesenchymal stem cells (MSCs) from the adjoining host tissues to create osteoprogenitor cells, later the osteoblasts are formed; osteoinduction is the capacity of the biomaterial to encourage the formation of bone cells. Growth factors such as bone morphogenetic proteins (BMPs), including BMP-2 and BMP-7, transforming growth factor- (TGF-), fibroblast growth factor (FGF), insulin-like growth factor (IGF), and platelet-derived growth factor (PDGF) have been shown to have this capability[32-34]. The graft's ability to operate as a permanent, biodegradable scaffold known as osteoconduction allows for the mechanical support of new bone and angiogenesis from the margins of the defect into and onto its surfaces. New bone development is started or induced by this trait [32-34].Last but not least, osseointegration is the ability of the graft to adhere to the adjacent bone without a layer of fibrous connective tissue in between, allowing for the inclusion of the graft at the place of installation [33]. These techniques may categorize all bone grafts and materials used as bone graft substitutes[30]. Only autografts have all of the characteristics above among all forms of bone transplants. Few characteristics out of four of the supreme bone graft material osseointegration, osteoconduction, and maybe osteoinduction are present in allografts and xenografts, and they lack osteogenic qualities [33,35]. In certain circumstances, bone transplants are necessary to maintain the structure while encouraging bone healing. Bone grafts like cortical and vascularized bone grafts are good choices when structural support is needed.

Table 1: Commonly used natural tissues and biomaterial graft[36]

Bone replacement graft materials
Human bone grafts tissues a) Autografts -Extra-oral -Intra-oral b) Allografts -Fresh or frozen bone -Freeze-dried bone allograft -Demineralized freeze-dried bone allograft (DFDBA)
Non-human source materials a) Xenografts -Bovine hydroxyapatite -Porcine bone -Equine bone -Coralline calcium carbonate
Synthetic materials (Alloplasts) a) Bioactive glasses b) Calcium phosphates -Hydroxyapatite -Tricalcium phosphate -Other calcium phosphates (Brushite, monetite, calcium polyphosphates/CPP) c) Calcium sulfate

Fig1a. Extraction socket

Fig1b. Graft material placement in socket followed by extraction

Fig1c. Post-operative socket

4. AUTOGRAFTS

Autografts are those taken from one place and replaced into a different site of the same individual[37]. They can be cortico-cancellous grafts that combine cortical and cancellous (non-vascularized or vascularized) bone types [38]. Survivor cells and bone-building peptides are present in fresh autografts[2]. They are the greatest material currently accessible from a biological standpoint since they have zero immunogenicity. After transplantation, they stay alive immediately, and their absence of immunogenicity enhances the possibility that the graft will be incorporated into the host site [39]. Moreover, fresh autografts' osteogenic, osteoinductive, and osteoconductive properties are optimal because they include MSCs, osteogenic bone marrow-derived cells, and growth factors[31 40]. Autografts have no associated possibility of spreading viruses in addition to providing skeletal reinforcement for surgically placed devices and eventually growing into technically efficient structures as they progressively replace nearby bone through creeping replacement[30]. The biggest disadvantage is that autografts must be taken from a different body region, requiring further surgery and increasing the risk of discomfort, morbidity, and problems at the donor site [39]. If extensive grafting is required, enough autograft quantities might not be available; hence other bone graft materials must be taken into account[11, 41]. The tissues from the grafts were harvested from a variety of locations. Possible sources for grafts include the iliac wing or crest, the closest or distal part of the tibia and radius, the nearby humerus, the end of the distal ulna, the ribs, the calcaneus, and the nearest olecranon[42-47]. Each of these sources has benefits and drawbacks. In 18 patients, Kitzinger et al. compared the iliac crest and the distal radius as the sources of bone graft; they found that the distal part of the radius was a better alternative because, in their situation, it eliminated the need for general anesthesia, cut down on the length of the procedure, and required less surgical exposure[48]. The best autografts for actual bone transplantation are cancellous or pedicled, circulated cortical autografts[49, 50]. The success of autogenic bone grafting depends on several factors, including the osteogenic cells' ability to survive and proliferate, the conditions at the site of the transplantation bed, the type of graft utilized, how it is handled, and how the graft is shaped to match the host's bone during surgery[45]. Although a fresh autologous graft can assist the genesis, conduction, integration, and stimulation of new bone formation, a bone graft substitution might not be required to possess all the mentioned characteristics to be clinically successful naturally. If minimal concentration and dosage criteria are satisfied when formative chemicals are locally given on a scaffold, stem cells from the mesenchymal layer are eventually recruited to the area and have the potential of consistently stimulating the formation of new bone[30].

5. ALLOGRAFTS

The allograft can be used as a substitute for autogenous bone transplant since it may cause harvesting-related difficulties and has a cap on the amount of graft that may be taken from the patient. As the donor screening methods were developed, the risk of infection decreased[51]. Bone allograft benefits include unrestricted material usage, no donor-site morbidity, and accessibility to mechanical support in various forms and dimensions. The most common methods for storing bone allograft are freezing and drying, and vacuum packaging. However, the drawbacks of the allograft include concerns that the structural quality of the bone may deteriorate and that sterilizing and storing it will kill any living osteogenic cells. Compared to an autogenous transplant, these mechanisms reduce the allograft's ability to mend the bone and cause a loss of osteogenic and osteoinductive activity. As a result, it is largely employed in osteoconduction by giving some mechanical support. Among the major issues with homologous bone is that there is still a risk of infection from viruses and other agents despite meticulous screening of donors and plasma samples. However, with a risk ratio of 1:1.6 million, there were barely two cases of HIV infection that were documented [52, 53]. Even the many sterilization techniques now in use cannot eradicate these kinds of infections. The most often employed approach in individual medical facilities is freezing or freezing-drying, which can completely reduce the possibility of viral infection[52, 54, 55]. Ethylene oxide gas cannot enter the cortical bone, despite some individuals emphasizing that it can stop viral infection[56]. Other techniques of sterilization, like irradiation, can be used[52]. Due to the allograft's lack of osteogenesis and poor osteoinductivity, as well as the effects of sterilization and storage on osteoconductivity and osteoinductivity, the bone union rate after allograft inclusion may be low[57, 58]. The allogeneic bone integrates similarly to nonvascularized autogenous bone grafts. However, the period of incorporation relies on the dimensions of the allograft. This characteristic is partly explained by the absence of cells needed for bone regeneration and immune responses that develop during the incorporation of allogeneic bone in the donor location [55, 59, 60]. Since it lacks structural stability, allo-cancellous bone is frequently used to treat incomplete bone defects instead of segmented or whole-bone deficiencies in clinical settings. Clinically, it is frequently employed to pack the bone defect and enhance spinal fusion, particularly in revision arthroplasty. Two well-known ossification processes are intramembranous ossification and enchondral ossification over the transplant bone's surface. Allogeneic bone is surrounded by an exterior callus with bridging enchondral bone growth, and at the same time, cortical bone resorption and creeping replacement take place. The two bones are thus joined as though by welding[61]. Additionally, only the junction undergoes fusion, and the innermost portion of a transplanted bone retains most of its dead bone trabecular for several years[62]. The third to sixth month is now when bone strength is at its lowest, and the first to second year is when it gradually improves [61, 63].

