Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/3nzjgm04

"A REVIEW ON UNEVELING THE MIRACLE MEDICINAL BENEFITS FOR MAINTAINING HEALTHY BONES FROM *CISSUS QUANDRANULARIS* AND *PITHECELLOBIUM DULCE*"

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Abstract: This study examines the medicinal properties of two plants, *Cissus quadrangularis* and *Pithecellobium dulce*, which have been used in traditional medicine for centuries. The plants' phytochemical profiles reveal a diverse range of bioactive compounds, including alkaloids, flavonoids, saponins, and phenolic acids. The study investigates the pharmacological actions of these plants, including their anti-inflammatory, anti-diabetic, hepatoprotective, and antioxidant effects. *Cissus quadrangularis* is found to have bone protective properties, with the potential to treat postmenopausal osteoporosis. Its anti-inflammatory activity is associated with luteolin and β-sitosterol. The plant also shows anti-diabetic potential by modulating the antioxidant defense system. *Pithecellobium dulce* exhibits anti-inflammatory activity, with its saponin content showing potential against exudative and proliferative phase inflammation. The plant also demonstrates antitubercular activity, with its alcoholic extract showing highest activity against Mycobacterium tuberculosis. The study highlights the potential of these plants as a source of new drugs and their contribution to alternative medicine. The findings provide a comprehensive overview of the medicinal properties of *Cissus quadrangularis* and *Pithecellobium dulce*, highlighting their potential for future research and development. The study's results support the use of these plants in traditional medicine and suggest their potential for use in bone disease.
Overall, this study demonstrates the potential of *Cissus quadrangularis* and *Pithecellobium dulce* as valuable resources for the development of new drugs and highlights the importance of preserving traditional knowledge and exploring the medicinal properties of plants.

1. INTRODUCTION:

The word Bone is derived from the Latin word **"Osteo"** and that being the case all the bone related diseases follow with the same i.e. Osteoporosis, Osteoarthritis, et*cissus* The adult human skeleton has a total of 213 bones, excluding the sesamoid bones. The appendicular skeleton has 126 bones, axial skeleton 74 bones, and auditory ossicles six bones. Each bone constantly undergoes modeling during life to help it adapt to changing biomechanical forces, as well as remodelling to remove old, microdamaged bone and replace it with new, mechanically stronger bone to help preserve bone strength. [1] The four general categories of bones are long bones, short bones, flat bones, and irregular bones. Long bones include the clavicles, humeri, radii, ulnae, metacarpals, femurs, tibiae, fibulae, metatarsals, and phalanges. Short bones include the carpal and tarsal bones, patellae, and sesamoid bones. Flat bones include the skull, mandible, scapulae, sternum, and ribs. Irregular bones include the vertebrae, sacrum, coccyx, and hyoid bone. Flat bones form by membranous bone formation, whereas long bones are formed by a combination of endochondral and membranous bone formation.[2] Long bones, however, are the most commonly loaded structures and therefore strongest load-bearing bones in the body, predominantly in the appendicular skeleton.[3] They comprise of a hollow cylindrical shaft known as the diaphysis, a cone-shaped proximal and distal metaphysis, and rounded proximal and distal epiphysis, each portion has different architectural features which are organised and configured to withstand and manage different physical loads during regular activities of daily living.[4] Bone is a structurally complex and sophisticated biomaterial. It must be rigid and stiff to withstand forces and accommodate loading, yet be flexible and elastic to deform and absorb energy. [5] It must shorten and widen under compression, yet lengthen and narrow under tension, whilst also withstanding torsional and shear forces in isolation and in combination without experiencing catastrophic failure. In order to manage these contradictory and paradoxical requirements, the skeleton contains two macroscopic osseous tissues (trabecular and cortical bone) which are architecturally and functionally different.[6] In its entirety, skeletal mass consists of approximately 20% trabecular tissue and 80% cortical tissue, which co-exists at various proportions in all bones through-out the body in accordance with the functional and regional demands of each individual bone.[7] The structural intricacies and interactions between these two osseous tissues, enable long bones to be remarkably light yet durable and strong in order to facilitate locomotion.[8]

