Role of Herbal Drugs in the Treatment and Rehabilitation of Femur Fracture: A Comprehensive Review

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ABSTRACT

Femoral fractures are major musculoskeletal injuries that may cause prolonged immobility, impaired functional recovery and, in some patients, delayed union or non-union. Surgical fixation restores mechanical stability; however, successful repair also depends on vascular supply, inflammatory regulation, recruitment of progenitor cells, osteoblast differentiation and coordinated bone remodelling. Medicinal plants and their phytoconstituents have attracted research interest because several demonstrate osteogenic, angiogenic, antioxidant or anti-inflammatory activities in experimental models. This narrative review discusses the potential contribution of selected herbal agents to femoral fracture healing and postoperative rehabilitation, with emphasis on Cissus quadrangularis, Epimedium brevicornum (icariin), Panax ginseng and Panax notoginseng (ginsenosides), Drynaria fortunei (naringin), Astragalus membranaceus (astragaloside IV), Curcuma longa (curcumin) and Salvia miltiorrhiza (tanshinones and salvianolic acids). Reported mechanisms include modulation of Wnt/β-catenin, BMP-2/Smad, MAPK/ERK and PI3K/Akt-related signalling, regulation of RUNX2 and alkaline phosphatase, effects on the OPG/RANKL axis, and support of vascular development. The review also considers the biological phases of secondary fracture healing and the relationship between controlled mechanical loading and functional rehabilitation. Although preclinical findings are encouraging, evidence that these agents improve human femoral fracture union, permit earlier weight-bearing or prevent muscle atrophy remains limited. Product standardization, pharmacokinetic characterization, toxicity assessment and evaluation of interactions with anticoagulants and other perioperative medicines are essential before routine clinical use can be recommended.

Keywords: Femoral fracture; bone regeneration; medicinal plants; Cissus quadrangularis; osteogenesis; angiogenesis; callus formation; phytotherapy; rehabilitation.

INTRODUCTION

The femur is the largest weight-bearing bone in the human body and is essential for standing, walking and lower-limb function. A fracture may therefore have substantial consequences for mobility, independence, quality of life and healthcare utilization. In younger adults, femoral shaft fractures are commonly associated with high-energy trauma, including road traffic accidents, whereas fragility fractures in older adults are often associated with falls and reduced bone strength. Displacement of fracture fragments may be influenced by the powerful surrounding muscle groups, including the quadriceps, hamstrings and hip adductors. Restoration of alignment and mechanical stability is consequently a central component of treatment.

Intramedullary nailing and locking-plate fixation are established methods for stabilizing many femoral fractures. Nevertheless, fixation alone cannot guarantee successful union. Vascular compromise, extensive soft-tissue injury, bone loss, infection, age-related changes and metabolic disorders may adversely affect repair. Delayed union and non-union can prolong protected weight-bearing, increase the need for additional intervention and impede return to daily activities. Biological support of fracture repair is therefore an important area of investigation.

Medicinal plants contain diverse classes of secondary metabolites, including flavonoids, phytosterols, saponins, polyphenols and terpenoids. Experimental studies have explored whether selected constituents influence osteoblast differentiation, osteoclast activity, collagen synthesis, oxidative stress, inflammatory signalling and

angiogenesis. The present review organizes the material in the supplied source document into a focused discussion of fracture biology, selected herbal agents, rehabilitation and translational limitations. It is a narrative synthesis of the material provided; it should not be interpreted as a systematic review or meta-analysis.[1]

Biology Of Femoral Fracture Healing

Primary and secondary bone healing

Fracture healing occurs through primary (direct) or secondary (indirect) repair, depending substantially on the mechanical environment. Primary healing is associated with close anatomical apposition and rigid fixation, with very limited interfragmentary movement. Osteoclast-mediated cutting cones cross the fracture interface and are followed by osteoblast deposition of new bone; prominent callus formation is generally absent. Secondary healing is common in many femoral fractures treated with fixation methods that permit controlled micromotion. It involves both intramembranous and endochondral ossification and proceeds through inflammatory, soft-callus, hard-callus and remodelling stages.[2]

