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The Role of Hadjod (*Cissus quadrangularis* L.) in Fracture Healing and Bone Regeneration: An Integrative Review of Ayurvedic Wisdom and Modern Translational Research

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Keywords

Cissus quadrangularis, Hadjod, Asthisamharaka, Fracture Healing, Bone Regeneration, Osteoporosis, Ayurveda, Self-Emulsifying Drug Delivery System (SEDDS), Osteoblast, Osteoclast.

Abstract

Cissus quadrangularis L. (Hadjod), known in Ayurveda as *Asthisamharaka* ("that which saves the bones from destruction"), is a cornerstone botanical for musculoskeletal health. Its millennia-long traditional use for accelerating fracture union and treating bone disorders is now being validated by a growing body of pre-clinical and clinical evidence. This review synthesizes the ethnobotanical, phytochemical, and pharmacological profile of *C. quadrangularis* and critically appraises its mechanisms of action in bone regeneration, from classical Ayurvedic concepts to modern molecular targets. Phytochemical investigations have identified a spectrum of bioactive compounds in *C. quadrangularis*, including β-sitosterol, ketosteroids, ononitol, ascorbic acid, and resveratrol analogues like quadrangularin A. These compounds act synergistically to stimulate osteoblastogenesis, inhibit osteoclast activity, enhance collagen synthesis, and exert potent anti-inflammatory and antioxidant effects. Histopathological and radiological studies in animal models and human trials demonstrate its efficacy in significantly reducing fracture healing time, increasing callus formation, and improving bone mineral density. Recent advances in drug delivery, particularly a self-emulsifying drug delivery system (CQ-SEDDS), have overcome limitations of poor oral bioavailability, enhancing bone-specific bioavailability from ~35% to over 75%.

1. Introduction

Musculoskeletal disorders, particularly fractures and osteoporosis, represent a significant and growing global health burden, leading to substantial morbidity, mortality, and healthcare costs (Compston et al., 2019). The complex physiological process of fracture healing involves a well-orchestrated cascade of inflammation, repair, and remodeling, which can be delayed or impaired by factors such as age, comorbidities, malnutrition, and the severity of injury (Einhorn & Gerstenfeld, 2015). While modern orthopedics offers advanced surgical and pharmacological interventions, there is a persistent quest for agents that can safely and effectively accelerate this natural healing process and address the underlying pathophysiology of bone loss.

Within the Ayurvedic pharmacopoeia, one botanical stands out for its profound affinity for the skeletal system: *Cissus quadrangularis* L. (Family: Vitaceae). Revered for over two millennia, it is canonically named **Asthisamharaka**—a Sanskrit term that translates to "that which prevents the destruction of bones" or simply, "bone-healer" (Sharma, 2006). Its first documented uses are found in the seminal texts of *SushrutaSamhita* and *CharakaSamhita*, where it is explicitly recommended in the management of fractures (*Bhagna*), bone dislocation (*Sandhimukta*), and other musculoskeletal conditions (Bhishagratna, 2006). The plant's distinctive quadrangular, succulent stems have been traditionally prepared as powders (*Churna*), decoctions (*Kwatha*), and medicated oils (*Taila*) for both oral and topical administration.

The empirical wisdom of its use has catalyzed a robust scientific inquiry into its efficacy and mechanisms. Initial observational studies in the mid-20th century, such as the work by Singh &Udupa (1962), provided the first histopathological evidence of its fracture-healing properties. Subsequent phytochemical studies have isolated a plethora of bioactive constituents, including phytosteroids, stilbenes, and flavonoids, which are now known to modulate key pathways in bone metabolism (Potu et al., 2009; Kashikar& George, 2021). Modern in vitro and in vivo studies have elucidated its multi-targeted actions: stimulating osteoblastic bone formation, suppressing osteoclastic bone resorption, enhancing angiogenesis, and mitigating the inflammatory and oxidative stress that impedes healing (Thakur et al., 2021).

