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THERAPEUTIC POTENTIAL AND PHARMACOLOGICAL INSIGHTS OF *CISSUS QUADRANGULARIS* LINN: A COMPREHENSIVE REVIEW

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ABSTRACT: *Cissus quadrangularis* Linn (CQ), a perennial medicinal herb of the Vitaceae family, has gained significant attention due to its extensive pharmacological and therapeutic properties. Commonly referred to as "Hadjod" or "Bone Setter," it is widely used in traditional medicine systems such as Ayurveda, Unani, and Siddha for its bone-healing, anti-inflammatory, and antimicrobial benefits. The plant's bioactive compounds include flavonoids, triterpenoids, stilbenes, phytosterols, calcium oxalate, and essential vitamins, which contribute to its pharmacological versatility. CQ exhibits diverse therapeutic activities, including anti-ulcer, antioxidant, anti-inflammatory, hepatoprotective, gastroprotective, antiosteoporotic, and antimicrobial properties. Its ability to enhance bone regeneration and mineralization has been widely studied, particularly in the context of osteoporosis and fracture healing. In addition, the plant demonstrates free radical scavenging, antibacterial, anti-hemorrhoidal, and hepatoprotective effects through its bioactive phytoconstituents. Its extracts show efficacy against various pathogens, promote gastrointestinal health, and have potential applications in managing oxidative stress-related disorders. This review provides an in-depth overview of the botanical, chemical, and pharmacological attributes of *Cissus quadrangularis* Linn, emphasizing its traditional uses and modern therapeutic potential. The evidence underscores its role as a valuable medicinal plant with applications in healthcare and drug discovery.

INTRODUCTION: The pharmaceutical industries heavily rely on natural products for the creation of new pharmaceuticals, and plants play a significant part in the drug discovery process [1]. According to a WHO research, folk medicine is the primary form of healthcare for 80% of people Sworldwide [2]. India has been blessed with a wealth of expertise in the field of medicine through its cultural traditions and heritage, including Ayurveda, Homeopathy, Unani, and Siddha [3, 4].

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Medicinal plants are the essential source for indigenous medical systems in India, and tribal people have always valued these plants much for their spiritual, medical, and cultural purposes [5]. In traditional medicine, *Cissus quadrangularis* Linn (CQ) is a medicinal herb with renowned health benefits [6].

Cissus quadrangularis is a perennial plant commonly known as Hadjod. It is belonging to family Vitaceae. This plant is also referred to as Adamant creeper, Square stalked vine, veldt grape, hadjod and pirandai, Sannalam, Nalleru, Vajravelli, Mangara valli, and devil's backbone [7]. It is a wandering shrub that is edible distinguished by a thick, quadrangular, meaty stem. Cissus is a genus of the Vitaceae family consisting of 800 species divided into 13 genera throughout the world in the

hotter regions of India, Sri Lanka, Malaya, Java, and West Africa [8, 9]. Out of these, 8 genera and 63 different species are found in India. It is a fleshy cactus-like, jointed climber. It is a 1.5 m tall plant with branches that have quadrangular sections and internodes that are 1.2 to 1.5 cm broad and 8 to 10 cm long. There is a leathery edge at every aspect. At the nodes are the 2 to 5 cm wide toothed trilobe leaves. Each node has a tendril coming out of the side that faces it. Little white, yellowish, or greenish flower racemes and globular fruit that become red when ripe [10].

FIG. 1: *CISSUS QUADRANGULARIS* LINN.

FIG. 2: STEMS AND LEAVES

Vernacular Name [11]:

English: Edible stemmed vine, Adamant creeper, Bone setter

Hindi: Hadjod, Hadjora, Hadsarihari, Harsankari, Kandvel

Bengali: Har, Harbhanga, Hasjora, Horjora

Gujarati: Chodhari, Hadsand, Hadsankal, Vedhari

Kanada: Mangarahalli

Malyalam: Cannalamparanta, Peranta

Marathi: Horjora, Harsankar, Kandavel, Nalllar

Tamil: Piranti, Vajjravalli

Telugu: Nalleru, Nelleratiga, Vajravalli

Oriya: Hadavhanga

Urdu: Harjora, Hadsankal

Taxonomy of *Cissus quadrangularis* [12, 13, 14]:

Kingdom: Plantae

Subkingdom: Tracheobionta

Super Division: Spermatophyta

Division: Magnoliophyta

Class: Magnoliopsida

Subclass: Rosidae

Order: Vitales

Family: Vitaceae

Genus: Cissus

Species: Quadrangularis.

