Review Article **AJCRR (2020) 4:18**

American Journal of Clinical Research and Reviews (ISSN:2576-0505)

A Systemic Review on the Pharmacognosy, Phytochemistry, Pharmacological and Clinical aspects of Edible stemmed vine, *Cissus quadrangularis* L

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ABSTRACT

Cissus quadrangularis Linn. belonging to the family Vitaceae is a common perennial climber, which is distributed throughout India. This square stemmed vine is widely used in traditional systems of medicines and parts like stem, roots and shoots are the most important parts, which are used medicinally. The article reveals 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. Many extensive research works had been done to prove its biological activities and pharmacology of its extracts. The current review deals with the enormous amount of updated information of scientific research and reports available in different aspects of this plant involving phytochemical, pharmacology, toxicological and clinical works. This review also includes reports on pharmacognosy, variants and traditional medicinal uses of the plant.

Keywords: *Cissus quadrangularis*; *Vitis quadrangularis*; Vitaceae; Bone Fracture; Edible stemmed vine

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How to cite this article:
Anoop Austin. A Systemic Review on the Pharmacognosy, Phytochemistry, Pharmacological and Clincal aspects of Edible stemmed vine, *Cissus quadrangularis* L. American Journal of Clinical Research and Reviews, 2020; 4:18

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Introduction

Cissus quadrangularis Linn. (Vitaceae) is a succulent perennial climber widely distributed among the hotter parts of India. In English it is called as Edible-stemmed Vine. Based on morphological characters three different variants have been identified, they are square - stemmed, round-stemmed and flat- stemmed. Frequently available varieties are square-stemmed and round-stemmed. These are rich in source of ascorbic acid, carotene A, anabolic steroid substance and calcium. The round-stemmed variety is characterised by the presence of wingless stem. Anatomical section of the stem shows a deposit of characteristic acicular or needle shaped calcium oxalate crystals, raphides and intrafasicular cambium. Medicinal properties of *Cissus quadrangularis* were described by Kirthikar and Basu (1980), Anonymous (1986), and Nadkarni (1989). Stem, stem juice, young shoots and total ash from young shoots are being used. The roots are useful as alterative, diaphoretic, stomachic, emmenagouge and antirheumatic. It is useful in fractures of the bones, dyspepsia, indigestion, otorrhoea, epistaxis, scurvy, asthma, irregular menstruation (Anonymous, 1986 and Nadkarni, 1989). Indigestion, dyspepsia, diarrhea, fistula is treated and it is an appetizer (Nadkarni, 1989). Urinary tract infection, eczema, poisonous bites, asthma, obesity, menstrual problems are also treated (Kirthikar and Basu, 1980).

Fig 1. Flowering twig

Medical literatures are abound with various types of *C. quadrangularis*. In the works of Madayan and Citraputhran (1987) three types are reported viz., four angled or square stemmed as *C. quadrangularis*, acrid taste as *C. setosa* and red coloured as C. *vitiginea*. Warrier *et al.* (1994) noted that two sided variety of *C. quadrangularis* was found in gardens. Singh and Arora (1978) mentioned that *Cissus* is edible and Sansevieria is non edible.

Ethnobotanical information

Flowering period of *C. quadrangularis* was observed at July to December (Giles Lal and Livingstone, 1978). Varied medicinal uses of *C. quadrangularis* has been reported in ethnomedical works (Sen and Dash, 2012). *C. quadrangularis* is used for stomach aches (Nagaraju and Rao, 1990) and amenorrhea (Sen and Dash, 2012). Tender shoots are macerated with juvenile leaves of *Pergularia daemia* and *Wrightia tinctoria*, along with a few pieces of garlic and pepper are used to treat whooping cough (Reddy *et al.,* 1989). This is also used for irregular menstruation (Anonymous, 1903), amenorrhea (Ahmad, 1957) and fractured bones (Nagaraju and Rao, 1990; Kumar and Prabhakar, 1987). In Sudan, the juice is used to cure camel wounds (Elhamidi, 1970). Entire plant of *C. quadrangularis* is used for setting fractured bones (Girach *et al.,* 1994), body pain (Jain, 1989; Bhat *et al.,* 1990), rheumatic back pain (Nagaraju and Rao, 1990) and as a “cure-all” medicine (Schmucker *et al.,* 1969). The dried entire plant of *Cissus* species is used for

rheumatism (Miles, 1966), aphrodisiac (Kerharo and Bouquet, 1950) and as an abortifacient (Hafez, 1982).

