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Cissus quadrangularis: An Herbal Remedy Climbing Towards Health & Wellness

Review Article

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Abstract

Traditional medical systems, such as Ayurveda and Siddha, have long acknowledged the many medicinal uses of the succulent plant *Cissus quadrangularis* (CQ), which is a member of the Vitaceae family. Popularly known as "Harjor" or "Bone Setter," CQ has attracted the attention of scientists due to its powerful ability to reduce inflammation, act as an antioxidant, alleviate pain, and rebuild bone. Plants with a high concentration of bioactive components, such as flavonoids, triterpenoids, ketosteroids, and phenolic compounds, have a wide range of potential medicinal uses. It is a potential natural option for osteoporosis and bone injuries, as shown in preclinical and clinical research that it speeds up fracture healing, increases bone mineral density, and modulates osteoblastic activity. In addition to its effects on bone health, CQ shows promise in the treatment of metabolic diseases like diabetes, obesity, and hyperlipidemia by influencing insulin sensitivity, suppressing hunger, and lipid metabolism. Its multifunctional botanical properties are further supported by its gastroprotective, antibacterial, and hepatoprotective activities. Based on molecular research, CQ is thought to exert its therapeutic effects by lowering oxidative stress and inflammatory cytokines and by influencing important cellular pathways such as NF-κB, MAPK, and PPARγ. Integration into evidence-based medicine is hindered by the lack of extensive clinical validation and standardized formulations, notwithstanding the therapeutic potential. By outlining current findings and pointing out areas where more study is needed, this review offers a comprehensive overview of *Cissus quadrangularis*' phytochemistry, pharmacology, and medicinal uses. The purpose of this paper is to encourage further research into this adaptable plant and its potential use in contemporary health and wellness programs.

Keywords: *Cissus quadrangularis*, Bone regeneration, Phytochemicals, Metabolic disorders, Anti-inflammatory activity.

Introduction

Historical Significance of Herbal Remedies

Herbal therapy has constituted the cornerstone of treatment for millennia, especially within traditional systems such as Ayurveda, Traditional Chinese therapy (TCM), and African ethnomedicine. These methods use plant-based medicines to tackle a range of conditions, from infections to chronic disorders, often using a holistic approach (1, 2). The worldwide revival of interest in phytotherapeutics arises from their comparatively low toxicity, cultural acceptance, and abundance of bioactive compounds, particularly when synthetic pharmaceuticals encounter issues such as resistance and adverse effects (3).

Rationale for Focusing on *Cissus quadrangularis*

Cissus quadrangularis, a succulent vine belonging to the Vitaceae family, has attracted interest for its historical use in the treatment of bone fractures, joint discomfort, obesity, and gastrointestinal disorders. In Ayurvedic and Siddha traditions, it is often referred to as the "Bone Setter" plant. Scientific research has substantiated several traditional assertions, emphasising its osteogenic, antioxidant, anti-inflammatory, and anti-obesity characteristics (5, 6). Its varied phytochemical composition and advantageous safety margin provide it a compelling prospect for integrative therapeutic advancement.

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Scope and Structure of the Review

This study compiles the most up-to-date information on *Cissus quadrangularis's* pharmacological properties, ethnomedicinal applications, phytochemistry, and therapeutic prospects. It provides an in-depth analysis of unanswered questions, regulatory concerns, and potential medicinal and nutraceutical uses.

Botanical Description and Phytochemistry

Botanical Classification and Morphology

- **Kingdom:** Plantae
- **Order:** Vitales
- **Family:** Vitaceae
- **Genus:** *Cissus*
- **Species:** *C. quadrangularis* L.

The plant is a perennial, fleshy climber with quadrangular, winged stems and tendrils. Its leaves are ovate to cordate, and it bears small greenish flowers and berries. The plant thrives in arid and semi-arid regions and is easily propagated via stem cuttings (7).

Geographical Distribution and Habitat

Cissus quadrangularis is widely distributed across tropical and subtropical zones of Asia and Africa. It is native to India and Sri Lanka but is also found in Myanmar, Thailand, and parts of Africa (8).

Phytochemical Profile

The plant is a reservoir of biologically active compounds, including ketosteroids, flavonoids, triterpenoids, stilbenes, phytosterols, ascorbic acid, and carotenoids (9). These constituents are distributed in various parts: stem, leaves, and roots.

Table 1: Active Constituents and Their Roles (9)

Phytochemical	Reported Activity
Ketosteroids	Bone healing, anabolic effect
Quercetin	Antioxidant, anti-inflammatory
β-Sitosterol	Anti-inflammatory, cholesterol-lowering
Ascorbic acid	Antioxidant, immune support
Calcium	Bone mineralization
Carotene	Antioxidant, vision support
Triterpenoids	Anti-inflammatory, hepatoprotective
Flavonoids	Antioxidant, cardioprotective

Traditional and Ethnomedicinal Uses

Applications in Ayurveda, Siddha, and Folk Medicine

In Ayurveda, *C. quadrangularis* is used under names like "Asthisamharaka" (bone protector) for treating fractures and sprains. Siddha medicine utilizes it for hemorrhoids, bone strengthening, and metabolic disorders. Folk healers employ stem paste or decoctions for wound healing, hemorrhoids, and menstrual disorders (10,11).

