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Pharmacognostical, Phytochemical and Pharmacological Overview: *Cissus quadrangularis* Linn.

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ABSTRACT

Cissus quadrangularis (Linn) has been used by the common man in India, and neighboring countries, Pakistan, Sri Lanka, Malaysia for promotion of fracture healing and well known as "Hadjod". It is also known as *Vitis quadrangularis* Wall. belongs to family Vitaceae. It is a common perennial climber, which is distributed throughout India, particularly in tropical regions. It requires warm tropical climate and propagated by stem cuttings. The plant is prescribed in the ancient Ayurvedic literature as a general tonic and analgesic, with specific bone fracture healing properties. The plant is believed to be useful in helminthiasis, anorexia, dyspepsia, colic, flatulence, skin diseases, leprosy, hemorrhage, epilepsy, convulsion, haemoptysis, tumors, chronic ulcers, swellings. The scrutiny of the present overview revealed pharmacognostical, phytochemical and some notable pharmacological activities of the plant such as Anti-osteoporotic activity**,** antioxidant, free radical scavenging, antimicrobial, antibacterial, bone healing, anti ulcer, analgesic and anti inflammatory, diuretic, Anabolic and Androgenic activity and toxicity studies.

Introduction

Cissus quadrangularis (Linn) has been used by the common man in India, and neighboring countries, Pakistan, Sri Lanka, Malaysia for promotion of fracture healing and well known as "Hadjod". It is also known as *Vitis quadrangularis* Wall. Belongs to family Vitaceae. It is a common perennial climber, which is distributed throughout India, particularly in tropical regions. It requires warm tropical climate and propagated by stem cuttings in the months of June and July [1].

Plant profile

It is a climbing herb, tendrils simple, opposite to the leaves, leafless when old. Leaves simple or lobed, cordate, broadly ovate or reniform, serrate, dentate, sometimes trifoliate and glabrous. Flowers small, greenish white, bisexual, tetramerous, in umbellate cymes, opposite to the leaves. Calyx is cup shaped. Fruit globose or obovoid fleshy berries, succulent, very acrid, dark purple to black, one seeded; seeds ellipsoid or pyriform. The stem is buff colored with a greenish tinge, dichotomously branched, sub- angular, glabrous, fibrous and smooth[2-3](Figure 1 & 2).

Fig.1: stem and leaf

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Fig.2: stem and fruit

Vernacular names[4]

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
Telgu: Nalleru, Nelleratiga, Vajravalli
Oriya: Hadavhanga
Urdu: Harjora, Hadsankal

Taxonomy of *Cissus quadrangularis*[5]

Kingdom: Plantae
Subkingdom: Tracheobionta
Super division: spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Rosidae
Order: Vitales
Family: Vitaceae
Genus: Cissus
Species: *quadrangularis*

Parts Used: Whole plant, root, stem, leaf

Distribution: Throughout India, particularly in hot parts.

Action and Uses

The plant is bitter, sweet, sour , thermogenic, laxative, anthelmintic, carminative, digestive, stomachic, depurative, homeostatic, aphrodisiac, anodyne, ophthalmic and union promoting. It is useful in helminthiasis, anorexia, dyspepsia, colic, flatulence, skin diseases, leprosy, haemorrhages, haemoptysis, ophthalmopathy, otorrhoea, chronic ulcers, tumours, haemorrhoids, epilepsy, convulsions, scanty menstruation, fractures, and swellings. The shoots are useful in colonopathy, scurvy, otorrhoea, asthma, burns, and wounds. Powdered roots as well as the stem paste are very specific for bone fractures. The stem is bitter and it is given internally and applied topically for broken bones, used in complaints of the back and spine, removes pus .Leaves and young shoots are powerful alteratives for bowel affections, juice of stem is useful in irregular menstruation.

