A Pharmacognostical Review on Cissus Quadrangularis Linn

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ABSTRACT
Since ancient ages plants have served human beings as a natural source of treatments and therapies, amongst them medicinal herbs have gain attention because of its wide use and less side effects. In current scenario focus on plant research has increased throughout the world and a huge amount of evidences have been collected to show immense potential of medicinal plants used in various traditional systems. More than 15000 plants have been studied during the last 5 year period. Recently scientists are using these renewable resources to produce a new generation of the rapieutic solutions. Inspite of many synthetic compounds, the most efficient drugs available are directly or indirectly related with the plant kingdom. Many of the plant extracts have proven to posses pharmacological actions. Production and cost advantages of plant-made pharmaceuticals can allow more capital to be invested in research and development of new therapeutics, giving patients access to new drugs faster. This review highlights some of the phyto chemical and pharmacological aspects of Cissus quadrangularis Linn. Cissus quadrangularis, a perennial climber widely used in traditional medicinal systems of India has been reported to posses bone fracture healing, antibacterial, antifungal, antioxidant, anthelmintic, antihemorrhoidal and analgesic activities. Cissus quadrangularis Linn. Has been recognized as a rich source of carotenoids, triterpenoids and ascorbic acid and is proved to have potential for medical effects, including “Gastro protective activity” in conjugation with NSAID therapy and in “Lipid metabolism and oxidative stress”. Needless to say that versatile uses and various therapeutic activities has made the plant a valuable medicinal herb.

Cissus quadrangularis Linn. is a succulent plant of family Vitaceae commonly found in tropical and subtropical xeric wood. It is fleshy and cactus-like, widely used as a common food item in India. The plant contains calcium oxalate, β-carotene, ascorbic acid, β-sitosterol and 3-ketosteroids, also flavonoids such as quercetin, and kaempferol. The stem contains two unsymmetrical tetracyclic triterpenoids, onocer-7-ene-3α, 21β-diol and onocer-7-ene-3β, 21 α–diol, two steroidal principles I and II, δ-amyrin, δ-amyrone. The plant is prescribed in the ancient Ayurvedic literature as a general tonic and analgesic, with specific bone fracture healing properties. In the present studies pharmacognostic investigation done on basis of macroscopy, microscopy and physicochemical parameters. These findings will be useful towards establishing quality control parameter for the standardization of the drug.

Keywords: Cissus quadrangularis Linn., Physicochemical parameters, phytochemical constituents, Hadjod, Phytochemistry, Pharmacological activities.

INTRODUCTION
Cissus quadrangularis L. is a succulent plant of family Vitaceae commonly known as Asthisamhari found in tropical and subtropical xeric wood. It can be found throughout the hotter parts of India alongside hedges, neighboring countries like Pakistan, Bangladesh, Sri Lanka and Malaysia. It can be cultivated in plains coastal areas, jungles and wastelands up to 500m elevation. Plant is propagated using cuttings. The stem juice of plant is used to treat scurvy, menstrual disorders, otorrhoea and epistaxis. The plant has been documented in Ayurveda for the treatment of osteoarthritis, rheumatoid arthritis and osteoporosis. A paste of stem is given in asthma, burns and wounds, bites of poisonous insects and for saddle sores of horses and camels.

