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Pharmacological and Therapeutic Activity of *Cissus quadrangularis*: An Overview

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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 therapeutic 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 phytochemical 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 "Gastroprotective 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.

KEYWORDS: Cissus quadrangularis, phytochemical constituents, Hadjod, Phytochemistry, Pharmacological activities.

INTRODUCTION

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 in Marathi, Haddjor in Punjabi, Hadbhanga in Oria, Vedhari in Gujrati, Perandi in Tamil, Nalleru in Telugu and Veldgrap, Edible Stemmed Vine in English.

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. [1, 2]

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 re-hydration, 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 [3], as well as its antioxidant and free radical scavenging activity *in vitro*.[4, 5] 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-amyrin, δ-amyrone, and flavanoids (quercetin) having different potential metabolic and physiological effects has also been reported. [6, 7]

CLASSIFICATION: [2, 20]

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

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 bowl 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, antiosteoporotic, gastroprotective, cholinergic activity as well as beneficial effects on cardiovascular diseases. [8]

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 acetylcholine like activity on isolated ileum of rabbit and uterus of rat. The action on dog blood pressure is analogous to muscarinic and nicotinic actions of acetylcholine. Ethyl acetate fractions of both fresh and dry stem extracts show antioxidant activity. The ethyl acetate extract and methanol extract of both fresh and dry stem further exhibit antimicrobial activity against gram-positive bacteria including Bacillus subtilis, Bacillus cereus, Staphylococcus aureus and Streptococcus species. Due to its widespread and versatile therapeutic uses as well as pharmacological actions, the present study highlighted the health promoting and therapeutic properties of *Cissus quadrangularis*. [9, 10, 11, 12]

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. [7, 11, 13, 14]

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 (Fig. 1) ($C_{30}H_{52}O_2$ m.p. 200 – 202 °C) and onocer - 7 ene – 3 β, 21 α diol (Fig. 2) ($C_{30}H_{52}O_2$, m.p. 233 – 234 °C). It also contains two steroidal principles –

1. $C_{27}H_{45}O$, melting point 249-252 °C
2. $C_{23}H_{41}O$, 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-3 β 21 α diol (Fig 1) ($C_{30}H_{50}O_3$, m.p. 235-237 °C). [15, 16, 17, 18, 19]

Seven new compounds are also reported which are 4-hydroxy 2 methyl-tricos-2 ene -22- one, 9-methyl-octadec-9-ene, heptadecyl- octadecanoate, icosanyl-icosanoate, 31-methyl tritiacontan-1-ol, 7- hydroxy-20- oxo- docosanyl cyclohexane 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. [20, 21, 22]
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. [23, 24, 25, 26]
Analysis of the toxicants 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 tartarate is also reported. [27, 28]
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. [29, 30]
Recently three new stilbene derivatives, quadrangularins A, B and C were isolated from *Cissus quadrangularis* together with resveratrol, piceatannol, pallidol 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 CO_2, leads to formation of calcite crystals of highly irregular morphology, indicating that bioorganic molecules present in the extract modulate the crystal morphology.[31, 32, 33]

STRENGTH AS PER AYURVEDIC PHARMACOPOEIA OF INDIA: [1, 2, 16, 19]

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
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

TOXICITY STUDY:
Toxicity study was conducted to evaluate the three-month sub chronic toxicity of *Cissus quadrangularis* powder in five groups of 12 Wistar rats of each sex. Water control group received orally 10 ml of water/kg BW/day. The dried stems powder was given orally to the four treatment groups at the doses of 0.03, 0.3, 3.0 and 30 g/kg BW/day, which were equivalent to 1,10, 100 and 1000 fold of the therapeutic dose in human respectively, the last group was the recovery group. No difference of initial or final body weights between *Cissus quadrangularis* treated and control groups was detected.
It was found that *Cissus quadrangularis* did not produce any significant dose-related changes of hematological parameters of serum clinical chemistry and no histopathological lesion of any internal organ that could be due to the toxic effect of *Cissus quadrangularis* was observed. The result indicated that *Cissus quadrangularis* at the doses given did not produce any toxicity in the rats during the administration period of 3 months. [34]

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, sulpher and strontium by the osteoblasts in fracture healing. [35, 36]