6. XENOGRAFTS

Xenografts, called heterologous or xenogenic grafts, are an additional option for autogenous bone transplants [64]. One person's xenografts are removed and implanted in another individual with different species. If xenogenous bone grafts could be treated to make them safe for transplantation in people, there would be an endless supply of material [64]. The risk of prion infections and zoonotic diseases like bovine spongiform encephalitis (BSE) spreading through products made from cattle is a severe concern[10, 65]. Like allografts, xenografts undergo processing that partly reduces their bone-forming and partially osteoinductive capabilities to equalize their antigenic features and prevent the spread of infection. Xenografts have poor clinical results. However, new information has been offered[67]. Research has used various bone transplants to treat pathologic bone fractures, non-unions, and bony deformities[66-69]. Autologous bone grafts are the gold standard in most of them, and alternative treatments are compared with autologous bone grafts[70]. Keskin et al. investigated how autologous bone marrow helped rabbits with ulnar bone defects stuffed with cow xenografts mend[4]. A bony defect in the ulna was created. To treat the anomalies in the bones, xenografts obtained from cows, a xenograft and bone marrow transplant, or, on the fifth day after the wound was filled, a xenograft and autogenous bone graft were employed. They discovered that when xenografts were combined with autogenous red bone marrow, their drawbacks were offset, significantly enhancing their incorporation into the recipient bed. Additionally, they concluded that the spongy xenograft may offer bone marrow cells a favorable substrate for osteogenesis. Additional research has revealed that bone marrow injection, as opposed to bone grafting, may have more positive outcomes with fewer complications in bone repair [71]. Recently, the effects of xenogenic bovine fetus DBM, commercial DBM, omentum, omentum-calf fetal DBM, cortical autograft, and xenogenic cartilage powder were investigated on the healing of tibial lesions in a dog model[72]. The susceptibility to infection associated with allografts and xenografts can be reduced or removed by acellularizing tendons, ligaments, and other soft and hard connective tissues. It may be advantageous for enhancing the integration of grafts [73-76].

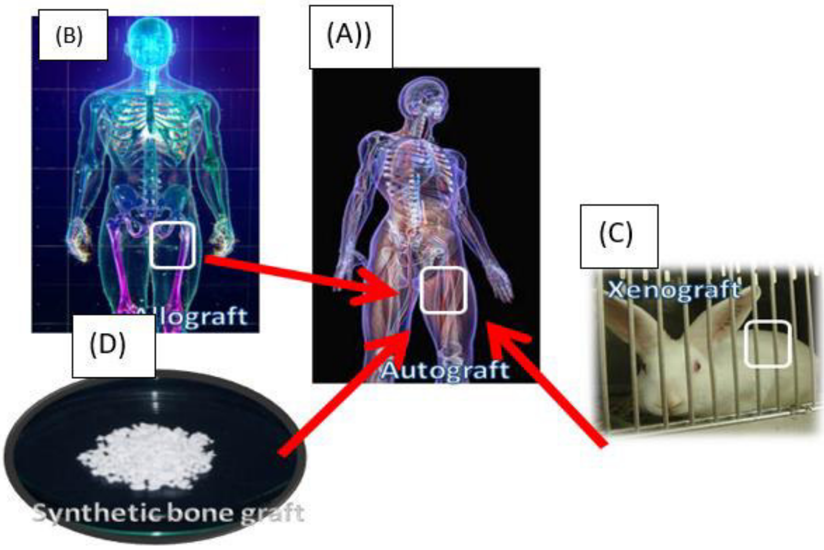

Fig 2: Types of bone grafts[77]

(A)Autograft: To fill the bone deficiency, the surgeon removes the bone from one site and incorporates it into another site of the same person. (B&C) Allograft and Xenograft: The bone transplant is taken from a human giver or an animal. Xenografts risk trigger an immune reaction and spread bacterial and viral infections and zoonotic diseases. (D)Synthetic bone graft: There are several kinds of artificial grafts. These grafts are secure and do not require a second surgical site.

7. IMMUNE RESPONSES

By generating pro-inflammatory cytokines, including interleukin-2 (IL-2), interferon (IFN), and tumor necrosis factor (TNF), which activate macrophages, Th1 cells can lead to poor remodeling of tissues and refusal of each allograft and xenograft transplants[28, 77]. Instead of stimulating macrophages, Th2 cells produce IL-4, IL-5, IL-6, and IL-10 cytokines, which are likely related to graft integration[28, 77]. Macrophages can be categorized as M1 or M2 cells depending on how their receptors express, function, and release cytokines[78]. Rat M1 macrophages express CD68 and CD80 on their surface and produce large amounts of cytokines that promote inflammation, including IL-12 and TNF. Rat M2 macrophages, on the other hand, exhibit CD163 surface markers, produce large quantities of IL-10 and TGF-, prevent the generation of cytokines that promote inflammation, and support favorable tissue remodelling[78, 79]. The Th2 lymphocyte response, which is advantageous for tissue remodeling, is induced by M2 macrophages. The extracellular matrix (ECM) of the scaffold, which contains cellular material, modifies the recipient's immune response after implantation by altering the phenotype of macrophages and lymphocytes; this might affect the result of tissue remodeling in terms of acceptance or rejection[78, 79, 80]. A cellular transplant can cause connective tissue to deposit and the rejection of the graft by inducing an M1 macrophage and Th1 lymphocyte response. An acellular graft induces an M2 macrophage and Th2 lymphocyte response, which results in greater beneficial tissue remodeling and graft acceptance[78].

Table-2: Advantages and disadvantages of some biological and synthetic tissue-engineered polymers [77]

Tissue-engineered polymer	Advantages	Disadvantages
Collagen	most important ECM component, high availability, simplicity of purification from live creatures, non-antigenicity, biodegradability, biocompatibility, and bioreabsorption, non-toxic biological plastic due to high tensile strength, and formulation in a variety of forms	Pure type I collagen is expensive, isolated type I collagen varies, hydrophilicity causes swelling and faster release, bovine spongiform encephalopathy (BSF) and mineralization are side effects, and limited cell differentiation and poor bone-forming capacity are further factors.
Chitosan	The material's biocompatibility, adsorption capabilities, capacity to promote cell differentiation, encouragement of osteoblast development and separation in cell culture, porous structure, flexibility, good structural properties, and appropriateness for cell ingrowth are only a few of its qualities.	Low solubility, insufficient capacity to create new bone, allergic responses, and non-osteoconductive
Alginate	Non-toxic; biodegradable; less costly; fast to set; simple to mix, handle, and utilise	Low mechanical stability (microparticles made exclusively with calcium alginate), poor dimensional stability, untidy to deal with, and less precise replication of detail
Calcium phosphate	outstanding biological qualities, probable resorbability, ideal bone-implant contact, simple surgical preparation, small bone defect, full adaptation to the bone cavity, outstanding biocompatibility, bioactivity, good molding capabilities, and simple manipulation	Low flexural/tensile strength, brittleness, and mechanical resistance

8. ETHNOPHARMACOLOGICAL USE OF MEDICINAL PLANTS IN OSTEOINTEGRATION

The World Health Organization estimates that about 80% of the world's population still relies on such plants as their primary source of medicines and that about 50,000 plant species have been registered for their medicinal uses[81]. The scientific community has investigated and validated several plants that indigenous and underprivileged communities have historically used as sources of raw materials and to create new biomaterial prototypes[82, 83]. For human survival and well-being, as well as preserving biodiversity, forests' ecosystem services are essential. Indigenous peoples worldwide use the forest for various purposes, including agriculture, fishing, hunting, medicine, building materials, and implements. These uses are particularly prevalent in underdeveloped areas where it is difficult to obtain traditional medicines. More than 25% of medicines available today come from medicinal plants. Although it differs between nations, the global market for herbal medicines has grown over the past ten years in tandem with pharmaceutical and clinical research [84]. Researchers conducted ethnopharmacological studies in communities and tribes worldwide, including India, Cameroon, the Philippines, Bangladesh, Brazil, and Southeast Asia. They examined the effectiveness of using traditional medicinal plants to treat various diseases, concentrating on those that could heal bone fractures. These plants were used in various ways, including topical application as pastes and systemic application as infusions and teas, depending on the type of bone fracture. The positive effects of using herbal extracts traditionally to repair bone fractures are frequently mentioned, but there aren't many studies to back them up. As a result, medicinal plants as complementary therapies hold promise for bone regeneration because they are biocompatible, convenient to use and store, and have been shown to promote osteogenesis[85]. The main functions and mechanisms of the medicinal plants mentioned in the research literature concerning the process of bone repair have been listed:

8.1. *Dysphania ambrosioides*

The Brazilian and Latin American populations have long used *Dysphania ambrosioides (L.)* Mosyakin and Clemants (*syn. Chenopodium ambrosioides L.*) as a traditional remedy for inflammatory conditions and treating bruises and fractures [86-88]. *D. ambrosioides* acts as an important osteointegration agent, demonstrating the importance of medicinal plants in phytomedicine production [85].