In India, it's widely used to make traditional remedies. Because of its a bone-healing and bone-joining property it helps to lessen pain and bone brawniness so it is known as "Hadjod" [15, 16]. Studies on *Cissus quadrangularis* toxicity show that its extract has no harmful effects [17].

Plant Propagation: It can be directly grown in prepared beds with a moderate supply of water and suitable substratum to climb. A 30 cm long mature stem was removed from their mother plant without damage for propagation. It requires a warm tropical climate. It is propagated using the stem cutting methods in the months of June to July. The plant is efficiently reproduced using its mature stem cuttings. A disease-free, healthy, and mature plant of *Cissus quadrangularis* L. was used as a source of stem cuttings for further development [18].

Microscopic Characters of Stem: The mature stem section has a squarish shape and each annular point has a pronounced protrusion; The cortex is made up of 8–16 layers of thin-walled, circular to oval sparenchymatous cells; there are four patches

of collenchymatous cells embedded in the cortical region like an umbrella arching over large vascular bundles; the projected portion of the angular region contains cortical cells filled with brown-red contents; the epidermis is single layered, covered externally with thick cuticle; the epidermal cells are short, rectangular, and tangentially elongated, followed by two to three layers of cork and a single-layered cork cambium; endodermis is not separate; The stele is made up of several different-sized vascular bundles grouped in a ring and divided by parenchymal rays; in each angular section, there are three to four bigger vascular bundles. Vascular bundles of the collateral and open types, capped by a erenchymatous sheath that is well-developed in bigger bundles, are located beneath the collenchymatous patch, while the remaining bundles are smaller; The cambium and interfascicular cambium are clearly separated; a broad pith made up of thin-walled, circular to oval parenchymatous cells occupies the central region; idioblasts with raphides and isolated acicular crystals of calcium oxalate are found in the cortex's outer region as well as in several cells there; rosette crystals of calcium oxalate are also present in the majority of the cells in the cortical region; and starch grains are distributed throughout the pith and cortical regions [19].