Pharmacognostical studies

Little work has been carried out on *C. quadran gularis*. Shah (1958) proposed square and round stemmed variants of *C. quadrangularis*. Kannan (1998) carried out pharmacognostical work on this plant. Square, round and flat stemmed variants of *C. quadrangularis* were described by Kannan and Jegadeesan (1999). Austin *et al.* (2004c) carried out Pharmacognostical studies on its variant I & II. The stem is dumbbell shaped in variant I (Fig 2) and rectangular in variant II (Fig. 3). Leaf shows striation of epidermal cells in variant I whereas absent in variant II. Microscopical sections demonstrated difference among variants (Nagani, *et. al.,* 2011).

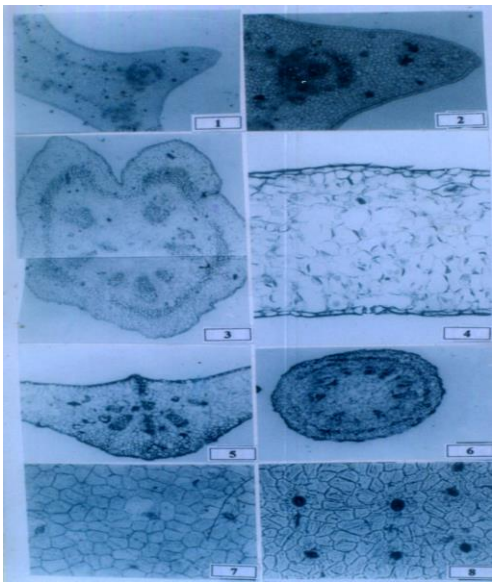


Fig. 2. Anatomical details of *C. quadrangularis* variant I

1: TS of young stem (x 47); 2: TS of young stem – A portion enlarged (x 113); 3: TS of petiole (x 32); 4: TS of leaf lamina (x 250); 5: TS of leaf midrib (x 46); 6: TS of young tendril (x 47); 7: Epidermal peeling of leaf upper surface (x 200); 8: Epidermal peeling of leaf lower surface (x 200)

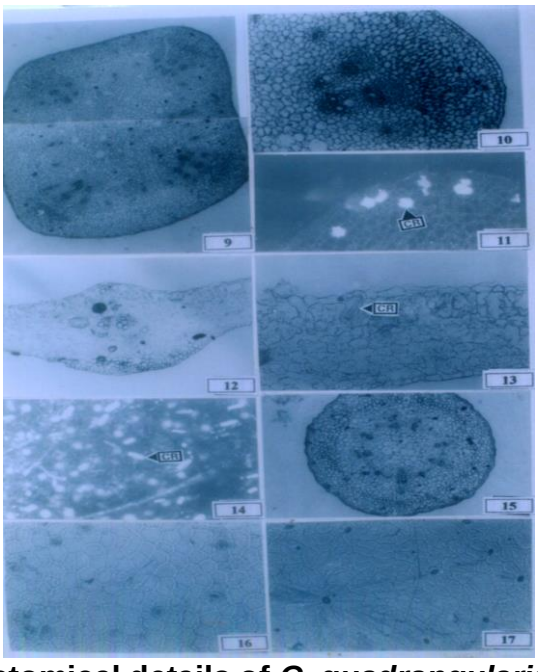


Fig. 3. Anatomical details of *C. quadrangularis* variant II

9: TS of young stem (x 40); 10: TS of young stem – A portion enlarged (x 110); 11: TS of young stem under polarised light showing the calcium oxalate crystals (x 110) (CR : crystal); 12: TS of leaf midrib (x 46); 13: TS of leaf lamina (x 132) (CR : crystal); 14: Surface view of cleared leaf under polarised light showing the calcium oxalate crystals (x 85) (CR : crystal); 15: TS of young tendril (x 60); 16: Epidermal peeling of leaf upper surface (x 87); 17: Epidermal peeling of leaf lower surface (x 90)