8.2. *Piper sarmentosum*

Southeast Asia has a *Piper Sarmentosum (Ps)* plant, typically used as a food flavoring [90]. Its extract has been used in Malaysia to treat menstrual irregularities, coughs, and toothaches[91]. There have been claims that various Ps plant extracts have anti-inflammatory, antimicrobial, antioxidant, and anticarcinogenic properties[92].

8.3. Cissus quadrangularis

Cissus quadrangularis, a perennial plant called linn, is primarily found in the world's hottest regions, including India, Sri Lanka, tropical Africa, South Africa, Thailand, Java, and the Philippines[93]. The plant treats irregular menstruation, bloody diarrhea, skin issues, earaches, and hemorrhoids. It accelerates the healing of bone fractures, as mentioned in ancient medical systems like Ayurveda. Beyond bone remineralization, plant phytoconstituents are notable and support their various therapeutic activities[94]. Singh et al. evaluated osteopontin expression during treatment with *C. quadrangular* extract capsules orally in a study with patients who had mandibular fractures compared to the control group. Rats given systemic *C. quadrangular* showed complete restoration of the normal bone composition following fracture in 4 weeks as opposed to 6 weeks for controls. The period it took for bones to heal was shortened by about two weeks. Indications of quicker bone remodeling include the total weight of the fractured bone returning to normal much sooner than in controls. The treated group experienced an acceleration of all events, including fibroblastic, collagenous, and osteochondral, in 10 to 14 days[95].

8.4. Cannabis sativa L. (Cs)

Since ancient times, people have used *Cannabis sativa L. (Cs)* for therapeutic and recreational purposes. Its medicinal applications have been documented as far back as ancient China, medieval Persia, and 14th-century Europe. These applications include the treatment of headaches, fever, gastrointestinal issues, malaria, and even as an antibiotic. The plant contains over 100 compounds, but 11-Tetrahydrocannabinol (THC) and Cannabidiol are the two most prevalent ones (CBD). Both influence the endocannabinoid system, which all mammals have as a physiological regulator. It also possesses several therapeutic properties, including appetite stimulants, antiemetic, antitumor activity, analgesic, anti-inflammatory, anxiolytic, and anticonvulsant. However, its medicinal use is still restricted due to side effects, social stigma, and legislation[96-98].

8.5. Ricinus communis L.

Originally from southern Asia, the castor bean *(Ricinus communis L.)* plant is now widely distributed, particularly in tropical and subtropical areas. According to reports, the plant has larvicide, antitumor, anti-implantation, anti-inflammatory, antidiabetic, central analgesic, antioxidant, anti-implantation, anti-implantation, anti-asthmatic, antitumor, and antitumor. These uses result from specific plant constituents being present[99, 100]. Polyurethane, a polymer with excellent properties, is produced by extracting castor oil from the fruit of *R. communis*. To find biomaterials that can be used as growth promoters and molecule carriers that will aid in the healing of significant bone defects, such as grafts, many current studies in bone tissue engineering have focused on plant polymers. These polymers act as bone cement[101]. Del Carlo et al. discovered that castor bean polymer stimulates osteogenesis and osteoconduction when combined with calcium, particularly when stem cells are present because they promote the movement of perivascular tissues, capillaries, and osteoprogenitor cells[102].

8.6. Ulmus wallichiana

The South Himalayan plant *Ulmus wallichiana Planch* is a significant one used to treat bone fractures in humans and animals. Swarnkar et al. showed the effectiveness of this compound in osteoblast induction and differentiation in osteoblast cultures extracted from rat calvaria to study bone differentiation promoted by naringenin. Utilizing computed tomography to analyze the rat calvaria's bone microarchitecture and fluorescent bone marking to identify new bone formation, the effectiveness in vivo was assessed[92].

8.7. Bixa Orellana L

The native Brazilian plant *Bixa Orellana L* grows in other parts of South and Central America. Tryptophan, methionine, and lysine are the amino acids, carotenoids (bixin and norbixin), and fatty acids that make up its chemical makeup. It also contains small amounts of linoleic and oleic acid[103]. Alves et al. examined the healing potential of polystyrene membrane coated with norbixin and collagen (PSNC) and photobiomodulation (PBM) laser (780 nm) in rats with calvarial bone defects. They were employed to gauge the progress of bone repair[104]. Animal model studies have demonstrated that using various biomaterials, either with or without the PBM laser, increased bone consolidation[105, 106].

8.8. Pueraria Lobata

Traditional medicine frequently used to stop the loss of bone density is Puerariae root, also known as Ge Gen, which is derived from *Pueraria lobata* root[107]. When studied in a bone defect healing model in mice, puerarina, one of the main phytoestrogens isolated from Gegen root (*Pueraria Lobata Willd.*), acted as a potent osteogenic agent, proving to be safe and ideal in bone defect repair[108]. *Pueraria lobata* and *Salvia miltiorrhiza* were used in a rat model study of calvary defect that combined collagen structure and herbal extracts to show that these species accelerated osteogenesis when used separately with the collagen matrix[109].

8.9. Radix salviae miltiorrhizae

Another popular and well-known medicinal plant is Danshen, *Radix salviae miltiorrhizae*. Danshen has been shown in one study to increase local bone neoformation in fractures that were experimentally induced in rabbit parietal bone, demonstrating its efficacy in promoting the healing of bone fractures. Additionally, it can be used as a bone graft, particularly in circumstances where vascular responses are compromised, enhancing the local vascular response. The *Radix salviae miltiorrhizae* plant contains salvianolic acid B (ASB), which has been described as a potent anabolic agent. So it has improved the healing of osteoporotic fractures when studied against glucocorticoid-induced osteoporosis[110]. It was discovered that ASB and its analogs could boost angiogenesis, lessen bone marrow adipogenesis, and promote osteocyte and lacunar canaliculi growth. In turn, this would increase the volume of blood vessels to supply nutrition to the bone and could be used as a bone graft, especially in situations where vascular responses are compromised[111].