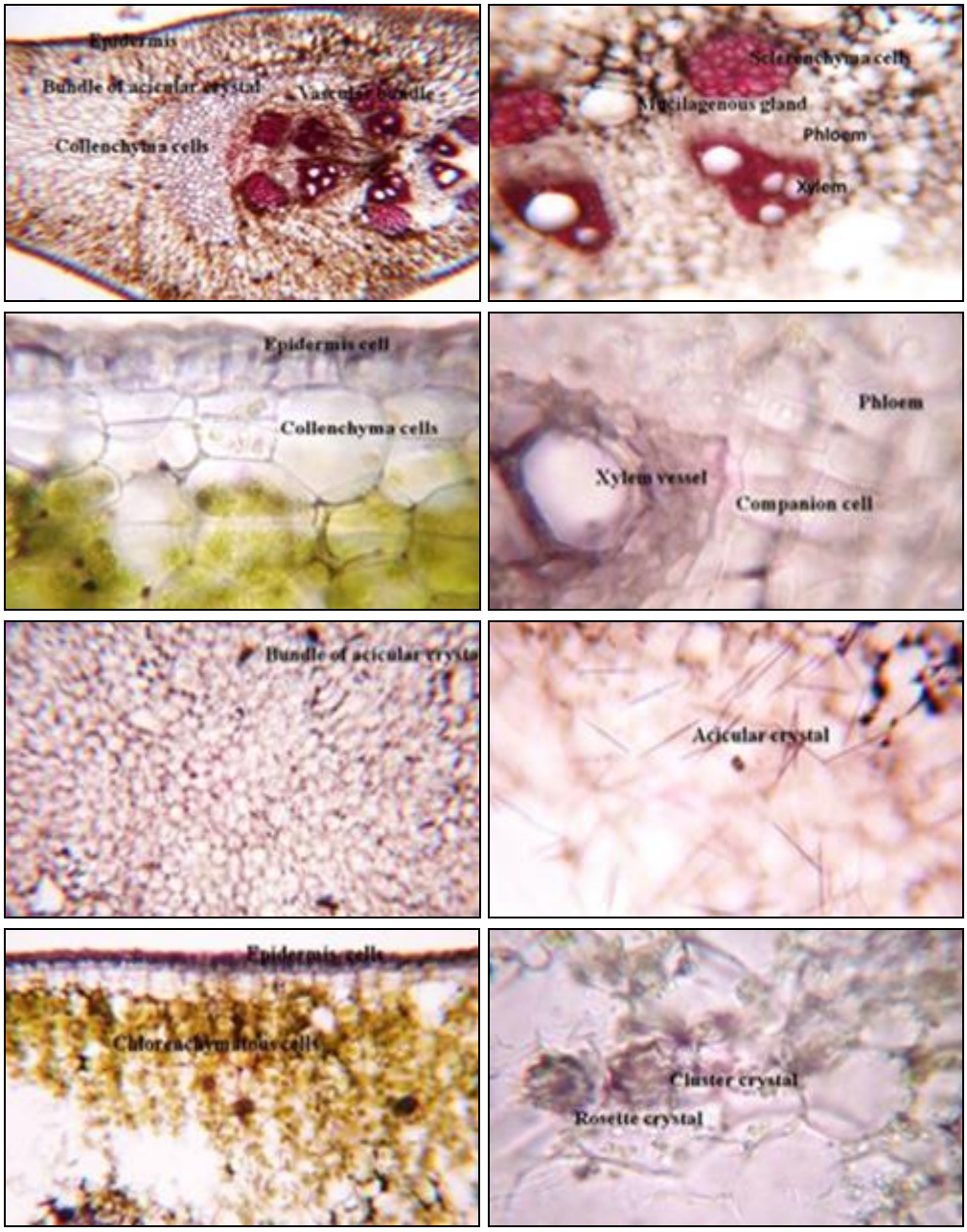

FIG. 3: MICROSCOPIC CHARACTERS OF STEM

Microscopic Characters of Leaf: On both surfaces, a leaf has a single layer of epidermis. Its thin cuticle covers the upper epidermisis. They both have anomocytic stomata. There are extremely few simple covering trichomes on each epidermis. § The lamina's transverse view reveals a single layer of closely packed palisade cells beneath the top epidermis. The midrib displays 5-7 layers of thick wall collenchyma that are densely packed on both surfaces. Mesophyl and vascular bundle that are pliable [20].

Powder Character of the Plant: The powder has actinocytic stem stomata and is creamish brown in color. Calcium oxalate crystals in bundles, rosettes, and clusters are dispersed. The majority of starch grains are simple, with helical, annular, and pitted vessels. Cluster crystals of calcium oxalate are observed in mucilage cavities surrounded by an epithelial layer and pieces of pericyclic fibers connected to idioblasts [21, 22].

Chemical Constituent of the Plant: There are several components in the plant, including flavonoids like quercetin, daidzein, and genistein, triterpenoids like friedelin, vitamin "C," stilbene derivatives like quadrangularin A, resveratrol, and piceatannol, iridoids like 6-0-meta-methoxybenzozyl catapol, picroside, and pallidol, and phytosterols like β-sitosterol and calcium [23, 24]. The antimicrobial, anti-inflammatory, anti-diarrheal, and anti-cancer [25-27] qualities of CQ flavanoids are well-established. Terpenoids are well known for their anti-tumor properties; they work by targeting the enzymes cyclooxygenase, phospholipases, and lipoxygenase. They also have a significant anti-inflammatory effect. According to numerous research, stilbenes have anti-inflammatory, anti-cancer, oestrogen receptor alpha agonist, and apoptosis-stimulating properties. Plants create primary metabolites to meet their basic needs, and secondary phytometabolites are primarily responsible for self-defense. The plant is abundant in phenols, vitamins, carotenes, calcium, potassium, iron, copper, cadmium, calcium oxalate, zinc, lead, and other substances [28].

Chemical Constituents in Different Parts [29-36]:

Stem: The plant's stem contains calcium oxalate, 31 methyl tritiacontanoic acid, taraxeryl acetate, taraxeroliso-pentadecanoic acid, β-amyrins, β-sitosterol, ketosetosterol, phenols, tannins, vitamin A, and carotene.

Aerial Part: It also contains calcium ions and phosphorus. 7-Oxo-Onocer-8-ene-3 β 21-α diol is a novel asymmetric tetracyclic triterpenoid found in the plant's aerial portions.

Leaves: Parthenocissus, pallidol, piceatanon, resveratrol, and alicyclic lipids are all found in leaves.