Inflammatory and soft-callus phases

Immediately after injury, damaged vessels produce a fracture haematoma and fibrin-rich clot. Platelets, inflammatory cells and local tissues release mediators such as IL-1, IL-6, TNF-α, TGF-β and PDGF. These signals contribute to recruitment of skeletal stem/progenitor cells and mesenchymal stromal cells. Macrophages remove damaged tissue and help regulate the transition from an inflammatory environment towards tissue repair. In regions of relative hypoxia, HIF-1α signalling contributes to chondrogenic differentiation. Chondrocytes produce a cartilage-rich soft callus containing extracellular-matrix components, including type II collagen and proteoglycans, which temporarily stabilizes the fracture.[3]

Hard-callus formation, angiogenesis and remodelling

As repair progresses, hypertrophic chondrocytes increase expression of factors associated with matrix mineralization and vascular development, including alkaline phosphatase (ALP) and vascular endothelial growth factor (VEGF). New vessels deliver oxygen, nutrients, mineral ions and osteoprogenitor cells. The cartilage matrix is progressively resorbed and replaced by woven bone through coordinated activity of chondroclast/osteoclast-lineage cells and osteoblasts. RUNX2 is an important transcriptional regulator of osteoblast differentiation. The hard callus bridges the fracture gap and provides increasing mechanical strength. During subsequent remodelling, woven bone is gradually replaced by organized lamellar bone, with osteoclast and osteoblast activity coordinated in part through the receptor activator of nuclear factor-κB ligand (RANKL)/osteoprotegerin (OPG) system.

Osteogenesis and angiogenesis are interdependent processes. The development of specialized CD31-high/endomucin-high (Type H) vessels has been associated with osteogenic activity in bone. This osteo-angiogenic relationship provides a biological rationale for investigating phytochemicals that may influence both bone-forming cells and vascular development.[4]

Phytochemical Classes And Potential Mechanisms

The source material describes several phytochemical groups with potential relevance to skeletal repair. Phytosterols and ketosteroid fractions, including β-sitosterol-associated constituents reported in Cissus quadrangularis, have been investigated for effects on osteoblast differentiation, ALP activity and collagen deposition. Flavonoids and related glycosides, including icariin and naringin, have been studied in relation to Wnt/β-catenin and BMP-2/Smad signalling, osteogenic gene expression and regulation of osteoclast activity. Triterpenoid saponins, including ginsenosides and astragaloside IV, have been examined for effects on PI3K/Akt/mTOR, HIF-1α and angiogenesis. Polyphenols such as curcumin and resveratrol have been investigated for antioxidant and inflammation-modulating effects, including regulation of NF-κB-associated pathways. Tanshinones and salvianolic acids have been studied for vascular and osteogenic effects.[5]

Selected Medicinal Plants And Bioactive Constituents

Cissus quadrangularis Linn

Cissus quadrangularis is traditionally associated with bone injury management and is among the most frequently discussed plants in the source document. Its reported constituents include ketosteroids, phytosterols such as β-sitosterol, triterpenoids, and flavonoids including quercetin and kaempferol; stilbenes such as resveratrol and piceatannol are also described. Experimental work suggests that extracts may influence the differentiation of bone-marrow-derived mesenchymal stromal cells towards osteoblasts. Proposed mechanisms include regulation of RUNX2 and p38/MAPK signalling, increased ALP activity, collagen synthesis and extracellular-matrix mineralization. Animal fracture models have reported changes in callus development and radiographic or biomechanical measures, including resistance to torsional or compressive loading. Anti-inflammatory and analgesic effects have also been proposed through modulation of inflammatory mediators such as TNF-α and myeloperoxidase-associated responses. These observations are not sufficient to establish improved union, earlier knee mobilization or earlier weight-bearing in patients with femoral fractures.[6,7]

Epimedium brevicornum Maxim. and icariin

Epimedium brevicornum contains icariin, a prenylated flavonol glycoside, and related metabolites such as icariside II. Preclinical findings described in the source material associate icariin with activation of Wnt/β-catenin and MAPK/ERK signalling and increased expression of osteogenic markers, including RUNX2, Osterix and osteocalcin. Icariin has also been investigated for effects on VEGF and basic fibroblast growth factor (bFGF), which participate in endothelial-cell proliferation and vascular development. Modulation of the OPG/RANKL balance has been proposed as a mechanism affecting osteoclast formation and bone remodelling. Research under metabolic stress conditions, including diabetes- or osteoporosis-related models, is of interest, but human femoral-fracture efficacy and safety remain to be established.[8]