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. [37, 38]
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 mucopolysaccharide 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. [39, 40, 41]
Radioactive calcium (Ca^{45}) studies indicated that *Cissus quadrangularis* causes less lowering of calcium (Ca^{45}) uptake in the treated animals while in the control animals there was a greater decrease in the calcium (Ca^{45}) uptake in the first week followed by a gradual increase in the subsequent weeks which reached its maximum in the 4^{th} weeks the calcium (Ca^{45}) uptake in the treated group came to normal at the end of 5^{th} 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 6^{th} 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. [42, 43, 44, 45, 46]

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. [47, 48]
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. [49, 50, 51, 52]

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 11^{th} 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 11^{th} 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 peristoneal 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. [53, 54]

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 inorganic 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 Skiagram 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 5^{th} 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 the 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. [55, 56]

Phosphorus (P^{32}) 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. [57, 58]

Analgesic activity:

The analgesic effect of the drug as observed by Haffner's tail flip and Eddy's hot plate methods were dose related. There was increase in reaction time even with such small dose as 1/40 th of the LD_{50} . The effect lasted for about 4 hrs. Cissus quadrangularis exhibited significant analgesic activity compared to that of Aspirin when tested using Haffner's clip and Eddy's hot plate methods. The extract was found to be effective by both oral and i.p. routes significantly ($P<0.001$) and reaction time was found to be increased by both methods. The duration of analgesic activity was from 2 to 4 hr and optimum effect was observed at $1/20^{th}$-$1/10^{th}$ of LD_{50} dose. The extract compared well with Acetylsalicylic acid. [59, 60]

The analgesic effect of this plant when used in bone fractures may be of great value in relief of pain which is a constant feature in these cases. As it compared well with acetyl salicylic acid in its analgesic response the nature of its chemically active constituents needs to be explored. [61]

Antiosteoporotic activity:

Osteoporosis, a silent epidemic, has become a major health hazard in the recent years afflicting over 2000 million people worldwide. It is a chronic, progressive condition associated with micro-architectural deterioration of bone tissue that results in low bone mass. The leading cause of osteoporosis is the lack of certain hormones, particularly estrogen in women and androgen in men as well as Imbalance in the activities of osteoblasts and osteoclasts cells lead to osteoporosis in postmenopausal women. In osteoporosis the bones begin to deteriorate due to calcium deficiency. In menopause, the decrease in hormones affects the body's ability to maintain calcium levels resulting in an increased loss of minerals from the bone. Postmenopausal women are at particular risk to

osteoporosis because the loss of estrogen associated with the menopause leads to bone loss of much greater magnitude than expected on the basis of age alone. Treatment focuses on slowing down or stopping the mineral loss thereby preventing bone fractures and controlling the pain associated with the disease. Many synthetic agents such as estrogens in hormone replacement therapy, selective estrogen receptor modulators like raloxifen and droloxifen, bisphosphonates and calcitonin have been developed to treat osteoporosis but each one of them is associated with side effects such as hypercalcemia, hypercalciurea, increased risk of endometrial and breast cancer, breast tenderness, menstruation, thromboembolic events, vaginal bleeding and hot flushes. [46, 47, 48, 49]

Cissus quadrangularis significantly inhibits antianabolic effects and exerts some beneficial effects on recovery of bone mineral density in postmenopausal osteoporosis. A study was conducted in which ethanol extract of *Cissus quadrangularis* was evaluated for its anti-osteoporotic activity in ovariectomized rat model of osteoporosis at two different dose levels of 500 and 750mg/kg per day. Healthy female albino rats were divided into five groups of six animals each. [50, 52, 53, 54]

The first group served as control. All the remaining groups were ovariectomized. Group 2 was fed with equivolume of saline and served as ovariectomized control. Group 3-5 were orally treated with Raloxifen (5.4mg/kg) and ethanol extract of *Cissus quadrangularis* (500 and 750mg/kg), respectively. 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. [55, 56, 57, 62]

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. [63, 64, 65] 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. [66-70] 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. [71-79]

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. [80]

Another study was performed to evaluate the effect of the methanolic extract of *Cissus quadrangularis* against free radical damage. The test extract exhibited significant inhibition in DPPH free radical formation, superoxide radical production and lipid peroxide production in erythrocytes. The activities of liver marker enzymes and antioxidant defense enzymes in rat liver homogenate were assessed in control and experimental animals. [81, 82, 83, 84]