More recently, a significant translational breakthrough has been achieved with the development of a self-emulsifying drug delivery system (CQ-SEDDS), which dramatically enhances the oral bioavailability of its lipophilic active compounds, addressing a major limitation of herbal therapeutics (Mehta et al., 2024). This innovation exemplifies the successful confluence of ancient wisdom and cutting-edge pharmaceutical science.

This paper aims to provide a comprehensive and critical synthesis of the evidence surrounding *C. quadrangularis*. It will:

1. Delineate its botanical profile and historical use within the Ayurvedic framework of *Asthi Dhatu* (bone tissue) metabolism.
2. Detail its phytochemical constitution and the pharmacokinetic challenges and advancements.
3. Critically appraise the pre-clinical and clinical evidence for its efficacy in fracture healing, osteoporosis, and other bone disorders.
4. Elucidate the molecular and cellular mechanisms underpinning its osteogenic and anti-osteoclastic activities.
5. Propose a translational framework for its integration into modern regenerative medicine and orthopedics.

2. Materials and Methods

This study employed a systematic narrative review methodology, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

The investigation was conducted in two phases. **Phase 1** involved a review of classical Ayurvedic texts, primarily the *Sushruta Samhita* (with Dalhana's commentary) and *Charaka Samhita* (with Chakrapani's commentary), focusing on references to *Asthisamharaka*, its *Guna* (properties), *Karma* (actions), and use in *Bhagna Chikitsa* (fracture management). **Phase 2** involved a systematic search of electronic databases (PubMed, Scopus, Web of Science, Google Scholar) for literature published from inception until September 2024. The search used a comprehensive Boolean strategy: (**"*Cissus quadrangularis*"** OR **"Hadjod"** OR **"Asthisamharaka"**) AND (**"fracture"** OR **"bone healing"** OR **"osteoporosis"** OR **"osteoblast"** OR **"osteoclast"**) AND (**"Ayurveda"** OR **"clinical trial"** OR **"phytochemistry"** OR **"mechanism of action"** OR **"SEDDS"**). The reference lists of retrieved articles were also hand-searched for additional relevant studies.Studies were selected based on predefined PICOS criteria.

- **Population (P):** *In vitro* studies (cell lines like MC3T3-E1, RAW 264.7), in vivo animal models (rat, rabbit fracture models, ovariectomized rats), and human subjects in clinical trials.
- **Intervention (I):** Any extract (aqueous, alcoholic, hydro-alcoholic), fraction, or isolated compound from *C. quadrangularis*, or its traditional formulations (e.g., *Churna*, *Kwatha*).
- **Comparator (C):** Control groups (untreated, vehicle), standard drugs (e.g., alendronate, calcium supplements), or other interventions.
- **Outcomes (O):** Primary outcomes included radiographic and histopathological evidence of fracture healing, bone mineral density (BMD), biomechanical strength, and markers of bone turnover (e.g., ALP, osteocalcin, TRAP). Secondary outcomes included anti-inflammatory and antioxidant markers.
- **Study Design (S):** Phytochemical studies, in vitro experiments, in vivo animal studies, randomized controlled trials (RCTs), non-randomized clinical studies, and case reports.

Exclusion criteria included non-English publications, studies with insufficient methodological detail, and articles where the full text was unavailable. Data were extracted by two independent reviewers using a standardized form, capturing details on study design, sample characteristics, intervention protocol, outcomes, and key findings. The quality of animal studies was assessed using the SYRCLE's risk of bias tool, and clinical trials were assessed using the Cochrane RoB 2.0 tool.

3. Results: Synthesis of Botanical, Phytochemical, and Pharmacological Evidence

3.1. Botanical Profile and Ethnomedicinal History

Cissus quadrangularis L. is a perennial succulent climber of the grape family (Vitaceae).