Anatomical characters:

The following distinguishing stem anatomical features are noted among the variants. In variant I, the stem has a dumbbell shaped outline with slight modifications. The four corners are extended forming the wing of the stem (Fig. 1,2). It has three cellular zones as in the general pattern. However, the mature stem is distinguished by the presence of a patch of sclerenchymatous cells at the four corners below the epidermis. In variant II, the outline of the stem is more or less rectangular in shape with blunt corners (Fig. 9,10). Striation of epidermal cells are common in variant I (Fig. 8), but absent in variant II. Large sized mucilage cells and raphides of calcium oxalate crystals are frequently observed in the pith and cortex. Anatomical characters of stem, petiole, leaf and tendril of the two variants do not show any marked variations.

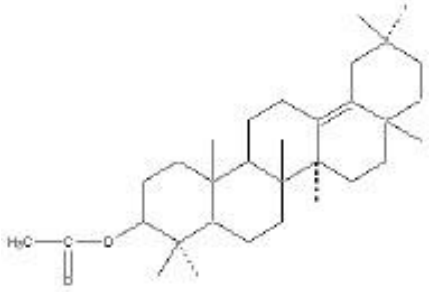
Phytochemical studies

Chemical constituents of various parts of *Cissus* spp. were analyzed by various workers. The entire plant of *C. quadrangularis* from India was studied by Bhutani *et al.* (1984). It contains 0.14% of Amyrin delta triterpene and 0.1% of Amyrone delta triterpene. The presence of 0.0003% of Arborenol iso-triterpene was found by Pluemjai and Saifah (1986). Udupa *et al.* (1965) reported the presence of keto steroid and Sen (1964) reported the presence of Oxosteroid. Prasad (1980) reported the presence of steroid having melting point 13°C. The presence of docosan-1-ol cyclohexane, 7-hydroxy-alkane and 20-oxo-friedelan-3-one triterpene were present in the aerial parts was reported by Gupta and Verma (1990). Pluemjai and Saifah (1986) found the presence of 0.00024% of friedelinol epi-triterpene in the entire plant from Thailand. Gupta and Verma (1991) found the presence of heptadecyl octadecanoate alkane and icosanyl icosanoate alkane from the aerial parts of the plant collected in India.

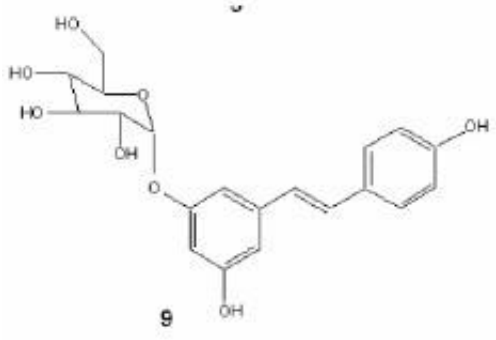
The presence of octadec-9-ene, 9-methyl alkene, oxo pentacosanoic acid, iso lipid in the aerial parts from India was also reported. Pluemjai and Saifah (1986) found the presence of 0.00022% of lupenone triterpene in the entire plant from Thailand. The entire plant from India contains 0.006% of onocer-7-ene-3-α-21-β-diol triterpene, 0.003% of onocer-7-ene-3-β-21-α-diol triterpene and β-sitosterol was reported by Bhutani *et al.* (1984). The presence of 0.0023% of onocer-8-ene-3-β-21-α-diol, 7 triterpene in the aerial parts from India was reported by Gupta and Verma (1991). The presence of β-sitosterol in the entire plant from Thailand was reported by Pluemjai and Saifah (1986).

