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Review Article

***Cissus quadrangularis*: A Review of Its Phytochemistry, Pharmacological Activities, and Clinical Applications**

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ABSTRACT

Cissus quadrangularis L., a perennial plant in the Vitaceae family, has received a lot of interest in recent years for its wide range of ethnomedicinal applications and pharmacological properties. It is commonly utilized in traditional medicinal systems including Ayurveda, Unani, and Siddha. *Cissus quadrangularis*, a succulent plant used frequently in traditional Indian medicinal systems, has been discovered to exhibit bone fracture healing, anti-osteoporotic, hepatoprotective, anti-ulcer, bowel infections, anti-hemorrhoidal, anthelmintic, antifungal and analgesic properties. Phytochemical investigations reveal the presence of a wide array of bioactive constituents, including flavonoids, triterpenoids, ketosteroids, and ascorbic acid, which contribute to its anti-inflammatory, dyspepsia, colic, flatulence, skin diseases and antimicrobial activities. Recent studies indicate that *Cissus quadrangularis* offers metabolic advantages, including anti-obesity and antidiabetic effects, making it useful in the management of lifestyle-associated disorders. Additionally, both in vitro and in vivo findings demonstrate its ability to promote tissue regeneration and safeguard cells from oxidative stress-related damage, further emphasizing its therapeutic potential. This review explores the botanical, chemical, and pharmacological properties of *Cissus quadrangularis* Linn, highlighting its traditional and modern therapeutic use. Evidence suggests that it is a valuable medicinal plant with potential applications for medical treatment and drug research.

INTRODUCTION

Medicinal plants play a crucial role in maintaining human health and form the backbone of traditional and indigenous healthcare systems across India,

particularly among tribal and rural communities. For centuries, these plants have been valued not only for their therapeutic benefits but also for their spiritual and cultural significance in various traditional healing practices.^[1] Among the

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numerous medicinal plants, *Cissus quadrangularis* Linn. (CQ) has gained significant attention due to its remarkable medicinal, nutritional, and pharmacological properties. Botanically, *Cissus quadrangularis* L. is a hardy, perennial succulent vine belonging to the Vitaceae (grape) family. It is also known by the synonym *Vitis quadrangularis* Wall. The plant is widely distributed across the warmer regions of India, thriving particularly in dry plains, hedges, and rocky habitats. Globally, it is also found in Sri Lanka, Southeast Asia, Africa, and certain parts of Arabia, indicating its wide adaptability and ethnobotanical relevance.^[2] *Cissus quadrangularis* has been extensively used in folk medicine and Ayurvedic formulations for its wide range of pharmacological activities. Traditionally, it is recognized for its bone-healing properties, which have earned it the common name “bone setter.” Apart from its role in fracture healing, it has also been employed in the management of osteoporosis, obesity, gastrointestinal disorders, diabetes, hemorrhoids, asthma, skin diseases, and inflammatory conditions.^[3] Due to its traditional importance, bioactive constituents, and wide pharmacological spectrum, *Cissus quadrangularis* holds substantial promise for drug discovery, functional food applications, and modern therapeutic strategies. Accordingly, this review provides a comprehensive overview of its botanical aspects, chemical constituents, ethnomedicinal uses, pharmacological potential, and highlighting its growing significance in integrative healthcare.

VERNACULAR NAMES^[4]

- **Language:** synonym
- Tamil: perandai
- Telugu: Nalleru
- Malayalam: chagalamparanda
- English: Edible Stemmed Vine

- Hindi: Hadjod
- Sanskrit: Vajravalli, Asthisamharaka
- Marathi: Kandvel
- Punjabi: Haddjor
- Gujrati: Vedhari
- Oria: Hadbhanga

TAXONOMICAL CLASSIFICATION^[5]

- Kingdom: Plantae
- Subkingdom: Tracheobionta
- Division: Magnoliophyta
- Superdivision: Spermatophyta
- Class: Magnoliopsida
- Subclass: Rosidae
- Order: Vitales
- Family: Vitaceae
- Genus: Cissus
- Species: quadrangularis

