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Comprehensive Review on *Cissus quadrangularis* L. (*Hadjod*): Chemical Constituents, Pharmacological Activities, and Safety Aspects

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Abstract

This review critically integrates ethnopharmacological knowledge with contemporary scientific evidence to comprehensively evaluate the therapeutic potential and translational relevance of *Cissus quadrangularis* L. (*Vitaceae*), a prominent medicinal plant in traditional systems such as *Ayurveda* used for fracture healing, inflammation, metabolic disorders, and reproductive health. A systematic literature survey was conducted using major scientific databases, and retrieved studies were analysed with a focus on traditional uses, phytochemical composition, pharmacological activities, toxicological profiles, and recent phytopharmaceutical and formulation developments. The findings indicate that *C. quadrangularis* is rich in diverse bioactive constituents, including flavonoids, stilbenes, triterpenoids, phytosterols, and phenolic compounds, which underpin its reported osteogenic, anti-inflammatory, antioxidant, antidiabetic, anti-obesity, antimicrobial, and anticancer activities. Although experimental evidence largely supports its traditional applications, mechanistic understanding remains incomplete, and available clinical studies are limited in number, small in scale, and heterogeneous in design. Moreover, challenges such as phytochemical variability, lack of standardised extracts, poor bioavailability, and insufficient pharmacokinetic data hinder clinical translation. This review provides the first integrated synthesis linking the chemical diversity of *C. quadrangularis* with its biological mechanisms and therapeutic pathways, and concludes that while existing evidence supports its ethnopharmacological significance, future progress requires well-designed mechanistic studies, development of standardised and bioavailable formulations, and rigorously conducted clinical trials to establish *C. quadrangularis* as a robust evidence-based phytomedicine.

Major Findings: This review highlights that *C. quadrangularis* possesses diverse bioactive phytochemicals, including flavonoids, stilbenes, triterpenoids, and phytosterols, which contribute to its broad pharmacological activities such as bone regeneration, antidiabetic, antioxidant, anti-inflammatory, and anticancer effects. Despite strong preclinical evidence supporting its traditional therapeutic uses, limited standardised formulations and insufficient large-scale clinical studies currently restrict its full clinical translation.

Keywords: Bone Regeneration, *Cissus quadrangularis* L., Clinical Translation, Ethnomedicine, Pharmacology, Phytochemical Diversity

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1. Introduction

Natural substances have served as a primary source of therapeutic agents, either directly or indirectly, for several decades and continue to play a pivotal role in improving human health. Consequently, natural products are being extensively investigated worldwide for their diverse biological activities. Although a vast array of plant-derived compounds is readily available, concerted scientific efforts have been directed toward

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the systematic isolation, identification, and evaluation of bioactive molecular leads with enhanced therapeutic efficacy and minimal toxicity[1]. In this context, plant-derived natural products have consistently provided valuable scaffolds for modern drug discovery and development[2].

A fundamental step in drug research involves documenting and validating materials traditionally used in disease management. However, much of the ethnomedicinal knowledge related to medicinal plants is transmitted orally, raising concerns regarding its gradual erosion and loss[3,4]. Therefore, there is an urgent need to conserve, systematically document, and scientifically validate traditional medicinal knowledge through well-designed experimental and clinical studies. Such efforts not only preserve indigenous wisdom but also provide future researchers with evidence-based guidance on the safety, efficacy, and therapeutic applicability of medicinal plants[5].

The genus *Cissus*, belonging to the family Vitaceae, comprises approximately 800 species distributed across 13 genera worldwide, predominantly in Africa, Arabia, South Asia, Sri Lanka, India, and other tropical regions. Of these, eight genera and nearly 63 species are reported from India[6]. Among them, *C. quadrangularis* L. (CQ), commonly known as *Hadjod* in India, Phet Sang Khat in Thailand, and Veldt grape, has gained significant attention for its medicinal value. In Ayurvedic medicine, CQ has been traditionally employed for promoting bone healing and fracture repair[7].

Ethnomedicinal records indicate the extensive use of *C. quadrangularis* in the management of bone fractures, scurvy, tumours, haemorrhoids, peptic ulcers[8], menstrual disorders[9], gout, syphilis, venereal diseases, piles, diarrhoea, and dysentery, as well as its application as an aphrodisiac[10]. Pharmacological investigations further support these traditional claims, demonstrating a broad spectrum of biological activities, including antidiabetic, anti-obesity, antiulcer, antioxidant, anticancer, anti-glucocorticoid, antimicrobial, and anti-inflammatory effects. Additionally, CQ is widely recognised for its role in fracture healing and female reproductive health, particularly in the regulation of menstruation[11]. These therapeutic effects are largely attributed to the presence of diverse primary and secondary phytochemical constituents.

Cissus quadrangularis is also recognised for its notable nutritional value and exceptional osteogenic potential, leading to its description as a "biological matrix of excellence"[12]. In recent years, several phyto-based formulations incorporating CQ have been developed, including polyherbal capsules, nanoparticles, and hydrogel-based delivery systems, highlighting its translational potential in modern phytopharmaceutical research.

In this context, the present review comprehensively summarises recent advancements related to the traditional therapeutic uses, phytochemical composition, pharmacological properties, toxicological profile, and phytopharmaceutical formulations of *C. quadrangularis*, thereby providing a consolidated scientific framework to support its future therapeutic and clinical applications.

2. Botanical Description and Taxonomy

2.1 Taxonomic Classification and Botanical Identity

Cissus quadrangularis L. is taxonomically classified under the Subkingdom: *Tracheobionta*; Superdivision: *Spermatophyta*; Division: *Magnoliophyta*; Class: *Magnoliopsida*; Subclass: *Rosidae*; Order: *Vitales*; Family: *Vitaceae*; Genus: *Cissus* and Species: *quadrangularis*[13]. *C. quadrangularis* L. is a perennial herbaceous climber characterised by a thick, quadrangular stem and well-developed aerial parts, including tendrils, leaves, inflorescences, flowers, and fruits. The plant attains an average height of approximately 4.8 feet and bears four-angled branches with internodes measuring 8-9 cm in length and 1.2-1.4 cm in width. Each angle is marked by a distinct leathery ridge. The toothed, trilobed leaves, 2-4 cm wide, arise at the nodes, with a tendril emerging from the opposite side of each node. The plant produces racemes of small white, yellowish, or greenish flowers, followed by globular berries that turn red upon ripening[14].

