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Review Article

Vine of Vitality: Exploring *Cissus* Benefits

P. S. Malusare, Dr. P. G. Kale*, K. R. Pawar, M. S. Nalawade

Abhinav Education Society's College of Pharmacy, (B. Pharm), Narhe, Pune.

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ABSTRACT

Cissus quadrangularis, commonly known as "Hadjod," is a tropical plant renowned for its wide range of medicinal properties, particularly in traditional healing systems such as Ayurveda and African medicine. This review explores the numerous health benefits associated with Cissus, focusing on its potential to promote bone health, aid in weight management, improve metabolic function, reduce inflammation, and enhance recovery from physical injuries. Its bioactive compounds, including flavonoids, alkaloids, and tannins, have been shown to possess anti-inflammatory, antioxidant, and analgesic properties. Additionally, Cissus has garnered attention for its role in supporting joint health, reducing oxidative stress, and potentially improving glucose metabolism, making it a promising natural supplement for various conditions. Through an examination of clinical studies and traditional uses, this paper aims to provide a comprehensive understanding of Cissus quadrangularis therapeutic potential, its mechanisms of action, and its evolving role in modern healthcare, promote innovation, and guide future research in Laser-Induced Breakdown Spectroscopy.

INTRODUCTION

The World Health Organization (WHO) estimates that between 20,000 and 35,000 plant species are used by various ethnic groups around the globe for medicines, cosmetics, health supplements, and treatments. Approximately 80% of individuals in underdeveloped nations use traditional medicine to maintain their health and vitality.[1] In India, people from all backgrounds use plants with healing properties. These plants are part of traditional medicine systems like Siddha, Ayurveda, and Unani, and they are also made into products by the pharmaceutical industry. Developing local medicines and using medicinal plants for treating diseases can bring significant economic advantages. The healing power of these plants comes from specific chemical substances that have clear effects on the human body.[2] Plant extracts and bioactive compounds have the potential to be used in the treatment of various diseases and may be incorporated by pharmaceutical companies to develop innovative

***Corresponding Author:** Dr. P. G. Kale
Address: *Abhinav Education Society's College of Pharmacy, (B. Pharm), Narhe, Pune.*
Email ✉: priyanka7337@gmail.com

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drug formulations.[3] Plants produce secondary metabolites that have important health benefits. These include properties that can fight oxidation, allergies, infections, skin conditions, rheumatoid arthritis, itching, worms, high blood sugar, and cancer.[4]

Cissus quadrangularis, commonly referred to as "Hadjod," is a perennial plant belonging to the Vitaceae family.This plant is recognized by various other names, such as Adamant creeper, Square stalked vine, veldt grape, devil's backbone, asthisamharaka, and pirandai, in addition to Sannalam, Nalleru, Vajravelli, and Mangara valli. While it is indigenous to India, Bangladesh, and Sri Lanka, it can also be located in Southeast Asia and Africa. Brazil and the southern region of the United States are both engaged in its importation. [5] The plant is a climbing herb that lives for many years. It has a thick, four-sided stem and other parts that grow above the ground, like Vines, foliage, blossoms, and produce.The stem of *Cissus quadrangularis* contains many important natural compounds. [6]

Fig 1: *Cissus quadrangularis* plant

The plant has a variety of ethnobotanical applications.The leaves and stem of *Cissus quadrangularis* Linn are abundant in phytochemicals such as alkaloids, amino acids, flavonoids, steroids, reducing sugars, gums, tannins, and saponins, terpenoids and large stilbene derivatives. which may provide health advantages. Extracts from its stem and root exhibit antioxidant properties, aid in the healing of bone fractures, and possess antimicrobial effects. The juice extracted from the stem is utilized for addressing various health issues, including scurvy, irregular menstrual cycles, ear discharge, and nosebleeds. Additionally, the stem extract is particularly rich in calcium and phosphorus.[7] *Cissus quadrangularis* is utilized for a variety of treatments, including the healing of fractures, ulcer reduction, parasite elimination, fungal infections, hemorrhoid relief, pain alleviation, and antibacterial properties. Hemorrhoids, leprosy, epilepsy, indigestion, skin burns, dysentery, intestinal issues, and hunger stimulation are among the conditions for which it is most beneficial.To identify and isolate plant materials, several analytical techniques are employed, including Ultraviolet and Infrared Spectroscopy, along with chromatographic methods like Thin Layer Chromatography (TLC). The selection of the method primarily depends on the solubility and volatility of the compounds involved. [8] Medical literature contains many types of *Cissus quadrangularis*. Madayan and Citraputhran (1987) identified three types: the four-angled or square-stemmed type called *C. quadrangularis*, the acrid-tasting type known as C. setosa, and the red-colored type referred to as C. vitiginea. Warrier et al. (1994) observed that a two-sided variety of *C. quadrangularis* was present in gardens.[9]

History:

Cissus quadrangularis, often called "Veldt grape," "Hadjod," or "Devil's backbone," is a plant found in India, Southeast Asian countries, and Africa. This plant belongs to the Vitaceae family and has a long history of use in Ayurvedic and Siddha medicine.In Ayurveda, it is known as "Asthisamharaka," which means "bone setter," because it is believed to help heal bones. It has also been used for issues like obesity, hemorrhoids, and gout. This plant is popular in Thailand for its medicinal properties. In African medicine, it is used similarly to Ayurveda. The entire plant is employed in the treatment of a range of medical

conditions.*Cissus quadrangularis*is a traditional remedy that has gained recognition in many regions due to its widespread growth. Since the 20th century, research has backed its traditional uses, showing benefits in bone healing, antioxidant effects, and potential help with osteoporosis, diabetes, and obesity. Traditionally, it was mainly used for women's health issues (like menopause and menstrual problems) and bone conditions. Other traditional uses include its believed anti-ulcer, anti-hemorrhoid, pain relief, and wound healing properties.[5,10,11]

