CHAPTER 73

PHYTOCHEMISTRY AND PHARMACOLOGICAL PROPERTIES OF *CISSUS QUADRANGULARIS* L.

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ABSTRACT

Cissus quadrangularis L., a square stemmed perennial vine belonging to the family Vitaceae, is widely used in traditional systems of medicine for various disorders. The plant has been reported to contain flavonoids, triterpenoids, phytosterols, glycosides and also a rich source of calcium. The chapter explores a wide number of phytochemical constituents that had been isolated from the plant, which plays major role including gallic acid derivatives, steroids, iridoids, flavonoids, stilbenes, and triterpenes, which possesses activities like anti-inflammatory, anti tumor, gastro protective, antioxidant, antimicrobial and various other important medicinal properties.

Biomolecules and Pharmacology of Medicinal Plants, Volume 2: T. Pullaiah (Ed.)

73.1 INTRODUCTION

Cissus quadrangularis L. is a perennial climber of the family Vitaceae. The plant is native of tropical Africa, Arabia, India, and Sri Lanka. It is commonly known as adamant creeper, veldt grape, devil's backbone, and bone setter. The plant is a rambling shrub, stem 4-winged, contracted at the nodes, internodes 4–15 cm long, tendrils stout. The leaves are simple, broadly ovate or reniform, chordate, petioles 6–12 mm long. Flowers are greenish yellow or reddish in umbellate cymes. Berries globose, red when ripe.

The plant is well cited for its medicinal uses in both Ayurvedic and Unani systems (Shirwaikar et al., 2003). The plant is well known for its anthelmintic, aphrodisiac, and antiasthmatic properties. The stem is bitter, applied for fractured bones and spine complaints. The plant is used to reduce the size of hemorrhoids and associated pain and inflammation (Lans, 2006). This chapter deals with phytochemical and pharmacological properties of *C. quadrangularis* till date.

73.2 PHYTOCHEMICALS

Phytochemical analysis of the plant revealed the presence of various phytoconstituents such as flavonoids, triterpenoids, vitamin C, stilbene derivatives, and many others. Major components of the plant include ascorbic acid, triterpene, β-sitosterol, ketosteroid, two asymmetrical tetracyclic triterpenoids, and calcium. Two steroidal principles and two asymmetric tetracyclic triterpenoids namely, onocer-7 ene 3 α, 21 β-diol and onocer-7 ene-3 β, 21 α-diol were reported from the stem (Bhutani et al., 1984). Seven new compounds were isolated and characterized as 4-hydroxy-2-methyl-tricos-2-en-22-one, 9-methyl-octadec-9-ene, heptadecyl octadecanoate, icosanyl icosanoate, 31-methyl-tritriacontan-1-ol, 7-hydroxy-20-oxo-docosanyl cyclohexane, and 31-methyltritriacontanoic acid from the plant. Taraxeryl acetate, friedelan-3-one, taraxerol, and isopentacosanoic acid were also isolated from this plant (Gupta and Verma, 1991). Stem extract contains a high percentage of calcium ions and phosphorus (Deka et al., 1994). Three new stilbene derivatives, quadrangularins A, B, and C have been isolated from the stem and characterized using 2D NMR (Adesanya et al., 1999). Jakikasem et al. (2000) reported the presence of β-sitosterol, δ-amyrin, δ-amyrone, and quercetin. *Cissus* contains ascorbic acid and carotene at a concentration of 479 mg, and 267 units respectively per 100 g of freshly prepared paste (Austin and Jagdeesan, 2002; Chidambara et al., 2003). Chemical characterization of the

plant showed polyphenols such as quercetin, daidzein, and genistein (Singh et al., 2007). Ecosyl eicosanoate, tetratriacontanol, tetratriacontanoic acid, α-amyrin, and β-sitosterol were reported from the leaf of plant (Jainu and Devi, 2009*)*. 7-Oxo-onocer-8-ene-3 β-21 α-diol, a new asymmetric tetracyclic compound was isolated and characterized through spectral studies from aerial parts of the plant (Jain et al., 2009). Thakur et al. (2009) reported the presence of δ-amyrin acetate, hexadecanoic acid, and transresveratrol-3-*O*-glucoside (Piceid) in the plant. Other compounds reported from the plant include resveratrol, piceatannol, pallidol, perthenocissin, and ketosteroid (Mishra et al., 2010). Rao et al. (2011) reported melanin promoting compound lupeol.

Stem powder contains a total of 4.33/100 g alkaloids, 7.86/100 g of flavonoids, 2.60/100 g of tannin, 3.85/100 g of saponin, 0.322/100 g of phenol, and 234/100 g of glycosides (Nawghare et al., 2017). The phytochemical compounds like saponins, alkaloids, protein, tannins, phenols, carbohydrates, terpenoids, and glycosides are highly present in methanolic stem extracts (Saranya and Rani, 2017). Four flavonoids quercetin, kaempferol 3-*O*-rhamnoside, quercetin 3-*O*-rhamnoside (quercitrin), and vitexin have been isolated and characterized by LC/MS/MS analysis, from the leaves of *C. quadrangularis* (Jain et al., 2017).