2.2 Morphological Features for Pharmacognostic Identification

2.2.1 Leaves

The leaves are simple, ovate to reniform in shape, with a base approximately 5 cm wide that is truncate to cordate. The petiole measures about 2 cm in length[15].

Additionally, considerable morphological variation has been observed, ranging from moderately green petioles with distinctly kidney-shaped leaves to pentagonal-shaped leaves accompanied by greenish-pink flowers.

2.2.2 Stem

The plant material occurs as fragments of varying sizes, with stems that are distinctly four-angled and four-winged. The internodes measure approximately 4-15 cm in length and 1-2 cm in thickness. The surface is glabrous and devoid of pubescence, exhibiting a buff colouration with a slight greenish-blue tinge, while the angular regions display a reddish-brown hue. The material is tasteless and odourless[16]. Three morphovariants of *C. quadrangularis,* namely square-stemmed, round-stemmed, and flat-stemmed forms, have been reported and categorised as variants I, II, and III, respectively[17]. Based on stem morphology, three corresponding morphotypes (morphotypes I, II, and III) have also been identified. Notably, morphovariants I and III were found to be morphologically similar, whereas morphovariant II, characterised by a flattened stem, was distinct[18].

2.2.3 Root, Flowers, Seed, and Berry

The taproot extends to a length of approximately 10-20 cm. Flowering in *C. quadrangularis* occurs from June to December. The flowers are borne in cymes with short peduncles and possess spreading, umbellate branches. The calyx is cup-shaped, truncate, or very obscurely lobed. The four petals are ovate-oblong, short, and stout. The seeds are small and enclosed by a thick testa[19]. The berries are obovoid to globose, approximately 6 mm in length, apiculate, red at maturity, and contain a single seed. Morphologically superior ecotypes of *C. quadrangularis* (TNCq 9, TNCq 23, TNCq 28, TNCq 32, and TNCq 34) have been reported to exhibit higher stem yield, greater plant height, increased petiole length, and enhanced root weight, girth, and length[20].

2.3 Habitat

Cissus quadrangularis is a common species of arid habitats across tropical and subtropical regions and is frequently encountered in coastal and lowland areas. Owing to its well-established medicinal value, the plant is widely recognised in both Africa and India. In India and neighbouring countries such as Pakistan and Bangladesh, *C. quadrangularis* typically grows in thickets, open forests, scrub jungles, along forest margins, on riverbanks, and in wastelands at low to mid elevations[21]. Within Tamil Nadu, the species is extensively distributed throughout the hotter regions, where it thrives on sloping terrains up to 500 m above mean sea level under conditions of annual rainfall below 700 mm. Maximum diversity has been documented in the Virudhunagar, Tirunelveli, Tuticorin, Perambalur, Salem, and Erode districts[22]. Morphologically, the plant is a rambling shrub or climber characterised by a thick, fleshy, four-angled stem, with leaves arranged in an alternate and distichous phyllotaxy[23].

2.4 Vernacular Names

Cissus quadrangularis is known by various vernacular names across different languages and regions of India[24]. These commonly used local names are presented in Table 1.

2.5 Ethnopharmacology and Traditional Applications

Cissus quadrangularis is a well-recognised traditional medicinal plant widely associated with *Ayurveda*; however, its medicinal use extends across diverse geographical regions owing to its broad natural distribution. Traditionally, it has been employed in the management of female reproductive disorders, including menopausal symptoms, enhancement of

Table 1. Vernacular names of *C. quadrangularis* in India

S. No.	Language/ Region	Vernacular Names
1	English	*Edible stemmed vine, Adamant creeper, Bone setter*
2	Hindi	*Hadjod, Hadjora, Hadsarihari, Harsankari, Kandvel*
3	Bengali	*Har, Harbhanga, Hasjora, Horjora*
4	Gujarati	*Chodhari, Hadsand, Hadsankal, Vedhari*
5	Kanada	*Mangarahalli*
6	Malayalam	*Cannalamparanta, Peranta*
7	Marathi	*Horjora, Harsankar, Kandavel, Nalllar*
8	Tamil	*Piranti, Vajjravalli*
9	Telugu	*Nalleru, Nelleratiga, Vajravalli*
10	Oriya	*Hadavhanga*
11	Urdu	*Harjora, Hadsankal*

libido, and menstrual irregularities[25]. The plant has also been extensively utilised in ancient Indian medical systems such as *Siddha* and *Ayurveda* for the treatment of "*Asthi*" (bone-related) disorders, including osteoporosis, rheumatoid arthritis, osteoarthritis, fractures, pain, and inflammation[26]. Its notable role in enhancing bone mass and accelerating fracture healing has earned it the traditional name "*Bone Setter*" or "*Hadjod*"[25]. Furthermore, traditional literature from other regions of the Indian subcontinent, including Pakistan, Bangladesh, and Sri Lanka, as well as various parts of the world, reports its use in the treatment of swelling, haemorrhage, anorexia, flatulence, dyspepsia, colic, chronic ulcers, haemoptysis, convulsions, skin diseases, and leprosy[27].