Common names/Regional names :

English: Vegetable with edible stems
Sanskrit : Asthissamdhani
Hindi: Kandvel, Hadjod, Hadjora,and Hadsarihari
Bengali: Hasjora, Horjora
Gujarati: Vedhari, Hadsankal
Kannada : Mangroli
Malayalam: Peranta, Cannalam Paranta
Marathi: Kandavel, Harsankar, and Horjora
Punjabi: Haddjor
Tamil: Perandai, Pirantai
Telugu: Vajravalli, Nelleratiga, and Nalleru [12]

Synonym:

Cissus bifida scum. and thonn
Cissus edulis Dalz.
Cissus quadrangular Salisb.
Cissus quadrangulus L.
Cissus Succulenta (gulpin) Burtt Davy
Cissus tetragona Harv.
Cissus triandra Schum. And Thonn
Saelanthus quadragonus Forssk
vitis succulent Galpin

Taxonomical Classification: [13]

Table 1: Taxonomy of *Cissus quadrangularis*

Sr. No	Taxonomy	Overview
1	Kingdom	Plantae
2	Sub Kingdom	Tracheobionta
3	Phylum	Tracheophyta
4	Division	Magnoliophyta
5	Super Division	Spermatophyta
6	Class	Magnoliopsida
7	Sub Class	Rosidae
8	Family	Vitaceae
9	Sub Family	Vitoideae
10	Genus	Cissus
11	Species	Quadrangularis
12	Order	Vitales

Geographical Distribution:

About 800 species of Cissus plants, which belong to the Vitaceae family, are distributed throughout 13 genera in regions such as Africa, Arabia, South Asia, Sri Lanka, and India. In India, there are 8 genera and 63 species. This plant grows well in warm places such as India, Sri Lanka, Bangladesh, Malaya, West Africa, and Thailand. It has many medicinal properties because of its different plant compounds and is mostly found in tropical and subtropical regions. States such as Assam, Kerala, Odisha, Madhya Pradesh, Tamil Nadu, and Uttar Pradesh are especially impacted. It is commonly called 'Hadjod' or 'Asthisamharaka' in the area and is often used to treat issues with bones, muscles, and ligaments. [14,15]

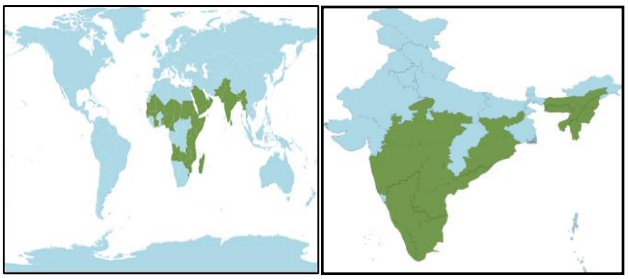


Fig 2: World and India map of *Cissus quadrangularis*(https://indiaflora-ces.iisc.ac.in/herbsheet.php?id=2619&cat=13) The green surface area on map shows the distribution area of *Cissus quadrangular*

Benefits of Ayurveda:

Rasa - Sweet

Guna - Light, Dry, Clear

Veerya - Sweet

Vipaka - Sweet

Doshaghnata - Reduces Kapha and Vata, Increases Pitta

Morphological Description: [16,17]

Table 2: The macroscopic characteristics of *Cissus quadrangularis*

Part	Description	Picture
Stem	Plant's stem is wet, thick, long, soft, and dark green. It is smooth, has four sides, and has wing-like edges. The stem is narrow at the joints. When the stem is young, it has sharp angles, long tendrils, and is mostly simple, while older stems are nearly without leaves.	
Leaves	Leaves on the plant are simple and oval-shaped. They can be whole or heart-shaped, with small teeth or wavy edges. The leaves may have 3 to 7 lobes, with the top lobe being triangular or somewhat spoon-shaped. They are slightly pointed and thin, smooth on both sides, measuring about 3 to 5 cm by 5 to 3 cm.	
Flower	A stem holds a flower that can be pink or white and is around 2 mm long. The green, cup-like hypanthium of the flower is 2 mm wide and may be flat or slightly lobed. The ovate-oblong, pointy, hooded-tipped petals are separated into four halves, each 1.5 mm long. The ovary is smooth, has a tiny stigma, and a slender style.	
Fruit	The plant's fruit is spherical, red, juicy, very acidic berries with a solitary seed that range in diameter from 6 to 10 mm. The oblong and smooth seeds have a width of 4 to 8 mm. Usually, June and July are when flowers and fruit appear.	
Tendrile	Tendrils are elongated, thin, and spirally twisted structures. They are unbranched and emerge from the nodes situated opposite the leaves. Initially green in color, they transition to brown upon drying. In their fresh state, they exhibit a smooth and pliable texture.	

Root	The roots exhibit a cylindrical shape, with a slight tapering and potential for irregular branching. Their texture can vary between fibrous and fleshy. Externally, the coloration ranges from light yellowish-brown to dark brown, while the internally is pale yellow to white.	