9. DISCUSSION

Numerous studies have demonstrated that various factors, including composition, fabrication technique, structural details at the macroscopic and microscopic levels, mechanical properties, premodification, and whether growth factors are coated on the scaffolds, affect their capacity to repair and regeneration. Plants used to treat bones must exhibit significant properties through their active constituents, exhibiting the following activities: antimicrobial; antioxidant, important in scavenging free radicals that delay bone healing; osteogenic activity, promoting increased osteoblast proliferation, osteocytes, and osteoclasts; angiogenic activity, acting on the supply of nutrients to the fracture bed, stimulating collagen production; and estrogenic activity, to control edema and pain production of chemical mediators are essential along its anti-inflammatory property. In 2014, B Santhosh Kumar and T Hemalatha conducted a study that showed that implants made up of Biphasic calcium phosphate–casein bone graft fortified with *Cassia occidentalis* have better mechanical and osteoinductive capabilities. Additionally, the BCP-casein-CO implant has good cytocompatibility and promotes cell growth and proliferation. The BCP-casein-CO implant's mechanical strength is sufficient to support bone tissue engineering and regeneration[112]. Another study was conducted on rat calvaria to assess the potential of herbal plants, carried out by Dong-Hwan Lee and Il-Kyu Kim in 2017. Histological analyses revealed that Danshen and Ge Gan extractions increased bone formation activity when used with collagen matrix in this in vivo experiment on rat calvarial bone defect. This effect most likely has angiogenesis as its mechanism[109]. Vicente F. Pinheiro Neto and Rachel M. Ribeiro compared the use of *Chenopodium ambrosioides* to other bone grafts already used in surgical procedures, such as *Ricinus communis* (castor oil) polyurethane and autogenous bone marrow, for the osseointegration of fractures in rabbits[113]. According to the data, the fact that *C. ambrosioides* graft and autogenous bone marrow have a stronger capacity to promote bone regeneration than castor oil graft indicates that the medicinal plant may have therapeutic advantages for bone tissue[114]. Guo-Chung Dong[115], Hueih Min Chen[116], Ricky W.K. Wong, and A. Bakr M. Rabie[117] contrasted the quantity of new bone that Gusuibu in collagen grafts generated to the amount that bone and collagen grafts produced. Compared to defects transplanted with bone and collagen, defects grafted with Gusuibu had 24% and 90% more new bone, respectively. In the passive control group, no bone developed. Later they concluded that Gusuibu may be employed as a bone graft material and has the impact of increasing new bone growth locally in collagen grafts. Shivaji Kashte, RK Sharma, and Sachin Kadam[118] found that the PCL-GO-CQ scaffold's synergistic combination of graphene oxide and *Cissus quadrangularis* callus extract increased the osteoblastic differentiation, osteoconduction, and osteoinduction potential of the material, making it an excellent choice for bone regeneration and bone tissue engineering applications. The innovative PCLGO-CQ scaffolds, made utilizing a layer-by-layer technique, have great promise for in vivo bone tissue engineering and follow-up research on bone tissue regeneration[119]. Susmita Bose, Naboneeta Sarkar, and Dishary Banerjee[120-121] indicated that recent advancements in manufacturing using additives, together with the increasing clinical need for biomedical implants, were substantially responsible for the rapid adoption of specific to patient's synthetic bone transplants[122]. However, due to implant failure, synthetic implants have a limited lifespan and have short-term therapeutic success, necessitating revision procedures, particularly in younger patients. These above studies show that using medicinal plants in conjunction with collagen or other shows us improved bone health, hastens regeneration, and can be used as a bone graft material. Thus this all gives us a thought about studying such biomaterials and implementing them in medical practices. It initiates us to intensify the study related to various molecules available to us naturally.

10. CONCLUSION

The studies which have been conducted shown that using medicinal plants as a way to speed up bone healing is effective in promoting tissue regeneration. The traditional uses of plants brought by communities like Asia, Africa, and South America have been crucial as a foundation for research into medicinal herbs and as an immediate remedy for pain relief and bone lesion healing. As discovered by ethnopharmacological studies, the traditional use of medicinal plants has been supported by scientific research, demonstrating that these biomaterials have curative, anti-inflammatory, antioxidant, and osteogenic activities and can transmit significant signals for bone cell recruitment. Thus, medicinal plants are a valuable source of new biomaterials for medical practice. To develop regenerative therapies that enhance patient care and lower the cost of conventional treatment, it is crucial to study further various molecules made available by nature.

11. AUTHORS CONTRIBUTION STATEMENT

Sayali Raut prepared the manuscript under the guidance of Dr. Priyanka Paul Madhu and Dr. Amit Reche. All the authors read and approved the final version of the manuscript.

12. CONFLICT OF INTEREST

Conflict of interest declared none.

13. REFERENCES

1. Kumar P, Vinitha B, Fathima G. Bone grafts in dentistry. J Pharm Bioallied Sci. 2013 Jun;5; Suppl 1:S125-7. doi: 10.4103/0975-7406.113312, PMID 23946565.
2. Brydone AS, Meek D, Maclaine S. Bone grafting, orthopedic biomaterials, and the clinical need for bone engineering. Proc Inst Mech Eng H. 2010 Dec;224(12):1329-43. doi: 10.1243/09544119JEIM770, PMID 21287823.
3. Dimitriou R, Jones E, McGonagle D, Giannoudis PV. Bone regeneration: current concepts and future directions. BMC Med. 2011 Dec;9(1):66. doi: 10.1186/1741-7015-9-66, PMID 21627784.
4. Keskin D, Gündoğdu C, Atac AC. Experimental comparison of bovine-derived xenograft, xenograft-autologous bone marrow, and autogenous bone graft for treating bony defects in the rabbit ulna. Med Princ Pract. 2007;16(4):299-305. doi: 10.1159/000102153, PMID 17541296.