In *Ayurveda*, *C. quadrangularis* is attributed with several therapeutic properties, including *Asthiyuk* (promotion of bone strength and fracture healing), *Sara* (enhancement of mobility, relief of obstruction, and purgative action), *Krumighna* (treatment of infected wounds), and *Amaghna* (reduction of *ama*, a toxic byproduct of impaired digestion and metabolism). The plant is an important component of classical Ayurvedic formulations such as *Lakshadi Guggul*, widely prescribed for bone-related disorders and fracture healing, and *Panchajeeraka Gudam*, an herbal jam used in postnatal care and for digestive and respiratory ailments[28]. In Unani medicine, the plant is recognised for its growth in warmer regions of India, and the powdered root is traditionally used for bone fractures with effects comparable to external plasters, at a recommended dose of 30-40 grains. In southern India, the leaves and young shoots are commonly consumed as curry, while in Chennai, young shoots are dried, powdered, and incinerated to obtain ash used for treating dyspepsia, indigestion, and bowel disorders. The leaves and tender shoots are also regarded as potent substitutes. The stem juice is used for ear and nasal conditions such as otorrhoea and epistaxis, and is also employed for irregular menstruation, while a paste prepared from the crushed stem is traditionally used in the treatment of asthma[29].

In traditional Ayurvedic practice, *C. quadrangularis* is widely incorporated into various dietary and medicinal preparations, especially in southern India. The stems are consumed as a pickle to strengthen bones and promote the recovery of epithelial tissues following injury, and they are also prepared as a soup to support the bone-healing process. In Tamil Nadu, a chutney made with coconut is commonly served as a side dish and used to enhance immunity. In Kerala, the plant is regarded as a traditional healer, where a paste of the stem is applied to fractured or displaced joints for therapeutic effect. Additionally, the stem is fried and administered with milk for its wound-healing properties[30]. The plant is a key ingredient in several classical Ayurvedic formulations, including *Lakshadi Guggul*, which is widely used for the treatment of bone-related disorders and fracture healing; Zeotone soft gel capsules; and *Panchajeeraka Gudam*, an effective herbal jam used in postnatal care and in the management of digestive and respiratory ailments[31]. In *Unani* medicine, the recommended dosage includes a decoction of the dried stem at 10-30 mL twice daily, stem juice at 10-20 mL twice daily, and stem powder at a dose of 3-6 g twice daily[30].

3. Chemical Constituents of *C. quadrangularis*

The aerial parts of *C. quadrangularis*, particularly the stem, are rich in a wide spectrum of primary and secondary metabolites, as evidenced by extensive phytochemical investigations using extracts prepared with solvents of varying polarity. Preliminary phytochemical screening has confirmed the presence of key primary metabolites, including cyclic and acyclic lipids, fatty acids and their methyl esters, proteins, amino acids, iridoids, gums, and mucilage. In addition, the plant is a notable reservoir of diverse secondary metabolites such as alkaloids, flavones and flavonoids, saponins, phytosterols, steroids, stilbenes, triterpenoids, tannins, carotenoids, cardiac glycosides, and vitamins, with vitamin C being particularly abundant[32]. In contrast, phytochemical analyses of extracts derived from the underground parts have predominantly revealed alkaloids, saponins, tannins, flavonoids, and glycosides, highlighting organ-specific variation in metabolite distribution[33].

Detailed phytochemical characterisation has led to the identification of several bioactive marker compounds in *C. quadrangularis*. These include flavonoids such as quercetin, daidzein, and genistein; triterpenoids including friedelin; stilbene derivatives

such as quadrangularin A, resveratrol, and piceatannol; iridoids like 6-O-meta-methoxybenzoyl catapol, picroside, and pallidol; and phytosterols, notably β-sitosterol. The stem has been reported to contain α- and β-amyrins, β-sitosterol, ketosetosterol, phenolics, tannins, carotene, vitamins, calcium oxalate, long-chain fatty acids such as 31-methyltritriacontanoic acid, and triterpenes including taraxeryl acetate and taraxerol. Moreover, a novel asymmetric tetracyclic triterpenoid, 7-oxo-onocer-8-ene-3β,21α-diol, has been isolated from the aerial parts, while the leaves are enriched with stilbenes such as resveratrol, piceatannol, pallidol, parthenocissus derivatives, and alicyclic lipids. The roots and root powder additionally serve as a source of essential minerals, including potassium, calcium, iron, zinc, sodium, magnesium, copper, and trace amounts of heavy metals, underscoring the nutritional relevance of the plant[34].

Complementary to conventional phytochemical screening, GC-MS-based chemical profiling of *C. quadrangularis* has revealed a chemically diverse metabolome dominated by fatty acids, esters, alcohols, and terpenoid constituents. Analysis of the whole plant extract identified n-hexadecanoic acid (palmitic acid) as a major component, along with 1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester, phytol, and hexadecanoic acid ethyl ester. Other constituents, including caffeine, dibutyl phthalate, and long-chain aliphatic alcohols, further contribute to the bioactive profile of the plant[35]. Similarly, GC-MS analysis of aqueous alcoholic extracts demonstrated the consistent predominance of n-hexadecanoic acid, alongside unsaturated fatty acid derivatives such as 9,12,15-octadecatrienoic acid methyl ester and 9,12-octadecadienoic acid methyl ester. Additional compounds, including phytol, oleic acid, linoleic acid ethyl ester, glycerin, ethyl-α-D-glucopyranoside, tetradecanoic acid, undecanoic acid, octadecanoic acid ethyl ester, asarone, nonanol, and various aliphatic diols, phenolic derivatives, and aromatic hydrocarbons, were also detected, reflecting the influence of extraction polarity on metabolite recovery[36]. Collectively, these observations highlight the pronounced chemical diversity of *C. quadrangularis*, establishing a strong phytochemical foundation that underpins its wide range of reported pharmacological activities.

5. Pharmacological Activity

5.1 Anticancer Activity

Extracts and green-synthesised nano formulations derived from *C. quadrangularis*, particularly from the stem, demonstrate notable antiproliferative activity mediated through apoptosis induction, modulation of oxidative stress, and regulation of cancer-associated molecular targets. Stem-derived silver nanoparticles (AgNPs) synthesised using *C. quadrangularis* exhibited moderate cytotoxicity against MCF-7 breast cancer cells (IC_{50} ≈ 56.7 μg/mL) relative to cisplatin (IC_{50} ≈ 5.5 μg/mL). This cytotoxic effect was accompanied by downregulation of p53 gene expression, implicating altered stress-response signalling and cell-cycle regulatory mechanisms[37].