Microscopic Description:

T.S of stem:

The area in the middle of the stem shows four elongated wings, each about 1.4 mm thick and 5.8 mm long, with a central thickness of 1.8 mm. The epidermis is protected by a thick cuticle, featuring circular, thick-walled, tangentially elongated cells. Ground tissues consist of densely packed, thi n-walled parenchyma. Beneath the epidermis is a cork layer, followed by 8 to 16 layers of collenchymatous cells at angular points over vascular bundles. Each wing contains three collateral vascular bundles, surrounded by a sclerenchymatous sheath. The xylem is broad, angular, and thin-walled, with phloem cells surrounding it and thin-walled fibers enveloping the xylem. A distinct cambium and interfascicular cambium are present, along with a large central pith. Acicular calcium oxalate crystals arelso distributed throughout.[18]

T.S of leaf:

The cross-section of the leaf midrib reveals a convex surface on the adaxial side and a brief conical surface on the abaxial side. The midrib features a delicate epidermal layer composed of small, thick-walled, square-shaped cells. The adaxial ground tissue is characterized by densely packed, thick-walled circular cells, whereas the surrounding regions are comprised of fragmented, small lobed parenchyma cells. The vascular system is composed of four radiating arms of vascular strands, featuring two to three rows of xylem elements and phloem located at the outer edges. The xylem is characterized by its circular, narrow, and thick-walled cells. The leaf lamina displays a distinct dorsiventral structure, characterized by layers of spherical spongy parenchyma cells located on the abaxial surface, while the adaxial surface features a single row of cylindrical palisade cells.Calcium oxalate raphides are present in thick bundles throughout the mesophyll.[19]

T.S of root:

The cross-section of the secondary root is circular, in contrast to the rectangular shape of the primary root.The periderm is rectangular with a multilayered cortex. The main root contains dispersed cells with calcium and tannin deposits, a substantial pith, and nearly three medullary rays at each corner, while the secondary root has evenly spaced medullary rays.[20]

Microscopy by powder:

Under a microscope, the powder showed slender lignified xylem fibers that taper at the ends and round or oval parenchyma cells that might be seen alone or in clusters. The narrow, elongated vessel elements have partially scalariform pits and uniseriate, horizontally elliptical lateral wall pits. Calcium oxalate crystals were also identified in the form of raphides and druses, along with cyclocytic stomata that were surrounded by one or two layers of subsidiary cells.[21]

Cultivation:

The medicinal herb *Cissus quadrangularis*, often called "Hadjod" or "bone setter," is indigenous to Africa and India. With internodes with four wings and tendrils at the nodes, this shrubby climber can grow to a height of approximately 1.5 meters. The internodes of its joined stems are 8–10 cm length and 1.2–1.5 cm broad. The plant rarely blooms, but

when it does, it produces meaty berries as fruit and tiny, bisexual, greenish-white flowers across from the leaves. Propagation primarily occurs from May to July, utilizing seeds and stem cuttings; however, the viability of seeds is often low. Warm tropical temperatures are ideal for *Cissus quadrangularis*, which grows up to 500 meters above sea level in wastelands, woods, and coastal plains. Plant material consists of quadrangular, 4-winged stem segments that are 4 to 15 cm long and 1 to 2 cm thick. It usually flowers from June to December. Established vines have a 20-foot spread.[22]

Phytochemical Screnning: [23,24,25]

Table 3: Phytochemical test of *Cissus quadrangularis*

Phytoconstituents	Test Name	Petroleum Ether Extract	Chloroform Extract	Ethanol Extract	Aquous Extract
Alkaloids	Marquis reagent	+	+	+	-
	Wagner's reagent	+	+	+	+
	Mayer test	+	+	+	+
Flavonoids	Ammonia test	+	+	+	+
	Sodium hydroxide test	+	+	+	+
Flavones	Sulphuric acid test	+	+	-	+
Terpenoids	Salkowski test	+	+	+	+
Phytosterols	Lieberman Burchard	+	+	+	-
Phenol	5% aq Fe Cl_3	-	-	+	-
Tannins	Alcholic Ferric chloride	-	-	+	-
Saponins	Foam test	-		+	
Glycoside	1% aq Fe Cl_3 test	+	+	+	+
	Sodium hydroxide test	+	+	+	+
Cardiac glycosides	Kellar kiliani test	+	+	+	+
Cardiac glycosides	Borntrager's test	-	-	-	-

Chemical Constituents:

Flavonoids such as quercetin, daidzein, and genistein; triterpenoids including friedelin; vitamin C; stilbene derivatives like quadrangularin-A, resveratrol, and piceatannol; iridoids such as 6-O-meta-methoxy-benzozyl catapol, picroside, and pallidol; as well as phytosterols like β-sitosterol and calcium represent significant components of the plant.[26] A variety of compounds have been extracted from plants, including flavonoids such as kaempferol and quercetin, stilbene derivatives known as quadrangularins A, B, and C, as well as other substances like phyto-sterols and resveratrol. The stem extract is especially high in phosphate and calcium, which are necessary for the formation of bones. [27]

Chemical constituents in the leaves:

Resveratrol, piceatannol, pallidol, parthenocissus, and alicyclic lipids are among the phytochemicals

found in the leaves. The compounds identified through gas chromatography-mass spectrometry (GC-MS) analysis of the ethanolic extract comprise n-hexadecanoic acid, phytol, bis(2-methylpropyl) ester, ethyl ester, 1,2-benzenedicarboxylic acid, caffeine, hexadecanoic acid, 3-dodecanol, dibutyl phthalate, and pentane,1,1-diethoxy.[28]