5. Athanasiou. 1ABCDEFG VT, Papachristou2ACDE DJ, Panagopoulos1BCDE A, Saridis1BCDF A, Scopa3ABCDEF CD, Megas1ABCDEFG P. Histological comparison of autograft, allograft-DBM, xenograft, and synthetic grafts in a trabecular bone defect: an experimental study in rabbits. Med Sci Monit. 2010;16(1):31.
6. Ehrler DM, Vaccaro AR. The use of allograft bone in lumbar spine surgery. Clin Orthop Relat Res. 2000 Feb 1;371:38-45;(371):38-45. doi: 10.1097/00003086-200002000-00005, PMID 10693548.
7. Shafiei Z, Bigham AS, Dehghani SN, Nezhad ST. Fresh cortical autograft versus fresh cortical allograft effects on experimental bone healing in rabbits: radiological, histopathological and biomechanical evaluation. Cell Tissue Banking. 2009 Feb;10(1):19-26. doi: 10.1007/s10561-008-9105-0, PMID 18626789.
8. Parizi AM, Oryan A, Shafiei-Sarvestani Z, Bigham AS. Human platelet-rich plasma plus Persian Gulf coral effects on experimental bone healing in a rabbit model: a radiological, histological, macroscopical and biomechanical evaluation. J Mater Sci Mater Med. 2012 Feb;23(2):473-83. doi: 10.1007/s10856-011-4478-1, PMID 22057970.
9. Yazar S. Onlay bone grafts in head and neck reconstruction. Plast Surg. 2010 Aug (Vol. 24, No. 03, pp. 255-261);24(3):255-61. doi: 10.1055/s-0030-1263067, PMID 22550447.
10. Moshiri A, Oryan A. Role of tissue engineering in tendon reconstructive surgery and regenerative medicine: current concepts, approaches, and concerns. Hard Tissue. 2012 Dec 29;1(2):11.
11. Oryan A, Alidadi S, Moshiri A. Current concerns regarding the healing of bone defects. Hard Tissue. 2013;2(2):1-2.
12. Seeman E. Bone modeling and remodeling. Crit Rev Eukaryot Gene Expr. 2009;19(3):219-33. doi: 10.1615/critreveukargeneexpr.v19.i3.40, PMID 19883366.
13. Nair AK, Gautieri A, Chang SW, Buehler MJ. Molecular mechanics of mineralized collagen fibrils in bone. Nat Commun. 2013 Apr 16;4(1):1724. doi: 10.1038/ncomms2720, PMID 23591891.
14. Jäger I, Fratzl P. Mineralized collagen fibrils: a mechanical model with a staggered arrangement of mineral particles. Biophys J. 2000 Oct 1;79(4):1737-46. doi: 10.1016/S0006-3495(00)76426-5, PMID 11023882.
15. Gupta HS, Seto J, Wagermaier W, Zaslansky P, Boesecke P, Fratzl P. Cooperative deformation of mineral and collagen in bone at the nanoscale. Proc Natl Acad Sci USA. 2006 Nov 21;103(47):17741-6. doi: 10.1073/pnas.0604237103.
16. Fratzl P, Weinkamer R. Nature's hierarchical materials. Prog Mater Sci. 2007 Nov 1;52(8):1263-334. doi: 10.1016/j.pmatsci.2007.06.001.
17. Currey JD. The relationship between the stiffness and the mineral content of bone. J Biomech. 1969 Oct 1;2(4):477-80. doi: 10.1016/0021-9290(69)90023-2, PMID 16335147.
18. Agna JW, Knowles HC, Alverson G. The mineral content of normal human bone. J Clin Invest. 1958 Oct 1;37(10):1357-61. doi: 10.1172/JCI103725, PMID 13575536.
19. Lieberman JR, Friedlaender GE, editors. Bone regeneration and repair: biology and clinical applications. Humana Press; 2005 Feb 17.
20. Frost HM. Intermediary organization of the skeleton. (No Title). 1986.
21. Kimmel DB. A paradigm for skeletal strength homeostasis. J Bone Miner Res. 1993 Dec;8;Suppl 2:S515-22. doi: 10.1002/jbmr.5650081317, PMID 8122521.
22. Raisz LG. Physiology and pathophysiology of bone remodeling. Clin Chem. 1999 Aug 1;45(8 Pt 2):1353-8. PMID 10430818.
23. Parfitt AM. Osteonal and hemi-osteonal remodeling: the spatial and temporal framework for signal traffic in adult human bone. J Cell Biochem. 1994 Jul;55(3):273-86. doi: 10.1002/jcb.240550303, PMID 7962158.
24. Doblaré M, Garcıa JM, Gómez MJ. Modeling bone tissue fracture and healing: a review. Eng Fract Mech. 2004 Sep 1;71(13-14):1809-40. doi: 10.1016/j.engfracmech.2003.08.003.
25. Martin AD, McCulloch RG. Bone dynamics: stress, strain, and fracture. J Sports Sci. 1987 Jun 1;5(2):155-63. doi: 10.1080/02640418708729773, PMID 3326949.
26. Einhorn TA, Gerstenfeld LC. Fracture healing: mechanisms and interventions. Nat Rev Rheumatol. 2015 Jan;11(1):45-54. doi: 10.1038/nrrheum.2014.164, PMID 25266456.
27. Sela JJ, Bab IA. Healing of bone fracture: general concepts. Princ Bone Regen. 2012:1-8.
28. Allman AJ, McPherson TB, Badylak SF, Merrill LC, Kallakury B, Sheehan C, et al. Xenogeneic extracellular matrix grafts elicit a TH2-restricted immune response1. Transplantation. 2001 Jun 15;71(11):1631-40. doi: 10.1097/00007890-200106150-00024, PMID 11435976.
29. Parikh SN. Bone graft substitutes: past, present, future. J Postgrad Med. 2002 Apr 1;48(2):142-8. PMID 12215702.
30. Greenwald AS, Boden SD, Goldberg VM, Khan Y, Laurencin CT, Rosier RN. Bone-graft substitutes: facts, fictions, and applications. Bone Joint Surg. 2001 Nov 1;83(2);Suppl 2 Pt 2:S98-103.
31. Keating JF, McQueen MM. Substitutes for autologous bone graft in orthopedic trauma. J Bone Joint Surg Br. 2001 Jan;83(1):3-8. doi: 10.1302/0301-620x.83b1.11952, PMID 11245534.
32. Nandi SK, Roy S, Mukherjee P, Kundu B, De DK, Basu D. Orthopaedic applications of bone graft & graft substitutes: a review. Indian J Med Res. 2010 Jul 1;132(1):15-30. PMID 20693585.
33. Albrektsson T, Johansson C. Osteoinduction, osteoconduction and osseointegration. Eur Spine J. 2001 Oct;10;Suppl 2:S96-101. doi: 10.1007/s005860100282, PMID 11716023.
34. Di Martino A, Liverani L, Rainer A, Salvatore G, Trombetta M, Denaro V. Electrospun scaffolds for bone tissue engineering. Musculoskelet Surg. 2011 Aug;95(2):69-80. doi: 10.1007/s12306-011-0097-8, PMID 21399976.
35. Scaglione M, Fabbri L, Dell'Omo D, Gambini F, Guido G. Long bone nonunions treated with autologous concentrated bone marrow-derived cells combined with dried bone allograft. Musculoskelet Surg. 2014 Aug;98(2):101-6. doi: 10.1007/s12306-013-0271-2, PMID 23700322.