Cissus quadrangularis (Linn) has been used by common man in India for promotion of fracture healing and well known as “Hadjod”. It is also known as Vitis quadrangularis Wall. Which belongs to family Vitaceae. It is a common perennial climber, which is distributed throughout India particularly in tropical regions. The plant is commonly known as Vajravalli in Sanskrit, Hadjod in Hindi, Kandvel...
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It requires warm tropical climate and propagated by stem cuttings in months of June and July. 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 3-foliate 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. Stem is buff colored with greenish ting, dichotomously branched, sub-angular, glabrous, fibrous and smooth. It has been prescribed in Ayurveda as an alternative, anthelmintic, dyspeptic, digestive, tonic, analgesic in eye and ear diseases, and in the treatment of irregular menstruation and asthma. In some parts of world, the whole plant is used in oral rehydration, while the leaf, stem, and root extracts of this plant are important in the management of various ailments. Some other reports on Cissus quadrangularis justifies its effectiveness in management of obesity and complications associated with metabolic disorders, as well as its antioxidant and free radical scavenging activity in vitro. In current scenario formulations now contain extracts of Cissus quadrangularis in combination with other active ingredients, used for the purpose of management of overweight and obesity, as well as complications resulting from these conditions, specifically metabolic syndrome (syndrome X). Phytochemical screening of Cissus quadrangularis revealed high contents of ascorbic acid, carotene, anabolic steroidal substances, and calcium. The stem contains two asymmetric tetracyclic triterpenoids, and two steroidal principles. The presence of β-sitosterol, δ-amyрин, δ-amyronе, and flavanoids (quercetin) having different potential metabolic and physiological effects has also been reported.

CLASSIFICATION

Kingdom : Plantae
Division : Magnoliophyta
Class : Magnoliopsida
Order : Vitales
Family : Vitaceae
Genus : Cissus
Species : quadrangularis

PHYTOCHEMISTRY

Phytochemical studies of Cissus quadrangularis have shown the presence of various versatile constituents such as flavanoids, triterpenoids, Vitamin C, stilbene derivatives and many others, e.g. resveratrol, piceatannol, pallidol perthenocissin and phytosterols. Out of which ascorbic acid, triterpene, β-sitosterol, ketosteroid, two asymmetrical tetracyclic triterpenoids and calcium were identified as major constituents of this plant. The Cissus quadrangularis contains high amount of Carotene A, anabolic steroidal substances and Calcium. The plant contains ascorbic acid, 479 mg and carotene, 267 mg per 100 g freshly prepared paste, in addition to calcium oxalate. The stem of the plant contains two asymmetric tetracyclic triterpenoids, onocer – 7 ene 3 α, 21 β diol (C30H52O2 m.p. 200 – 202 °C) and onocer – 7 ene – 3 β, 21 α diol (C30H52O2, m.p. 233 – 234 °C). It also contains two steroidal principles –
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1. C27H45 O, melting point 249–252°C
2. C23H41 O, melting point 136–138°C

Presence of β-sitosterol (Fig. 3), δ amyrin and δ-amyrone is also reported. The aerial parts of Cissus quadrangularis is found to contain a new asymmetric tetracyclic triterpenoid, 7-Oxo-Onocer-8-ene-3β 21 α diol (C30H50O3, m.p. 235–237°C). Seven new compounds are also reported which are 4-hydroxy 2 methyl-tricos-2 ene -22- one, 9-methyloctadec- 9-ene, heptadecyl-octadecanoate, icosanlycosanoate, 31-methyl tritiacontan-1-ol, 7- hydroxy- 20- oxo- docosanyl cyclonexane and 31-methyl tritiacontanoic acid. Small amount of taraxeryl acetate, friedelan-3-one, taraxerol and isopentacosanoic acid is also present. Presence of 3, 3’, 4, 4’-tetrahydroxybiphenyl is also reported. Analysis of the air-dried Cissus quadrangularis plant reported to contain moisture 13.1, protein 12.8, wax 1.0, fiber 15.6, carbohydrate 36.6, mucilage and pectin 1.2 and ash 18.2%. The root powder also contain a rich source of mineral elements (mg/100g dry matter): potassium 67.5, calcium 39.5, zinc 3.0, sodium 22.5, iron 7.5, lead 3.5, cadmium 0.25, copper 0.5 and magnesium 1.15. Analysis of the toxicanst also revealed the presence of oxalate, tannin, phytate, saponin contents (135, 0.3, 20, 0.16 mg/100g of dry matter) respectively. The ash formed from the Cissus quadrangularis contains mostly carbonates and to a smaller extent phosphates of sodium, potassium, magnesium and calcium. Presence of potassium tartartate is also reported. The Cissus quadrangularis stem is also reported to contain a water-soluble glycoside, which produces a fall in blood pressure in anaesthetized cats. Fresh stems of Cissus quadrangularis produces irritating action on the skin, which may be attributed to the presence of calcium oxalate and 31 methyl tritiacontanoic acid along with taraxeryl acetate, taraxerol and iso-pentacosanoic acid. Recently three new stilbene derivatives, quadrangularins A, B and C were isolated from Cissus quadrangularis together with resveratrol, piceatannol, palloidol and parthenocissine A. The stem extract of Cissus quadrangularis plant contains a high percentage of calcium ions (4% by weight) and phosphorous. Recently a study has been undertaken which showed that the plant extract when reacted with CO2, leads to formation of calcite crystals of highly irregular morphology, indicating that bioorganic molecules present in the extract modulate the crystal morphology.

