

A Phytochemical and Pharmacological Review of an Indian Plant: *Cissus quadrangularis*[†]

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Abstract: *Cissus quadrangularis* (Vitaceae) is a common perennial succulent climber plant belonging to the Vitaceae family. The plant has a strong pharmacological profile with a variety of phytoconstituents and is geographically distributed throughout tropical and subtropical regions of the world. It is prominently found in India, Pakistan, and Bangladesh. The plant is found all over India, but its presence is dominantly observed in states such as Assam, Kerala, Odisha, Madhya Pradesh, Tamil Nadu, and Uttar Pradesh. The plant in India is popularly called 'Hadjod' or 'Asthisamharaka' and is very well established as a medicine related to the management of bone, muscles, and ligament issues. Traditionally, almost all aerial and underground parts have medicinal value, but the stem is most commonly used. Phytochemicals studies performed on the plant revealed the presence of a variety of constituents, viz., tannins, proteins, carbohydrates, phenol flavonoids, triterpenoids, phytosterols, glycosides, saponins, vitamin C, and alkaloids. In addition, these plants are also a rich source of calcium. The systematic review also established the pharmacological role of the plant as a bone setter and fractured bone healer; its antimicrobial, anti-diabetic, anti-inflammatory, anti-obesity, and anti-oxidant effects; bone turnover; cardiovascular and hepatoprotective properties; and many more. The current review article carried out a detailed discussion of its phytochemical and pharmacological potential.

Keywords: fracture healing; *Cissus*; wound healing; analgesic; anti-inflammatory



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1. Introduction

India is a country full of fauna and flora and holds a strong tradition of using flora and fauna as food supplements and medicines. As per the available data, it was estimated that the total number of higher plant species found on earth is 250,000, and of this number, approximately more than 70,000 plants are medicinal. In India alone, over 45,000 plant species exist, making India the world's 12th biodiversity center [1,2]. In addition to this rich fauna and flora, the very existence of an alternative system of medicines, namely Siddha, Ayurveda, Unani, Naturopathy, and homeopathy, in India officially established a very long, safe, and continuous use of herbs [3,4]. As of now, by carrying out a systematic literature study, it was evident that India presented about 8000 medicinal plant species from different alternative systems of medicine. In terms of numbers, around 700 medicinal plant species are reported from Ayurveda, 600 species are reported from Siddha, 600 species of plants are reported from Amchi, 700 medicinal plant species are reported from Unani, 67 medicinal plant species are reported from Rigveda, 81 medicinal plant species are reported from Yajurveda [1,2], etc. Apart from the prescription drugs of alternative systems, plants are popularly used by millions of Indians as health food, spices, home remedies, and over-the-counter (OTC) drugs. The market for medicinal plants in India stood at INR 4.2 billion

(USD 56.6 million) in 2019 and is expected to increase at a CAGR of 38.5% to INR 14 billion (USD 188.6 million) by 2026. The total world herbal trade is currently assessed at USD 120 billion [2,5].

The present review study is designed by considering the rich tradition of India's medicinal plants. The study has a prime focus to introduce one of the important plants of Ayurveda, named *Cissus quadrangularis*, which is popularly called 'Had-Jod' or 'Asthisamharaka'. The article makes an effort to present detailed phytochemicals and the pharmacological potential of the plant, with superficial information about traditional claims and future perspectives related to the plant.

2. Plant Description

2.1. Habitat

Cissus quadrangularis is a common plant in the arid habitat of tropical and subtropical regions and is very often found in coastal and lowland areas. The plant is very well known in Africa and India for its medicinal uses. In India and the subcontinent of India such as Pakistan and Bangladesh, the *Cissus* plant can be found in thickets, open forests, scrub jungles, along forest borders, on riverbanks, and wastelands at low and medium elevations [6].

2.2. Synonyms

This aggressively growing plant is identified by several international names and regional names; some important international names of *Cissus quadrangularis* are Veldt grape, adamant creeper, cactus vine, kangaroo vine, stemmed vine, veldt grape, and winged tree bine, and the Indian regional names are Had-Joad, Asthisamharaka, Pirandai, and Hadsankal [6–8].

2.3. Botanical Description

The plant is a perennial herbaceous climber comprising a thick quadrangular stem along with other aerial components such as tendrils, leaves, inflorescence, flowers, and fruits [5,7]. The detailed part-wise description of the *Cissus quadrangularis* is described below and shown in Figure 1.

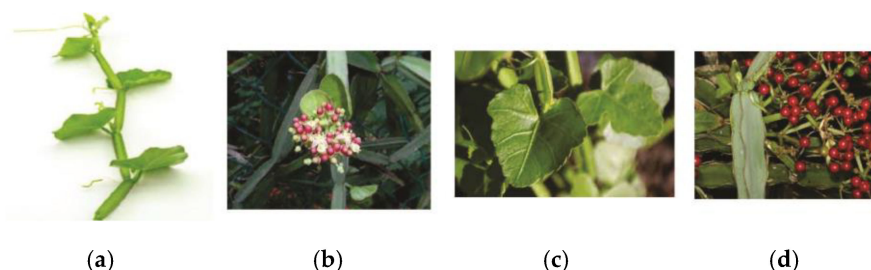


Figure 1. *Cissus quadrangularis* plant parts: (a) stem bearing all parts of the plant, (b) flower and inflorescence, (c) typical leaf of the plant, and (d) fruits of the plant.