Bone is generated, regulated and maintained by an interaction of four key cells: osteoblasts, osteoclasts, osteocytes and extra-cellular lining cells. [9] Osteoblasts are anabolic in nature, producing new bone material by synthesizing and calcifying newly generated collagen. Osteoblasts are uniquely adaptable and compatible, transforming into bone lining cells (surrounding the extra-cellular matrix) and osteocytes (embedded within the bone matrix) during the osteogenic process.[10] Conversely, osteoclasts are a catabolic cell which degrades, dissolves and resorbs bone material, often as a response to material damage or disuse. Osteoclasts have a limited lifespan, undergoing apoptosis (programmed cell death) within 2 to 4 weeks of osteoclastogenesis. Osteoblasts and osteoclasts work independently during bone creation and formation (modelling), and co-operatively via a basic multi-cellular unit (BMU) during bone maintenance and homeostasis (remodelling). [11] Osteocytes are central to bone development and renewal as the most abundant residential cell in bone, accounting for approximately 90% to 95% of all bone cells. Specifically, osteocytes are descendants of osteoblasts produced during ontogenesis, which subsequently become entombed within the mineralised collagen matrix. [12] Osteocytes form a well-connected network of sensory channels to detect environmental alterations and communicate reactionary processes to osteoblasts, bone lining cells and fellow osteocytes. This network is explicitly formed by dendritic connections (~60 to 80 per osteocyte) which proliferate through canaliculated passages to provide a functional and mechanosensitive platform integral to the detection of mechanical load and associated micro damage. [13] This mechanically sensitive function, known as mechanotransduction, enables bone to physiologically detect and convert mechanical energy into proportionate biochemical signals in order to promote growth and repair processes. The process of mechanotransduction, including how bones sense mechanical changes, are described further under the Bone Adaptation section of this review.[14]

Bone growth, development and preservation is largely reliant upon hormonal regulation, globally controlling skeletal homeostasis somewhat independently of mechanical loads through-out the lifespan in order to facilitate non-mechanical functions of bone.[15] Specifically, the endocrine system serves to maintain bone mineral deposition and homeostatic cellular balance through continual, non-mechanically induced generation and regeneration of bone during biological growth and maturation.[16]While the endocrine system does not explicitly strive to optimise bone strength, endocrine status can have a profound, indirect and negative impact on structural integrity and mechanical competency when irregular hormonal environments arise.[17] Endocrine activity therefore forms a central component of a complex biological system that mediates calcium-phosphate balance, energy metabolism and bone mineralisation in response to dynamic and volatile physiological requirements. [18] In this regard, endocrine function majorly influences bone health and metabolism, ascending into domination through adulthood and advanced ageing. [19]