36. Sheikh Z, Hamdan N, Ikeda Y, Grynpas M, Ganss B, Glogauer M. Natural graft tissues and synthetic biomaterials for periodontal and alveolar bone reconstructive applications: a review. Biomater Res. 2017 Dec;21(1):9. doi: 10.1186/s40824-017-0095-5, PMID 28593053.
37. Zimmermann G, Moghaddam A. Allograft bone matrix versus synthetic bone graft substitutes. Injury. 2011 Sep 1;42;Suppl 2:S16-21. doi: 10.1016/j.injury.2011.06.199, PMID 21889142.
38. Pereira-Júnior OC, Rahal SC, Iamaguti P, Felisbino SL, Pavan PT, Vulcano LC. Comparison between polyurethanes containing castor oil (soft segment) and cancellous bone autograft in the treatment of segmental bone defect induced in rabbits. J Biomater Appl. 2007 Jan;21(3):283-97. doi: 10.1177/0885328206063526, PMID 16543284.
39. Janicki P, Schmidmaier G. What should be the characteristics of the ideal bone graft substitute? Combining scaffolds with growth factors and/or stem cells. Injury. 2011 Sep 1;42:S77-81. doi: 10.1016/j.injury.2011.06.014.
40. Oryan A, Meimandi Parizi A, Shafiei-Sarvestani Z, Bigham AS. Effects of combined hydroxyapatite and human platelet-rich plasma on bone healing in a rabbit model: radiological, macroscopical, histopathological and biomechanical evaluation. Cell Tissue Banking. 2012 Dec;13(4):639-51. doi: 10.1007/s10561-011-9285-x, PMID 22180011.
41. Gomes KU, Carlini JL, Biron C, Rapoport A, Dedivitis RA. Use of allogeneic bone graft in maxillary reconstruction for installation of dental implants. J Oral Maxillofac Surg. 2008 Nov 1;66(11):2335-8. doi: 10.1016/j.joms.2008.06.006, PMID 18940502.
42. Patel JC, Watson K, Joseph E, Garcia J, Wollstein R. Long-term complications of distal radius bone grafts. J Hand Surg Am. 2003 Sep 1;28(5):784-8. doi: 10.1016/s0363-5023(03)00364-2, PMID 14507508.
43. Lee M, Song HK, Yang KH. Clinical outcomes of autogenous cancellous bone grafts obtained through the portal for tibial nailing. Injury. 2012 Jul 1;43(7):1118-23. doi: 10.1016/j.injury.2012.02.021, PMID 22459896.
44. Mauffrey C, Madsen M, Bowles RJ, Seligson D. Bone graft harvest site options in orthopedic trauma: a prospective in vivo quantification study. Injury. 2012 Mar 1;43(3):323-6. doi: 10.1016/j.injury.2011.08.029, PMID 21917258.
45. Vittayakittipong P, Nurit W, Kirirat P. Proximal tibial bone graft: the volume of cancellous bone, and strength of decancellated tibias by the medial approach. Int J Oral Maxillofac Surg. 2012 Apr 1;41(4):531-6. doi: 10.1016/j.ijom.2011.10.023, PMID 22133867.
46. Bayod J, Becerro-de-Bengoa-Vallejo R, Losa-Iglesias ME, Doblaré M. Mechanical stress redistribution in the calcaneus after autologous bone harvesting. J Biomech. 2012 Apr 30;45(7):1219-26. doi: 10.1016/j.jbiomech.2012.01.043, PMID 22349115.
47. Goyal T, Sankineani SR, Tripathy SK. Local distal radius bone graft versus iliac crest bone graft for scaphoid nonunion: a comparative study. Musculoskelet Surg. 2013 Aug;97(2):109-14. doi: 10.1007/s12306-012-0219-y, PMID 22968662.
48. Kitzinger HB, Karle B, Prommersberger KJ, van Schoonhoven J, Frey M. Four-corner arthrodesis–does the source of graft affect bony union rate? Iliac crest versus distal radius bone graft. J Plast Reconstr Aesthet Surg. 2012 Mar 1;65(3):379-83. doi: 10.1016/j.bjps.2011.09.043, PMID 22015143.
49. Yazar S. Onlay bone grafts in head and neck reconstruction. Plast Surg. 2010 Aug (Vol. 24, No. 03, pp. 255-261);24(3):255-61. doi: 10.1055/s-0030-1263067, PMID 22550447.
50. Rizzo M, Moran SL. Vascularized bone grafts and their applications in the treatment of carpal pathology. Plast Surg. 2008 Aug (Vol. 22, No. 03, pp. 213-227);22(3):213-27. doi: 10.1055/s-2008-1081404, PMID 20567715.
51. Manyalich M, Navarro A, Koller J, Loty B, De Guerra A, Cornu O et al. European quality system for tissue banking. InTransplantation Proc. 2009 Jul 1 (Vol. 41, No. 6, pp. 2035-2043);41(6):2035-43. doi: 10.1016/j.transproceed.2009.06.157, PMID 19715826.
52. Centers for Disease Control (CDC). Transmission of HIV through bone transplantation: case report and public health recommendations. MMWR Morb Mortal Wkly Rep. 1988 Oct 7;37(39):597-9. PMID 3138522.
53. Buck BE, Malinin TI, Brown MD. Bone transplantation and human immunodeficiency virus: an estimate of the risk of acquired immunodeficiency syndrome (AIDS). Clin Orthop Relat Res. 1976-2007 Mar 1;240:129-36;(240):129-36. PMID 2645073.
54. Pelker RR, Friedlaender GE. Biomechanical aspects of bone autografts and allografts. Orthop Clin North Am. 1987 Apr 1;18(2):235-9. doi: 10.1016/S0030-5898(20)30387-4, PMID 3561975.
55. Hamer AJ, Strachan JR, Black MM, Ibbotson CJ, Stockley I, Elson RA. Biomechanical properties of cortical allograft bone using a new method of bone strength measurement: a comparison of fresh, fresh-frozen and irradiated bone. J Bone Joint Surg Br. 1996 May;78(3):363-8. PMID 8636167.
56. Prolo DJ, Pedrotti PW, White DH. Ethylene oxide sterilization of bone, dura mater, and fascia lata for human transplantation. Neurosurgery. 1980 May 1;6(5):529-39. doi: 10.1227/00006123-198005000-00006, PMID 6997770.
57. Herron LD, Newman MH. The failure of ethylene oxide gas-sterilized freeze-dried bone graft for thoracic and lumbar spinal fusion. Spine. 1989 May 1;14(5):496-500. doi: 10.1097/00007632-198905000-00004, PMID 2658125.
58. An HS, Simpson JM, Glover JM, Stephany J. Comparison between allograft plus demineralized bone matrix versus autograft in anterior cervical fusion. A prospective multicenter study| a prospective multicenter study. Spine. 1995 Oct 1;20(20):2211-6. PMID 8545714.
59. Stevenson S, Emery SE, Goldberg VM. Factors affecting bone graft incorporation. Clin Orthop Relat Res. 1976-2007 Mar 1;324:66-74;(324):66-74. doi: 10.1097/00003086-199603000-00009, PMID 8595779.
60. Sandhu HS, Grewal HS, Parvataneni H. Bone grafting for spinal fusion. Orthop Clin North Am. 1999 Oct 1;30(4):685-98. doi: 10.1016/s0030-5898(05)70120-6, PMID 10471772.
61. Enneking WF, Campanacci DA. Retrieved human allografts: a clinicopathological study. Retrieved Human Allografts. Bone Joint Surg. 2001 Jul 1;83(7):971-86. doi: 10.2106/00004623-200107000-00001.