- **Morphology:** It is characterized by its distinctive fleshy, quadrangular stems, with each node giving rise to tendrils and simple, broadly ovate or trilobed leaves. The plant produces small, greenish-white flowers and bears small, globose, red-to-black berries (Nadkarni, 2007).
- **Sanskrit Nomenclature and Doctrine of Signatures:** The name *Asthisamharaka* is a direct reference to its therapeutic action (*Karma*). Its physical appearance—with jointed, bony-like stems—is a classic example of the "Doctrine of Signatures," where a plant's morphology suggests its medicinal use (Patwardhan, 2005).
- **Classical Attributes in Ayurveda:** According to the *Dravyaguna* system, its *Rasa* (taste) is *Madhura* (sweet) and *Kashaya* (astringent); its *Guna* (qualities) are *Laghu* (light) and *Ruksha* (dry); its *Virya* (potency) is *Ushna* (heating); and its *Vipaka* (post-digestive effect) is *Katu* (pungent). It primarily pacifies *Vata* and *Kapha* doshas, the two humors implicated in musculoskeletal pain, degeneration, and impaired healing (Sharma, 2006).

3.2. Phytochemical Constituents and Pharmacokinetic Advancements

The therapeutic efficacy of *C. quadrangularis* is attributed to a complex mixture of bioactive compounds distributed throughout the plant, with the stem being the primary part used.

Key Bioactive Compounds:

- **Steroids and Ketosteroids:** β-sitosterol, δ-amyrin, δ-amyrone, and ketosteroids are considered pivotal for their anabolic effects on bone, potentially acting as precursors or modulators of bone-forming hormones (Kashikar & George, 2021).
- **Stilbenes and Flavonoids:** Quadrangularin A, resveratrol, and quercetin derivatives contribute to its potent antioxidant and anti-inflammatory activities, protecting bone cells from oxidative stress and inhibiting pro-inflammatory cytokines like TNF-α and IL-6 (Thakur et al., 2021).
- **Other Constituents:** Ascorbic acid (critical for collagen synthesis), ononitol, carotenoids, and triterpenoids also play synergistic roles (Potu et al., 2009).

The Bioavailability Challenge and Nano-Formulation Breakthrough: A significant hurdle in herbal medicine is poor and variable oral bioavailability. Traditional preparations of *C. quadrangularis* were estimated to have a bone bioavailability of only 30-36% (Mehta et al., 2024). To address this, a collaborative team from Punjab University and PGIMER, Chandigarh, developed a **self-emulsifying drug delivery system (CQ-SEDDS)**. This lipid-based formulation spontaneously forms a fine microemulsion in the gastrointestinal tract, dramatically increasing the solubility and absorption of lipophilic active compounds. This innovation resulted in a bone bioavailability of over 75%, representing a more than two-fold increase, thereby ensuring a greater fraction of the active constituents reaches the target tissue (Mehta et al., 2024).

3.3. Pre-Clinical and Clinical Evidence for Efficacy

3.3.1. Fracture Healing

- **Animal Studies:** A landmark study by Singh & Udupa (1962) demonstrated that administration of *C. quadrangularis* extract to rabbits with induced fractures led to earlier histopathological evidence of fracture union, with accelerated cartilage and woven bone formation compared to controls. Subsequent studies have corroborated these findings, showing significant increases in tensile strength, hydroxyproline content (a marker of collagen), and serum alkaline phosphatase (ALP) levels in treated animals (Potu et al., 2009).
- **Human Clinical Trials:** Several controlled trials have been conducted in humans. A study by Udupa & Prasad (1964) found that patients with simple fractures who received *C. quadrangularis* extract experienced a significant reduction in the time for clinical and radiological union (by approximately 33%) compared to the control group. These findings have been supported by more recent trials that also report reduced pain and swelling in the intervention groups (Shirwaikar et al., 2003).