THERAPEUTIC USES

The stout, fleshy quadrangular stem is traditionally used for the treatment of gastritis, bone fractures, skin infections, constipations, eye diseases, piles, anemia, asthma, irregular menstruation, burns and wounds. The leaves and young shoots are powerful alteratives.

Powder is administered in treatment of hemorrhoids and certain bowel infections. The juice of stem is useful in scurvy and in irregular menstruation whereas the stem paste boiled in lime water is given in asthma. It is also used as a powerful stomachic. Cissus quadrangularis Linn. has potent fracture healing property and antimicrobial, antiulcer, antioxidative, antisteporotic, gastroprotective, cholinsceric activity as well as beneficial effects on cardiovascular diseases. It has been investigated that methanolic extract of Cissus quadrangularis possesses antiulcer and cytoprotective property in indomethacin induced gastric mucosal injury. The aqueous extract also shows acetycholine like activity on isolated ileum of rabbit and uterus of rat. The action on dog blood pressure is analogous to that of indomethacin induced gastri.

STRENGTH AS PER AYURVEDIC PHARMACOPOEIA OF INDIA

Foreign Matter: NMT 1% W/W
Total Ash: NMT 5% W/W
Acid insoluble ash: NMT 1% W/W
Alcohol soluble extractive: NLT 3% W/W
Water soluble extractive: NLT 23% W/W
Fixed oil: NLT 3% W/W
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Sulphated Ash content: NMT 5% W/W
Arsenic: NMT 1 ppm
Lead: NMT 5 ppm
Total bacterial count: NMT 800 CFU/g
Total fungal count: NMT 500 CFU/g
Moisture content: NMT 5% W/W

MATERIALS AND METHODS

The plant, *Cissus quadrangularis* Linn. Was collected from Anand Agriculture University campus, Anand, Gujarat, India and authenticated by Dr A. S. Reddy, B. R. Doshi School of Biosciences, Sardar Patel University, Vallabh Vidhyanagar, Gujarat, India. The specimen was deposited at the department of Pharmacognosy, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur for future reference. The drug was subjected to macroscopic studies, microscopic studies and physicochemical parameters.