Panax ginseng and Panax notoginseng (Araliaceae): ginsenosides

Panax species contain dammarane-type saponins, including ginsenosides Rg1 and Rb1 and metabolites such as ginsenoside Compound K. Preclinical investigations have explored their potential to promote osteogenesis and angiogenesis, including the development of Type H vessels in fracture callus. Proposed pathways include PI3K/Akt/mTOR and VEGF/VEGFR2 signalling, with possible effects on BMP-2 and osteocalcin expression. Panax notoginseng-containing preparations have also been discussed in relation to postoperative bleeding and haematoma. Because some preparations may affect haemostasis or interact with medicines, potential benefits must be weighed against bleeding and interaction risks. Clinical evidence for improved femoral union, reduced blood loss or better rehabilitation outcomes remains limited.[9]

Drynaria fortunei (Polypodiaceae; Gusuibu) and naringin

Drynaria fortunei is a traditional medicinal fern whose reported constituents include naringin and neoeriocitrin. Experimental studies described in the source material suggest that naringin may promote osteoblast differentiation and matrix formation through BMP-2/Smad1/5/8 signalling, with increased expression of RUNX2, ALP and type I collagen. It may also influence RANKL-induced NF-κB and MAPK pathways involved in osteoclast differentiation. Changes in trabecular bone indices, including bone-volume fraction and trabecular thickness, have been reported in preclinical contexts. These findings provide a rationale for further study in settings of reduced loading, but do not demonstrate prevention of disuse bone loss or improved human femoral-fracture union.[10]

Astragalus membranaceus (Fabaceae; Huangqi) and astragaloside IV

Astragalus membranaceus contains polysaccharides, isoflavones and triterpenoid saponins. Astragaloside IV has been investigated for tissue-protective, antioxidant and angiogenesis-related effects. Proposed mechanisms include modulation of PI3K/Akt/GSK-3β signalling, stabilization of HIF-1α and regulation of VEGF and bFGF expression. These effects may be relevant to injured tissues exposed to hypoxia or oxidative stress. The source

document also discusses possible immunomodulatory effects involving TNF-α and IL-6. Claims that astragaloside IV prevents muscle wasting, preserves quadriceps mass or improves clinical fracture union remain unconfirmed.[11]

Curcuma longa L. (Zingiberaceae) and curcumin

Curcumin is a major polyphenolic constituent of turmeric and has been widely investigated for anti-inflammatory and antioxidant properties. It may modulate NF-κB-associated signalling and inflammatory mediators such as IL-1β, TNF-α and inducible nitric oxide synthase. The effect of inflammation modulation requires particular care in fracture repair because the early inflammatory response is a necessary part of normal healing; excessive suppression may be counterproductive. Curcumin has also been studied in relation to BMP-2/Smad/RUNX2 signalling and in biomaterial or scaffold systems designed for bone-defect repair. Its bioavailability, formulation, dose, interactions and clinical effects on femoral fracture healing require further evaluation.[11]

Salvia miltiorrhiza Bunge (Lamiaceae; Danshen): tanshinones and salvianolic acids

Salvia miltiorrhiza contains lipophilic diterpenoid quinones, including tanshinone IIA and cryptotanshinone, and hydrophilic phenolic compounds such as salvianolic acid B. Experimental findings described in the source material suggest that salvianolic acid B may influence osteogenic differentiation through ERK signalling, ALP activity, osteocalcin expression and mineral deposition. Tanshinone IIA has been investigated for effects on endothelial migration and capillary-like tube formation through VEGF/VEGFR2-related mechanisms. Although vascular support is biologically important in fracture repair, claims of improved microcirculation or faster femoral union in patients remain insufficiently supported. Potential effects on bleeding and anticoagulant medicines require attention.[12]