Roots: A consistent supply of mineral resources, such as potassium, calcium, zinc, sodium, iron, lead, cadmium, copper and magnesium, is frequently offered by root powder.

TABLE 1: THE SUMMARY OF CHEMICAL COMPOUNDS IN *CISSUS QUADRANGULARIS* LINN

Types of compounds	Compound	Plant part
Flavonol	Kacmpferol	Stem
	Quercetin	
Tetracyclic triterpenoid or saponin	Lupeol	Stem
Calcium oxalate	Calcium oxalate	Stem
Stilbene	Pallidol	Stem
	Parthenocissin	Stem
	Quadrangularin A	Stem
	Quadrangularin BQuadrangularin C	Stem
	Piceatannol	Stem
	Oxo-steroid	Stem
	Steroid	Whole plant
	Keto-steroid	Whole plant
		Whole plant
Potassium and phosphorus	δ-amyrin	Whole plant
triterpene Anabolic steroids	δ-amyrone	
	β-sitosterol	
Vitamin- c	Vitamin- c	whole plant

α-carotene	Chomolipid hydrocarbon	whole plant
Alkene alkaloid and alkenone	--	Aerial part

Therapeutic uses: Traditionally, the sturdy, juicy quadrangular stem has been used to cure burns, wounds, anemia, asthma, piles, eye disorders, gastritis, one fractures, skin infections, constipation, and irregular menstruation. The young shoots and leaves have strong alterative properties. Hemorrhoids and certain bowl infections are treated with powder. The stem paste heated in lime water is used to treat asthma, while the stem juice is helpful for scurvy and irregular menstruation. It's also utilized as a potent stomachic. Strong fracture healing properties, antibacterial, antiulcer, antioxidant, anti-osteoporotic, gastroprotective, cholinergic, and heart disease-preventive properties are all exhibited by *Cissus quadrangularis* Linn [37].

The antiulcer and cytoprotective properties of Cissus quadrangularis methanolic extract have been studied in relation to indomethacin-induced gastric mucosal damage. Additionally, the aqueous extract exhibits acetylcholine-like action on the rat uterus and isolated rabbit ileum. Acetylcholine's muscarinic and nicotinic effects on blood pressure in dogs are comparable. Both fresh and dry stem extracts exhibit antioxidant activity in their ethyl acetate fractions. Both the fresh and dry stem's ethyl acetate and methanol extracts further demonstrate santibacterial efficacy against gram-positive bacteria, such as Streptococcus species, Staphylococcus aureus, Bacillus subtilis, and Bacillus cereus. The current study emphasized the health-promoting and therapeutic qualities of Cissus quadrangularis because of its numerous and varied medicinal applications as well as pharmacological effects [38, 39, 40].

Pharmacological Activities:

Anti-ulcer Activity: Any disruption in the biological membrane that prevents the organs to which the membrane belongs from functioning normally is called an ulcer. There is a noticeable effect of CQ extract on peptic ulcers [41]. By increasing glycoprotein levels and decreasing gastric secretions, methanol extract exhibits strong antiulcer activity, as demonstrated by an experimentally induced ulcer in a rat model. It also produces a healing effect through an antioxidative mechanism when aspirin causes gastric mucosal destruction in rats. According to studies on gastric juice and mucosa, cissus at a dose of 500 mg/kg administered for 10 days significantly increases mucosal defense elements including mucin formation, mucosal cell multiplication, and cell life span, and β-sitosterol and triterpenoids [42] protect gastrointestinal injury. It is quite effective at curing peptic ulcers [43, 44].

Antibacterial and Antimicrobial Activity: The CQ's stem and root have strong antibacterial activity. Alcoholic preparations of the CQ's aerial portions have antiprotozoal action against both E. coli and *Entamoeba histolytica* [45, 46]. Primarily, these have been documented against *Salmonella typhi, Bacillus subtilis*, L. acidophilus, *Streptococcus pyogenes, Escherichia coli, Proteus mirabilis, Staphylococcus aureus, Pseudomonas aeruginosa* [47], *S. mutans*, and *Staphylococcus aureus*. Dichloromethane and 90% methanol extracts from the stem exhibit antibacterial action against *P. aeruginosa* and *E. coli*. It demonstrates that the Salmonella microbe is mutagenicity averse. Alcoholic extracts provide antiprotozoal action against *E. histolytica* [41] in the aerial portion. The growth of E. coli is significantly inhibited by plant-mediated CaO nanoparticles [48].