Presence of β-sitosterol in the aerial parts in India was reported by Desai *et al.* (1996) and Gupta and Verma (1991). The presence of taraxerol triterpene, taraxerol acetate triterpene, tricos-2-en-22-one, 4-hydroxy-2-methyl alkene, YL-tritriacontan-1-ol, 31-methyl alkane, tritriacontanoic acid, 31-methyl alkane in the aerial parts from India was studied by Gupta and Verma (1991). The absence of tannins by hide test in the aerial parts of *C. quadrangularis* was reported by Atal *et al.* (1978).

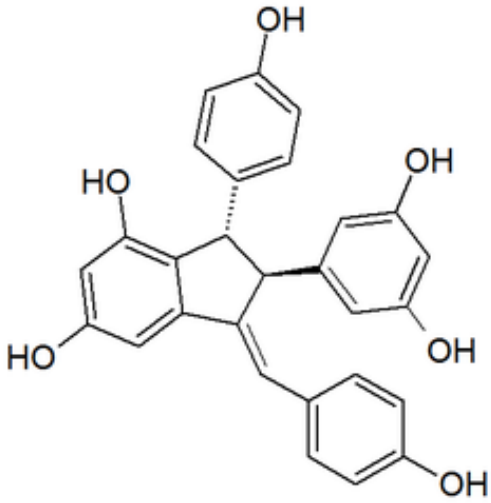
Two new iridoids 6-*O*-[2,3-dimethoxy]-*trans*-cinnamoyl catalpol and 6-*O-meta*-methoxy-benzoyl catalpol along with a known iridoid picroside 1, two stilbenes quadrangularin A and pallidol, quercitin, quercitrin, β-sitosterol and β-sitosterol glycoside were isolated from *Cissus quadrangularis* Linn and were reported by Singh *et. al.,* (2006). In methanolic extract of *C. quadrangularis* 25.63% of n-Hexadecanoic acid was reported which is suggested to be an anticancer compound (Ramasamy *et. al*., 2012).



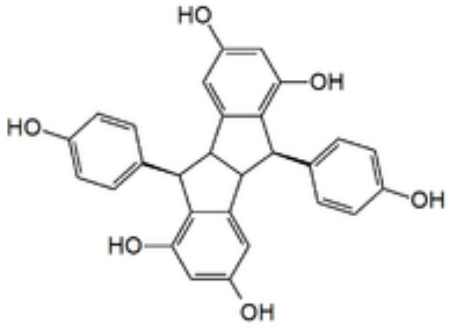
1: *δ-Amyrin acetate*



9: *Trans-resveratrol-3-O-glucoside*



Quadrangularin A



Pallidol

Variants are not much studied on phytochemical contents and seasonal variations. Austin *et al.* (2004a) conducted detailed study on these aspects. They found out that total ash (11.88 %),

acid insoluble ash (5.7 %), LOD (91 %), solubility in alcohol (6 %) and successive extractives in alcohol (18.64 %) was high in variant I, whereas, water soluble ash (6.62 %), sulphated ash (18.33 %), successive extractives in petroleum ether (3.3 %), benzene (1.24 %), chloroform (0.48 %) and water (24.92 %) yielded high in variant II (Austin *et al.,* 2004b). Variant I contains seven amino acids viz.,arginine, threonine, phenylalanine, cystine, amino-n-butryic acid, lysine, an histidine. Cystine, arginine, threonine, leucine and cystine are present in variant II. Alkaolids, saponins and terpenoids were identified by TLC patterns which showed difference among the variants and seasonal samples. Fingerprinting techniques were evolved. Variant I contain 0.85 % of calcium, 7.74 % of ascorbic acid, 4.32 % of β sitosterol and 8.93 % of amino acids in variant I whereas Variant II contain 0.76 % of calcium, 5.64 % of ascorbic acid, 3.03 % of β sitosterol and7.28 % of amino acids.Comparative studies on the seasonal influence demonstrated an high content before flowering period compared to vegetative period.