Cultural Relevance and Regional Practices

The plant holds ethnobotanical significance in Indian tribal medicine, where its stem is chewed fresh or prepared into poultices. In parts of Africa, it is administered orally for gastric ulcers and topically for wounds. Its wide usage across continents signifies its cultural integration into traditional health systems (12).

Pharmacological Properties and Mechanisms of Action

Anti-inflammatory and Analgesic Activity

Cissus quadrangularis exhibits potent anti-inflammatory effects through inhibition of cyclooxygenase (COX) and lipoxygenase (LOX) pathways. Its steroidal constituents suppress pro-inflammatory cytokines such as TNF-α and IL-6, alleviating pain and swelling in models of arthritis and inflammation (13, 14).

Bone Healing and Osteoprotective Mechanisms

The plant promotes bone regeneration by enhancing osteoblast proliferation and mineral deposition. Key mechanisms include increased alkaline phosphatase (ALP) activity and collagen matrix formation. Animal models show faster fracture healing and increased callus formation (15, 16).

Antioxidant and Cytoprotective Effects

Rich in flavonoids, ascorbic acid, and carotenoids, *C. quadrangularis* effectively neutralizes reactive oxygen species (ROS). It elevates endogenous antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT), thus protecting cells from oxidative damage (17, 18).

Antimicrobial and Anthelmintic Properties

Ethanolic and aqueous extracts of the stem exhibit antibacterial activity against *E. coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. These effects are mediated by membrane disruption and enzyme inhibition in microbes (19).

Anti-obesity and Metabolic Effects

The plant reduces body weight, LDL-cholesterol, and leptin levels in obese models, potentially via appetite suppression and enhanced lipid metabolism. It has been suggested to modulate peroxisome proliferator-activated receptors (PPARs) and AMPK pathways (20, 21).

Other Therapeutic Activities

Gastroprotective: Enhances mucin secretion and reduces gastric acidity, aiding ulcer healing.

Hepatoprotective: Reduces hepatic transaminases and improves liver histology in toxin-induced damage models (22, 23).

Preclinical and Clinical Evidence

In Vitro Studies

Numerous in vitro assays show antioxidant, anti-inflammatory, and osteogenic effects. The stem extract enhances osteoblast differentiation and reduces lipid accumulation in adipocytes (24, 25).

In Vivo Animal Studies

Animal models confirm fracture healing, anti-ulcer, hepatoprotective, and hypolipidemic effects. Rat models of bone fractures treated with extracts show significantly faster union and increased bone density (15, 16)

Human Clinical Trials

Several small-scale trials in India and Africa reported improvements in fracture healing, lipid profiles, and body weight. However, most studies are limited by small sample sizes, lack of blinding, or short durations (26, 27).

Safety, Efficacy, and Dosing

C. quadrangularis is considered safe at doses up to 3 g/day in adults. Mild gastrointestinal discomfort has been reported in some cases. Long-term toxicity remains under-researched (28).

Formulations and Delivery Systems

Traditional Preparations

Used as powdered stem, decoctions, or pastes in Ayurveda and Siddha medicine, often administered with milk or ghee for enhanced absorption (27).

Modern Herbal Formulations

Available as capsules, tablets, and syrups marketed for bone health, weight management, and joint support. Standardized extracts with quantified ketosteroid content are gaining popularity (28).

Nanoformulations and Bioavailability Enhancement

Recent innovations include nanoemulsions and liposomal formulations to enhance the solubility and intestinal uptake of hydrophobic phytoconstituents. These systems show promise in improving systemic availability and targeted delivery (29, 30).

Toxicology and Safety Profile

Acute and Chronic Toxicity Studies

Cissus quadrangularis has demonstrated a high safety margin in preclinical studies. Acute oral toxicity testing in albino rats revealed no signs of mortality or behavioral toxicity at doses up to 5000 mg/kg (31). Sub-chronic administration (1000 mg/kg/day for 90 days) caused only mild hepatic changes at high doses in Wistar rats (32). Chronic exposure (up to 6 months) did not induce significant hematological or histopathological alterations (33).

Genotoxicity assays, including Ames tests and micronucleus tests, reported no mutagenic potential (34). Reproductive toxicity studies showed no teratogenic or embryotoxic effects in rodent models (35).

Herb-Drug Interactions

Studies on human liver microsomes suggest *C. quadrangularis* may inhibit CYP3A4, potentially affecting the metabolism of drugs like simvastatin and warfarin (36). Co-administration with NSAIDs like ibuprofen occasionally caused mild gastrointestinal discomfort, likely due to additive mucosal effects (37).