The aqueous extract of CQ has been shown to have antibacterial properties against *Helicobacter pylori* [49]. CQ's aqueous extract has antifungal and antibacterial properties against Pseudomonas aeruginosa [50] and Mucor sp. According to one experiment, CQ's ethyl acetate, ethanol, and methanol extracts had strong anti-*Kebsiella pneumoniae* action, with respective zones of inhibition of 22, 11, and 10mm [51]. A significant antibacterial tendency against cariogenic microorganisms [47] is revealed by CQ. The extracts of chloroform and ethyl acetate do not significantly inhibit Proteus mirabilis [52] and *Penicillium* sp. *Staphylococcus aureus, B. subtilis, Streptococcus species*, and *B. cereus* were among the Gram-positive bacteria that were relatively more vulnerable to the CQ extract than were the Gram-negative bacteria, *E. coli* and *P. aeruginosa*, which exhibit great resistance [53].

Antiosteoporotic Activity: Osteoporosis is a long-lasting, degenerative disorder that causes reduced bone mass due to micro-architectural bone tissue degradation. Lack of specific hormones, especially estrogen in women and androgen in males, along with an imbalance in the activity of osteoblasts and osteoclasts cells, are the main causes of osteoporosis in postmenopausal women. Because of a calcium deficit, osteoporosis causes the bones to weaken [54]. In postmenopausal osteoporosis, Cissus quadrangularis has some positive effects on bone mineral density recovery and considerably limits anabolic effects. An investigation was carried out to assess the anti-osteoporotic properties of Cissus quadrangularis ethanol extract at two distinct dose levels of 500 and 750 mg/kg daily in an ovariectomized rat model of osteoporosis. The results evaluated using biomechanical, biochemical, and histological parameters demonstrated a clear antiosteoporotic action of the plant's ethanol extract [55, 56].

Central Nervous System Activity: The root extract has depressive properties in the central nervous system, as evidenced by a reduction in exploratory behavior. Root methanol extract includes saponins that have strong hypnotic effects and prevent mice's spontaneous motor activity [57].

Analgesic and Stimulatory Activity: Because of flavonoids and β-sitosterol, methanol extract has analgesic, non-inflammatory, and venotonic effects on hemorrhoids. Methanol extract's β-sitosterol does have the capacity to lower MPO enzymes. This suggests that the flow of neutrophils into the inflammatory tissue has significantly decreased. Rats' neutrophils that are activated by aspirin-induced tissue injury benefit from ethanol extract [58].

Bone Healing Activity: The plant's alcoholic extract paste was applied both topically and intramuscularly to help albino rats heal fractures more quickly. The development of cortical bone and trabeculae in the fetal femur is improved by 95% ethanol extract, which may be linked to the high levels of calcium, phosphorus, and phytoestrogenic steroids. It has also been demonstrated to affect early regeneration and rapid mineralization of the bone fracture healing process [59].

Antioxidant and Free Radical Scavenging Activity: Due to the presence of β-carotene it may be exhibit strong antioxidant and free radical scavenging activity *in-vitro* and *in-vivo* systems [60].

Anti-inflammation: CQ may have an anti-inflammatory impact since it contains flavonoids, primarily beta-sitosterol and luteolin [61, 62]. One of the key ingredients in Ayurvedic medication formulation, "Laksha Gogglu," is also found in C. quadrangularis and has the ability to reduce swelling, relieve pain, treat related illnesses associated with fractures, and improve fracture healing [63, 64]. The EPP-induced rat ear oedema generation model is employed in the anti-inflammatory activity test, which is highly helpful for screening and examining inflammatory activity. Bradykinin, histamine, PGs, and serotonin are among the inflammatory mediators released in this model. These mediators are effective in increasing vascular permeability, promoting vasodilation, and causing oedema [65]. The CQ holdback effect on the development of ear oedema in the EPP-induced model [62] is demonstrated by experiments. Pro-inflammatory substances including TNFα and iNOS are inhibited by CQ, which also has anti-inflammatory properties [66].