62. Finkemeier CG. Bone-grafting and bone-graft substitutes. J Bone Joint Surg Am. 2002 Mar 1;84(3):454-64. doi: 10.2106/00004623-200203000-00020, PMID 11886919.
63. Ullmark G, Obrant KJ. Histology of impacted bone–graft incorporation. J Arthroplasty. 2002 Feb 1;17(2):150-7. doi: 10.1054/arth.2002.29393, PMID 11847612.
64. Develioglu H, Unver Saraydin SU, Kartal U. The bone-healing effect of a xenograft in a rat calvarial defect model. Dent Mater J. 2009;28(4):396-400. doi: 10.4012/dmj.28.396, PMID 19721275.
65. Oryan A, Moshiri A, Meimandi Parizi AH, Raayat Jahromi A. Repeated administration of exogenous sodium-hyaluronate improved tendon healing in an in vivo transection model. J Tissue Viability. 2012 Aug 1;21(3):88-102. doi: 10.1016/j.jtv.2012.06.002, PMID 22766020.
66. Emami MJ, SAEIDINASAB H, ORYAN A, MEIMANDI PA. The effect of bone marrow graft on bone healing: a radiological and biomechanical study.
67. Bigham AS, Dehghani SN, Shafiei Z, Nezhad ST. Experimental bone defect healing with xenogenic demineralized bone matrix and bovine fetal growth plate as a new xenograft: radiological, histopathological and biomechanical evaluation. Cell Tissue Banking. 2009 Feb;10(1):33-41. doi: 10.1007/s10561-008-9107-y, PMID 18810656.
68. Keles GC, Sumer M, Cetinkaya BO, Tutkun F, Simsek SB. Effect of autogenous cortical bone grafting in conjunction with guided tissue regeneration in the treatment of intraosseous periodontal defects. Eur J Dent. 2010 Oct;4(4):403-11. doi: 10.1055/s-0039-1697860, PMID 20922160.
69. Faldini C, Miscione MT, Acri F, Chehrassan M, Bonomo M, Giannini S. Use of homologous bone graft in the treatment of aseptic forearm nonunion. Musculoskelet Surg. 2011 Apr;95(1):31-5. doi: 10.1007/s12306-011-0117-8, PMID 21442290.
70. Price CT, Connolly JF, Carantzas AC, Ilyas I. Comparison of bone grafts for posterior spinal fusion in adolescent idiopathic scoliosis. Spine. 2003 Apr 15;28(8):793-8. PMID 12698123.
71. Emami MJ, Oryan A, Meimandi-Parizi A, Kasraee R, Tanideh N, Mehrabani D. Bone marrow transplantation and autogenic cancellous bone grafting in healing of segmental radial defects: an animal study. J Appl Anim Res. 2006 Sep 1;30(1):69-72. doi: 10.1080/09712119.2006.9706827.
72. Bigham-Sadegh A, Karimi I, Alebouye M, Shafie-Sarvestani Z, Oryan A. Evaluation of bone healing in canine tibial defects filled with cortical autograft, commercial-DBM, calf fetal DBM, omentum and omentum-calf fetal DBM. J Vet Sci. 2013 Sep 1;14(3):337-43. doi: 10.4142/jvs.2013.14.3.337, PMID 23820162.
73. Elder BD, Eleswarapu SV, Athanasiou KA. Extraction techniques for the decellularization of tissue-engineered articular cartilage constructs. Biomaterials. 2009 Aug 1;30(22):3749-56. doi: 10.1016/j.biomaterials.2009.03.050, PMID 19395023.
74. Vavken P, Joshi S, Murray MM. Triton-X is the most effective among the three decellularization agents for ACL tissue engineering. J Orthop Res. 2009 Dec;27(12):1612-8. doi: 10.1002/jor.20932, PMID 19504590.
75. Zhang AY, Bates SJ, Morrow E, Pham H, Pham B, Chang J. Tissue-engineered intrasynovial tendons: optimization of acellularization and seeding. J Rehabil Res Dev. 2009 Apr 1;46(4):489-98. doi: 10.1682/jrrd.2008.07.0086, PMID 19882484.
76. Gui L, Chan SA, Breuer CK, Niklason LE. Novel utilization of serum in tissue decellularization. Tissue Eng Part C Methods. 2010 Apr 1;16(2):173-84. doi: 10.1089/ten.TEC.2009.0120, PMID 19419244.
77. Oryan A, Alidadi S, Moshiri A, Maffulli N. Bone regenerative medicine: classic options, novel strategies, and future directions. J Orthop Surg Res. 2014 Dec;9(1):18. doi: 10.1186/1749-799X-9-18, PMID 24628910.
78. Badylak SF, Gilbert TW. Immune response to biologic scaffold materials. Semin Immunol. 2008;20(2):109-16. doi: 10.1016/j.smim.2007.11.003, PMID 18083531.
79. Brown BN, Valentin JE, Stewart-Akers AM, McCabe GP, Badylak SF. Macrophage phenotype and remodeling outcomes in response to biologic scaffolds with and without a cellular component. Biomaterials. 2009 Mar 1;30(8):1482-91. doi: 10.1016/j.biomaterials.2008.11.040, PMID 19121538.
80. Valentin JE, Stewart-Akers AM, Gilbert TW, Badylak SF. Macrophage participation in the degradation and remodeling of extracellular matrix scaffolds. Tissue Eng Part A. 2009 Jul 1;15(7):1687-94. doi: 10.1089/ten.tea.2008.0419, PMID 19125644.
81. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014 Jan 10;4:177. doi: 10.3389/fphar.2013.00177, PMID 24454289.
82. Ngueguim FT, Khan MP, Donfack JH, Siddiqui JA, Tewari D, Nagar GK et al. Evaluation of Cameroonian plants towards experimental bone regeneration. J Ethnopharmacol. 2012 May 7;141(1):331-7. doi: 10.1016/j.jep.2012.02.041, PMID 22414477.
83. Zhao S, Baik OD, Choi YJ, Kim SM. Pretreatments for the efficient extraction of bioactive compounds from plant-based biomaterials. Crit Rev Food Sci Nutr. 2014 Jan 1;54(10):1283-97. doi: 10.1080/10408398.2011.632698, PMID 24564586.
84. RajeswarPegu A, Tamuli R. Assessment of human-wildlife conflicts in poba reserved Forest, Dhemaji District, Assam. INDIA.
85. Pinheiro Neto VF, Ribeiro RM, Morais CS, Vieira DA, Guerra PC, Abreu-Silva AL et al. Chenopodium ambroisioides in the repair of fractures in rabbits. Int J Pharmacol. 2015 Jan 1;11(7):732-7.
86. Lorenzi H, Matos FJ. Plantas Medicinais no Brasil, nativas e exóticas. Nova Odessa. I plantarum. 2002;364.
87. Grassi LT. Chenopodium ambrosioides L. Erva de Santa Maria (amaranthaceae): estudo do potencial anti-inflamatório, antinociceptivo e cicatrizante.
88. Pinheiro Neto VF, Araújo BM, Guerra PC, Borges MO, Borges AC. Efeito do cataplasma das folhas de mastruz (Chenopodium ambrosioides) na reparação de tecidos moles e ósseo em rádio de coelho. J Bras Fitomed. 2005;3(2):62-6.
89. Coutinho JM, Lins Neto EM, Monteiro JM. Plantas medicinais utilizadas na Comunidade Santo Antônio, Currais, Sul do Piauí: um enfoque etnobotânico. Baptistel AC. Rev Bras Plant Med. 2014;16:406-25.