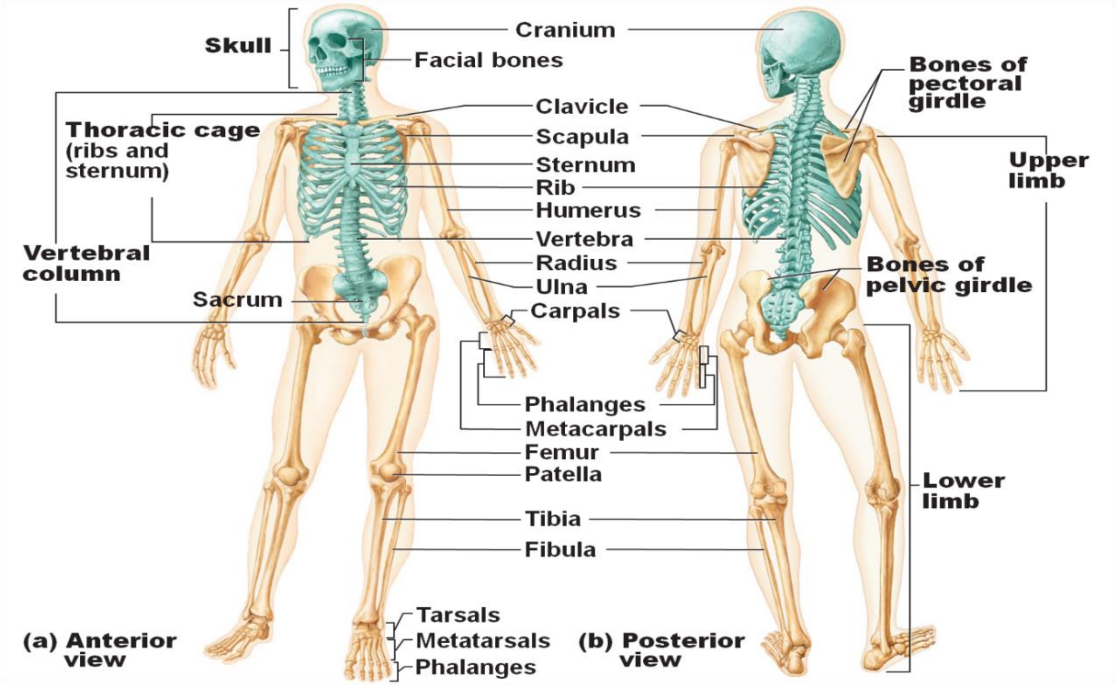

Figure 1 Diagrammatic Representation of Skeletal System

The World Health Organization (WHO) defines traditional medicine as "the sum of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement, or treatment of physical and mental illness," whether these practices are based on explicable theories, beliefs, or experiences. Indian Traditional Medicine, the world's oldest system of medicine, has contributed significantly to the care and wellbeing of people throughout its history.[20] Ayurveda, Siddha, and Unani, Yoga, Naturopathy, and Homoeopathy are six of India's ancient medical traditions. The most well-known of these ancient practices is Ayurveda. The ancient Ayurvedic remedies are used by over 70% of India's rural population. [21]

2. CISSUS QUANDRANULARIS:

2.1. Taxonomical classification: [22]

Kingdom	*Plantae*
Subkingdom	*Tracheobionta*
Super division	*Spermatophyta*
Division	*Magnoliophyta*
Class	*Magnoliopsida*
Subclass	*Rosidae*
Order	*Rhamnales*
Family	*Vitaceae*
Genus	*Cissus L.*
Species	*Cissus quadrangularis L.*

2.2. Vernacular names: [23]
- **Sanskrit**: Asthisamharaka
- **Hindi** : Hadjod, Hadjora, Hadsarihari, Harsankari, Kandvel
- **Gujarati** : Chodhari, Hadsand, Hadsankal, Vedhari
- **English**: Edible stemmed vine, Adamant creeper, Bone setter

2.3. Geographical Distribution: [24]
The plant is extensively spread in tropical and subtropical locations across the world, including India, Sri Lanka, South Africa, Thailand, Java, and the Philippines. The plant's complete structure (root, stem, and leaves) has been noted for therapeutic purposes in both the Ayurvedic and Unani systems.

2.4. Botanical Description:

(a) (b) (c) (d)

Figure 2 . 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

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 [25, 26]. The detailed part-wise description of the *Cissus quadrangularis* is described below and shown in Figure 2
.

2.4.1 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.

2.4.2 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 cuspidate; membranous; glabrous on both sides; 3-5 × 5-3 cm; and stipules ovate or cuneate, obtuse, and deciduous.