2.3.1. Stem

The stem of the plant is moist, thick, long, fleshy, deep green in color, glabrous, quadrangular, angel-winged, constricted at nodes, and slightly downy. When young, the stem shows branches that are sharply angular or winged, exhibits long tendrils, and is simple, and it is almost leafless when old.

2.3.2. Leaves

Leaves on the stem of the plant are simple ovate or reniform; entire or cordate; serrulate dentate or crenate-serrate; 3–7 lobed; terminal lobe triangular or sub-spathulate; subacute or \pm cuspidate; membranous; glabrous on both sides; 3–5 \times 5–3 cm; and stipules ovate or cuneate, obtuse, and deciduous.

2.3.3. Inflorescence

The inflorescence found in the plant is umbellate cyme with peduncles that are 1–2.5 cm long. The stem shows the presence of tendrils that are long, slender, and simple.

2.3.4. Flower

Stem bears a flower comprising pink to white colors and is approximately 2 mm long. The hypanthium of the flower is cup-like, truncate or obscurely lobed, green in color, and 2 mm wide. Petals are four in number and distinct, ovate-oblong, acute, and hooded at the apex. The size of the petal is 1.5 mm in length. The flower is disc-shape and is longer than the ovary. The ovary present in the flower is glabrous, with a slender style and small stigma.

2.3.5. Fruit

The fruit of the plant comprises berries that are globose, red, succulent, very acidic, 6–10 mm in diameter, and single-seeded. The seeds are obovoid smooth and measure 4–8 mm across. The flowering and fruiting time is identified to take place in June–July [6,8].

3. Phytochemical Profile

The aerial portion, particularly the stem of *Cissus quadrangularis*, demonstrated the presence of several important primary and secondary metabolites. The study, performed for the presence of preliminary phytoconstituents, was carried out on an extract prepared using different solvents, which was found to exhibit the presence of important primary metabolites, namely lipids (cyclic and acyclic), fatty acids, methyl esters, protein, amino acid, iridoids, gums, and mucilage. The extracts of the plant also showed the presence of a few important secondary metabolites, namely alkaloids, flavones and flavonoids, saponins, phytosterols, steroids, stilbenes, triterpenoids, tannins, carotene, cardiac glycosides, and vitamins (especially vitamin C) [9,10]. On the other hand, the extracts prepared from the underground parts of the plant using different solvents showed a wide array of compounds when examined for phytochemical profile, namely alkaloids, saponins, tannins, flavonoids, and glycosides [11].

4. Traditional Uses

The detailed study of the traditional literature available on *Cissus quadrangularis* in India and abroad established its use in the management of several issues of humans and animals in all parts of the world [12,13]. The Indian traditional system of treatment, namely Siddha and Ayurveda, extensively used the plant for the management of 'Asthi', i.e., bone-related issues such as fracture, pain, inflammation, osteoporosis, rheumatoid, and osteoarthritis [2,7]. The traditional literature of other Indian subcontinents such as Pakistan, Bangladesh, Sri Lanka, etc., and even other parts of the world also claimed the use of the plant in the treatment of swelling, hemorrhage, hemorrhage, anorexia, flatulence, dyspepsia, colic, chronic ulcer, hemoptysis, convulsion, skin diseases, leprosy, and helminthiasis [7,9,14].

5. Pharmacological Profile

This review highlights some of the phytochemical and pharmacological aspects of *Cissus quadrangularis*. The prominent traditional actions of the plant are fracture healing and producing antibacterial and antifungal, antioxidant, anthelmintic, anti-hemorrhoidal, and analgesic effects. The other potential medical effects include gastroprotective activity, NSAID, and producing antioxidants in lipid metabolism and oxidative stress. All these above-mentioned versatile uses and various therapeutic activities make the plant a valuable medicinal herb [15]. The details of pharmacological activities are explained in detail in the following discussion.

5.1. Actions Related to Bones

The *Cissus quadrangularis* plant is a well-established herb in the management of bone-related ailments, and in line with this fact, several studies were conducted using different animal models and even human subjects. All these studies now establish that the plant has a potential role in the management of bone fracture, osteoporosis, and the maintenance of bone density. The core understanding of all these studies proposes that the plant has unidentified anabolic steroids that are responsible for action via the estrogenic receptor of the bone. The efficacy of the plant for the early ossification and remodeling of bones can better stimulate metabolism and the fast uptake of minerals, viz., calcium, sulfur, and strontium by osteoblast [15].

5.2. Analgesic and Anti-Inflammatory Activity

The plant was tested for analgesic and anti-inflammatory activity using the extract that was prepared using a different solvent. The summaries of all observations are as follows.