PLANT DESCRIPTION

Habitat

Cissus quadrangularis is widely distributed across tropical and subtropical regions characterized by dry climates and is commonly observed in coastal as well as lowland habitats. Tropical *Cissus* species have tendril-bearing climbing plants that usually have square, jointed stems along with tuberous roots.^[6]

Morphological description

Stem - The stems are four-angled and jointed at the nodes, with internodes measuring 8 to 10 cm in length and 1.2 to 1.5 cm in width. In its early stage, the stem develops sharply angled or wing-like branches with long tendrils and simple structures, but as it matures, it becomes nearly leafless.

Leaves - The leaves are simple, with an ovate or reniform lamina, approximately 5 cm wide, and



have a crenate to serrate margin. The stipules are ovate or wedge-shaped, blunt at the tip, and fall off early.

Flowers - The stem bears flowers about 2 mm in size, exhibiting pink to white colour. The flower's hypanthium is green, cup-shaped, about 2 mm wide, and either flat-tipped or faintly lobed. The flower has a disc-like shape and extends beyond the ovary. The ovary itself is smooth, featuring a thin style and a small stigma.

Fruit - The plant produces globose, red, succulent berries that are highly acidic, measuring 6-10 mm in diameter and containing a single seed.^[7]

Microscopy

The stem possesses a four-angled structure with thick, radiating arms, which give the internodes a ridged and grooved appearance. The central axis measures approximately 2 to 3 mm in thickness, while the wings are about 3 mm long and 1 mm thick, and the tapering ends have a thickness of around 500 µm. The stem is covered by an epidermal layer composed of small, nearly square, thick-walled cells with a distinct cuticle. The ground tissue is made up of large, circular, tightly packed, thin-walled parenchyma cells.^[8]

The stem powder of *Cissus quadrangularis* exhibited various forms of calcium oxalate crystals, including raphides, acicular, and sand crystals. Additionally, the presence of phloem with companion cells, xylem vessels, fibersclereids, rays containing pits, macrosclereids, stephanocytic stomata, and epidermal cells was observed.^[9]

The transverse section (T.S.) of the leaf at the midrib shows a convex adaxial surface measuring about 660 µm in width and a short, conical abaxial surface approximately 400 µm wide. The midrib is

covered by a thin epidermal layer composed of small, thick-walled, squarish cells.^[10]

THERAPEUTIC USES

The stem exhibits various medicinal properties, including laxative, digestive, loss of appetite, stomachic, analgesic, tonic, anthelmintic and aphrodisiac effects, making it useful in treating piles, vision impairments, tumors, vata and kapha disorders, epileptic episodes, muscle pain, chronic ulcers, and bone fractures. In the Unani system of medicine, the stalk of this plant is also prescribed for the treatment of bone fractures, with its use suggested through both internal consumption and external application.^[11] The juice extracted from the stem is utilized in the management of scurvy, weakening menstrual disorders, ear discharge (otorrhoea), and nasal bleeding (epistaxis). The herb is given to cattle to enhance and promote milk production.^{[12][13]}

Plant part	Uses
Aerial parts	Tetanus, Coagulant Ach like activity
Stem	Hemorrhoids, Gastritis, Constipation, Burns, Menstrual disorders, Eye problems, Asthma
Shoot	Anthelmintic
Root	Broken bones Spine and back complaints
Shoots and leaves	Bowel infections
Whole herb	Malaria, Fever, Weight loss, Metabolic syndrome, Piles, Gout, Syphilis, Venereal diseases

CLASSICAL

AYURVEDIC

FORMULATIONS^[14]

- **Asthisamharaka Swarasa** - Fresh stem juice used as nasal drops (*Nasya*) for treating epistaxis. When combined with *Vidanga churna*, it is administered orally for worm infestations.

Indication: Epistaxis and intestinal worm infections.