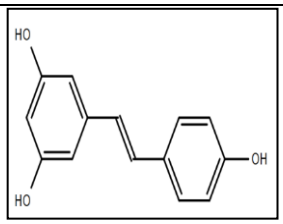
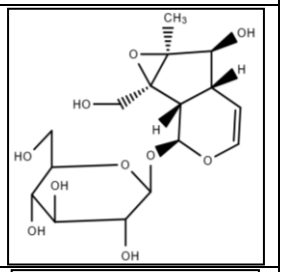
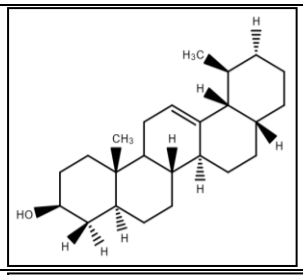
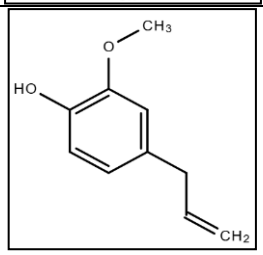
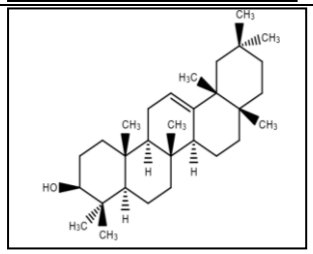
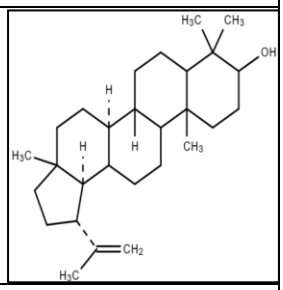
Chemical constituents in the stem:

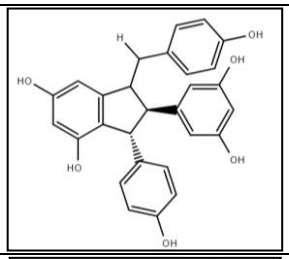
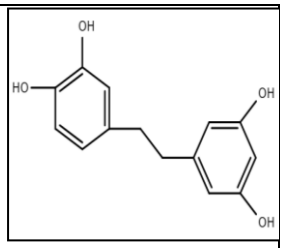
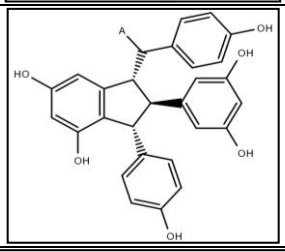
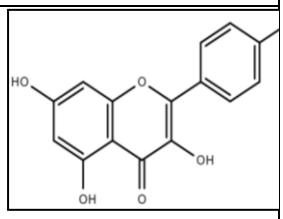
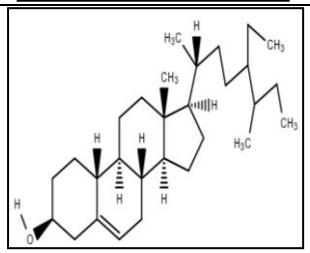
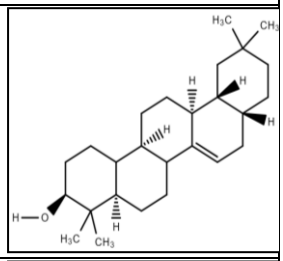
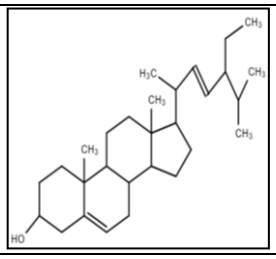
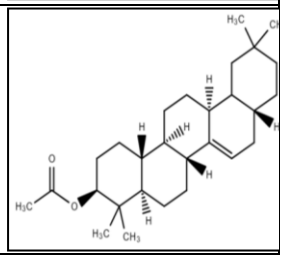
The stem of the plant contains a variety of substances, including vitamins, carotene, calcium oxalate, 31-methyl tritiacontanoic acid, taraxeryl acetate, taraxerol, iso-pentadecanoic acid, phenolic compounds, tannins, A and β-amyrins, β-sitosterol, ketosetosterol, as well as calcium and phosphorus ions. The aerial parts, in contrast, are characterized by the presence of 7-Oxo-Onocer-8-ene-3 β 21-α diol, a novel tetracyclic triterpenoid. The stem extract is notable for containing 4% by weight of calcium ions, along with phosphorus, calcium oxalate, 31-methyl tritiacontanoic acid, taraxerol acetate, taraxerol, and iso-pentadecanoic acid. Phytochemical analyses have also identified alpha and β-amyrins, β-sitosterol, ketosetosterol, phenolic compounds, saponins, carotene, neophytadiene, and 1-octadecyne.[29,30]

Chemical constituents in the root:

Powder of root is a source of minerals like potassium, calcium, zinc, sodium, iron, lead, cadmium, copper, and magnesium in the concentration of (mg/100g dry matter): 67.5, 39.5, 3.0, 22.5, 7.5, 3.5, 0.25, 0.5, and 1.15, respectively. Various toxic substances are also identified like oxalate, tannin, phytate, and saponin. [31]

Table 4: Chemical constituents present in *Cissus quadrangularis*

Compound	Structure	Compound	Structure
Resveratrol		Catapol	
α-Amyrin		Eugenol	
β-Amyrin		Lupeol	
Quadrangularin A		Piceatananol	

			
Quadrangularin B		Kaemeferol	
Beta-sistosterol		Taraxerol	
Stigmasterol		Taraxeryl acetate	

Pharmacological Activity:

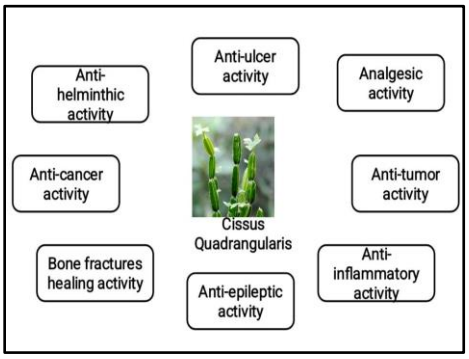


Fig 3: The *Cissus quadrangularis* therapeutic properties

Anti-Cancer Activity:

The plant's alcoholic extract shown anticancer effects on a range of cell lines, including those linked to kidney, breast, colon, skin, and cervical malignancies.[32]

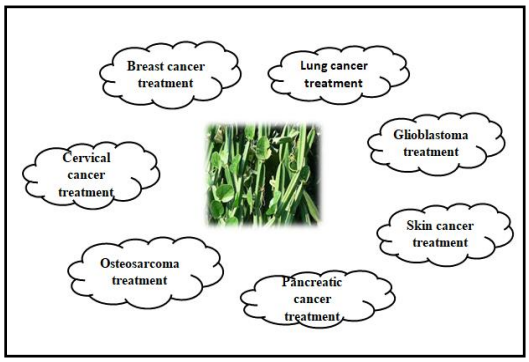


Fig 4: The *Cissus quadrangularis* anticancer activity

Table 5: Efficacy of phytochemicals from *Cissus quadrangularis*in cancer treatment

Name of the phytochemical/ extract from *Cissus quadrangularis*	Parts used	Active against	Mode of action	Ref. No
Ethanol-based extract.	Stem	Skin cancer (A431 cells)	CQ extract caused damage to A431 cells and triggered cell death (apoptosis).	[33]
Gamma-Tocopherol	Stem	Oral cancer	CQ caused cancer cells in the mouth to stop growing and made them die by blocking their normal cycle of division at an early stage.	[34]
Quercetin and rutin are flavonoids	Aerial part	Breast carcinoma	Decreased the survival rate of breast cancer cells..	[35]
Epi-glut-5(6)-en-ol and betulinic acid	Stem	Non-small cell lung carcinoma (NCI-H226) and colorectal cancer (HCT-116) cell lines.	It exerts cytotoxic effects on both colon cancer cells and lung cancer cells.	[28]
Lupeol	Stem	MCF -7 Cells associated	Showed a significant ability to boost melanin	[28]

		with breast cancer	production, linked to higher extract concentration, while inhibiting cancer cell proliferation.	
Methanolic extract	Aerial part	MG63 (Osteosarcoma cell line)	The methanolic extract of CQ reduces the proliferation of MG63 cells in a dose-dependent fashion.	[32]
Ethanol based extract	Stem	Squamous cell carcinoma (oral epidermoid carcinoma cells derived from KB).	Membrane blebbing, cellular shrinkage, and a loss of membrane asymmetry were observed in KB cells following the treatment.	[36]
Chloroform and ethanol extracts.	Aerial part	EAC (Enriched Ascites Carcinoma) cell line	It exhibited an antagonistic effect on the Ascites carcinoma cells, resulting in cytotoxicity.	[36]

Bone Fracture Healing Activity:

Cissus quadrangularis is a source of vitamins and steroids that enhance bone fracture healing. The anabolic elements facilitate the prompt recovery of connective tissues and enhance the rapid mineralization of the callus. In rat studies, systemic administration of *Cissus quadrangularis* led to complete restoration of normal bone composition within four weeks post-fracture, compared to six weeks for the control group, reducing healing time by about two weeks. Additionally, the fractured bone's weight returned to near-normal levels sooner, indicating more efficient remodeling. The healing phases were accelerated by 10 to 14 days in the *Cissus quadrangularis* group.[37]

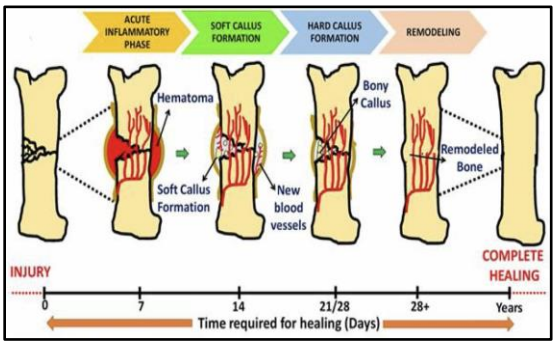


Fig 5: A diagrammatic illustration depicting the various stages of bone healing, from the initial injury to the final remodeled bone.[42]

The mechanism by which *Cissus quadrangularis* facilitates bone regeneration is as follows:

Bioactive compounds derived from CQ have the ability to regulate gene expression associated with bone remodeling, thereby affecting both osteoblastogenesis (the process of bone formation) and osteoclast genesis (the process of bone resorption). Mitogen-activated protein kinases (MAPKs) are crucial regulators of bone mass, significantly influencing the functions of both osteoblasts and osteoclasts. In osteoblasts, MAPK phosphorylation activates nuclear factor kappa-B (NFκB), while in osteoclasts, its dephosphorylation inhibits late differentiation markers like matrix metalloproteinases (MMPs), which are linked to extracellular matrix degradation. Thus, MAPK signaling promotes osteoblastogenesis and suppresses osteoclastogenesis. Research indicates that the dephosphorylation of MAPK plays a role in the inhibition of MMPs, which in turn contributes to the degradation of cartilage and bone. Furthermore, CQ facilitates the differentiation and mineralization of osteoblasts through the activation of activator protein-1 (AP-1) via c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK). Inhibitors of JNK, MAPK, and ERK reduce alkaline phosphatase (ALP) activity, indicating CQ's role in regulating osteoblasts via the MAPK pathway. Additionally, MAPK facilitates the movement of β-catenin into the nucleus through the Wnt/β-catenin signaling pathway, which in turn stimulates osteoblast differentiation by increasing the expression of runt-related transcription factor 2 (Runx2), bone morphogenetic proteins (BMPs), and alkaline phosphatase (ALP).CQ-E has been shown to enhance ALP activity and tissue mineralization. Sirtuin 1 (SIRT1) is essential for osteoblastogenesis, interacting with Runx2 to promote its deacetylation during ossification. Osteoblasts increase osteoprotegerin (OPG) levels, enhancing osteoblast-related gene expression (COL1A1, osteocalcin, osteopontin) and exhibiting anti-resorptive properties by down-regulating RANK and inhibiting NFATc1, while increasing apoptosis-related genes like Caspase-3 within osteoclasts. The OPG to RANK ligand (RANKL) ratio in osteoblasts further reduces osteoclast progenitor differentiation. Molecular docking studies have revealed that quercetin and rutin present in the CQ-E fraction act as enhancers of hydroxyproline, alkaline phosphatase (ALP), and osteoprotegerin (OPG), while simultaneously inhibiting the receptor activator of nuclear factor kappa-B ligand (RANKL) within osteoblasts. Additionally, resveratrol, which is derived from CQ, contributes to the enhancement of bone micro-architecture by elevating the OPG to RANKL ratio and decreasing the expression of the osteoclastic gene TRAP5b. It also modulates FOXO1 and FOXO3 expression via the SIRT1 pathway, promoting antioxidant enzymes and

Runx2, highlighting its dual anabolic and anti-resorptive effects in bone remodeling.[38,39,40,41,42]

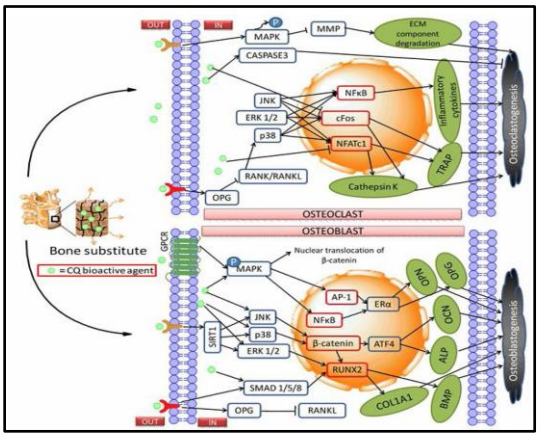


Fig 6 : A diagram illustrating the orthopedic use of bioactive compounds from *Cissus quadrangularis* through bone substitutes, emphasizing their roles in promoting osteoblastogenesis and osteoclastogenesis for bone remodeling.[42]

Anti-Inflammatory and Pain-Relieving Properties:

Methanol based extract of *Cissus quadrangularis* exhibits analgesic, anti-inflammatory, and venotonic properties beneficial for hemorrhoid treatment. Its anti-inflammatory effects are primarily due to flavonoids like luteolin and β-sitosterol, which reduces the enzyme MPO, indicating decreased neutrophil infiltration in inflamed tissues. Ethanol extract protects neutrophils from aspirin-induced damage in rats. Both methanolic (90%) and dichloromethane extracts inhibit the COX-2 enzyme, while the extract's vitamin content enhances its effects beyond those of durabolin. Luteolin inhibits lipo-oxygenase enzymes, and β-sitosterol reduces edema from arachidonic acid, acting as a dual inhibitor of its metabolism. The extract's anti-inflammatory efficacy is confirmed by its ability to inhibit COX, 5-LOX, and TNF-Alpha, with an active fraction showing an IC50 of 550 µg/ml. In vitro studies demonstrated a dose-dependent reduction in COX, iNOS, and TNF-Alpha levels. Research on analgesic and antipyretic properties suggests that its effectiveness is similar to that of aspirin, successfully alleviating acetic acid-induced writhing in mice and reducing hyperpyrexia. The remarkable anti-inflammatory and cartilage-regenerative characteristics of *Cissus quadrangularis*, along with its mechanism of action that includes the inhibition of MMP and ROS, are of considerable importance. Furthermore, we suggest that survivin is crucial for chondroprotection and osteogenesis by blocking the p38 MAPK signaling pathways.[43,44,38]

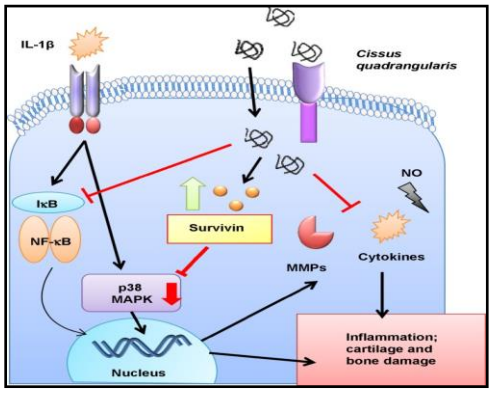


Fig 7: *Cissus quadrangularis* mitigates catabolic processes associated with IL-1β-induced inflammation and cartilage deterioration by decreasing the levels of pro-inflammatory cytokines and matrix metalloproteinases (MMPs).
(IL-1β = interleukin-1β; MAPK = mitogen-activated protein kinase; MMPs = matrix metalloproteinases; NO = nitric oxide; NF-κB = nuclear factor kappa B)[38]

Anti-Diabetic Activity:

The ethanolic extract of the plant offers protection against diabetic nephropathy in rats subjected to high-fat diets and streptozotocin-induced diabetes by improving insulin resistance, as well as normalizing creatinine levels and lipid profiles.It restores albuminuria, enhances creatinine clearance, and improves glomerular filtration rate while modulating SIRT1 and DNMT1 expression. The extract protects against renal inflammation, oxidative stress, and fibrosis by downregulating TGFβ, col1/3, and Smad2/3. It additionally reduces serum glucose concentrations, inhibits weight loss, and enhances glucose absorption in diabetic rats induced by alloxan. The ethyl acetate fraction derived from the stem exhibits notable antidiabetic properties, leading to elevated blood glucose levels and inflammatory markers, while simultaneously decreasing the activity of antioxidant enzymes. It stimulates the mRNA expression of IL-6, TNFα, and NF-κB in adipose tissue and improves the histopathological conditions of the liver and pancreas in diabetic rats, showing effectiveness comparable to that of metformin. Administered at 100 mg/kg, this fraction lowers blood glucose by modifying carbohydrate-metabolizing enzyme activities, significantly enhancing pyruvate kinase and hexokinase while decreasing other enzyme activities, thus impacting carbohydrate metabolism in diabetes models. The rhizome extract of *Cissus quadrangularis* demonstrates a notable anti-diabetic effect in rats induced with Alloxan, successfully managing blood glucose levels. Furthermore, the ethanolic extract (EECQ) offers protection against steatohepatitis associated with type 2 diabetes by inhibiting NOX4.[45,46,47,48,49]

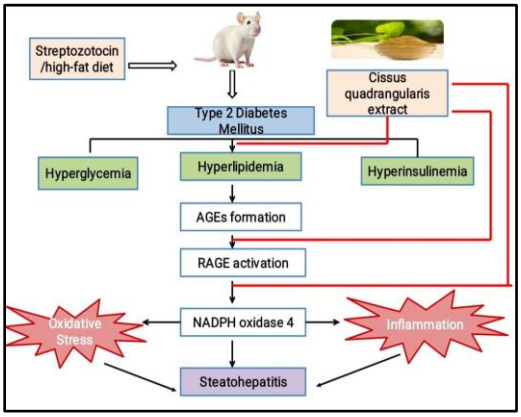


Fig 8: Inhibits NOX4, protecting against steatohepatitis caused by type 2 diabetes

Anthelmintic Activity:

The methanol stem extract exhibits notable anthelmintic activity against Pheretima posthuma, with effectiveness that is comparable to that of the pharmaceutical agent albendazole. [50] The alcoholic infusion of root similarly induced paralysis within 8.33 minutes and led to mortality at 18.50 minutes, demonstrating its effectiveness against *Pheretima posthuma* and showing results comparable to those of piperazine citrate.[51] Additionally, a concentrated methanol extract derived from the aerial portions of the plant exhibits significant adulticidal effects, inhibiting

88% of egg hatching in the ruminant parasite *Haemonchus contortus*. [52]

Antimicrobial Activity:

The methanolic extract obtained from the plant has exhibited significant antiviral properties against herpes simplex virus types HSV1 and HSV2, which are known to cause skin infections in humans, while simultaneously displaying no cytotoxic effects on vero cells. [53] The petroleum ether extract derived from the plant demonstrates antibacterial activity against Gram-positive bacteria, notably *S. Aureus* and *B. cereus* in addition to Gram-negative pathogens like *S. typhi* and *Ecoli*. Furthermore, the methanol extract sourced from the stem has shown antimicrobial efficacy against specific avian microorganisms, including various *Escherichia* species. Additionally, the ethanol extracts obtained from the shoots have been effective against a range of pathogenic bacteria, including *Ecoli, P. Species, S. Aureus, B. subtilis,* and *Klebsiella pneumonia*.[54]

Adiposity-reducing activity:

The ethanolic extract of the plant exhibits anti-hyperlipidemic effects and has potential in reducing the concentrations of phospholipids, cholesterol, HDL, and TG in animal models that are fed high-fat diets.[55] The aqueous extracts obtained from the leaves and stems of the plant, when given at a dosage of 300 mg, have shown efficacy in reducing body fat as well as decreasing both systolic and diastolic blood pressures, TG levels, waist and hip measurements, fasting blood glucose, total cholesterol, and leptin levels. Furthermore, these extracts are linked to an increase in adiponectin levels and HDL-cholesterol in human subjects. [56]

Anti-Ulcer Activity:

The extract of *Cissus quadrangularis* exhibits significant efficacy against peptic ulcers. The methanol extract demonstrates notable anti-ulcer properties, as evidenced by experiments conducted on a rat model, which show an enhancement in glycoprotein levels and a reduction in gastric secretions. Furthermore, it promotes recovery from gastric mucosal injury caused by aspirin in rats through an antioxidative mechanism. Research on gastric juice and mucosa indicates that a dosage of 500 mg/kg of *Cissus quadrangularis* administered over a period of ten days markedly enhances mucosal protective factors, including the production of mucin, the proliferation of mucosal cells, and their lifespan. Furthermore, gastric damage is mitigated by the presence of β-sitosterol and triterpenoids, indicating a strong potential for healing peptic ulcers. Prior to the induction of ulcers using ethanol and indomethacin, the extract of *Cissus quadrangularis* led to a notable decrease in ulcer formation when compared to the control group. This extract exhibited a protective effect that was dosage-dependent across both ulcer models. Significant reductions ($p < 0.05$) in the number of ulcer lesions were observed in rats that received different doses of the extract in conjunction with ranitidine (100 mg/kg body weight), relative to the control groups in both experimental setups.[57]

Anti-Fungal Activity:

The antifungal properties of *Cissus quadrangularis* extract were assessed by comparing its effectiveness to that of fluconazole, which acted as the standard reference medication. The study utilized the conventional agar-well diffusion method, and the antifungal efficacy was assessed by measuring the diameter of the inhibition zone present on the surfaces of the Petri dishes.. The results indicated that *Cissus quadrangularis* extract exhibited notable antifungal activity, particularly the diethyl ether extract, which demonstrated significant effectiveness against *Aspergillus flavus*.[44]