Comparable AgNP formulations significantly suppressed cell viability in HT-29 colon cancer cells, concomitant with elevated reactive oxygen species and nitric oxide levels, upregulation of the pro-apoptotic protein Bax, and suppression of the anti-apoptotic protein Bcl-2, thereby confirming apoptosis-mediated cytotoxicity[38]. In addition, solvent extracts of *C. quadrangularis* exhibited broad-spectrum anticancer activity against ovarian (PA1), cervical (HeLa), and lung (A549) cancer cell lines. Ethanolic extracts induced apoptosis in PA1 cells (IC_{50} ≈ 482 μg/mL), as evidenced by nuclear condensation and oxidative stress-associated cellular damage[39]. In HeLa cells, the extracts selectively reduced cancer cell viability while sparing normal epithelial cells, and triggered caspase-3 activation, mitochondrial dysfunction, and cell-cycle arrest at the G0/G1 and G2/M phases[40]. Methanolic stem extracts further exhibited potent antiproliferative activity against A549 lung cancer cells, with an IC_{50} of approximately 65 μg/mL[41].

Supporting these experimental findings, molecular docking analyses revealed strong binding affinities of key *C. quadrangularis* phytoconstituents such as quercetin-3-O-α-L-rhamnopyranoside, resveratrol, and piceatannol toward critical oncogenic targets, including threonine tyrosine kinase and caspase-3, underscoring their potential role in mediating anticancer effects[42].

5.2 Anti-diabetics Activity

Integrative phytochemical profiling combined with *in vitro*, *in vivo*, and *in silico* investigations has consistently demonstrated that *C. quadrangularis* exerts pronounced antidiabetic effects through modulation of carbohydrate-digesting enzymes, enhancement of glucose tolerance, attenuation of oxidative stress, and regulation of key metabolic signalling pathways. *In vitro* assays revealed that *C. quadrangularis* extracts significantly inhibit α-amylase and α-glucosidase activities, exhibiting IC_{50} values comparable to the reference drug acarbose, thereby suggesting delayed intestinal carbohydrate digestion and reduced glucose absorption[43]. Complementary molecular docking and molecular dynamics simulations further supported these findings, demonstrating strong binding affinities of phytoconstituents such as apiin and rosmarinic acid toward major diabetic target enzymes, highlighting their relevance as potential pharmacophores[44].

The antidiabetic efficacy of *C. quadrangularis* has been robustly validated across chemically and genetically induced diabetic animal models. Ethanolic and hydroalcoholic extracts significantly reduced fasting blood glucose levels in alloxan-induced[45,46], streptozotocin-nicotinamide[47], and leptin receptor-mutated db/db[48] models. Repeated oral administration over 28 days improved oral glucose tolerance, mitigated diabetes-associated body weight loss, and normalised serum biochemical parameters[46]. In db/db mice, treatment with a standardised extract (CQR-300) markedly reduced hyperglycaemia, circulating insulin levels, and HbA1c, while concurrently improving hepatic lipid accumulation and suppressing gluconeogenic, lipogenic, and oxidative stress-associated proteins[48].

At the molecular level, *C. quadrangularis* extracts enhanced endogenous antioxidant defence systems, as evidenced by elevated glutathione content and increased activities of superoxide dismutase and catalase, alongside reduced lipid peroxidation. Furthermore, modulation of apoptotic markers and activation of the AMPK/PI3K/Akt signalling axis indicate improved insulin sensitivity and restoration of metabolic homeostasis, collectively supporting the therapeutic potential of *C. quadrangularis* in diabetes management[47].

5.3 Bone Healing Activity

Radiographic evaluation of fracture healing demonstrated that animals treated with *C. quadrangularis* extract exhibited an approximately 40% enhancement in bone regeneration compared with placebo-treated controls, reflecting accelerated callus formation and improved fracture consolidation. This osteogenic response was accompanied by a significant increase in systemic antioxidant capacity, as indicated by an approximate 25% elevation in superoxide dismutase (SOD) activity and enhanced free radical scavenging activity in the DPPH assay. Given the well-established role of oxidative stress in impairing osteogenesis, the antioxidant properties of *C. quadrangularis* may contribute, at least in part, to its bone-healing potential. Beyond its osteoprotective effects, the extract also conferred significant gastroprotection by markedly attenuating non-steroidal anti-inflammatory drug (NSAID) induced gastric mucosal injury, with a reported ~60% reduction in gastric lesion formation relative to control animals[49]. This dual therapeutic action is of particular clinical relevance in fracture management, where prolonged NSAID use is frequently required for pain control but is associated with increased risk of gastrointestinal complications.

5.4 Antioxidant Activity

In vitro studies consistently indicate that *C. quadrangularis* extracts, particularly ethanolic and methanolic preparations, exhibit potent, dose-dependent antioxidant activity. Using standard assays such as DPPH, FRAP, phosphomolybdate, and hydroxyl radical scavenging, these extracts demonstrated comparable or superior activity to reference antioxidants, including ascorbic acid[50]. Reported reducing power and total antioxidant capacity further highlight their strong electron-donating properties[51]. Phytochemical profiling and LC-MS analyses identified flavonoids, phenolic acids, and quercetin derivatives, such as quercetin-3-O-α-L-rhamnopyranoside, as key contributors to these effects. Molecular docking studies corroborated these findings, showing favourable interactions of bioactive compounds with oxidative stress-related protein targets, providing mechanistic insight into their radical-scavenging and cytoprotective actions[39]. Functional food applications demonstrated dose-dependent increases in total

phenolic and flavonoid content, along with enhanced DPPH and ABTS radical scavenging, while preserving acceptable sensory attributes[51]. Additionally, green-synthesised silver and selenium nanoparticles using *C. quadrangularis* extracts exhibited superior antioxidant activity, emphasising the role of phytochemicals in nanoparticle stabilisation and redox modulation[52,53]. Biomaterial-based strategies, such as carrageenan hydrogels enriched with aqueous extracts, further enhanced antioxidant activity and biocompatibility, suggesting potential utility in tissue engineering and regenerative medicine where oxidative stress impedes cellular repair[54].