2.4.3 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.
2.4.4 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. [27]
2.4.5 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 in place in June–July. [28]

2.5. Phytochemical Profile: [29, 30, 31]

Plant parts	Phytochemical Constituents
Aerial Portion (Stem)	Alkaloids, Flavones and flavonoids ,Saponins ,Phytosterols, Lipids (cyclic and acyclic), Fatty acids, Methyl esters
Underground Parts	Alkaloids, Saponins, Tannins, Flavonoids, Glycosides

2.6 Pharmacological action:

2.6.1 Bone Turnover activity:

Cissus quadrangularis was examined for bone protecting characteristics and investigated to determine the mechanism by which it benefits bone [32]. It protected the microarchitecture of the long bones against ovariectomy-induced bone loss by reducing inflammation and modulating the bone morphogenetic protein and Wingless-related integration site (Wnt) signaling pathways. The findings suggested that the plant may be used to treat postmenopausal osteoporosis without causing any negative effects. The petroleum ether extract of *Cissus quadrangularis* considerably enhanced the thickness of both cortical and trabecular bone, indicating that the plant has considerable anti-osteoporotic action. Furthermore, the extract decreased bone loss, as demonstrated by weight increase in the femur, and it also reduced osteoplastic activity, promoting bone creation [33, 34].

Furthermore, the percentage of total length of ossified cartilage (bone) in pups was greater, indicating that maternal administration of Cissus *quadrangularis* petroleum ether extract during pregnancy can accelerate fetal bone formation throughout the intrauterine developing phase [35]. In another investigation, ethanol extract demonstrated strong restorative progress with mineralization, somewhat well-distributed osteocytes, and full healing with fundamental properties of normal bone [36].

The ability of *Cissus* quadrangularis to stimulate osteoblast development of the mouse pre-osteoblast cell lines was investigated by Tasadduq et al. [37]. Alkaline phosphatase activity, an early osteoblast marker, was significantly upregulated in response to the ethanolic extract, suggesting that the extract promoted osteoblast differentiation. Toor et al. [38] investigated the osteogenic potential of Cissus, and found that the plant's ethanolic extract promoted early callus remodelling and expedited fracture healing. The impact of the hexane and dichloromethane fraction on the mineralization and differentiation of mouse pre-osteoblast cell line was also investigated by the authors [39].

Human osteoplastic SaOS-2 cell DNA production has increased after treatment with *Cissus* quadrangularis, suggesting that these cells are proliferating more quickly [40]. The study also showed that increased mRNA and protein expression of Runx2, a crucial transcription factor involved in the regulation of bone matrix protein, mediates the anabolic effects of the ethanolic extract of *Cissus* quadrangularis in human osteoblast-like cells. *Cissus* quadrangularis has been shown to have osteogenic potential in the healing of mandibular fractures; it reduces pain, oedema, and fracture mobility while hastening the repair of fractured jaw bones [41, 42].

2.6.2 Anti-inflammatory activity:

Panthong et al.'s research [43] demonstrated *Cissus* quadrangularis’s anti-inflammatory properties, which are linked to luteolin and β-sitosterol. Similarly, at a dose level of 50 mg/kg, the methanolic root extract of *Cissus* quadrangularis shown a potent activity of 4.16 [44]. In RAW 264.7 macrophage cells, lipopolysaccharide-induced nitric oxide generation was potently and dose-dependently reduced by an ethyl acetate extract of *Cissus* quadrangularis [45]. Both the nuclear translocation of p65 NF-κB and the mRNA and protein expressions of inducible nitric oxide synthase were inhibited by the extract. Subsequent research revealed that the extract alone promoted dose- and time-dependent heme oxygenase-1 gene expression at the protein and mRNA levels.