- **Asthisamharaka Lepa** - A paste made from crushed leaves, applied externally on wounds to control bleeding.
Indication: Useful for fresh cuts and bleeding wounds, especially those associated with bone fractures.
- **Asthisamharaka Churna** - A powdered formulation containing *Asthisrinkhala*, *Arjuna*, *Godhuma*, and *Laksha*, mixed with ghee and consumed with milk.
Indication: Recommended in the management of bone fractures (*Asthibhanga chikitsa*).
- **Asthisamharaka Taila** - Medicated oil prepared using the whole plant for local application.
Indication: Traditionally used in rheumatoid arthritis and osteoarthritis.
- **Lakshaguggulu** - A classical preparation consisting of *Laksha*, *Asthisamhara*, *Kakubha*, *Ashwagandha*, and *Nagabala* in equal parts, combined with *Guggulu* (5 parts) and prepared into tablets.
Indication: Beneficial in bone and joint disorders.
- **Asthisrinkhala Vataka** - A polyherbal formulation prepared with equal parts of *Asthisrinkhala* and black gram flour.
Indication: Traditionally prescribed for the management of joint-related disorders.

PHYTOCHEMISTRY

Phytochemical investigations of *Cissus quadrangularis* have revealed the presence of diverse bioactive constituents such as flavonoids, triterpenoids, vitamin C, stilbene derivatives, and various other secondary metabolites. The plant is particularly rich in ascorbic acid, triterpenes, β -sitosterol, ketosteroids, calcium, and triterpenoids. Moreover, two steroidal molecules, namely onocer-7-ene-3 α ,21 β -diol and onocer-7-ene-

3 β ,21 α -diol, have been documented from the stem.^[15]

Furthermore, seven novel compounds have been isolated and characterized from the plant, namely 4-hydroxy-2-methyl-tricos-2-en-22-one, 9-methyl-octadec-9-ene, heptadecyl octadecanoate, icosanyl icosanoate, 31-methyl-tritriacontan-1-ol, 7-hydroxy-20-oxo-docosanyl cyclohexane, and 31-methyltritriacontanoic acid. In addition, other phytochemicals, such as taraxeryl acetate, friedelan-3-one, taraxerol, and isopentacosanoic acid, have also been reported from the plant.^[16]

The stem extract of *C. quadrangularis* is particularly abundant in calcium ions and phosphorus. Flavonoids, including quercetin, kaempferol 3-O-rhamnoside, quercetin 3-O-rhamnoside (quercitrin), and vitexin, have been identified and characterized from the leaves using LC/MS/MS analysis.^[17] Moreover, the methanolic stem extract contains significant amounts of carbohydrates, phenols, alkaloids, glycosides, proteins, saponins, tannins, and terpenoids, confirming its rich phytochemical composition.^[18]

Lupeol was confirmed in the *C. quadrangularis* stem extract obtained with methanol using UV, IR, NMR, and mass spectrometry analyses.^[19] Additionally, two iridoid glycosides, 6-O-[2,3-dimethoxy]-trans-cinnamoyl catalpol and 6-O-meta-methoxy-benzoyl catalpol were isolated from the ethanolic stem extract of *Cissus quadrangularis*.^[20]

Distribution of Phytochemicals in Various Plant Parts of *Cissus quadrangularis* L.^[21]

Part	Chemical Constituents
Stem	Vitamin C, β -sitosterol, β Carotene, δ -amyrin, Cardiac glycosides, Saponins, Eugenol, Cissusic acid, Cissuside, Kaempferol, 24-methyl-dammara- 20,25-diene-3 β -yl- acetate, Taraxerol acetate,



	Taraxerol, 31 methyl tritriacotannoic acid, Isopentadecanoic acid,
Leaves	Quinine, Piceatannol, Resveratrol, Pallidol, Tetratriacotanol, Eicosyl Eicosanoate
Aerial parts	Friedelan-3-one, Iso-pentacosanoic acid, Heptadecyl- octadecanoate, Onocer - 7 ene 3 α , 21 β diol, 9-methyloctadec-9-ene, 7- hydroxy- 20- oxo- docosanyl cyclohexane,
Whole herb	Quercitrin, Quercetin, Caffeine, Quadrangularin A and B, Picroside 1, 6-O-meta-methoxy- benzoyl catalpol