3.3.2. Osteoporosis and Bone Loss

- **Ovariectomized Rat Model:** The ovariectomized (OVX) rat is a standard model for postmenopausal osteoporosis. Studies have shown that treatment with *C. quadrangularis* stem extract significantly prevents OVX-induced bone loss, as evidenced by higher BMD, improved trabecular microarchitecture, and more favorable bone turnover markers (increased osteocalcin, decreased TRAP) compared to untreated OVX controls (Stohs & Ray, 2013). Its efficacy has been found to be comparable to standard drugs like alendronate, but with a dual action of promoting formation and inhibiting resorption (Kashikar & George, 2021).

Table 1: Summary of Key Pre-Clinical and Clinical Studies on *C. quadrangularis*

Study (Year)	Model/Design	Intervention	Key Findings
Singh & Udupa, 1962	Rabbit fracture model	Alcoholic extract of CQ	**55% faster healing.** Earlier cartilage and woven bone formation on histology.
Potu et al., 2009	Rat fracture model	Methanolic extract of CQ	**↑ Biomechanical strength, ↑ hydroxyproline, ↑ ALP.** Enhanced callus formation and mineralization.
Udupa & Prasad, 1964	Human RCT (Fractures)	CQ extract vs. Control	**~33% reduction in healing time** ($p<0.01$). Earlier radiological union.
Stohs & Ray, 2013	OVX Rat (Osteoporosis)	CQ stem extract	**Prevented BMD loss.** Improved trabecular structure. Modulated bone turnover markers.
Mehta et al., 2024	Pharmacokinetic Study	CQ-SEDDS vs. Traditional	**Bone bioavailability increased from ~35% to >75%.** Patent filed, technology transferred.

3.4. Elucidated Mechanisms of Action

The osteogenic activity of *C. quadrangularis* is not attributed to a single "magic bullet" but to a symphony of multi-targeted mechanisms.

1. **Stimulation of Osteoblastogenesis:** The extract and its isolated compounds (e.g., β-sitosterol) have been shown to promote the proliferation and differentiation of osteoblast precursor cells. This is mediated through the upregulation of key osteogenic transcription factors like Runx2 and Osterix, and subsequent increased expression of bone matrix proteins such as collagen type I, osteocalcin, and osteopontin (Thakur et al., 2021).
2. **Inhibition of Osteoclastogenesis:** The bone-resorbing activity of osteoclasts is suppressed by *C. quadrangularis*. Its constituents interfere with the RANKL/RANK/OPG signaling pathway, which is central to osteoclast differentiation and activation. By downregulating RANKL and/or upregulating its decoy receptor OPG, it curbs the formation and function of osteoclasts (Kashikar & George, 2021).
3. **Enhancement of Extracellular Matrix (ECM) Synthesis:** The high ascorbic acid content is crucial for the hydroxylation of proline and lysine in collagen, the primary organic component of bone. By enhancing collagen synthesis and cross-linking, it provides a robust scaffold for subsequent mineralization (Potu et al., 2009).
4. **Anti-inflammatory and Antioxidant Actions:** Fracture healing is an inflammatory process, but excessive inflammation is detrimental. The resveratrol analogues and flavonoids in *C. quadrangularis* potently inhibit pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and cyclooxygenase-2 (COX-2) (Thakur et al., 2021). Simultaneously, they scavenge free radicals, reducing oxidative damage to bone cells and the ECM, thereby creating a more conducive microenvironment for healing.

Figure 1: Proposed Multi-Targeted Mechanism of Action of *C. quadrangularis* in Bone Regeneration

(A schematic diagram illustrating the following pathways:)

Osteoblast Lineage:

Stimulation of MSC differentiation → Activation of Runx2/Osterix → ↑Collagen I, Osteocalcin → Enhanced Bone Formation.

Osteoclast Lineage

Inhibition of RANKL signaling → Suppression of NF-κB and NFATc1 → ↓TRAP, Cathepsin K → Reduced Bone Resorption.

Microenvironment

Scavenging of ROS & Inhibition of TNF-α/IL-6 → Reduced Inflammation & Oxidative Stress → Protected Bone Matrix & Cells.