Anti-Oxidant Activity:

Numerous studies have assessed the anti-oxidant properties of *Cissus quadrangularis* through both in-vivo and in-vitro analyses. A particular study

utilized two separate in-vitro techniques. The original method evaluated antioxidant activity by measuring the rate of lipid peroxidation in erythrocytes, utilizing the production of Thiobarbituric acid reactive substances (TBARS) as a marker, with Butylated hydroxytoluene (BHT) serving as the reference compound.The alternative approach utilized the decolorization of the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, employing Catechin as the standard reference compound. The extract of *Cissus quadrangularis* exhibited notable anti-oxidant activity in both methodologies, showing results comparable to those of the reference drugs.Additionally, an in-vivo investigation into the antioxidant properties of *Cissus quadrangularis* was performed using rats administered carbon tetrachloride (CCl4). This study involved the assessment of several enzymes, including Aspartate aminotransferase, Superoxide dismutase, catalase, and Glutathione peroxidase, which served as biomarkers. The results demonstrated that rats that received pretreatment with *Cissus quadrangularis* extract showed decreased levels of these enzymes, indicating the potential antioxidant activity of the plant.[58]

Anabolic and Androgenic Activity:

Cissus not only speeds up the process of bone remodeling but also greatly improves the tensile strength of bones. Clinical studies have demonstrated that Cissus can reduce fracture healing time to approximately 55-33 percent compared to control groups. The anti-glucocorticoid properties of Cissus are supported by various studies indicating that when bones are compromised due to cortisol treatment, the administration of Cissus extract halts the weakening caused by cortisol and initiates the healing process. Endogenous glucocorticoids, including cortisol, activate pathways that lead to the degradation of both bone and skeletal muscle tissue. Glucocorticoids are recognized for their role in facilitating muscle degradation through the activation of the Ubiquitin-Proteasome proteolytic pathway, a critical mechanism for eliminating damaged and dysfunctional proteins. Cissus *quadrangularis* contributes to the maintenance of muscle tissue during periods of physical and emotional stress by exerting both anabolic and anti-glucocorticoid effects, which is especially important for bodybuilders and athletes.[59]

Toxicity Study:

Before evaluating the pharmacological effects of natural drugs on animals, assessing their toxicity is crucial. Studies on CQL's toxicity profile have examined various factors, including study type, duration, animal subjects, extract type, dosage, and outcomes.In short-term toxicity tests on mice, a single oral dose of 2000 mg/kg of methanol and chloroform extracts showed no unusual behavior or mortality over 14 days. A long-term study conducted over 28 days demonstrated that a dosage of 400 mg/kg of the methanolic extract resulted in considerable weight loss, as well as an increase in packed cell volume and hemoglobin levels, suggesting possible advantages in the treatment of anemia. The chloroform extract administered at a dosage of 200 mg/kg resulted in only negligible alterations. The safety profile of CQL indicates an LD50 exceeding 2000 mg/kg. In a distinct study, subchronic and mutagenicity evaluations of the CQL extract (CRQ-300) were performed on Sprague Dawley rats at doses of 100, 1000, and 2500 mg/kg over a duration of 90 days. The results indicated no noticeable clinical signs of toxicity or mortality. Furthermore, the mutagenicity assessments confirmed the lack of genotoxic effects, thus supporting the safety profile of CRQ-300, with an LD50 exceeding 2500 mg/kg.[14] A study on toxicity was performed to assess the sub-chronic effects of *Cissus quadrangularis* powder over a duration of three months, involving five groups of 12 Wistar rats of both sexesThe control group was given a daily

dose of 10 ml of water for each kilogram of body weight. In contrast, the four treatment groups received the dried stem powder in different amounts: 0.03, 0.3, 3.0, and 30 grams per kilogram of body weight daily. These doses corresponded to 1, 10, 100, and 1000 times the therapeutic dose recommended for humans, respectively. The last group was identified as the recovery group. There were no notable differences in the initial or final body weights observed between the groups that received treatment with *Cissus quadrangularis* and the control group. The research indicated that *Cissus quadrangularis* did not induce any notable dose-dependent alterations in blood parameters or serum clinical chemistry. Furthermore, no detrimental lesions in any internal organs were associated with the toxic effects of *Cissus quadrangularis*. The findings suggest that Cissua quadrangularis, at the administered doses, did not induce any toxicity in the rats over the three-month period.[60]

CONCLUSION:

Cissus quadrangularis emerges as a plant with remarkable medicinal potential, offering a broad range of therapeutic benefits. Its efficacy in treating conditions such as bone fractures, arthritis, and obesity underscores its growing relevance in modern healthcare. The plant's diverse pharmacological effects can be attributed to its rich array of bioactive compounds, including flavonoids, alkaloids, and phenolics, which collectively contribute to its anti-inflammatory, antioxidant, and healing properties. While the evidence supporting its therapeutic value is promising, further research is essential to fully understand its mechanisms of action and long-term safety. Although toxicity appears to be minimal when used within recommended dosages, caution is advised, particularly with prolonged or excessive use. The increasing popularity of Cissus-based supplements and topical products reflects its rising demand, with an expanding number of patents signaling its potential in both the pharmaceutical and nutraceutical sectors.

As a natural remedy with significant health benefits, *Cissus quadrangularis* holds great promise for future clinical studies and may eventually find a more established place in mainstream medical practice. Its ongoing exploration could pave the way for its broader use as a complementary or alternative treatment in various therapeutic areas.

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