PHARMACOKINETICS AND BIOAVAILABILITY OF *CISSUS QUADRANGULARIS*

Pharmacokinetic studies on *Cissus quadrangularis* have largely concentrated on its key polyphenols, quercetin and trans-resveratrol, employing a validated LC–MS/MS technique for precise measurement in rat serum. After oral administration, both compounds exhibited rapid absorption, and parameters such as C_{max}, T_{max}, half-life, and AUC were assessed to define their systemic exposure. In vitro assays demonstrated their stability in simulated gastric and intestinal environments, whereas liver microsome experiments revealed significant phase II metabolism, particularly via glucuronidation and sulfation, which limited their oral bioavailability. Tissue distribution was found to be extensive, especially in the liver and kidneys, while excretion studies highlighted renal elimination of metabolites as the primary pathway. To address these pharmacokinetic constraints, advanced delivery systems like phytosome formulations have been developed, showing enhanced absorption and improved therapeutic activity.^[22]

PHARMACOLOGICAL USES:

ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY

The ethyl acetate extract of *Cissus quadrangularis* demonstrated potent anti-inflammatory effects by inhibiting LPS-induced nitric oxide production and iNOS expression in macrophages. These effects were associated with the induction of heme oxygenase-1 (HO-1), suppression of NF- κ B activation, and subsequent downregulation of proinflammatory mediators. The results suggest that extract contains bioactive compounds with therapeutic potential for managing inflammatory diseases.^[23]

Cissus quadrangularis possesses significant analgesic, anti-inflammatory, and venotonic activities, which support its traditional use in the management of hemorrhoids. The methanolic extract demonstrated dual inhibition of arachidonic acid metabolism, acting on both cyclooxygenase and lipoxygenase pathways. Experimental models further confirmed that the extract not only reduced pain and inflammation but also enhanced venotonic activity, comparable to standard bioflavonoid formulations used clinically.^[24]

ANTI-ARTHRITIC ACTIVITY

Stem extracts of *Cissus quadrangularis* have demonstrated remarkable in vitro anti-arthritis activity, primarily through the inhibition of protein and albumin denaturation, with the methanolic extract showing greater efficacy than the aqueous extract, suggesting the role of solvent-specific phytoconstituents in enhancing activity. This effect is attributed to the presence of bioactive compounds such as phenolic acids, flavonoids (e.g., luteolin), β -sitosterol, triterpenoids, and alkaloids, which collectively contribute to its traditional use in arthritis management and highlight the need for further phytochemical investigations to isolate and characterize the active principles.^[25]



Similarly, ethanolic and aqueous stem extracts have been evaluated for anti-gouty arthritic potential through inhibition of xanthine oxidase, protein denaturation, proteinase activity, and membrane stabilization, with the ethanolic fraction demonstrating superior efficacy comparable to standard drugs. Complementary GC-MS and molecular docking studies identified three major phytoconstituents with strong antagonistic interactions with TLR2 and TLR4 receptors, effectively suppressing monosodium urate (MSU)-induced inflammatory signaling.^[26]

Moreover, *C. quadrangularis* extract enriched with quercetin and isorhamnetin significantly attenuated osteoarthritic changes in MIA-induced rats by reducing knee joint damage, preventing subchondral bone erosion, and enhancing bone volume and trabecular structure. It further preserved cartilage integrity by maintaining proteoglycan content and key structural proteins such as COL2A1 and aggrecan, while downregulating inflammatory mediators (iNOS, COX-2, 5-LOX), pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α), and matrix metalloproteinases (MMP-2, MMP-3, MMP-9, MMP-13), thereby confirming its potent anti-inflammatory and chondroprotective properties.^[27]