Antihemorrhoidal Activity: Flavonoids are the main chemicals found in C. quadrangularis, according to a phytochemical analysis. The bioflavonoids have shown promise in the treatment of varicose veins and hemorrhoids, especially diosmin, hesperidin, and oligomeric proanthocyanidin complexes. These bioflavonoids have antagonistic effects on the biochemical mediators of inflammation, vasculoprotective effects, and phlebotonic activity. The flavonoids, particularly luteolin, and β-sitosterol may be responsible for the anti-inflammatory action already noted in the crude extract of C. quadrangularis. It is also possible that the flavonoids in the extract, which function similarly to diosmin and hesperidin, are responsible for the venotonic effect of C. quadrangularis. Since hesperidin and diosmin are used together to treat hemorrhoids, an extract that has the same anti-inflammatory and venotonic properties can likewise be utilized as an antihemorrhoidal medication [67].

Antioxidant: Key phytochemicals involved in oxidative stress-related disorders include carotenoids, steroids, calcium, and the ingestion of plant polyphenol antioxidants [68, 69]. By donating hydrogen radicals to primary radicals, which are subsequently reduced to non-radical chemical compounds and transformed into oxidized antioxidant radicals, antioxidants substances that hunt down free radicals play a significant role in preventing diseases caused by free radicals. CQ extract exhibits both anti-lipid peroxidative and free radical scavenging qualities [70]. *In-vitro* and *in-vivo* systems, the methanol extract of CQS exhibits strong antioxidant and free radical rummaging activity primarily due to the presence of β-carotene. It also inhibits the production of superoxide radicals, DPPH free radicals, and lipid peroxide in erythrocytes [68, 71]. Presence of flavonoids, indoles, photosteroid and keto compounds, and effective antioxidants [72]. Ethyl acetate from both fresh and dry stem extracts shows 64.8% antioxidant activity in the 1, 1diphenyl-2-picrylhydrazyl system and 61.6% in the β-carotene linoleic acid system [73].

Hepatoprotective Activity: *C. quadrangularis* methanol extract has hepatoprotective properties against rifampicin induced hepatotoxicity in rats. It was determined that its antioxidant activity, particularly the presence of β-carotene, may be responsible for the hepatoprotective mechanism. The plant's insulin-sensitizing and antioxidant properties provide hepatoprotection. Additionally, it demonstrated anti-lipid peroxidative and free-radical scavenging properties, and by boosting the activity of antioxidant enzymes, it lessened liver damage [74].

Gastro Protective Activity: Due to its abundance of carotenoids, triterpenoids, and ascorbic acid, Cissus quadrangularis is well recognized in traditional medicine for treating gastrointestinal diseases. Its function in human nutrition has also drawn a lot of interest. Numerous research has examined and demonstrated the preventive activity of Cissus quadrangularis extract (CQE) against gastrointestinal toxicity and the mechanism underlying its therapeutic action against aspirin-induced damage to the stomach mucosa [75].

CNS Depressant Activity: The CNS depressant activity of Cissus quadrangularis root extract is evidenced by reduced spontaneous motor activity, decreased exploratory behavior, impaired motor coordination, and potentiation of pentobarbitone-induced sleep. This activity is likely attributed to the saponin content present in the extract [76].

Miscellaneous Activity: The decoction made with Piper nigrum and *Zingiber officinale* soothes physical pain, while the dry powder made from the shoot can help with digestive problems. Stem paste has excellent cardiotonic properties and can be used for burns, insect bites, wounds, and muscle pain64. Additionally, it exhibits the ability to treat epilepsy, convulsions, leprosy, and camel and horse saddle sores. It is a major factor in weight loss and obesity reduction, and a mixture of stem powder pulses fried in sesame oil is used to treat a number of "Vata" illnesses [77, 78].

CONCLUSION: *Cissus quadrangularis Linn* emerges as a promising medicinal plant with diverse therapeutic applications and pharmacological properties. This comprehensive review highlights its traditional use in Ayurveda and its scientifically validated efficacy in managing bone health, fractures, inflammation, obesity, diabetes, and gastrointestinal disorders. The plant's bioactive compounds, including flavonoids, triterpenoids, and phytosterols, contribute to its wide-ranging biological activities. While the pharmacological potential of *C. quadrangularis* is significant, most studies have been preclinical or exploratory in nature, with limited clinical validation. Future research should focus on large-scale clinical trials, detailed toxicological evaluations, and the development of standardized formulations to ensure safety, efficacy, and reproducibility. Moreover, exploring synergistic effects with other medicinal plants and understanding molecular mechanisms can further enhance its therapeutic applications. In conclusion, *Cissus quadrangularis Linn* represents a valuable phytomedicine with a broad spectrum of health benefits, warranting further scientific exploration for its integration into modern medicine.

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