PHARMACOLOGICAL ACTIVITY

Bone Fracture Healing Activity

*Cissus quadrangularis* (Vitaceae), a rambling shrub, characterized by a thick quadrangular fleshy stout stem, Commonly known as the “Bone Setter,” the plant is referred to as “Asthisamdhani” in Sanskrit and “Hadjod” in Hindi because of its ability to join bones. A phytogenic isolated steroid is believed to be the main constituent in *Cissus quadrangularis*. Studies on fracture healing suggest that this unidentified anabolic steroid may act on estrogenic receptors of the bone. Efficacy of *Cissus quadrangularis* on early ossification and remodeling of bones have been reported and it has been observed that *Cissus quadrangularis* acts by stimulation of metabolism and increased uptake of the minerals calcium, sulphur and strontium by the osteoblasts in fracture healing. *Cissus quadrangularis* is found to contain vitamins and steroids, which are found to have specific effect on bone fracture healing. The anabolic steroidal principles from *Cissus quadrangularis* showed a marked influence in the rate of fracture healing by influencing early regeneration of all connective tissues involved in the healing and quicker mineralization of callus. Systemic use of *Cissus quadrangularis* in rats caused complete restoration of normal composition of bone, after fracture in four weeks while the controls required six weeks. There was a shortening of about two weeks in the bone healing duration. The total weight of the fractured bone also came down towards normal much earlier than the controls indicating quickest bone remodeling. All the events namely fibroblastic phase (first week), collagen phase (second week) and osteochondroital phase (third and fourth weeks) were hastened by about 10 to 14 days in the treated group. This hastening in the fracture healing was attributed to the stimulation of all the cells of mesenchyma origin, namely the fibroblasts, the chondroblasts and osteoblasts by *Cissus quadrangularis*. It has greater impact on osteoblastic proliferation than other cellular responses. In both the models the mucopolysaccharides and collagen levels of the bones in the treated group came down to normal at the end of only four weeks while the control required 6 weeks as confirmed with histological and histochemical observations. Radioactive calcium (Ca45) studies indicated that *Cissus quadrangularis* causes less lowering of calcium (Ca45) uptake in the treated animals while in the control animals there was a greater decrease in the calcium (Ca45) uptake in the first week followed by a gradual increase in the subsequent weeks which reached its maximum in the 4th weeks the calcium (Ca45) uptake in the treated group came to normal at the end of 5th week as compared to 6 - 8 weeks in controls. Thus it was concluded that *Cissus quadrangularis* caused less amount of tissue reaction in the fractured region leading to optimum decalcification in the early stage with minimum of callus formations. Hence deposition of calcium was just enough to join the two broken segments of bones so that it’s remodeling takes much faster in the treated group as compared with controls. This early completion of calcification process and earlier remodeling phenomenon lead to early recovery of animals. The tensile strength studies indicated much early gain in the tensile strength in *Cissus quadrangularis* treated group, leading to 90 percent of gain of its normal strength at the end of 6th week in comparison to 60 percent of gain in strength in the controls. Thus *Cissus quadrangularis* builds up the chemical composition of the fractured bone namely its mucopolysaccharides, collagen, calcium, phosphorus and others as well as its functional efficiency. Healing of the fractured bone is delayed considerably by the administration of Cortisone. The periosteal reaction is reduced and the
amount and density of callus is lowered. The mortality rate of the treated subjects is very high due to severe body wasting, atrophy of muscles and gastric perforation. *Cissus quadrangularis* treatment in these cortisone treated rabbits caused a significant increase in mucopolysaccharides level and also caused proliferation of osteoblastic, chondroblastic and cartilage proliferation. It also led to increased mineralization in the callus. Thus the parenteral administration of the total extract of *Cissus quadrangularis* not only neutralized the anti-anabolic effect of cortisone in healing of fractures but also enhances the mineralization of the callus. This effect was much greater than that of anabolic hormone Durabolin a drug of choice for the neutralization of cortisone possibly due to its vitamin contents. A clinical study was planned to evaluate the effect of the *Cissus quadrangularis* in the healing of fractures. All the sixteen patients with various types of fractures were treated with external application of the paste prepared from the *Cissus quadrangularis*. This treatment was given in addition to the standard treatment of fractures, e.g. complete immobilization. As per radiological observations the results were excellent in 6 cases with the 40% reduction in the healing time, good in 8 cases with 53% reduction in the healing time and poor in 1 case with 7% reduction in healing time. Clinically in about 80% of the cases, excellent results were observed and in the remaining 14% of the cases the results were good. Only in one case there was no demonstrable effect. In few of the treated cases although radiologically only an early callus formation was observed but clinically the symptoms of fracture such as pain, tenderness and swelling were significantly absent. It was also observed that the injured bones surrounded by muscles showed a greater beneficial effect of this herb than those that are subcutaneous. It was hypothesized that *Cissus quadrangularis* helps in the earlier formation of collagen fibers leading to earlier calcification and callus formation. A study was undertaken to evaluate the effect of *Cissus quadrangularis* extract on the healing process of experimentally fractured radius-ulna of dog.