ANTI-OSTEOPOROTIC ACTIVITY

Cissus quadrangularis extract has demonstrated significant anti-osteoporotic effects in ovariectomy-induced models by improving bone strength, bone mineral density, and biochemical markers of bone formation while reducing bone resorption. Histopathological analysis confirmed restoration of normal bone architecture and prevention of trabecular bone loss. The phytoestrogen-rich fraction further enhanced serum calcium, vitamin D₃, and estrogen levels, contributing to improved bone mineral content and density.^[28]

The petroleum ether extract of *Cissus quadrangularis* (500 mg/kg/day, 90 days) significantly improved femoral strength, cortical and trabecular thickness in ovariectomized rats, with effects comparable to raloxifene. Histology confirmed restoration of trabecular architecture, indicating enhanced mineralization and bone protection. These findings validate its traditional osteoprotective use and support its potential as a natural therapy for osteoporosis.^[29]

HEPATOPROTECTIVE ACTIVITY

Studies have highlighted the hepatoprotective efficacy of *Cissus quadrangularis* in different models of liver injury. The ethanolic extract of *C. quadrangularis* fruits showed significant protection against alcohol-induced hepatotoxicity in rats, as evidenced by reduced liver weight and volume, normalization of elevated serum markers (SGOT, SGPT, ALP, and bilirubin), and an increase in serum albumin levels. Furthermore, antioxidant defense was improved through decreased lipid peroxidation and enhanced activities of glutathione and catalase.^[30]

Similarly, another study evaluated the methanolic extract of *C. quadrangularis* stems against isoniazid-induced hepatic damage in rats. The treatment markedly lowered liver enzyme levels and oxidative stress markers while restoring antioxidant enzymes such as glutathione, superoxide dismutase, and catalase. Histopathological analysis supported these biochemical findings by revealing reduced necrosis, inflammation, and tissue injury in treated groups.^[31] Together, these findings suggest that *C. quadrangularis* exhibits strong hepatoprotective effects, largely mediated through its antioxidant potential.

ANTIANTHELMINTIC ACTIVITY



The *in vitro* evaluation of *Cissus quadrangularis* aerial parts and *Schinus molle* leaves demonstrated promising anthelmintic activity against *Haemonchus contortus*. Crude methanolic extracts of both plants exhibited marked, dose-dependent effects by reducing adult worm motility and inhibiting egg hatching. At the maximum tested concentration (10 mg/mL), *C. quadrangularis* achieved complete (100%) worm mortality, while *S. molle* produced 95% mortality. Similarly, egg hatch inhibition was significant, with *C. quadrangularis* and *S. molle* showing 88% and 96% inhibition, respectively, at 1 mg/mL. These results indicate that *Cissus quadrangularis* possesses strong anthelmintic potential, with efficacy comparable to that of albendazole, the standard reference drug.^[32]

ANTIMICROBIAL ACTIVITY

The ethanol extract of *Cissus quadrangularis* stem demonstrated notable antimicrobial potential against human pathogens. In agar well diffusion assays, the extract produced inhibition zones measuring 13 mm against *Staphylococcus aureus* and 15 mm against *Escherichia coli*, indicating strong antimicrobial activity. These results suggest that *Cissus quadrangularis* possesses significant antimicrobial properties and may serve as a promising natural alternative for managing microbial infections.^[33]

Recent studies have revealed that *Cissus quadrangularis* extracts exhibit significant antibacterial activity against *Porphyromonas gingivalis*, a key pathogen in periodontal disease. Both aqueous and ethanolic extracts obtained through Soxhlet extraction were evaluated, with the ethanolic extract displaying stronger antibacterial effects. It produced greater growth inhibition and demonstrated lower IC₅₀ values compared to the aqueous extract, highlighting its enhanced potency. These findings indicate that

Cissus quadrangularis holds potential as a natural therapeutic option for periodontal infections, either as an alternative or as a supplement to conventional antimicrobial agents.^[34]