Ayurvedic properties

Rasa-Madhura
Guna- Laghu,Ruksha,Sara
Veerya- Ushna
Vipaka -Madhura
Doshaghnata- Kaphavatashamaka,Pittavardhaka

Pharmacognostical overview[6-9]

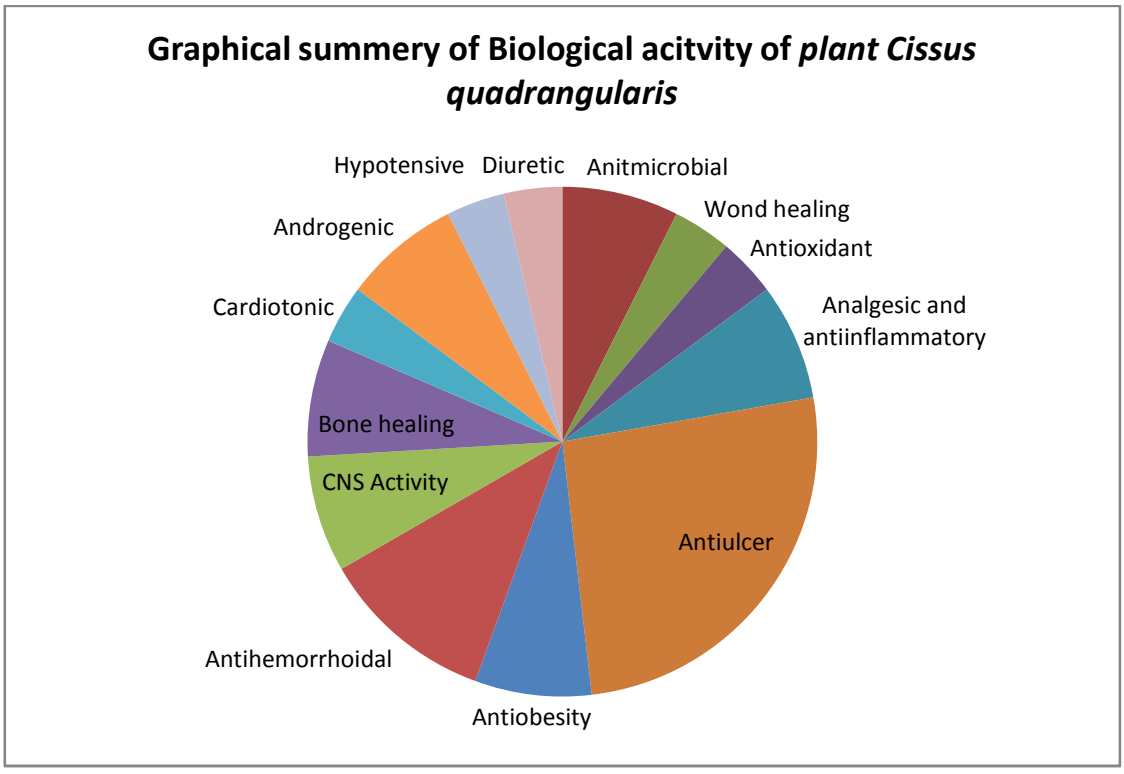
Fresh stem is thick, fleshy, succulent, quadrangular with acutely 4 angled or 4 winged internodes and contracted nodes. Fracture is short fibrous and fractured surface is greenish yellow in colour. Odour is distinct and taste acrid. Microscopically, a transaction of internode shows 4-angled outline. Epidermis consists of single row of cells covered with a thick cuticle and tubular cells. Numerous stomata are found on the epidermis. Actinocytic stomata transverse throughout the epidermis which, in surface view, are seen encircled by small cells forming a girdle like sheath, epidermis cells thick-walled rectangular to pentagular in surface view. Cortex is composed of thin walled several layers of thin walled parenchyma cells, parenchymatous cells containing chloroplasts, starch grains and raphides of calcium oxalates. Embedded in cortex are some secretory cells. At the corners internal to epidermis, 3 to 4 layers of compactly arranged sclerenchymatous cells are seen. Next to the sclerenchymatous zone are found 3 to 4 layers of rectangular cork cells, arranged completely without any intercellular space. The phellogen arises in the sub-epidermal layer, with the angles in cortex, collenchyma occurs in the form of discrete strands. Individual collenchyma cells are isodiametric with cellulosic thickenings