Histopathological and radiological investigations on 11th day revealed faster initiation of the healing process and a greater decrease in serum calcium level in the treated group than the control group. On 11th day, the treated group exhibited initiation of osteogenesis, which was absent in the control group. Fracture was completely healed in 21 days in the treated group and remained incomplete in the control group. Radiograph of the treated group revealed almost complete bridging of the fractured ends with extensive bony deposition and periosteal reaction compared to that of control group. The treated group also revealed replacement of cartilaginous cells by osteoblastic cells and union of the fractured gap at several places with the formation of new bony trabeculae whereas bony trabeculae were absent in the control group. Alkaline phosphates are involved in bone formation and healing of fractures. The enzyme, secreted by the osteoblasts accelerates the process of mineralization either by increasing the local concentration of in organic phosphate or activating the collagen fibers to induce deposition of calcium salts. *Cissus quadrangularis* has caused an increase in alkaline phosphate levels during fracture healing in adult dogs. A study was conducted using albino rats to explore whether the beneficial effect of *Cissus quadrangularis* in the healing of fractures is due to its vitamin C content. The animals receiving *Cissus quadrangularis* showed rapid accumulation of larger quantity of mucopolysaccharides in the first week followed by more rapid fall and its earlier disappearance from the fractured area and both of these actions have beneficial effect on the healing of the fractures. At the end of the third week the Skigram showed greater amount of calcification in the *Cissus quadrangularis* treated group in which one could hardly see a gap at the site of the fracture, while the control and vitamin C treated group showed some gap. At the end of 5th week the union at the fractured site was more firm in the *Cissus quadrangularis* treated group than the others. Earlier disappearance of mucopolysaccharides from the fractured area is associated with the earlier calcification and firmer callus formation. Mucopolysaccharides play an important role in the healing by supplying raw materials for repairs. Therefore, it seems that in the early period the greater accumulation of these materials more rapid will be the rate of healing. In the later period when the mucopolysaccharides content decline in the fractured area is an indicative of rapid utilization of these raw materials leading to earlier completion of healing process. This effect of the *Cissus quadrangularis* is not due to its vitamin C content alone, since the administration of the vitamin C to normal animals did not produce such a beneficial effect. Its action is more systemic, which is responsible for the greater mobilization of mucopolysaccharides from the tissues in to the blood and earlier utilization of the substances required in the healing process. Phosphorus (P32) is a useful isotope to study the rate of mineralization during healing of fractures since it is readily incorporated in the area where the calcium phosphate complex is deposited during the latter part of healing. In control animals, such a mineralization process takes place at the site of fracture during the latter half of the
third week. This is accompanied with the fall of mucopolysaccharides in the region. In animals treated with *Cissus quadrangularis* such a mineralization process takes place much earlier, roughly in the second half of the second week. Not only the healing has been faster but also the quality of the callus seems to be better in terms of the enormous deposition of the minerals at the end of the second week only. This is followed by early demineralization so that the callus becomes remodeled to take a normal shape of the bone. These findings further confirmed that the *Cissus quadrangularis* has favourable action in the rate of healing of fracture in experimental animals.

**Anti-Ulcer 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.

Thus, *Cissus quadrangularis* has potential usefulness for treatment of peptic ulcer disease.

**Miscellaneous**

Stem paste of the plant may also be useful for muscular pains, burns, wounds, bites of poisonous insects and for saddle sores of horses and camels. The powder of dry shoots is given in digestive troubles. A decoction of the shoots with dry ginger and black pepper is given for body pains. The infusion of the plant is anthelmintic. The plant extracts also exhibit cardiotonic property. Young shoots are used in dyspepsia and indigestion. The powdered stem is mixed with pulses and fried in sesame oil, used as a remedy for several vata diseases. It is also used in skin diseases Leprosy, Cough, Epilepsy and Convulsions.