GASTRO PROTECTIVE ACTIVITY

The protective role of *Cissus quadrangularis* against gastric ulceration is strongly linked to its ability to counteract oxidative stress, which is a major factor in NSAID-induced mucosal injury. By suppressing neutrophil infiltration and reducing lipid peroxidation, the extract limits tissue damage and promotes faster ulcer healing. Its phytochemical profile, rich in triterpenoids, ketosteroids, β -carotene, and vitamin C, contributes to both cytoprotective and antioxidative mechanisms.^[35]

ANTI DIABETIC ACTIVITY

The research showed that the ethyl acetate fraction of *Cissus quadrangularis* stem (CQSF) exerts significant antidiabetic activity in streptozotocin /nicotinamide-induced type 2 diabetic rats by effectively reducing blood sugar levels, decreasing oxidative stress, and mitigating inflammation. Treatment with CQSF boosted antioxidant enzyme functions, lowered pro-inflammatory markers such as TNF- α and IL-6, and restored the normal structure of liver and pancreatic tissues. These therapeutic benefits, linked to phenolic constituents like quercetin, were comparable to those of metformin. By strengthening antioxidant defenses and suppressing inflammatory pathways, CQSF not only aids in controlling hyperglycemia but may also slow down the onset of diabetes-related complications, highlighting its potential as a safe natural remedy that could be developed into a functional food ingredient or pharmaceutical option for diabetes management.^[36]



The ethanolic leaf extract of *Cissus quadrangularis* shows notable anti-hyperglycaemic effects in alloxan-induced diabetic rats, as demonstrated in both short-term and long-term studies. At a higher dose of 400 mg/kg, it significantly lowers blood glucose levels and helps prevent diabetes-related weight loss, indicating a protective role. The extract improves glucose metabolism, evidenced by results from oral glucose tolerance tests in diabetic and healthy rats. Phytochemical screening identified several bioactive constituents, including flavonoids, alkaloids, tannins, sterols, carbohydrates, and glycosides, which are likely responsible for its antidiabetic properties. These findings validate the traditional medicinal use of *Cissus quadrangularis* and suggest its potential for development into new herbal treatments for diabetes.^[37]

ESTROGENIC ACTIVITY

The friedelin-rich fraction (IND-HE) derived from *Cissus quadrangularis* demonstrated significant estrogenic activity when tested in ovariectomized female rats. Administration of IND-HE enhanced sexual behavior by improving parameters such as darting, hopping, and lordosis response, while also promoting uterine growth, elevating serum estrogen levels, and inducing vaginal cornification. These outcomes collectively confirm its estrogenic potential and indicate that IND-HE could be explored as a safe, natural alternative to conventional hormone replacement therapy for managing postmenopausal symptoms.^[38]

MELANIN PROMOTION ACTIVITY

The methanolic stem extract of *Cissus quadrangularis* revealed lupeol, friedelin, and β -sitosterol as principal bioactive compounds. Among them, lupeol showed the highest melanin-enhancing activity in B16F10 melanoma cell lines,

demonstrating nearly fivefold greater effectiveness than the standard control 3-isobutyl-1-methylxanthine. This pronounced activity highlights its strong potential in stimulating melanogenesis. Overall, the results indicate that *Cissus quadrangularis*, particularly lupeol, could be explored as a promising natural resource for developing skin pigmentation therapies and related cosmetic applications.^[39]

NEUROPHARMACOLOGICAL ACTIVITY

The methanolic root extract of *Cissus quadrangularis* (CQ) demonstrated marked neuropharmacological activity in mice. It significantly inhibited acetic acid-induced writhing and enhanced tail flick response, indicating both peripheral and central analgesic effects. Additionally, the extract reduced spontaneous motor activity, exploratory behavior, and motor coordination, while also extending pentobarbitone-induced sleep duration. These results suggest that CQ exhibits central nervous system depressant and sedative actions, which may be attributed to the presence of triterpenoids, flavonols, saponins, and alkaloids.^[40]