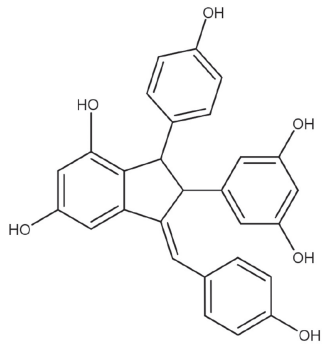
Phytochemical quantification clearly evidenced the presence of *n*-hexadecanoic acid (23.42%), 2-furancarboxaldehyde, 5-(hydroxymethyl)- (18.64%), 9,12-octadecadienoic acid, methyl ester (12.05%), Urs-12-en-24-oic acid, 3-oxo-, methyl ester, (+)- (6.73%), 4,8,13-cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)- (3.74%), 3,7,11,15 -tetramethyl-2-hexadecen-1-ol (3.30), propane, 1,1,3-triethoxy-(2.37%), vitamin E (2.33%), 2H-pyran, 2-(7-heptadecynyloxy) tetrahydro- (2.23%), 2(1H) naphthalenone, 3,5,6,7,8,8a –hexahydro -4, 8a-dimethyl-6-(1-methylethenyl)- (1.35%), 9-octadecenoic acid (Z)-, methyl ester (1.69%), 1,2-15,16-diepoxyhexadecane (1.64%), E-10-pentadecenol (1.10%), E-2-tetradecen-1-ol (0.80%), cyclopentane undecanoic acid, methyl ester (0.64%) and docosanoic acid, ethyl ester (0.44%) (Chenniappan et al., 2020).

73.3 PHARMACOLOGICAL USES

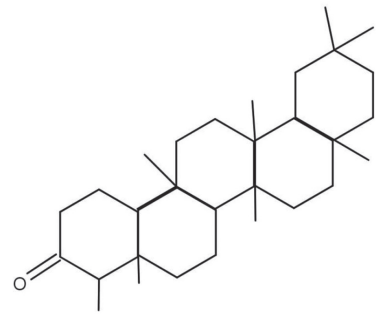
73.3.1 ANTIOXIDANT AND FREE-RADICAL-SCAVENGING ACTIVITY

Sathyaprabha et al. (2010) reported free-radical-scavenging property and antilipid peroxidative properties of the plant. Due to high β-carotene, the extract of *C. quadrangularis* exhibits significant antioxidant activity and

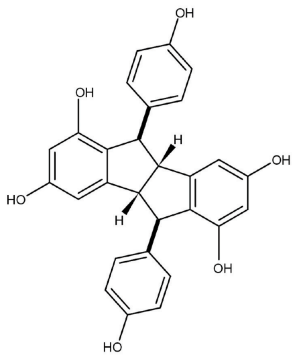
inhibition of lipid peroxide production in erythrocytes (Jainu and Devi, 2005; Palu et al., 2010). Further, the extract upregulates the antioxidants and endothelial nitric oxide synthase expression in H_2O_2 damaged human ECV304 cells (Sapsrithong et al., 2012).