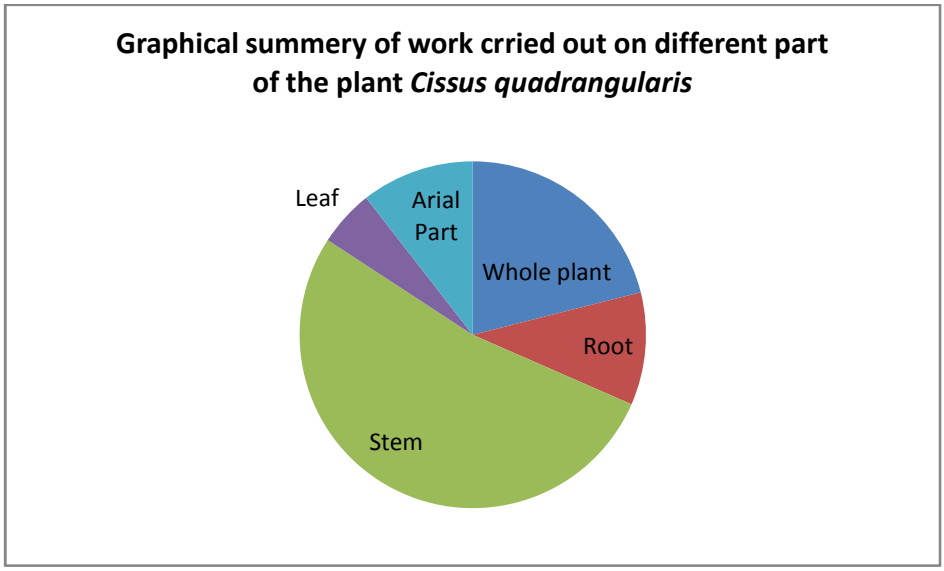
at their angles. Endodermis is not distinguishable .Vascular bundles are collateral, open and arranged in a ring around the large central pith. Discontinuous rings of vascular bundles, parallel to the undersurface of the epidermis, 3 to 4 vascular bundles under the wings more developed than the once at the flat sides, conjoint, collateral with a cap of vast fibres encircled by idioblast containing cluster crystals of calcium oxalate, with numerous air cavities throughout the section. In oldest stem, a complete ring of vascular strand with well developed cambium ring is seen except at the flat board side of the stem.

Phytochemical overview

- From the petroleum ether extract of *Cissus quadrangularis* Linn., three triterpenes and one phytosterol were isolated. The triterpene were identified as lupenone, epifriedlinol, isoaroborenol and the phytosterol as β-sitosterol[10].
- Four marker constituents, namely, onocer-7-ene-3 alpha, 21 beta-diol, delta-amyrin, delta-amyrone and 3,3',4,4'-tetrahydroxybiphenyl of an Ayurvedic crude drug *Cissus quadrangularis* Linn. are identified for standardisation purposes. 3, 3', 4, 4'-Tetrahydroxybiphenyl has been isolated for the first time from this drug. The contents of the marker constituents were quantitatively determined by HPTLC and HPLC methods in samples collected from five different geographic zones of India[11].
- A triterpene δ-amyrin acetate (1), aliphatic acid hexadecanoic acid (3) and stilbene glucoside trans-resveratrol-3-O-glucoside (9) were isolated for the first time from the stems of *Cissus quadrangularis*, along with previously reported compounds namely, δ-amyrone (2) δ-amyrin (4), β-sitosterol (5), kaempferol (6), quercetin (7) and resveratrol (8). The structure elucidation of the isolated compounds were performed by spectroscopic techniques (IR, UV, 1H-NMR, 13C-NMR and MS) and by direct comparison with literature[12].
- Two new iridoids 6-O-[2,3-dimethoxy]-trans-cinnamoyl catalpol (1) and 6-O-meta-methoxy-benzoyl catalpol (2) along with a known iridoid picroside 1 (3), two stilbenes quadrangularin A (4) and pallidol (5), quercitin (6), quercitrin (7), beta-sitosterol (8) and beta-sitosterol glycoside (9) were isolated from *Cissus quadrangularis* Linn. The compounds 3 and 7 are first reported from this plant. The structures were elucidated by analysis of their spectroscopic data and by direct comparison with literature. This is the first reported occurrence of iridoids in *C. Quadrangularis* [13].
- Phytochemical studies on methanolic extract reveals the presence of triterpenes including α and β amyrin, β-sitosterol, ketosteroid, phenol, tannin and vitaminC[14-17].

Pharmacological overview





Anti-osteoporotic activity

Ethanol extract of *Cissus quadrangularis* Linn was evaluated for its anti-osteoporotic activity in ovariectomized rat model of osteoporosis at two different dose levels of 500 and 750 mg/kg per day. The findings assessed on the basis of biomechanical, biochemical and histopathological parameters showed that the ethanol extract of the plant had a definite antiosteoporotic effect [18].