Comparative summary of selected herbal agents

Plant / constituent	Major phytochemical class	Proposed biological actions	Evidence status in source
Cissus quadrangularis	Phytosterols, ketosteroids, flavonoids, stilbenes	RUNX2/MAPK, ALP, collagen and callus development; possible anti-inflammatory effects	Preclinical; limited clinical observations
Epimedium / icariin	Prenylated flavonoid glycoside	Wnt/β-catenin, MAPK/ERK, VEGF; OPG/RANKL modulation	Predominantly preclinical
Panax species / ginsenosides	Triterpenoid saponins	PI3K/Akt/mTOR, VEGF/VEGFR2; osteo-angiogenic coupling	Predominantly preclinical
Drynaria / naringin	Flavonoid	BMP-2/Smad, RUNX2, ALP, type I collagen; RANKL-related effects	Predominantly preclinical
Astragalus / astragaloside IV	Triterpenoid saponin	PI3K/Akt/GSK-3β, HIF-1α, VEGF and bFGF	Preclinical; clinical benefit uncertain
Curcuma / curcumin	Polyphenol	NF-κB and oxidative-stress modulation; BMP-2/Smad/RUNX2	Preclinical and broader clinical research; femur-specific benefit uncertain
Salvia / tanshinones, salvianolic acid B	Diterpenoid quinones and phenolic acids	ERK-related osteogenic activity; VEGF/VEGFR2-related angiogenesis	Predominantly experimental

Herbal Adjuvants And Postoperative Rehabilitation

Recovery after femoral fixation requires both fracture consolidation and restoration of muscle strength, joint mobility, balance and gait. Restricted weight-bearing and prolonged inactivity may contribute to quadriceps weakness, reduced muscle activation, hip or knee stiffness and local bone loss. Herbal agents with proposed osteogenic, anti-inflammatory or antioxidant actions have therefore been considered as possible adjuncts. However, no herbal product discussed here should replace fixation, prescribed thromboprophylaxis, pain management or a supervised rehabilitation programme.[13]

Mechanobiology and Wolff's law

Bone adapts to its mechanical environment. Controlled axial loading can produce interstitial fluid movement within the lacunar-canalicular network and stimulate osteocyte mechanosensing through structures such as primary cilia, integrins and stretch-activated calcium channels. Mechanical signals may influence sclerostin and canonical Wnt/β-catenin activity, thereby affecting osteoblast-mediated formation and remodelling. This concept is commonly associated with Wolff's law. Nevertheless, excessive loading of an immature callus can compromise fixation or delay healing. Weight-bearing progression must therefore be determined by fracture pattern, fixation stability, imaging and the treating orthopaedic team.[13]

Phased rehabilitation framework

Phase I: Acute postoperative stage (approximately days 0–14)

Priorities include pain and swelling management, prevention of complications of immobility, maintenance of circulation and early activation of available muscle groups. Depending on the operation and the patient's condition, the programme may include ankle pumps, gentle quadriceps and gluteal isometric contractions, and assisted knee movement within prescribed limits. The source document identifies Cissus quadrangularis, Curcuma longa and Panax notoginseng as agents investigated for anti-inflammatory or tissue-protective effects; their ability to improve haematoma resolution, reduce analgesic requirements or preserve early osteogenic signalling is not clinically established.[14]

Phase II: Early callus formation and protected mobilization (approximately weeks 2–6)

Goals include maintaining hip and knee flexibility, preventing contractures and beginning protected mobilization when permitted. Exercises may include assisted knee flexion and extension, heel slides, gentle terminal knee extension and pelvic stabilization. Partial weight-bearing, if allowed, is performed with an appropriate walking aid. Icariin, ginsenoside Compound K and Cissus quadrangularis have experimental osteogenic signals involving RUNX2 and ALP; astragaloside IV has been investigated for antioxidant and tissue-protective actions. Evidence that these compounds prevent postoperative muscle wasting or accelerate human fracture healing is insufficient.[14]

Phase III: Bony-callus consolidation and progressive loading (approximately weeks 6–12)

This phase may involve gradual progression of weight-bearing, gait retraining, restoration of knee mobility and lower-limb strengthening, subject to clinical and radiographic review. Stationary cycling, low-resistance strengthening, supported squats, step-ups and balance activities may be introduced when appropriate. Naringin and icariin have been studied in relation to BMP-2/Smad and Wnt/β-catenin pathways. It remains unknown whether these agents enhance callus consolidation sufficiently to justify earlier loading or reduce fixation-related complications.[15]

Phase IV: Remodelling and functional rehabilitation (approximately months 3–12 and beyond)

Later rehabilitation focuses on progressive resistance exercise, quadriceps and hamstring strength, balance, coordination, gait symmetry and return to occupational or recreational activity. Cissus quadrangularis and naringin have been investigated for effects on bone turnover and the OPG/RANKL system. Evidence that they prevent disuse osteopenia, improve long-term cortical remodelling or reduce peri-implant refracture is limited.