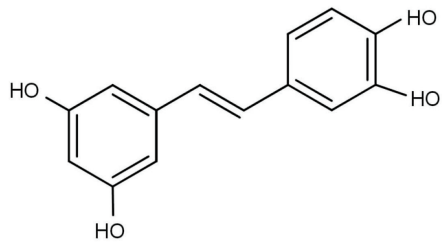
Quadrangularin A



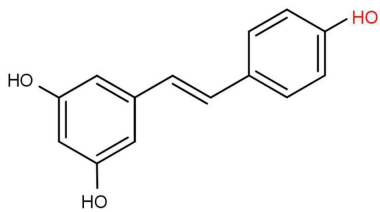
Friedelan-3-one



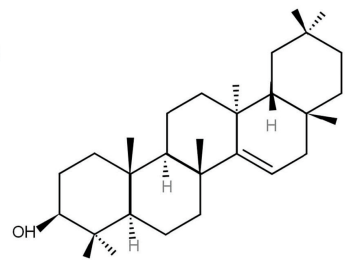
Pallidol



Piceatannol



Resveratrol



Taraxerol

73.3.2 ANTIMICROBIAL ACTIVITY

In *in vitro* conditions, chloroform extract of *C. quadrangularis* exhibited helicobactericidal activity (Austin et al., 2003). Ethyl acetate and methanol stem extracts, exhibited antimicrobial activity against *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, and *Streptococcus* species (Murthy et al., 2003). Methanol and aqueous extract was found to be active against against *Escherichia coli, B. subtilis, S. aureus*, and *Candida albicans* (Mishra et al., 2009). Nanoparticles synthesized from the plant showed significant antibacterial and antifungal activity. Silver chloride nanoparticles inhibited the growth of *Streptococcus pyogenes*, *S. aureus*, *E. coli*, and *Proteus vulgaris* (Gopinath et al., 2013). Calcium oxide nanoparticles showed maximum inhibition of *E. coli* (Marquis et al., 2016) and copper oxide nanoparticles showed antifungal activity against *Aspergillus niger* and *Aspergillus flavus* (Devipriya and Roopan, 2017). Studies on ethyl acetate and methanolic plant extracts showed significant antimicrobial activity against the avian pathogens (Kumar et al., 2017). Cysteine protease from *C. quadrangularis* showed maximum zone of inhibition against *B. cereus* (21 mm) and *Bacillus megaterium* (20 mm) (Muthu et al., 2017).

73.3.3 ANTIOSTEOPOROTIC AND BONE HEALING ACTIVITY

Early ossification and remodeling of bones by stimulation of metabolism and increased uptake of the minerals by the osteoblasts was reported from *C. quadrangularis* (Udupa et al., 1965; Prasad and Udupa, 1972). Biological studies of the plant revealed the antiosteoporotic and healing property of fractured bones (Deka et al., 1994). The phytoestrogen steroids isolated from plant showed influence on early regeneration and quick mineralization of bone (Chopra et al., 1999). External as well as intramuscular application of extract paste promotes rapid healing of fracture in *in vivo* rat model. A total of 95% of ethanolic plant extract promotes the development of cortical bone and trabeculae in foetal femur, and early regeneration and rapid mineralization of fractured bone. Whole plant extract at a dose of 500 and 750 mg/b.w. showed antiosteoporotic activity in ovraiectomized rat model (Guha Bakshi et al., 2001).

Shirwaikar et al. (2003) found that ethanolic extract is effective in ovariectomy-induced osteoporosis. The stem was found to contain high percentage of calcium and phosphorus and reduced the healing time between 33 and

55% in fractured bones (Enechi and Odonwodo, 2003). Maternal administration of plant extract can stimulate foetal bone growth during pregnancy (Potu et al., 2008). *Cissus* is a good candidate for preventing postmenopausal osteoporosis, enhances osteobastogenesis, and bone marrow mesenchymal stem cell proliferation (Potu et al., 2009; Singh et al., 2011). Muthusami et al. (2011) suggested molecular mechanism for the healing properties of the plant for fractures for the first time. Improved thickness of trabecular bone and periosteum was observed in neonatal rats treated with petroleum ether extract of *Cissus* (Srinivasa Rao et al., 2014).

73.3.4 ANTI-ULCER AND GASTRO PROTECTIVE ACTIVITY

Traditionally the plant is used to treat gastrointestinal disorders (Williamson, 2002). Methanol extract showed significant antiulcer activity by enhancing glycoprotein levels and decreasing gastric secretions. Antilipid peroxidating effect of methanol plant extract prevents gastric damage (Gutierrez and Vargas, 2006). The extract promotes ulcer protection by decreasing gastric secretions, gastric mucin content, and ulcer index. Significant antisecretory and cryoprotective property of *C. quadrangularis* was observed in experimental rats against ulceration (Mallika and Shyamala, 2003; Jainu et al*.,* 2006).

73.3.5 ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY

Methanol stem extract possess analgesic and anti-inflammatory effects and is due to flavonoids. Stem extract possess anti-inflammatory activity against cycloxygenase (Asolkar et al., 1992). The stimulatory effect of extract is probably due to vitamins and is greater than durabolin, metabolic hormone (Frank et al*.,* 1995). Ethanol extract possesses protective effect against neutrophils-mediated tissue damage. *C. quadrangularis* at a dose of 350 mg/kg showed analgesic activity in both central and peripheral analgesics, and significant antipyretic and anti-inflammatory activities. The activity is mainly due to carotene, phytosterol substances, calcium, sitosterol, amyrin, and amyrone (Mallika and Shyamala, 2003). Acetone fraction of *C. quadrangularis* (AFCQ) inhibited cycloxygenase (COX-1), cycloxygenase (COX-2), and 5 lipoxygenase (5-LOX) enzyme activity (Bhujade et al*.,* 2015).

73.3.6 CENTRAL NERVOUS SYSTEM ACTIVITY

Saponins in the methanol root extract showed potent sedative activity and inhibit spontaneous motor activity in an experimental study in rats. The root extract possesses CNS depressant activity. Screening against central nervous depressant resulted in increased muscle relaxation (Subhashri et al., 2013).