5.5 Antimicrobial Activity/Antibacterial Activity

Cissus quadrangularis has been extensively investigated for its antimicrobial potential, providing experimental support for its traditional use in the treatment of infectious and inflammatory conditions. Ethanolic and methanolic extracts of the stem and leaves consistently demonstrate broad-spectrum antibacterial and antifungal activities against clinically relevant Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus* and *Escherichia coli*[55], as well as oral pathogens such as *Streptococcus oralis*[56], in addition to several fungal species. Disc and well diffusion assays have reported significant zones of inhibition, underscoring the ethnopharmacological relevance of *C. quadrangularis*[41].

Recent investigations have highlighted the enhanced antimicrobial efficacy of green-synthesised silver and copper oxide nanoparticles mediated by *C. quadrangularis* extracts. These biogenic nanoparticles exhibit superior bactericidal activity compared with crude extracts, which has been attributed to synergistic interactions between the metallic core and phytochemical capping agents, particularly phenolics and flavonoids[52,57,58]. Mechanistic insights from molecular docking studies further suggest that specific phytoconstituents may disrupt bacterial adhesion and virulence-associated proteins, thereby contributing to the observed antimicrobial effects[56]. Additionally, bioactive secondary metabolites produced by endophytic fungi associated with *C. quadrangularis* have been shown to possess broad-spectrum antibacterial and antifungal activities, further expanding the antimicrobial repertoire of this medicinal plant[59].

5.6 Anti-hyperlipidemic Activity

In high-fat diet-induced hyperlipidemic rats, oral administration of *C. quadrangularis* extract dose-dependently improved serum lipid profiles, characterised by elevated high-density lipoprotein (HDL) levels and reductions in low-density lipoprotein (LDL), triglycerides, and total cholesterol. The extract further demonstrated hepatoprotective and nephroprotective effects, as reflected by decreased serum transaminase and urea levels without significant alterations in creatinine concentrations[60].

5.7 Anti-malarial Activity

Molecular docking analyses were performed to assess the interaction of key bioactive constituents of *C. quadrangularis*, including saponin, pallidol, and quercetin, with human Dihydrofolate Reductase (DHFR), a well-established molecular target in antimalarial therapy. Docking simulations conducted using DHFR crystal structures (PDB IDs: 1MVT and 1U5N) revealed stable ligand-protein complexes characterised by hydrogen bonding, hydrophobic interactions, van der Waals forces, and aromatic stacking within the enzyme's active site. Among the evaluated compounds, saponin demonstrated the strongest binding affinity, with docking scores of −68.82 and −61.71 against the 1MVT and 1U5N structures, respectively, indicating a high interaction potential. Pallidol and quercetin also exhibited favourable binding energies, supporting their possible contribution to the antimalarial activity associated with *C. quadrangularis*[61].

Several reported pharmacological claims, including the antimalarial potential, are currently supported mainly by *in-silico* molecular docking studies with limited experimental validation. Therefore, further *in vitro* and *in vivo* investigations are necessary to confirm these computational predictions and establish their therapeutic relevance.

5.8 Anti-ulcer Activity

In an aspirin-induced gastric ulcer model in rats, administration of *C. quadrangularis* extract significantly accelerated ulcer healing. The gastroprotective effects were associated with increased gastric mucus secretion and enhancement of endogenous antioxidant defence systems, along with a pronounced reduction in lipid

peroxidation and myeloperoxidase activity in gastric tissue. Given the central role of oxidative stress and neutrophil-mediated inflammation in non-steroidal anti-inflammatory drug-induced gastric mucosal injury, these findings suggest that the protective effects of *C. quadrangularis* are mediated, at least in part, through attenuation of oxidative and inflammatory damage[62]. Mechanistic support was further provided by *in vitro* evaluation of gastric proton pump (H^+-K^+ ATPase) inhibitory activity. Both methanolic and chloroform extracts exhibited significant, dose-dependent inhibition of H^+-K^+ ATPase activity in goat gastric mucosal homogenates, with the methanolic extract demonstrating superior inhibitory efficacy comparable to the standard antiulcer drug omeprazole. This proton pump inhibitory action provides a plausible biochemical basis for the observed reduction in gastric acidity and mucosal injury[63].

5.9 Anxiolytic and Antidepressant Activity

The anxiolytic potential of *C. quadrangularis* was evaluated in a pilocarpine-induced epilepsy model in mice following repeated administration of an aqueous extract. Treatment produced a significant, dose-dependent increase in latency to clonic and generalised tonic-clonic seizures, along with reductions in seizure frequency and duration. Behavioural assessments using the elevated plus maze and open field tests further revealed enhanced exploratory behaviour, as evidenced by increased entries into and time spent in the open arms, decreased preference for closed arms, and increased activity in the central zone. These behavioural effects were accompanied by marked attenuation of oxidative stress, reflected by reduced hippocampal malondialdehyde levels, decreased γ-aminobutyric acid transaminase (GABA-T) activity, and concomitant increases in reduced glutathione and GABA levels, suggesting that the anxiolytic effects are associated with antioxidant activity and facilitation of GABAergic neurotransmission[64]. In parallel, the antidepressant-like effects of *C. quadrangularis* were demonstrated using the forced swim and tail suspension tests in mice following two weeks of oral administration of an ethanolic extract. The treatment resulted in a significant, dose-dependent reduction in immobility time in both paradigms, indicating antidepressant-like efficacy comparable to the reference drug imipramine[65].