Similarly, cyclooxygenase and 5-lipoxygenase were inhibited by the plant's acetone extract, with IC50 values for cycloxygenase-1, cycloxygenase-2, and 5-lipoxygenase being 7 µg/ml, 0.4 µg/ml, and 20 µg/ml, respectively. Additionally, it exhibited anti-inflammatory action with an IC50 value of 65 µg/ml on the RAW 264.7 cell line. Furthermore, the extract demonstrated the suppression of proinflammatory mediators such as TNFα and inducible nitric oxide synthase, in addition to nuclear factor E2 p45-related factor 2 translocation and Heme oxygenase-1 upregulation [46]. When *Cissus* quadrangularis extract was administered, the aspirin-induced gastric lesions were significantly reduced. This was accompanied by an increase in uric acid, antioxidative enzymes, and SH groups as well as a significant decrease in the activities of lipid peroxidase, TNF-alpha, myeloperoxidase, and xanthine oxidase [47].

The anti-inflammatory and cartilage-regenerating characteristics of *Cissus* quadrangularis, as well as its mechanism of action through the inhibition of matrix metalloproteinase and reactive oxygen species, were verified by Kanwar et al. [48]. The plant treatment's hydroalcoholic extract significantly decreased oxidative stress, serum TNF-α levels, and the expression of angiogenesis and inflammation markers in synovium [49].

2.6.3 Anti-diabetic activity:

According to Lekshmi et al. [50, 51], *Cissus* quadrangularis stem extract may have anti-diabetic properties that are mediated via altering the antioxidant defense system. Because of the plant's high quercetin content, the ethyl acetate fraction may be useful as a dietary supplement to lessen the effects of diabetes. Moreover, the plant's antidiabetic properties are linked to enhancing the antioxidant defence system and reducing inflammatory reactions.

2.6.4 Hepatoprotective activity:

The hepatoprotective effect of *Cissus* quadrangularis methanol extract against rifampicin-induced hepatotoxicity in rats was studied by Swamy et al. [52]. It was determined that the antioxidant activity of hepatoprotection, particularly the presence of β-carotene, may be responsible for this process. The plant's insulin-sensitizing and antioxidant properties provide hepatoprotection [53]. Additionally, it demonstrated free-radical scavenging and antilipid peroxidative properties, and it reduced liver damage by raising the activity of antioxidant enzymes [54].

3. Pithecellobium dulce:

3.1. Taxonomical classification: [55]

Kingdom	Plantae
Phylum	Spermatophyta
Subphylum	Angiospermae
Class	Dicotyledonae
Order	Fabales
Family	Leguminosae
Genus	Pithecellobium
Species	*Pithecellobium dulce*

3.2 Vernacular names: [56]

- **Sanskrit:** Kodukkapuli
- **Hindi**: Vilayati imli, Jungli jilebi
- **Gujarati :** Vilayati Ambli
- **English**: Manila Tamarind, Monkey pod, Madras thorn II.

3.3 Geographical Distribution: [56]

The plant originated from Brazil, Argentina, Bolivia, Colombia, etc, *Pithecellobium dulce* is one of the species that has become widespread outside from its origin. It is one of 18 species in this genus.

It has been distributed naturally in many countries like India, Huawei, tropical Africa, and especially along the coast.

3.4 Biological Description: [57]

Pithecelobium dulce typically reaches a height of 10-15 m, however it can reach up to 18 m. Broad, spreading crown with sporadic branches up to 30 m in diameter; short, up to 1 m thick bole. Grey in color, the bark finally becomes rough, wrinkled, and peels.

The bi-pinnate leaves resemble Hardwicke binnata in that they have two pairs of two kidney-shaped leaflets that are each 2-2.5 × 1-2 cm. The tree seems to be evergreen because new leaves develop at the same time as old ones die off. At the base of leaves are thin spines that are 2 to 15 mm long and arranged in pairs.

The tiny white heads of blooms have a diameter of one centimeter. Every flower has a calyx and hairy corolla around roughly fifty slender stamens that are joined in a tube at the base. Pods are 1.5 cm by 10–15 cm, and as they ripen, their hue changes to a reddish-brown spiral. Each pod has five to ten glossy, black, two-centimeter-long seeds. This tree is simple to identify because to its distinctive grey bark and tightly coiled seed pods.