73.3.7 ANTIHEMORRHOIDAL ACTIVITY

The bioflavonoids, diosminin, hesperidin, and proanthocyanidins are used in the treatment of hemorrhoids and varicose veins (Panthong et al., 2006). Luteolin and β-sitosterol in the crude extract has antihemorrhoidal activity that suggested its possible use as antihemorrhoidal drug. It also has analgesic effect, which is useful in the treatment of painful hemorrhoid (Anitua et al., 2004).

73.3.8 ANTIDIABETIC ACTIVITY

The oral administration of *C. quadrangularis* extract reduced the body weight and blood glucose levels in obese patients (Oben et al., 2006, 2007). The ethanolic extract (60 μg/mL) exhibited 27.3% of inhibitory effect against the alpha amylase enzyme. Glucose uptake rate by yeast cell was increased with the increasing concentration of the ethanolic stem extract and decreased with the increasing intercellular glucose concentration (Rekha and Devika, 2018).

73.3.9 MELANIN PROMOTION ACTIVITY

Methanol crude extract along with its different fractions and control were studied in cell lines (B16F10 melanoma) for melanin promotion activity. The crude methanolic extract, fractions 2 and 4 and lupeol showed significant activity by producing more melanin in the cells (Rao et al., 2011).

73.3.10 ANTICANCER ACTIVITY

Resveratrol, a major constituent of *C. quadrangularis*, trigger the human tumour cells (Clement et al., 1998) but it did not show any cytotoxicity in

in vivo models (Delmas et al., 2006). *n*-Hexadecanoic acid reported from methanolic extract of *C. quadrangularis* is proved to be an anticancerous compound (Ramasamy et al., 2012). Nanoparticles synthesized from the plant were studied against anticancer activity (Subhashri et al., 2013). In a dose-dependent manner, the extract effectively inhibited the proliferation of MCF-7 cells with IC_{50} value of 40 μg/mL (Subramani, 2018). *In vitro* leukemic cytotoxic study in HL-60 cell lines with ethnolic extract exhibited dose-dependent free-radical activity (Dhanasekaran, 2020).

73.3.11 IMMUNOMODULATORY EFFECT

Yadav et al. (2014) studied immunomodulatory effect of ethanolic extract of *C. quadrangularis* using zinc sulfate turbidity test. Significant serum immunoglobulin levels were observed in experimental animals.

73.3.12 OBESITY AND WEIGHT LOSS

C. quadrangularis had a significant role in the management of weight loss and metabolic syndrome. Total weight was reduced significantly in about 123 over weight and obese persons with adverse side effects like headache, dry mouth, diarrhoea, eructation, gas, and insomnia. The action is due to the reduction of absorption of dietary fats and enhanced satiation (Oben et al., 2006). This study demonstrated significant reductions in weight, lowered serum lipids with consequent improvement of cardiovascular risk factors. The increase in plasma 5-HT and creatinine hypothesizes a mechanism for controlling appetite and increasing lean body mass (Subhashri et al., 2013). Blending of *C. quadrangularis* powder with rice flour as base with other ingredients like wheat flour and Bengal gram flours was more promising to treat obesity and oxidative stress associated problems (Malathi, 2014). A study from Nash et al. (2019) clearly elucidated decrease in body fat, blood pressures, total cholesterol, leptin levels, triglycerides, as well as fasting blood glucose levels.

73.3.13 ANTIPROTOZOAL ACTIVITY

Methanol and dichloromethane extract of plant were evaluated for anti-plasmodial activity. The whole plant showed good antiplasmodial activity (Pluemjai and Saifah, 1986).

73.3.14 MISCELLANEOUS ACTIVITY

The plant extract exhibits wound healing activity, cardio tonic, androgenic property, and molluscidal activity. Aerial parts possess hypotensive and diuretic activity. The plant formulation is used in the management of different metabolic syndromes (Mallika and Shyamala, 2005). *In vitro* anthelmintic activity was tested against *Haemonchus contortus* using methanolic extract of aerial parts of *C. quadrangularis.* At a concentration of 1 mg/mL, the extract exhibited 88% egg hatching inhibitory effect (Zenebe et al., 2017).

73.4 CONCLUSION

C. quadrangularis has been used as traditional medicine in different parts of the world for treating various disorders. Each part of the plant possesses therapeutic efficacy against different disorders. The major pharmacological properties include antioxidant, antimicrobial, bone healing, gastroprotective, analgesic, anti-inflammatory, antihemorrhoidal, antidiabetic, anticancerous, immunomodulatory, and antiobesity activity. This would provide a general idea about the modalities of action of the drug and its benefits. This would inquire to bridge the scientific rationale in developing and standardizing a novel drug. Thus, *C. quadrangularis* appears as a worthy plant for new drug formulations.

KEYWORDS

- ***Cissus quadrangularis***
- **phytochemical constituents**
- **quadrangularin A**
- **pharmacological properties**
- **bone healing activity**

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