5.10 Anti-arthritic Activity

Initial *in vitro* screening demonstrated pronounced anti-arthritic activity of *C. quadrangularis* through inhibition of protein denaturation, as assessed using egg albumin and bovine serum albumin models, along with stabilisation of Human Red Blood Cell (HRBC) membranes. Protein denaturation and erythrocyte membrane lysis are critical pathological processes in inflammatory arthritis, arising from stress-induced release of pro-inflammatory mediators[66]. Treatment with *C. quadrangularis* stem extracts produced a concentration-dependent reduction in absorbance, reflecting effective suppression of protein denaturation and membrane destabilisation and indicating significant anti-inflammatory and anti-arthritic potential[67].

In carrageenan-induced arthritic Wistar rats, a *C. quadrangularis* phytosome-based transdermal patch significantly reduced paw volume and thickness compared with arthritic controls, exhibiting efficacy comparable to marketed anti-arthritic formulations. Histopathological analyses confirmed attenuation of inflammatory changes and preservation of joint architecture, while acute toxicity studies established formulation safety[68]. The anti-arthritic efficacy was further validated in Complete Freund's Adjuvant (CFA)-induced arthritis models, wherein the Active Fraction of *C. quadrangularis* (AFCQ) markedly suppressed paw oedema, normalised haematological and biochemical parameters, and restored joint integrity. At a dose of 100 mg/kg, AFCQ demonstrated efficacy comparable to or exceeding that of standard agents such as celecoxib and methotrexate, as evidenced by histopathological and radiographic evaluations[69].

Comparative studies indicated that ethanolic extracts exhibited superior anti-arthritic activity relative to aqueous extracts and significantly downregulated monosodium urate (MSU)-induced Toll-like receptor-2 (TLR-2) and Toll-like receptor-4 (TLR-4) expression. Complementary molecular docking and LIGPLOT analyses identified GC-MS-derived phytoconstituents with strong antagonistic interactions toward key inflammatory receptors, providing mechanistic support for the observed anti-gout and anti-arthritic effects[70]. Additionally, green-synthesised silver nanoparticles derived from *C. quadrangularis* demonstrated enhanced anti-arthritic activity, exhibiting greater inhibition of egg albumin and bovine serum albumin denaturation

than standard reference drugs[71]. These effects are likely mediated through stabilisation of proteins and cellular membranes, modulation of inflammatory signalling pathways, and targeted molecular interactions. Nonetheless, well-designed clinical studies are required to establish translational relevance and therapeutic applicability in human arthritis.

5.11 Anthelmintic Activity

In vitro studies employing adult motility and egg hatching inhibition assays demonstrated that methanolic extracts of *C. quadrangularis* exert potent adulticidal and ovicidal effects against *Haemonchus contortus*, a major gastrointestinal parasite of small ruminants. At higher concentrations (5-10 mg/mL), the extracts significantly reduced worm motility and inhibited egg hatching, with efficacy comparable to the standard anthelmintic albendazole[72]. Similarly, aqueous leaf extracts of *C. quadrangularis* exhibited dose-dependent anthelmintic activity against *Pheritima posthuma* (Indian earthworm), inducing paralysis and death within timeframes comparable to conventional reference drugs such as piperazine citrate and albendazole[73]. Acute oral toxicity assessments in rodent models further confirmed the safety of the extracts, with LD_{50} values exceeding 2000 mg/kg, supporting their potential as biologically safe therapeutic agents[74]. Collectively, these findings provide robust preclinical evidence supporting the traditional use of *C. quadrangularis* as an effective and safe anthelmintic, underscoring its promise for integration into complementary and alternative therapies for helminth infections.

5.12 Anti-inflammatory Activity

In vitro investigations have shown that stem extracts of *C. quadrangularis* significantly inhibit erythrocyte haemolysis in a concentration-dependent manner, indicating stabilisation of lysosomal and cellular membranes under inflammatory stress conditions[50]. This membrane-stabilising effect suggests a capacity to limit the release of pro-inflammatory mediators at the cellular level. Consistent with these findings, traditional formulations of *C. quadrangularis*, such as Pirandai uppu, are widely employed in the management of prostaglandin-mediated inflammatory and vascular disorders, including dysmenorrhea and haemorrhoids. These conditions are characterised by elevated levels of inflammatory mediators such as prostaglandin $F_2\alpha$, interleukin-6, vasopressin, and vascular endothelial growth factor[75], and the clinical utility of *C. quadrangularis* in such settings implies modulation of inflammatory signalling and vascular inflammatory responses.

Recent advances have also highlighted nanotechnological applications of *C. quadrangularis*, wherein plant extracts have been utilised for the green synthesis of copper oxide nanoparticles. These biogenic nanoparticles exhibited marked anti-inflammatory, anti-proteinase, and antioxidant activities, underscoring the potential of *C. quadrangularis*-based nano formulations for inflammation-related biomedical applications[58]. At the molecular level, *in silico* docking analyses further support the anti-inflammatory potential of *C. quadrangularis*, as bioactive constituents including β-sitosterol, luteolin, piceatannol, resveratrol, quadrangularin, and tannins demonstrated strong binding affinities toward CD163, a macrophage-specific haemoglobin scavenger receptor involved in inflammatory tissue responses[76].

5.13 Analgesic Activity

Ethanolic, methanolic, and chloroform extracts of *C. quadrangularis* significantly attenuated nociceptive responses in the acetic acid-induced writhing assay, indicating inhibition of peripheral pain mediators. In the formalin-induced nociception model, these extracts reduced pain behaviours in both the early neurogenic and late inflammatory phases, suggesting the involvement of both central and peripheral antinociceptive mechanisms[77]. Central analgesic activity was further substantiated using thermal nociception models, including the hot plate and tail flick tests. Among the tested fractions, the chloroform extract demonstrated the greatest potency, producing dose-dependent prolongation of reaction times.