Pithecollobium or *Pithecolobium* is another common spelling of the genus. The Greek terms pithekos, which means "ape," and lobos, which means "lobe," are the source of the genus name, which refers to the pods' ear-like form. This species was imported to Coromandel, India, and was named and botanically documented there in 1795. The particular name, which means "sweet," most likely alludes to the pulp of the edible seeds.

3.5 Phytochemical Profile:[58, 59, 60, 61]

PLANT PARTS	PHYTOCHEMICAL COMPOUND
Bark	Flavonoid , Tannin, Sterol
Root	Isoflavonoid glycoside Genistein-4‟-O-L-rhamnopyranoside
Stem Bark	Prenylated flavonoid 3'-prenylapigenin-7-O-rutinoside
Leaves	Flavonoid, Polyol, Sugar, Fatty alcohol ,Sterol, Sterol glycoside ,Flavonoid glycoside
Seeds	Saponins, Triterpene, Triterpenoid saponin, Acylated triterpenoid, saponin, Flavonoid.
Fruit Pulp	Sterol glycoside, Sterol

3.6 Pharmacological Action:

3.6.1 Anti-Inflammatory Activity: [62]

Using models of formaldehyde-induced arthritis and carrageenan-induced oedema, the saponin (which contains two genin acids, oleanolic acid and echinocystic acid, with xylose, arabinose, and glucose as sugar moieties) extracted from *Pithecellobium dulce* fruits has been studied against the exudative and proliferative phase of inflammatory reaction in albino rats.

3.6.2 Antitubercular Activity: [63, 64]

The antimycobacterial activity of the leaf extracts in hexane, chloroform, and alcoholic solvents was investigated using the BACTEC460TB-Radiospirometric system. Comparing the alcoholic extract with common medications such as streptomycin, isoniazid, rifampicin, ethambutol, and pyrazinamide, the concentration of 20 mg/ml revealed the highest level of action.

3.6.3 Adulticidal Activity: [65]

The LC50 and LC90 values of *Pithecellobium dulce* leaves and seeds against Cx. quinquefasciatus were found to be 234.97, 309.24 ppm and 464.86, 570.80 ppm, respectively, among the five solvent extracts that were examined. The best potential against the mosquito that transmits filariasis, Cx. Quinquefasciatus, was found in the methanol extract of *Pithecellobium dulce* leaves.

3.6.4 Antioxidant properties: [66]

Pithecellobium dulce fruit was used to assess the antioxidant activity and extract anthocyanin. It is possible to assess the anthocyanin, flavanoids, and polyphenol antioxidants found in *Pithecellobium dulce* fruit pericarp *Pithecellobium dulce* was identified between fruit pods using the anthocyanin and phenolic content of the research, which also revealed two distinct extracts and free radical scavenging activities.

Conclusion:

The studies on *Cissus quadrangularis* and *Pithecellobium dulce* have demonstrated the significant medicinal potential of these plants. *Cissus quadrangularis* has shown promising results in treating postmenopausal osteoporosis, inflammation, and diabetes, while *Pithecellobium dulce* has exhibited anti-inflammatory, antitubercular, and adulticidal activities. The phytochemical profiles of these plants have revealed a diverse range of bioactive compounds, supporting their traditional uses and suggesting their potential for development into new drugs.Further research is needed to fully explore the medicinal properties of these plants, optimize their extraction and purification processes, and evaluate their safety and efficacy in clinical trials. However, the existing evidence suggests that *Cissus quadrangularis* and *Pithecellobium dulce* are valuable resources for the development of alternative and complementary therapies, and their preservation and further study are warranted. Overall, this research contributes to the growing body of evidence supporting the importance of traditional medicine and the potential of plant-based therapies to address various health concerns. By exploring the medicinal properties of plants like *Cissus quadrangularis* and *Pithecellobium dulce*, we may uncover new avenues for the prevention and treatment of diseases, improving human health and well-being.

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