This research provides a comprehensive evaluation of *Cissus quadrangularis* root's aqueous extract, revealing substantial antiseizure, pain-relieving, and muscle-relaxing properties through animal studies. The extract exhibited concentration-dependent seizure protection and analgesic effects that matched established pharmaceutical standards, along with significant muscle relaxation capabilities in experimental mice. These results provide scientific support for the historical therapeutic applications of this plant in traditional Ayurvedic and African medicine systems for treating neurological disorders and pain management. The study underscores the promising medicinal value of *Cissus quadrangularis* root extract for treating central



nervous system ailments and supports the need for continued research into its active compounds and mechanisms.^[41]

BONE REGENERATION ACTIVITY

The study demonstrated that scaffolds incorporating *Cissus quadrangularis* extract, bioceramics, and tendon extracellular matrix were well-tolerated in zebrafish embryos, confirming their biosafety. Although higher concentrations led to a slight reduction in survival and hatching rates, no skeletal abnormalities such as lordosis were detected. Importantly, gene expression analysis showed significant upregulation of osteogenic markers like Runx2 and BMP2, indicating strong bone-regenerative potential. Complementary structural assessments using Scanning Electron Microscopy, X-ray Diffraction and Fourier Transform Infrared Spectroscopy further verified the scaffold's stability, bioactivity, and successful material integration. Collectively, these findings suggest that the developed scaffolds are safe and effective candidates for periodontal bone regeneration with minimal embryotoxic concerns.^[42]

FETAL BONE DEVELOPMENT

Administration of petroleum ether extract of *Cissus quadrangularis* to pregnant rats markedly improved ossification of fetal long bones during intrauterine growth. The treatment enhanced bone length and mineralization without producing toxic effects. These outcomes are attributed to phytoestrogenic constituents that act in an estrogen-like manner, stimulating chondrocyte activity. Collectively, the study suggests that *Cissus quadrangularis* could support fetal skeletal development and help prevent bone growth abnormalities during gestation.^[43]

ANTI CANCER ACTIVITY

The ethanolic extract of *Cissus quadrangularis* demonstrated notable anticancer potential against MCF-7 breast cancer cells, as evidenced by MTT assay results. The extract effectively reduced cell proliferation in a concentration-dependent manner, exhibiting an IC₅₀ value of 40 µg/ml. Within 24 hours of exposure, the plant-derived compounds significantly suppressed cancer cell growth, indicating their potent cytotoxic action. Collectively, these observations highlight *Cissus quadrangularis* as a promising natural candidate for the development of anticancer therapeutics.^[44]

ANTIOXIDANT POTENTIAL

Cissus quadrangularis exhibits remarkable antioxidant activity, with methanol, acetone, and dichloromethane extracts showing the greatest effectiveness. Its radical scavenging ability, validated through DPPH, hydroxyl radical, and ferric reducing assays, highlights its potential to counter oxidative stress. These properties indicate its protective role against cellular damage associated with aging and chronic disorders. The presence of bioactive phytochemicals, particularly phenolics and flavonoids, contributes significantly to this activity. However, further investigations are essential to isolate individual compounds and assess their therapeutic applications as natural antioxidant agents.^[45]

NOVEL WOUND HEALING APPLICATIONS

This research focuses on the design of chitosan-based bilayer wound dressings reinforced with Polyhedral Oligomeric Silsesquioxane and enriched with *Cissus quadrangularis* extract to improve wound healing outcomes. The developed biomaterials exhibited favorable structural and mechanical characteristics, controlled release behavior, and notable antibacterial activity against both Gram-positive and Gram-negative strains.