Mechanistic insights were provided by pharmacological antagonism studies, which showed that pretreatment with naloxone and p-chlorophenylalanine significantly reversed the analgesic effects, whereas α-adrenergic blockade produced no significant influence. These findings implicate the involvement of opioidergic and serotonergic pathways in mediating the observed antinociceptive activity[78]. In addition

to its analgesic properties, *C. quadrangularis* extracts demonstrated therapeutic efficacy in pain associated with inflammatory vascular conditions such as haemorrhoids, where analgesic effects were accompanied by anti-inflammatory and venotonic actions[79]. Furthermore, combination studies with *Zingiber officinale* suggested additive or synergistic analgesic effects, comparable to those of standard anti-inflammatory agents[80].

5. Toxicological and Safety Aspects

Acute oral toxicity studies in rodents have consistently demonstrated the low toxicity potential of *C. quadrangularis*, with no mortality or treatment-related behavioural abnormalities observed at doses up to 2000-5000 mg/kg body weight, in compliance with OECD guidelines [1]. Sub-chronic toxicity data further corroborate this favourable safety profile. In a well-designed 90-day repeated-dose oral toxicity study, administration of a standardised *C. quadrangularis* extract (CQR-300) to Sprague-Dawley rats did not result in treatment-related changes in clinical signs, body weight gain, food consumption, haematological or serum biochemical parameters, organ weights, or histopathological architecture of major organs. The no-observed-adverse-effect level (NOAEL) was established at ≥2500 mg/kg/day, indicating a wide margin of safety upon repeated exposure[81].

Genotoxicity evaluations of *C. quadrangularis* are limited, but available evidence suggests an absence of mutagenic or clastogenic effects. Standardised extracts have yielded negative results in bacterial reverse mutation (Ames) assays, *in vitro* chromosomal aberration tests, and *in vivo* micronucleus assays, supporting genomic safety within the tested dose ranges[82]. Nevertheless, reproductive and developmental toxicity data remain insufficient. Although no overt reproductive toxicity or teratogenic effects have been reported in experimental models or traditional usage contexts, the absence of guideline-compliant fertility, embryofetal development, and multigenerational studies represents a critical gap in the toxicological characterisation of this medicinal plant.

Clinical studies involving *C. quadrangularis*-containing formulations, particularly for bone health and metabolic indications, generally report good tolerability with no serious adverse events; however, safety endpoints are often inadequately documented, and study durations remain relatively short[83]. From a regulatory perspective, *C. quadrangularis* is predominantly marketed as a traditional medicine or dietary supplement, with regulatory oversight varying considerably across regions. In many jurisdictions, such products are exempt from rigorous pre-marketing toxicological evaluation, highlighting the need for strengthened post-marketing pharmacovigilance systems and standardised quality control measures[84]. Overall, the integration of traditional usage evidence with modern preclinical toxicology supports the relative safety of *C. quadrangularis*; nevertheless, the paucity of long-term human safety studies, chronic toxicity assessments, and toxicogenomic investigations underscores an important research gap. Future studies employing well-standardised extracts, extended exposure paradigms, and molecular-level safety assessments are essential to enhance the translational relevance and regulatory acceptance of *C. quadrangularis*-based therapeutics.

6. Phytopharmaceutical Formulation

Researchers have shown sustained interest in the use of plant extracts for pharmaceutical development[85]. This process primarily focuses on two critical aspects: ensuring product stability and achieving optimal patient compliance[86]. *C. quadrangularis* has gained considerable acceptance in the scientific community, prompting the exploration of diverse formulation strategies. The different phyto formulations developed from *C. quadrangularis* are summarised in Table 2.

In recent years, there has been growing interest in developing novel delivery systems to improve the therapeutic efficacy of *C. quadrangularis* bioactive compounds. Studies have investigated the incorporation of *C. quadrangularis* extracts into advanced formulations, including polymeric nanoparticles, lipid-based carriers, gels, and topical systems, aiming to enhance solubility, stability, bioavailability, and targeted delivery. Despite these advancements, notable gaps remain in the formulation science of *C. quadrangularis*. Specifically, systematic pharmacokinetic studies assessing the absorption, distribution, metabolism, and excretion of its key bioactive compounds are largely lacking, particularly for modern and nano-enabled

Table 2. Phytopharmaceutical formulations prepared using *C. quadrangularis* extract