The methanolic extract demonstrated analgesic and anti-inflammatory activity. The study performed on mice showed a noteworthy reduction in the number of writhes in mice induced by acetic acid and also showed considerably reduced licking time in both phases of the formalin test. These responses in mice were suggestive of the peripheral and central analgesic activity of the plant. The rat model plant showed an effective anti-inflammatory property and showed an inhibitory effect on edema formation induced by ethyl phenylpropionate in rat ears as well as paw edema by carrageenin and arachidonic acid [16].

The ethanolic extract of the plant was also evaluated for analgesic, anti-inflammatory, and antipyretic activity in an albino rat model, and the result demonstrated a significant reduction in the edema produced by carrageenan and showed analgesic activity in the formalin test. The study suggested that the ethanolic extract may have central and peripheral effects, and these are the mechanisms of analgesia and anti-inflammation [17]. The *Cissus quadrangularis* plant was also evaluated in connection with its ability to inhibit the cyclooxygenase-I (COX-1) enzyme, which is one of the important components in pain and inflammation reactions [18]. The extract of the plant was assessed for the inhibition of COX-I using a COX-1 assay, and the response of the inhibition was reported in percentages [14]. In one more study, different extracts of *Cissus quadrangularis* were evaluated and found to have an inhibitory action on cyclooxygenase (COX-1), cyclooxygenase (COX-2), and 5-lipoxygenase (5-LOX) enzyme activity. The spectroscopic and polarographic methods were employed for the determination of the inhibition of enzymes.

The acetone extract had the most promising results, and when Western blot analysis was carried out, it demonstrated the downregulation of pro-inflammatory mediators as well as the upregulation of phase-II enzymes. The determined IC₅₀ values of the acetone extract for enzyme inhibition were 7 µg/mL, 0.4 µg/mL, and 20 µg/mL for COX-1, COX-2, and 5-LOX, respectively. The extract showed anti-inflammatory activity on the cell line (RAW 264.7) with an IC₅₀ value of 65 µg/mL. Furthermore, it showed the inhibition of pro-inflammatory mediators such as iNOS and TNFα, along with the translocation of Nrf-2 and upregulation of HO-1 [18].

A study using the ethyl acetate extract of *Cissus quadrangularis* also reported somewhat similar potential, and the results of this study showed the potent inhibition of lipopolysaccharide (LPS)-induced nitric oxide (NO) production. The plant showed the suppression of mRNA expression and inducible nitric oxide synthase (iNOS) proteins, and the inhibitory effects of plant NO production were abrogated by an HO-1 inhibitor, zinc protoporphyrin IX (ZnPP) [19].

5.3. Anti-Diabetic Activity

The anti-diabetic potential of the *C. quadrangularis* stem extract is mediated via the modulation of the antioxidant defense system. The ethyl acetate fraction that is rich in the quercetin supplementation of the plant might be beneficial as a food supplement for the

attenuation of diabetic complications. Furthermore, the antidiabetic activity of the plant is associated with potentiating the antioxidant defense system and suppressing inflammatory responses [20].

5.4. Wound Healing Activity

The methanolic and total aqueous extracts of the plant were analyzed for wound healing activity in rat animal models and were found to exhibit good wound healing activity, and this is probably due to the phenol constituents present in it. The activity was evaluated by using an ointment formulation made with 2% (*w/w*) of the methanolic extract and 2% (*w/w*) of the total aqueous extract, and both formulations exhibited significant wound healing activity [21].

6. Conclusions

The *Cissus quadrangularis* plant is a vine that grows in Africa and parts of Asia, including India. It is one of the most commonly used medicinal plants in Thailand and is also used in traditional African and Ayurvedic medicine. All parts of the plant are used for medicine. The phytochemical investigation of the plant shows the presence of many important primary and secondary metabolites, such as lipids (cyclic and acyclic), fatty acids, methyl esters, proteins, and amino acids; iridoids, gums, and mucilage; alkaloids, flavonoids, and flavones; saponins, phytosterols, flavonoids, steroids, stilbenes, and triterpenoids; tannins; carotene, enzymes, nicotinic acid, tyrosin, cardiac glycosides, saponins, and vitamins, especially vitamin C. The traditional literature on Indian systems of medicine, as well as the literature across the world, suggests that these plants have proven efficacy in treating various ailments, such as osteoporosis, bone, and muscle fracture; ligament damage; pain; and inflammation. Scientific investigations using animals and humans also established that the plant is a good wound and fracture healer. Major pharmacological activities established about this plant include antimicrobial, anti-diabetic, anti-inflammatory, anti-obesity, anti-oxidant, bone turnover, and cardiovascular and hepatoprotective activities. Furthermore, the most extensive clinical studies using standardized extracts of *Cissus* alone or in combination with other ingredients involve weight loss and the regulation of blood glucose and lipids. Thus, *Cissus quadrangularis* appears to be a worthy wound healer.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ECB2023-14557/s1>, Conference Poster: A Phytochemical and Pharmacological Review of an Indian Plant: *Cissus quadrangularis*.

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