Antioxidant activity

Extracts of *Cissus quadrangularis* Linn were tested for antioxidant activity by β-carotene linoleic acid model and also by 1, 1-diphenyl-2-picrylhydrazyl model. The ethyl acetate fraction of both fresh and dry stem extracts at a concentration of 100 ppm showed 64.8% antioxidant activity in the β-carotene linoleic acid system and 61.6% in the 1, 1-diphenyl-2- picrylhydrazyl systems[19].

Analgesic and Anti-inflammatory activity

The effects associated with haemorrhoid, i.e. analgesic and anti-inflammatory activities as well as the venotonic effect of the methanol extract of *C. quadrangularis* (CQ) were assessed in comparison with reference drugs. In the analgesic test, CQ provoked a significant reduction of the number of writhes in acetic acid-induced writhing response in mice. CQ also significantly reduced the licking time in both phases of the formalin test. The results suggest peripheral and central analgesic activity of CQ. In acute phase of inflammation CQ elicited the inhibitory effect on the edema formation of the rats' ear induced by ethyl phenylpropiolate as well as on the formation of the paw edema in rats induced by both carrageenin and arachidonic acid. It is likely that CQ is a dual inhibitor of arachidonic acid metabolism. In addition, CQ exerted venotonic effect on isolated human umbilical vein similarly to the mixture of bioflavonoids, i.e. 90% diosmin and 10% hesperidin. The results obtained confirmed the traditional use of *C. quadrangularis* for the treatment of pain and inflammation associated with hemorrhoid as well as reducing the size of hemorrhoids[20].

Antiulcer activity

Cissus quadrangularis is an indigenous plant commonly mentioned in Ayurveda for treatment of gastric ulcers. The ulcer-protective effect of a methanolic extract of *Cissus quadrangularis* was comparable to that of the reference drug sucralfate. Further, gastric juice and mucosal studies showed that Cissus at a dose of 500 mg/kg given for 10 days significantly increased the mucosal defensive factors like mucin secretion, mucosal cell proliferation, glycoproteins and life span of cells. The present investigation suggests that Cissus not only strengthens mucosal resistance against ulcerogens but also promotes healing by inducing cellular proliferation[21-28].

Toxicity studies

Toxicity study was conducted to evaluate the three-month subchronic toxicity of *C. quadrangularis* powder in five groups of 12 Wistar rats of each sex. Water control group received orally 10 ml of water/kg BW/day. It was found that *C. quadrangularis* did not produce any significant dose-related changes of hematological parameters or serum clinical chemistry, and no histopathological lesion of any internal organ that could be due to the toxic effect of *C. quadrangularis* was observed. The results indicated that *C. quadrangularis* at the doses given did not produce any toxicity in the rats during the administration period of 3 months[29].

Anabolic and Androgenic activity

In addition to speeding the remodeling process of the bone, *Cissus* also leads to a much faster increase in bone tensile strength. In clinical trials *Cissus* has led to a fracture healing time in the order of 55 to 33 percent of that of controls. *Cissus* exerts antiglucocorticoid properties is suggested by a number of studies where bones were weakened by treatment with Cortisol and upon administration of *Cissus* extract the Cortisol induced weakening was halted and the healing process begun.[30] Endogenous Glucorticoids including the body's endogenous hormone Cortisol activate pathways that degrade not only bone, but skeletal muscle tissue as well. Glucocorticoids induce muscle breakdown. They activate the so-called Ubiquitin-Proteasome pathway of proteolysis. This pathway of tissue breakdown is important for removing damaged and non-functional proteins. By exerting an anabolic, antiglucorticoid effect *Cissus* preserve muscle tissue during times of physical and emotional stress, which is of more interest to the average bodybuilder or athlete.[31]

Anti microbial and antibacterial activity

Methanol extract (90%) and dichloromethane extract of stems possess antibacterial activity against *S. aureus*, *E. coli*, and *P. aeruginosa* and mutagenicity against *Salmonella* microsome[32]. Antimicrobial activity has also been reported from stem and root extract. The alcoholic extract of aerial part was found to possess antiprotozoal activity against *Entamoeba histolytica*. Alcoholic extract of the stem showed activity against *E. coli*[33].