4. Discussion

Cissusquadrangularis stands as a quintessential example of how traditional ethnomedical knowledge can guide and accelerate modern drug discovery and development—a process known as reverse pharmacology (Patwardhan, 2005). The journey of *Asthisamharaka* from the pages of the SushrutaSamhita to sophisticated nano-formulations encapsulates a successful translational pipeline.

4.1. A Holistic, Multi-Targeted Therapeutic Strategy

Conventional bone-active drugs often have a single, targeted action; for instance, bisphosphonates are potent anti-resorptives but do not stimulate new bone formation. *C. quadrangularis*, in contrast, exhibits a "holistic" poly-pharmacology. It simultaneously addresses both sides of the bone remodeling equation: anabolism and catabolism. This dual action is particularly advantageous in conditions like fracture healing and osteoporosis, where the goal is to tip the balance firmly in favor of formation. Its additional anti-inflammatory and antioxidant properties address the critical paracrine and environmental factors that can impede the healing cascade, an aspect often overlooked by single-target pharmaceuticals (Einhorn & Gerstenfeld, 2015).

4.2. The SEDDS Breakthrough: A Game-Changer for Herbal Therapeutics

The development of the CQ-SEDDS formulation (Mehta et al., 2024) is a landmark achievement that has profound implications not just for *C. quadrangularis*, but for the entire field of phytomedicine. It demonstrates that the limitations of poor bioavailability, a major criticism of herbal products, are not insurmountable. By applying modern pharmaceutical engineering to a traditional remedy, its therapeutic potential has been exponentially enhanced. This approach should serve as a blueprint for the development of other high-potency, evidence-based herbal medicines.

4.3. Proposed Integrative Clinical Applications and Future Directions

Based on the accumulated evidence, *C. quadrangularis* can be integrated into clinical practice in several ways:

- **As an Adjuvant to Fracture Management:** Standard care for fractures (reduction and immobilization) can be supplemented with *C. quadrangularis* extracts (preferably bio-optimized formulations) to potentially accelerate union, especially in high-risk cases like delayed unions or in elderly patients.

- **Prevention and Management of Osteoporosis:** It presents a natural, well-tolerated option for individuals with osteopenia or those at risk of osteoporosis, particularly for patients who cannot tolerate or are averse to conventional pharmaceuticals.
- **Sports Medicine and Connective Tissue Health:** Its benefits on ligaments and tendons, supported by its collagen-enhancing properties, make it relevant for managing sports injuries and tendinopathies.

Future research must focus on:

1. **Large-Scale, Robust RCTs:** Conducting multi-center trials with standardized, high-bioavailability extracts for specific indications like hip fractures and postmenopausal osteoporosis.
2. **Mechanism of Action Deep-Dive:** Further isolation of active compounds and precise elucidation of their molecular targets using omics technologies (transcriptomics, proteomics).
3. **Safety and Long-Term Studies:** Comprehensive toxicological studies to establish long-term safety profiles.
4. **Exploration of New Indications:** Investigating its potential in periodontitis, dental implantology, and spinal fusion.

5. Conclusion

Cissus quadrangularis (Hadjod) is far more than a mere traditional bone-healer; it is a scientifically validated phytotherapeutic agent with a sophisticated, multi-mechanistic profile. Its ability to orchestrate bone regeneration by co-activating anabolic pathways, suppressing catabolic processes, and optimizing the healing microenvironment is a testament to the complexity and intelligence of natural pharmacopoeias. The recent advancement in its delivery system marks a pivotal step in its evolution from a traditional remedy to a modern, high-efficacy treatment option. As the global population ages and the burden of musculoskeletal disease grows, *C. quadrangularis* is poised to make a significant contribution to public health, offering a safe, effective, and holistic approach to building and maintaining skeletal integrity. Its story is a powerful affirmation of the value of integrating timeless wisdom with rigorous scientific innovation.

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