Regulatory Status and Quality Control

C. quadrangularis is listed in several traditional pharmacopeias and approved in India as a dietary supplement. However, standardization remains a major concern, with variability in active ketosteroid content across preparations. Quality control is typically performed via TLC, HPTLC, or HPLC methods (38, 39).

Challenges and Limitations in Research

Gaps in Mechanistic Understanding

While multiple pharmacological benefits have been documented, the precise molecular targets of *C. quadrangularis* constituents remain unclear. Most studies focus on gross outcomes rather than mechanistic pathways like receptor modulation or gene expression.

Standardization Issues

Variability in plant chemotypes, harvesting conditions, and extraction methods contribute to inconsistencies in bioactivity. Lack of standardized biomarkers for quality assurance limits reproducibility and clinical translation (40).

Clinical Trial Shortcomings

Human clinical studies are limited in number, often underpowered, and lack rigorous randomization, blinding, or placebo control. Many are conducted in regional settings without long-term follow-up or adverse event monitoring (41, 42).

Future Perspectives and Potential Applications

Role in Modern Integrative Medicine

Cissus quadrangularis is gaining recognition as a complementary remedy for bone health, obesity, and inflammatory conditions. Integration into orthopedic and metabolic care protocols is feasible, provided evidence-based dosing guidelines are developed.

Commercial and Nutraceutical Potential

The plant's use in sports nutrition, anti-obesity, and joint health supplements continues to rise. Patent activity around nanoformulations and standardized extracts has increased in the past decade (43). Market acceptance hinges on validated health claims and regulatory approval.

Research Directions and Innovations

Key future directions include:

- Pharmacokinetic profiling of active compounds
- Multi-omics approaches (transcriptomics, metabolomics) to elucidate mechanisms
- Large-scale, multicentric, randomized clinical trials
- Novel formulations (e.g., nanocarriers, bioadhesive gels)

Conclusion

Cissus quadrangularis, a climbing perennial herb deeply embedded in the pharmacopeias of Ayurveda, Siddha, and folk medicine, has emerged as a prominent candidate in the realm of evidence-based herbal therapeutics. Its historical use in fracture healing, inflammation, and gastrointestinal ailments has prompted an upsurge in scientific investigations aimed at validating and expanding its traditional applications.

The pharmacological breadth of *C. quadrangularis* is attributed to a diverse array of bioactive constituents, including ketosteroids, flavonoids (quercetin, kaempferol), triterpenoids, stilbene derivatives like resveratrol, and β-sitosterol. These compounds contribute to a wide range of therapeutic activities such as anti-inflammatory, analgesic, antioxidant, bone regenerative, hepatoprotective, antimicrobial, and anti-obesity effects. Mechanistic studies have demonstrated that these effects are mediated via multiple pathways, including COX-2 inhibition, NF-κB downregulation, and enhancement of osteoblastogenesis through upregulation of alkaline phosphatase and collagen synthesis. The herb also shows promise in modulating metabolic parameters such as lipid profiles and blood glucose levels, highlighting its potential role in metabolic syndrome management.

The safety profile of *C. quadrangularis* is generally favorable, with acute and sub-chronic toxicity studies in animal models reporting minimal adverse effects at high doses. Clinical trials, though limited in number and scale, have demonstrated efficacy in promoting bone healing, reducing weight, and alleviating joint pain with minimal side effects. However, concerns about herb-drug interactions, especially via cytochrome P450 inhibition, warrant more rigorous pharmacokinetic and toxicovigilance studies.

From a translational perspective, the herb has been incorporated into a variety of formulations, including powders, capsules, decoctions, and more recently, nanoformulations designed to improve bioavailability and target-specific delivery. These advancements open new avenues for its integration into mainstream pharmaceutical and nutraceutical sectors. However, lack of standardized extracts, poor regulation of commercial products, and inconsistencies in active constituent concentrations remain significant barriers to clinical and commercial success.

Despite its promise, several limitations persist. The majority of existing studies are preclinical, and those involving humans often suffer from methodological flaws such as small sample sizes, lack of blinding, and inadequate follow-up. Moreover, the absence of universal quality standards and authentication procedures undermines the reproducibility and scalability of research findings. There is also a paucity of mechanistic insights at the molecular and genomic levels, which could further solidify the herb's therapeutic legitimacy.

Looking forward, *Cissus quadrangularis* presents a compelling opportunity for integration into modern integrative and personalized medicine frameworks. To fully harness its therapeutic potential, future efforts should focus on conducting large-scale, randomized, placebo-controlled clinical trials with robust methodological designs. Standardization of extracts using modern analytical tools such as HPLC, LC-MS/MS, and NMR should be prioritized. Furthermore, exploration of gene-expression modulation, signal transduction pathways, and interaction with the human microbiome will provide a deeper understanding of its multifaceted pharmacology.

In conclusion, *Cissus quadrangularis* exemplifies the synergy between traditional wisdom and modern science. With continued research, quality control, and innovation, it is poised to become a cornerstone in the evolving landscape of botanical therapeutics for bone health, metabolic disorders, and beyond.

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