Bone healing activity

Paste of alcoholic extract of the plant was locally as well as intramuscularly facilitates rapid healing of fracture in albino rats[34]. Ethanol extract (95%) enhances the development of cortical bone and trabeculae in fetal fumor, which may be related to rich content of calcium, phosphorous and phytoestrogenic steroids and shown to influence early regeneration and quick mineralization of bone fracture healing process[35].

Central nervous system activity

The root extract possesses central nervous system depressant activity indicated by decrease in exploratory behavior. Methanol extract of roots contains saponins which show potent sedative activity and also inhibit spontaneous motor activity in mice[36-37].

Antihemorrhoidal Activity

As the combination of flavonoids (90% diosmin and 10% hesperidin) used clinically for the treatment of hemorrhoid was reported to have anti-inflammatory and analgesic activities as well as venotonic effect which is not reported previously. Phytochemical study of *C. quadrangularis* revealed that its major compounds are flavonoids. The bioflavonoids, particularly diosmin, hesperidin and oligomeric proanthocyanidin complexes have demonstrated potential in the treatment of hemorrhoids and varicose veins.[38] These bioflavonoids exhibit phlebotonic activity, vasculoprotective effects and antagonistic effect on the biochemical mediators of inflammation. The anti-inflammatory effect which is already been observed from the crude extract of *C. quadrangularis* could be produced by the flavonoids especially luteolin, and by β-sitosterol. The venotonic effect of *C. quadrangularis* may also be postulated to be due to the effect of flavonoids present in the extract which act in the same way as that of diosmin and hesperidin. As diosmin and hesperidin are used in combination (Daflon®) to treat hemorrhoid, the extract which produced the same activities (anti-inflammatory and venotonic) can also be used as antihemorrhoidal drug. Besides these effects, *C. Quadrangularis* also possesses the analgesic effect, which can be very useful in painful hemorrhoid. The present study proved the traditional use of *C. quadrangularis* as an antihemorrhoidal drug in Thai folk medicine.[39-40]

Antiobesity property

The studies with *Cissus quadrangularis* (CQ), *Sambucus nigra*, *Asparagus officinalis*, *Garcinia atroviridis*, ephedra and caffeine, Slimax (extract of several plants including *Zingiber officinale* and Bofutsushosan) showed a significant decrease in body weight. In 41 animal studies, significant weight loss or inhibition of weight gain was found. No significant adverse effects or mortality were observed except in studies with supplements containing ephedra, caffeine and bofutsushosan. In conclusion, compounds containing Ephedra, CQ, Ginseng, Bitter melon, and Zingiber were found to be effective in the management of obesity. Attention to these natural compounds would open a new approach for novel therapeutic and more effective agents [41].

The effects of the two formulations, *Cissus quadrangularis* only and a *Cissus quadrangularis/Irvingia gabonensis* combination, on weight loss in overweight and obese human subjects. Although the *Cissus quadrangularis*-only group showed significant reductions on all variables compared to the placebo group, the *Cissus quadrangularis/Irvingia gabonensis* combination resulted in even larger reductions. This apparently synergistic formulation should prove helpful in the management of obesity and its related complications[42].

Miscellaneous activity

Acetone and dichloromethane extract of the plant possess proteolytic activity against cysteine protease. An extract of the plant has wound healing activity and molluscidal activity. [43] The extract of the plant exhibits cardiotonic and androgenic property[44]. Ethanol extract (50%) of aerial parts possesses hypotensive activity and stem extract possess diuretic.

Discussion

Synthetic medicines have the drawback of side effects. Therefore peoples are moving towards herbal medicines and their combinations. Some diseases don't have any proper

treatment. Hence the only option remains folk medicines like *Coccolus hirsutus*, *Muraya coignii*, *Anogiessus latifolia* and many more. Now a days more emphasis is given to have better health instead of taking medicine, hence the use of Nutraceuticals is also increased[45-47]. Some herbal drugs which can be used as nutraceuticlas are *Typha angustifolia* and *Typha latifolia*, *wheat grass*, *Piper betle*, *Bamboo* etc[48-55].

Folk medicines have good scope for the new drug therapy as well as Nutraceuticals. This review article on *Cissus quadrangularis* will provide help to know the potency of the medicine for different diseases.

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Conflict of interest: We declare that we have no conflict of interest.

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