Return to unrestricted activity should be based on clinical assessment, healing and functional capacity rather than a fixed timetable.[15]

Safety, Toxicity And Herb–Drug Interactions

Product quality and toxicological assessment

Herbal medicines are chemically complex and may vary with species authentication, plant part, geographical origin, harvest conditions, extraction solvent, processing and storage. Standardization to defined marker compounds, contaminant testing and reproducible manufacturing are necessary for meaningful research and safe use. The source document highlights comfrey (Symphytum officinale) as an example of a plant with important toxicity concerns. Comfrey contains unsaturated pyrrolizidine alkaloids that can undergo metabolic activation and cause hepatic injury, including hepatic sinusoidal obstruction syndrome. Internal use is therefore a significant safety concern; topical preparations, where permitted, are subject to restrictions and should not be assumed to be risk-free.[16]

Interactions with anticoagulants and perioperative medicines

Patients with femoral fractures may require pharmacological thromboprophylaxis because trauma, surgery and immobility increase venous thromboembolism risk. Regimens may include direct oral anticoagulants, low-molecular-weight heparins or other agents according to clinical circumstances. The source material identifies Salvia miltiorrhiza, Panax ginseng and high-dose curcumin as botanicals of concern because of possible antiplatelet effects or interactions involving drug-metabolizing enzymes and transporters, including CYP3A4, CYP2C9 and P-glycoprotein. Such interactions may alter drug exposure or increase bleeding risk. Patients should disclose all herbal products to their surgical and pharmacy teams. Decisions about stopping or restarting a product must be individualized by the treating clinicians; patients should not independently discontinue prescribed anticoagulants.[16]

Clinical evidence limitations

Evidence must be interpreted according to study design. Cell-based and animal findings can identify plausible mechanisms but do not establish effective human doses, clinical benefit or safety in postoperative patients. Extracts may differ substantially in composition, and isolated compounds may not behave like whole-plant preparations. Potential interactions, effects on wound healing, bleeding, liver function and concomitant analgesic or anticoagulant therapy require prospective evaluation.

Research Gaps And Future Directions

Future work should move from mechanistic plausibility towards reproducible pharmaceutical products and clinically meaningful outcomes. Priorities include botanical authentication; chemical fingerprinting; quantitative standardization of marker compounds; stability testing; pharmacokinetic and bioavailability studies; dose-ranging and toxicology; and evaluation of interactions with anticoagulants and other perioperative medicines. Formulation approaches such as bone-targeted nanoparticles, stimuli-responsive carriers, hydrogels and bioactive scaffolds may improve local delivery or protect unstable constituents, but their performance and safety require validation.

Network pharmacology, molecular docking and artificial-intelligence-assisted analyses may help prioritize candidate compounds and targets, but computational predictions should be confirmed experimentally. Well-designed multicentre randomized controlled trials are needed to test whether standardized products improve outcomes beyond standard orthopaedic care. Relevant endpoints could include radiographic union, time to union, non-union rate, callus characteristics, bone-turnover markers such as P1NP and CTX, pain, adverse events, time to permitted full weight-bearing, quadriceps strength, gait performance and validated functional scores. Trials should prespecify fracture type, fixation method, timing, product composition and rehabilitation protocol.

CONCLUSION

Femoral fracture healing is a coordinated biological and mechanical process that depends on vascular development, progenitor-cell recruitment, osteoblast and osteoclast activity, callus formation and progressive remodelling. The medicinal plants discussed in this review contain constituents with experimental effects on osteogenic signalling, angiogenesis, inflammation and oxidative stress. Cissus quadrangularis, icariin, ginsenosides, naringin, astragaloside IV, curcumin and Salvia miltiorrhiza-derived compounds are therefore candidates for further investigation as adjuncts to conventional fracture care. However, current evidence does not establish that these agents reliably accelerate human femoral union, permit earlier weight-bearing or prevent muscle atrophy. Their use must not replace surgical stabilization or clinician-directed rehabilitation. Standardized formulations, robust safety and interaction studies, and adequately powered clinical trials are essential before any routine recommendation can be made.

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