90. Burkill IH. A dictionary of the economic products of the Malay Peninsula. A dictionary of the economic products of the Malay Peninsula. 2nd ed. Vol. 2; 1966.
91. Khatun MA, Harun-Or-Rashid M, Rahmatullah M. Scientific validation of eight medicinal plants used in traditional medicinal systems of Malaysia: a review. American-Eurasian J Sustain Agric. 2011 Jan 1;5(1):67-75.
92. Swarnkar G, Sharan K, Siddiqui JA, Mishra JS, Khan K, Khan MP, et al. A naturally occurring naringenin derivative exerts potent bone anabolic effects by mimicking estrogen action on osteoblasts. Br J Pharmacol. 2012 Mar;165(5):1526-42. doi: 10.1111/j.1476-5381.2011.01637.x, PMID 21864313.
93. Geissler PW, Harris SA, Prince RJ, Olsen A, Odhiambo RA, Oketch-Rabah H et al. Medicinal plants used by Luo mothers and children in Bondo district, Kenya. J Ethnopharmacol. 2002 Nov 1;83(1-2):39-54. doi: 10.1016/s0378-8741(02)00191-5, PMID 12413706.
94. Attawish A, Chavalittumrong P, Chivapat S, Chuthaputti A, Rattanajarasroj S, Punyamong S. Subchronic toxicity of Cissus quadrangularis Linn. Songklanakarin J Sci Technol. 2002;24:39-51.
95. Singh N, Singh V, Singh RK, Pant AB, Pal US, Malkunje LR et al. Osteogenic potential of Cissus quadrangular assessed with osteopontin expression. Natl J Maxillofac Surg. 2013 Jan;4(1):52-6. doi: 10.4103/0975-5950.117884, PMID 24163553.
96. de Carvalho CR, Franco PL, Eidt I, Hoeller AA, Walz R. Canabinoides e epilepsia: potencial terapêutico do canabidiol. VITTALLE-revista de ciências da saúde. 2017 Mar 26;29(1):54-63.
97. Gyles C. Marijuana for pets? Can Vet J. 2016 Dec;57(12):1215-8. PMID 27928166.
98. Landa L, SULCOVA A, Gbelec P. The use of cannabinoids in animals and therapeutic implications for veterinary medicine: a review. Vet Med. 2016 Mar 1;61(3):111-22. doi: 10.17221/8762-VETMED.
99. Kensa VM, Yasmin S. Phytochemical screening and antibacterial activity on Ricinus communis L. Plant Sciences Feed. 2011;1(9):167-73.
100. Rana M, Dhamija H, Prashar B, Sharma S. Ricinus communis L.—a review. Int J PharmTech Res. 2012 Oct;4(4):1706-11.
101. Abdul WM, Hajrah NH, Sabir JS, Al-Garni SM, Sabir MJ, Kabli SA et al. Therapeutic role of Ricinus communis L. and its bioactive compounds in disease prevention and treatment. Asian Pac J Trop Med. 2018 Mar 1;11(3):177.
102. Del Carlo RJ, Kawata D, Viloria MIV, Oliveira DR, Silva AS, Marchesi DR, et al. Polímero derivado de mamona acrescido de cálcio, associado ou não à medula óssea autógena na reparação de falhas ósseas. Cienc Rural. 2003;33(6):1081-8. doi: 10.1590/S0103-84782003000600013.
103. Shilpi JA, Taufiq-Ur-Rahman M, Uddin SJ, Alam MS, Sadhu SK, Seidel V. Preliminary pharmacological screening of Bixa orellana L. leaves. J Ethnopharmacol. 2006 Nov 24;108(2):264-71. doi: 10.1016/j.jep.2006.05.008, PMID 16963211.
104. Alves AMM, de Miranda Fortaleza LM, Filho ALMM, Ferreira DCL, da Costa CLS, Viana VGF et al. Evaluation of bone repair after application of a norbixin membrane scaffold with and without laser photobiomodulation (λ 780 nm). Lasers Med Sci. 2018 Sep;33(7):1493-504. doi: 10.1007/s10103-018-2506-9, PMID 29728942.
105. Soares LG, Magalhães EB, Magalhães CA, Ferreira CF, Marques AM, Pinheiro AL. New bone formation around implants inserted on autologous and xenografts irradiated or not with IR laser light: a histomorphometric study in rabbits. Braz Dent J. 2013 May;24(3):218-23. doi: 10.1590/0103-6440201302186, PMID 23969909.
106. Pinheiro AL, Santos NR, Oliveira PC, Aciole GT, Ramos TA, Gonzalez TA et al. The efficacy of the use of IR laser phototherapy associated with biphasic ceramic graft and guided bone regeneration on surgical fractures treated with wire osteosynthesis: a comparative laser fluorescence and Raman spectral study on rabbits. Lasers Med Sci. 2013 May;28(3):815-22. doi: 10.1007/s10103-012-1166-4, PMID 22833288.
107. Wang X, Wu J, Chiba H, Umegaki K, Yamada K, Ishimi Y. Puerariae radix prevents bone loss in ovariectomized mice. J Bone Miner Metab. 2003 Sep;21(5):268-75. doi: 10.1007/s00774-003-0420-z, PMID 12928827.
108. Yuan SY, Sheng T, Liu LQ, Zhang YL, Liu XM, Ma T et al. Puerarin prevents bone loss in ovariectomized mice and inhibits osteoclast formation in vitro. Chin J Nat Med. 2016 Apr 1;14(4):265-9. doi: 10.1016/S1875-5364(16)30026-7, PMID 27114313.
109. Lee DH, Kim IK, Cho HY, Seo JH, Jang JM, Kim J. Effect of herbal extracts on bone regeneration in a rat calvaria defect model and screening system. J Korean Assoc Oral Maxillofac Surg. 2018 Apr;44(2):79-85. doi: 10.5125/jkaoms.2018.44.2.79, PMID 29732313.
110. Wong RW, Rabie AB. Effect of Salvia miltiorrhiza extract on bone formation, The Japanese Society for Biomaterials, The Australian Society for Biomaterials, and the Korean Society for Biomaterials. J Biomed Mater Res A. 2008 May;85(2):506-12. doi: 10.1002/jbm.a.31577, PMID 17729265.
111. O'Brien KA, Ling S, Abbas E, Dai A, Zhang J, Wang WC, et al. A Chinese herbal preparation containing radix salviae miltiorrhizae, radix notoginseng, and borneol-um syntheticum reduces circulating adhesion molecules. Evid Based Complement Alternat Med. 2011 Jan 1;2011:790784. doi: 10.1093/ecam/nen060, PMID 18955365.
112. Kumar BS, Hemalatha T, Deepachitra R, Raghavan RN, Prabu P, Sastry TP. Biphasic calcium phosphate–casein bone graft fortified with Cassia occidentalis for bone tissue engineering and regeneration. Bull Mater Sci. 2015 Feb;38(1):259-66. doi: 10.1007/s12034-014-0799-2.
113. Pinheiro Neto VF, Ribeiro RM, Morais CS, Vieira DA, Guerra PC, Abreu-Silva AL et al. Chenopodium ambroisioides in the repair of fractures in rabbits. Int J Pharmacol. 2015 Jan 1;11(7):732-7.
114. Pinheiro Neto VF, Ribeiro RM, Morais CS, Campos MB, Vieira DA, Guerra PC et al. Chenopodium ambrosioides as a bone graft substitute in rabbits radius fracture. BMC Complement Altern Med. 2017 Dec;17(1):350. doi: 10.1186/s12906-017-1862-5, PMID 28676049.
115. Sun JS, Dong GC, Lin CY, Sheu SY, Lin FH, Chen LT et al. The effect of Gu-Sui-Bu (Drynaria fortunei J. Sm) immobilized modified calcium hydrogenphosphate on bone cell activities. Biomaterials. 2003 Feb

1;24(5):873-82. doi: 10.1016/s0142-9612(02)00372-1, PMID 12485805.

116. Dong GC, Chen HM, Yao CH. A novel bone substitute composite composed of tricalcium phosphate, gelatin, and Drynaria fortunei herbal extract, The Japanese Society for Biomaterials, The Australian Society for Biomaterials, and the Korean Society for Biomaterials. J Biomed Mater Res A. 2008 Jan;84(1):167-77. doi: 10.1002/jbm.a.31261, PMID 17607749.
117. Wong RW, Rabie B, Bendeus M, Hägg U. The effects of rhizoma Curculiginis and rhizoma Drynariae extracts on bones. Chin Med. 2007 Dec;2:13. doi: 10.1186/1749-8546-2-13, PMID 18093297.
118. Kashte S, Sharma RK, Kadam S. Layer-by-layer decorated herbal cell compatible scaffolds for bone tissue engineering: A synergistic effect of graphene oxide and Cissus quadrangularis. J Bioact Compat Polym. 2020 Jan;35(1):57-73. doi: 10.1177/0883911519894667.
119. Kashte S, Dhumal R, Chaudhary P, Sharma RK, Dighe V, Kadam S. Bone regeneration in critical-size calvarial defect using functional biocompatible osteoinductive herbal scaffolds and human umbilical cord Wharton's jelly-derived mesenchymal stem cells. Mater Today Commun. 2021 Mar 1;26:102049. doi: 10.1016/j.mtcomm.2021.102049.
120. Bose S, Sarkar N, Banerjee D. Natural medicine delivery from biomedical devices to treat bone disorders: a review. Acta Biomater. 2021 May 1;126:63-91. doi: 10.1016/j.actbio.2021.02.034, PMID 33657451.
121. Kalita SJ, Bose S, Hosick HL, Martinez SA, Bandyopadhyay A. Calcium carbonate reinforced natural polymer composite for bone grafts. MRS Online Proc Libr (OPL). 2002;724:N8-18.
122. Catledge SA, Fries MD, Vohra YK, Lacefield WR, Lemons JE, Woodard S et al. Nanostructured ceramics for biomedical implants. J Nanosci Nanotechnol. 2002 Jul 1;2(3-4):293-312. doi: 10.1166/jnn.2002.116, PMID 12908255.