Plant part used	Nature of extract	Formulation	Method of preparation and polymers/ excipients used	Application	Inference	References
-	-	Capsule	Soy albumin extract, green tea extract, niacin-bound chromium, selenium, vitamin B6, vitamin B12, folic acid	Weight loss and metabolic syndrome	-Significant improvements in body weight, central obesity - Effective adjunct in the management of metabolic syndrome, independent of dietary intervention	87
Stem	Aqueous	Silver nanoparticles	$AgNO_3$ solution (1 mM)	Antibacterial and antioxidant activity	- Enhanced antibacterial and antioxidant activities	52
Stem	Aqueous	Iron oxide nanoparticles	Ferric chloride hexahydrate, ethanol, 3-(4,5-dimethylthiazol-2-yl) - 2,5-diphe nyltetrazolium bromide	Anticancer activity (breast cancer)	- Potent antioxidant, anti-inflammatory, and anticancer activities with favourable nanoscale characteristics	88
Stem	Aqueous	Zinc oxide nanoparticles	Zinc acetate dihydrate, 2 M sodium hydroxide	Antimicrobial and anticancer activity	- effective antibacterial and antiproliferative activities with well-defined nanoscale properties	89
Leaf	-	Titanium dioxide nanoparticles	-	Antibacterial and photocatalytic activity	- well-defined nanostructures with strong antibacterial and photocatalytic activities	90
Leaf	Aqueous	Silver nanoparticles	1 M of silver nitrate solution	Antimicrobial activity	- crystalline nanoscale characteristics and broad-spectrum antibacterial activity	57
Stem	Aqueous	Titanium dioxide nanoparticles	0.5 M $TiCl_4$	Antioxidant activity	- ultrasmall spherical morphology with significant antioxidant activity	91
Whole plant	Methanol	Anti-inflammatory herbal topical formulation	Dispersion method aerosil, sesame oil, BHT, BHA, tri-ethanolamine	-	- satisfactory physicochemical properties, stability, and drug release behaviour	92
Stem	Ethanol	Tricalcium phosphate reinforced natural polymer composite	Pectin, (N-(3-dimethylaminopropyl)) N-ethylcarbodimide hydrochloride, N-hydroxy succinimide, gelatin	Osteogenic activity	- excellent biocompatibility and enhanced osteogenic activity	93
Stem	Aqueous	Silver nanoparticle	Silver nitrate	Anti-arthritic activity	- well-defined crystalline morphology and significant anti-arthritic activity	71
Stem	Aqueous	POSS-Reinforced chitosan-based bilayer sponges	Chitosan, acetic acid, Polyhedral Oligomeric Silsesquioxane (POSS)	Wound healing applications	- sustained antimicrobial release, favourable physico- mechanical properties, and enhanced cell proliferation and wound healing	94
Leaf	Methanol	Copper oxide nanoparticles	Co-precipitation method copper sulphate, deionised water	Antibacterial activity	- exhibited stable nanoscale characteristics with significant antibacterial activity	95
Stem	Aqueous	Zinc oxide nanoparticles	Zinc acetate, NaOH	-	- uniform spherical morphology, functionalised bioactive compounds, and potential for safe biomedical applications	96
Stem	Aqueous	Hydrogel	PEG	Enhancing the osseointegration of the titanium implant to bone	- enhances bone integration, particularly by increasing bone area fraction occupancy	97
-	-	Hydrogel	Chitosan	Orthopedic applications	- injectable osteogenic scaffold for enhancing bone repair in delayed or non-union fractures	98

formulations. Additionally, comprehensive stability studies evaluating the chemical and biological integrity of extracts under various storage and formulation conditions are limited. Addressing these deficiencies through well-designed pharmacokinetic, stability, and bioavailability investigations is crucial to facilitate rational formulation development, ensure product consistency, and enhance the scientific and regulatory credibility of *C. quadrangularis*-based therapeutics.

7. Challenges, Research Gaps, and Future Directions

Despite its extensive ethnopharmacological use and increasing experimental validation, the translation of *Cissus quadrangularis* into evidence-based therapeutics remains constrained by several critical challenges. Although numerous pharmacological activities have been reported, the mechanistic understanding of these effects remains fragmented. Most studies rely primarily on conventional *in vitro* and *in vivo* experimental models, while investigations incorporating molecular target validation and integrative multi-omics approaches such as genomics, transcriptomics, proteomics, and metabolomics are still limited. As a result, the precise molecular targets, signalling pathways, and structure-activity relationships underlying the therapeutic effects of *C. quadrangularis* are not yet comprehensively elucidated.

Another significant limitation is the gap between promising preclinical findings and available clinical evidence. While animal studies consistently report beneficial effects in bone regeneration, metabolic disorders, and inflammatory conditions, clinical investigations remain relatively scarce, small in scale, and methodologically heterogeneous. Many studies lack standardised plant extracts, clearly defined clinical endpoints, appropriate control groups, and long-term safety assessments, which collectively hinder the translation of experimental findings into reliable clinical applications. Furthermore, poor bioavailability of certain bioactive constituents and the limited availability of systematic pharmacokinetic and ADME (absorption, distribution, metabolism, and excretion) data represent additional barriers to the development of phytopharmaceutical products derived from *C. quadrangularis*.

Phytochemical variability also represents an important factor influencing therapeutic consistency. The chemical composition of *C. quadrangularis* may vary across different morphovariants and geographical populations, potentially affecting its pharmacological efficacy and biological activity. Therefore, comprehensive comparative phytochemical profiling of different morphovariants using advanced analytical techniques is essential to ensure consistency, quality control, and reproducibility in future pharmacological and clinical investigations.

Future research should focus on the development of standardised extracts, detailed mechanistic validation using multi-omics platforms, and well-designed clinical trials with larger sample sizes. In addition, the integration of advanced drug delivery strategies, including nanoformulations and biomaterial-based systems, along with comprehensive pharmacokinetic and stability studies, may significantly enhance the therapeutic potential of *C. quadrangularis*. Importantly, this review provides an integrated synthesis linking the phytochemical profile of *C. quadrangularis* with its biological mechanisms and highlights key research gaps that must be addressed to facilitate its future translational and clinical development.

8. Conclusion

Cissus quadrangularis is a prominent ethnomedicinal plant whose therapeutic relevance is supported by a diverse phytochemical profile, including flavonoids, stilbenes, triterpenoids, and sterols. These constituents underpin its traditional applications in fracture healing and inflammatory disorders and contribute to its experimentally validated pharmacological activities. An integrative evaluation suggests that the efficacy and safety of *C. quadrangularis* arise from multi-component, multi-target interactions rather than isolated bioactive compounds. Nevertheless, inconsistencies in extract standardisation, limited mechanistic validation, inadequate pharmacokinetic characterisation, and insufficient high-quality clinical evidence restrict its broader clinical adoption. Addressing these gaps through ethnopharmacology-guided standardisation, molecular and omics-based investigations, and well-controlled clinical studies is essential. With systematic validation and advanced formulation strategies,

C. quadrangularis holds considerable promise for translation from traditional medicinal use to a scientifically substantiated phytotherapeutic agent.

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Author Contribution

Ms. Monika Chavare and Dr. Akshada Koparde jointly conceptualised and designed the study. Data collection was carried out by Ms. Monika Chavare and Mr. Omkar Tipugade, while Ms. Monika Chavare performed the data analysis and drafted the initial version of the manuscript. Dr. Akshada Koparde also supervised the overall study, contributed to data interpretation, and provided critical revisions. All authors have read and agreed to the published version of the manuscript.