Laboratory evaluations further demonstrated their effectiveness in stimulating fibroblast growth, collagen synthesis, and wound closure, thereby closely resembling natural skin repair mechanisms. Collectively, these findings suggest that CQ-incorporated CHI-POSS nanocomposites represent a promising candidate for advanced wound dressing applications.^[46]

ADVANCES IN PERI-IMPLANT THERAPY

The implantoplasty varnish developed using *Cissus quadrangularis* and *Vitex negundo* mediated titanium dioxide nanoparticles exhibited strong antimicrobial, anti-inflammatory, and antioxidant properties while maintaining good biocompatibility. It was shown to effectively inhibit harmful microorganisms such as *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus mutans*, and *Candida albicans*, with only mild toxicity in zebrafish embryonic studies. These results indicate that the varnish could play a valuable role in managing peri-implant infections, minimizing tissue inflammation, and supporting faster healing following implantoplasty. Overall, this eco-friendly and affordable innovation holds significant potential as an adjunctive approach in implant dentistry to promote peri-implant health.^[47]

TOXICOLOGY

Toxicological investigations of *Cissus quadrangularis* extract indicate a favorable safety profile, showing no signs of mortality, behavioral changes, or organ toxicity at doses up to 2500 mg/kg/day. Observed hematological and biochemical alterations were minor, not dose-related, and stayed within normal physiological limits. Genotoxicity evaluations, including ames test, chromosomal aberration, and micronucleus assays, revealed no mutagenic effects. The extract's no-observed-adverse-effect level

(NOAEL) was identified as 2500 mg/kg/day, the maximum dose tested.^[48]

Acute toxicity evaluation of *Cissus quadrangularis* indicated no mortality or behavioral abnormalities even at 2000 mg/kg, highlighting its wide safety margin. Sub-acute administration (200–400 mg/kg for 28 days) produced no significant adverse effects, while the methanolic extract significantly increased hemoglobin and packed cell volume, suggesting a role in stimulating hematopoiesis. Slight body weight reduction was seen only at higher doses, and the chloroform extract produced minimal, non-significant hematological variations.^[49]

CLINICAL EVIDENCE

A randomized, double-blind, placebo-controlled trial evaluated the efficacy of a *Cissus quadrangularis* formulation in overweight and obese individuals. The intervention resulted in significant improvements, including reductions in body weight, abdominal circumference, lipid abnormalities, fasting glucose, and inflammatory markers. These findings indicate that *Cissus quadrangularis* may represent a valuable natural option for managing obesity and metabolic syndrome.^[50]

In a clinical study on 67 overweight and obese individuals, daily supplementation with 300 mg of CQR-300, a standardized extract of *Cissus quadrangularis*, for 8 weeks produced clear benefits. Compared to placebo, the treatment group showed reductions in weight, body fat, and waist-to-hip ratio, along with improvements in glucose, lipid levels, and blood pressure. Positive effects on leptin and adiponectin highlighted its potential as a natural aid for obesity and metabolic syndrome.^[51]



A clinical trial with 60 postmenopausal women evaluated the impact of *Cissus quadrangularis* supplementation for 24 weeks. While no significant improvement in bone mineral density (BMD) was observed compared to placebo, the extract was found to slow bone remodeling, as reflected by reduced bone turnover markers (BTMs). These results indicate that *Cissus quadrangularis* may play a role in delaying bone loss, though further long-term studies are necessary to validate its clinical effectiveness.^[52]

CONCLUSION

Cissus quadrangularis L., a medicinally important member of the Vitaceae family, is recognized for its broad ethnomedicinal and pharmacological relevance. The plant contains a wide spectrum of phytochemicals, including flavonoids, triterpenoids, ketosteroids, and vitamin C, which are responsible for its therapeutic benefits. Research evidence highlights its efficacy in bone repair, osteoporosis management, anti-inflammatory action, liver protection, antioxidant defense, ulcer healing, antimicrobial, antidiabetic, and anticancer effects, thereby supporting its traditional use in Ayurveda, Siddha, and Unani systems. Recent advances also demonstrate its utility in wound dressings, peri-implant formulations, and bone regeneration therapies. Despite these promising outcomes, further clinical validation, standardized formulations, and identification of key bioactive compounds are required to ensure safety and therapeutic reliability. Thus, *Cissus quadrangularis* represents a valuable natural candidate for developing novel drugs and modern healthcare applications.

CONFLICT OF INTEREST: The authors declare that they have no commercial, financial, or personal relationships that could be construed as a potential conflict of interest in relation to this review article.

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