Carbon tetrachloride (CCl_4) caused a significant increase in aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT), alkaline phosphatase (ALP) and decrease in superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and reduced glutathione (GSH), which was reverted by *Cissus quadrangularis* pretreatment. The results obtained suggest that *Cissus* showed inhibition of lipid peroxidation, free radical production and increase in antioxidant enzymes activities, which reveal its antioxidant property. It can be concluded that the free radical scavenging activity of the plant extract may be responsible for the therapeutic action against tissue damage. [85, 86, 87, 88]

The stem part of *Cissus quadrangularis* contains vitamin C, carotenoids, calcium, steroidal and these are known to be excellent antioxidants and numerous studies suggest that dietary intake of plant polyphenol antioxidants may have positive effects in oxidative-stress related pathologies. These antioxidative constituents present in *Cissus* might be responsible for the free radical scavenging activity, antilipid peroxidative and antisuperoxide formation. [89, 90, 91, 92]

Parasympathomimetic activity

Aqueous extract showed acetylcholine like activity on isolated ileum of rabbit and rat, uterus of rat, dog tracheal muscle and ileum in situ of dog. The responses on dog blood pressure were analogous to Muscarinic and Nicotinic actions of Acetylcholine. It was ineffective on frog rectus muscle.

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. [93]

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. [94]

Anti-inflammatory activity:

Studies have revealed that oral administration of phenidone produced marked inhibition of the paw edematous response induced by arachidonic acid injection. CQ exerted inhibitory effect on the edema formation in this animal model. It has been observed that flavanoids, several flavones, flavonols, flavanols and flavanonols are inhibitors of lipoxygenase, especially luteolin which is one of the compounds found in *C. quadrangularis*. In this regard, it has been previously shown that at least flavonoid, one of the major components of *C. quadrangularis*, inhibits the inflammatory process. Furthermore the anti-inflammatory activity of β sitosterol was also demonstrated which is another active constituent of *C. quadrangularis*. *The result of the study confirmed the finding that C. quadrangularis have an* inhibitory effect on edema induced by both carrageenin and arachidonic acid. Taken together, it is evident that both cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism are inhibited by *C. quadrangularis*. It is therefore suggested that *C. quadrangularis* is a dual inhibitor of arachidonic acid metabolism. [95]

Cissus also posses anti-inflammatory activity on a mg per mg basis comparable to aspirin or ibuprofen. *Cissus quadrangularis* constitutes one of the ingredients of an Ayurvedic preparation, 'Laksha Gogglu', which has been proved to be highly effective in relieving pain, reduction of swelling and promoting the process of healing of the simple fractures as well as in curing the allied disorders associated with fractures. It acts by preventing the conversion of arachidonic acid to inflammatory prostaglandins. [96, 97, 98]

Recently anti-inflammatory activity assay of *Cissus* extract was performed. Cyclooxygenase is a key enzyme in the prostaglandin biosynthetic pathway, which is important in the inflammatory process. The ability to inhibit the COX-1 activity was used to evaluate the anti-inflammatory activity of *Cissus* extract. The anti-inflammatory activity of the extract was expressed as the percentage of inhibition of prostaglandin synthesis using a COX-1 assay. The amount of (^{14}C)-labelled prostaglandin synthesized was measured using a scintillation counter after removing the unmetabolized (^{14}C)-Arachidonic acid substrate by column chromatography. The percent inhibition of prostaglandin synthesis was calculated. [99, 100]

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. [101] 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 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. [102, 103]

Gastroprotective Activity:

Cissus quadrangularis is well known for the treatment of gastric disorders in traditional medicine, owing to its rich source of carotenoids, triterpenoids and ascorbic acid, and has received considerable attention regarding its role in human nutrition. A number of studies have analysed and revealed the effect against gastric toxicity and the gastroprotective effect of *Cissus quadrangularis* extract (CQE) along with its mechanism underlying the therapeutic action against the gastric mucosal damage induced by aspirin. [63, 64, 67] The studies have investigated the effect of CQE on the course of experimentally induced gastric ulcer by analyzing the levels of tumor necrosis factor-α (TNF-α), interleukines, microvascular permeability, activity of nitric oxide synthase-2 (NOS-2), mitochondrial antioxidants, lipid peroxidation and DNA damage. The investigational findings have shown significant increase in vascular permeability, NOS-2 activity. Levels of TNF-α and interleukines were monitored and oxidative damage were noted in aspirin administered rats. The optimum protective dose of 500 mg/kg of extract was given for the pretreatment of gastric ulcers with different doses of CQE (250, 500 and 750 mg/kg) for 7 days which significantly attenuated these biochemical changes caused by aspirin in rats. [69, 70] The results showed ulcer protection by 40, 71.2 and 72.6%, respectively, as compared to ranitidine (RTD) (30 mg/kg) by 71.9% in the aspirin model. In addition, the findings of the studies have shown that administration of aspirin increases lipid peroxidation status, xanthine oxidase (XO), myeloperoxidase and decrease in superoxide dismutase (SOD), catalase (CAT) and selenium–glutathione peroxidase activities in the gastric mucosa, resulting in mucosal damage at both cellular and subcellular level which were reversed by CQE. [71] In addition, CQE prevents oxidative damage of DNA by reducing DNA fragmentation indicating its block on cell death. Pretreatment with CQE ameliorated the observed effect significantly in the gastric mucosa of ulcerated rats. Ulcer protection in CQE treated rats was also confirmed by histoarchitecture, which was comprised of reduced size of ulcer crater and restoration of mucosal epithelium. These findings suggest that the gastroprotective activity of CQE could be mediated possibly through its antioxidant, antiapoptotic effects as well as by the attenuation of the oxidative mechanism and neutrophil infiltration. Triterpenoids and β-sitosterols present in *Cissus quadrangularis* possess antilipidperoxidative effect and have a pivotal role in the gastroprotective effect of CQE. [76, 79]

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: [1, 2, 4, 5]

Decoction of dried stalks: 10-30 ml bid

- Juice: 10-20 ml bid
- Powder: 3-6 g bid

AYURVEDIC PREPARATIONS:

- Flexi-Muv Oil (Anti-inflammatory, Anti-arthritic)
- Boneforte Capsule (Calcium supplement)
- Laksha Gogglu (Analgesic, anti-inflammatory)

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.

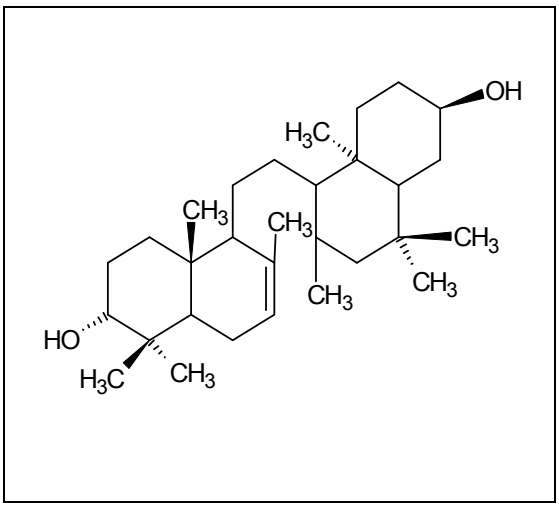

Fig. 1 Onocer-7-ene, 3-α, 21-β diol

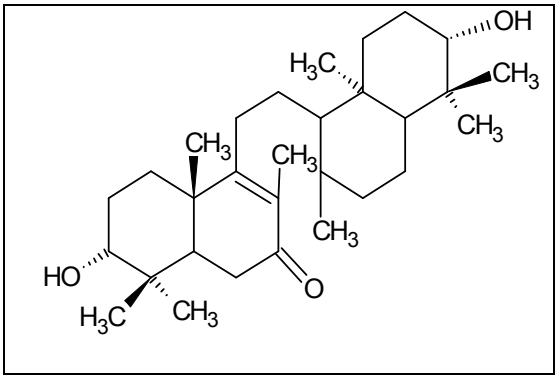

Fig 2. 7-oxo-onocer-8-ene.3-β. 21-α diol

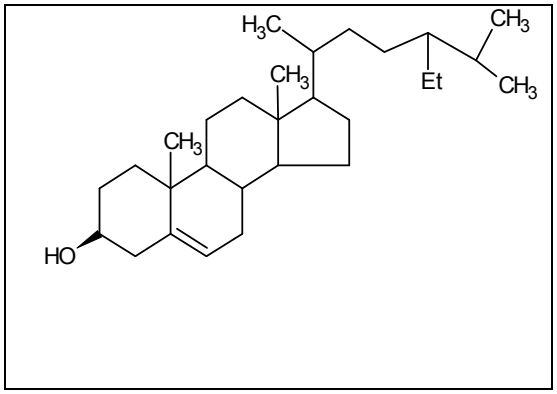

Fig. 3 β-sitosterol

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