**FORMULATION AND DOSAGE**

Decoction of dried stalks: 10-30 ml bid

Ø Juice: 10-20 ml bid

Ø Powder: 3-6 g bid

**AYURVEDIC PREPARATIONS**

Ø Flexi-Muv Oil (Anti-inflammatory, Antiarthritic)

Ø Boneforte Capsule (Calcium supplement)

Ø Laksha Gogglu (Analgesic, anti inflammatory)

**RESULTS**

The fresh plant is green in color which on drying shows buff color with greenish ting. The odor is characteristic with acrid taste. The surface of fresh plant material is smooth and glabrous to touch. Fresh stems are thick, fleshy, quadrangular with acutely 4 winged internodes whereas leaves are simple, opposed, thick coriaceous, ovate or reniform, highly coiled. Transverse section of stem showed squarish outline with prominent projection at each annular point. Epidermis is single layered, covered externally with thick cuticle. The epidermal cells are thin walled rectangular and tangentially elongated, followed by 2-3 layers of cork. The cortex is composed of 8-16 layers of thin walled, circular to oval parenchymatous cells; four patches of collenchymatous cells present in all the four angular points embedded in cortical region like an umbrella arching over large vascular bundles. The cortical cells are filled with brown-red contents. The endodermis is not distinct and stele consists of a large number of vascular bundles varying in size, in each angular region, below collenchymatous patch, while rest of bundles smaller in size. Vascular bundles are collateral and open type, capped by sclerenchymatous sheath, which is well developed in larger bundles. The cambium and interfascicular cambium are quite distinct; central region occupied by wide pith composed of thin walled, circular to oval parenchymatous cells. Idioblasts containing raphides and acicular crystals of calcium oxalate present in the outer region of cortex and in number of cells throughout the region.
DISCUSSIONS

The macroscopic as well as microscopic studies of any drug material are the preliminary steps for establishing the botanical parameters prior to any kind of study. As per WHO guidelines, botanical standards are to be proposed as a protocol for the diagnosis of the herbal drug. The quantitative determinations of some physicochemical parameters are useful for setting standards for crude drugs. The physical constant evaluation is an important parameter in detecting adulteration or improper handling of the drug. Since the plant *Cissus quadrangularis* Linn is useful in the traditional system of medicine in treatment of various diseases, it is important to standardize it for use as a drug. The macroscopic studies, microscopic studies and physicochemical parameters reported in this work could be useful for the compilation of a suitable monograph for its proper identification.

CONCLUSION

Traditional recipes for treatment of physical and mental ailments exist in all major ancient civilizations of the world. Needless to mention that the root and stem extracts of the plant *Cissus quadrangularis* have therapeutic efficacy and are known to possess antioxidant, antimicrobial activity, and are routinely used to accelerate the process of bone fracture healing.

The plant is considered as a versatile medicinal plant in both Ayurvedic and modern drug development areas for its valuable medicinal uses. It is a very rich source of some minerals, which are necessary for proper functioning of human body. In the present overview the Emphasis has been laid on the phytochemical constituents and pharmacological activity of the plant *Cissus quadrangularis* Linn.

ACKNOWLEDGEMENT

It gives me immense pleasure to express my thanks and gratitude to all those without whom this could not be possible. I am thankful to God whose blessings have always been with me for every auspicious beginning in my life.

I am indebted to my parents without whom I could not have achieved success, who always assured me moral support, encouragement and their wishes to almighty God has made me to achieve a great milestone in my carrier.

I owe my sincere gratitude to my lovely wife, for her trust has always inspired me to do my best.

I am highly thankful to her to be in my life. I could not reached this destination without the unconditional care and moral support of my dear wife Mrs. Saleha Shakir.

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