Microbiological Studies

Antibacterial, antifungal, antiviral, antiamoebic, antischistosomal molluscocidal and insecticidal activities of *Cissus* spp. have been carried out. The antibacterial activity of *C. quadrangularis* was carried out by Dhawan *et al.* (1977) against *Bacillus subtilis, Escherichia coli, Salmonella typhosa, Staphylococcus aureus* and *Agrobacterium tumefaciens* (plant pathogen). The antifungal activity of the same was carried against *Microsporum canis, Trichophyton mentagrophytes* and *Aspergillus niger* (plant pathogens) and the antiyeast activity was studied against *Candida albicans* and *Cryptococcus neoformans*. The cell culture for cytotoxic activity of the extracts was also carried out by the same authors.

The insecticidal activity of *C. quadrangularis* was evaluated by Atal *et al.* (1978) against *Musca domestica* and *Tribolium castaneum*. The mutagenic activity of *C. quadrangularis* was analysed by Sivaswamy *et al.* (1991) by means of Ames test. It was active against *Salmonella typhimurium* TA1537 and *S. typhimurium* TA98 at the concentration of 1 mg/plate but inactive against *S. typhimurium* TA1535 and S. typhimurium TA1538. The molluscocidal activity of *C. quadrangularis* against *Biomphalaria pfeifferi* and *Bulinus truncates* was carried out by Abdel-Aziz *et al.* (1990). Ethanolic extract (50%) was active against *Entamoeba histolytica* at a concentration of 125 μg/ml. Dhar *et al.* (1968) also continued amoebicidal activities of ethanolic extracts of the same plant.

Austin *et al.* (2004a, 2004b) found out its activity against *Helicobacter pylori.* Variant I was found to be effective than variant II and samples collected before flowering season were more potent. This activity helps in treating the patients with PUD.

Methanolic and ethyl acetate extracts of *C. quadrangularis* demonstrated high inhibitory activity against the bacterial strains viz., *Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus* pyogenes*, Salmonella typhi* and *Streptococcus pyogenes*. On the contrary, petroleum ether, ethanol, and water extracts, did not demonstrate any inhibition. Further, *E.coli* did not respond to any of the extracts used (Kashikar and George, 2006). On the contrary, Chloroform extract of *C. quadrangularis* demonstrated antibacterial activity against, *E. coli, Pseudomonas putida, Staphylococcus aureus* and *ß-hemolytic streptococcus* (Selvamaleeswaran *et. al*., 2016). It was also interesting to note that ethanol, methanol, and ethyl acetate extracts exhibited maximum activity against *Klebsiella pneumonia* (Mummed *et. al*., 2016). Partially purified methanolic extract of *C. quadrangularis* demonstrated antiviral activity against HSV type 1 and 2 viruses at 1:400 dilution. The effect was due to the presence of steroids and terpenoids in the extract (Balasubramanian, *et. al.*, (2010).

Pharmacological studies

Many pharmacological studies were carried out to reveal various activities of all parts of *C. quadrangularis*. Review resulted in many new inputs on bone fracture, Mucoprotective, Arthritis, Haemerrhoids, anabolic effects etc.

Bone fracture

The fracture healing effects of the entire plant of *C. quadrangularis* was studied by Chopra *et al.* (1976). Intra-muscular route of aqueous extract in dogs was effective at a dose of 1 mg/kg. The histo-chemical and biochemical effects of the fracture healing effects of *C. quadrangularis* was carried out by Udupa and Prasad (1964) in dogs. There was an increase in tensile strength in treated animals, which correlated with an increase in the components of the bone, such as muco-polysaccharides, collagen, Ca and P. There was 90% gain in normal strength at the end of 6 weeks compared with 60% gain in controls. The Ca^{45} uptake studies indicated earlier completion of calcification and earlier remodeling phenomena (Udupa *et al.,* 1965).

Sham operated or ovariectomized, two month old C57BL/6 mice (Jameela Banu *et al.,* 2012), which were fed with *C. quadrangularis* clearly demonstrated a normal trabecular number, thickness, and connectivity density, among the 2 models except cortical bone mineral content in the proximal tibia, which concludes inhibited bone loss in the cancellous and cortical bones of femur and proximal tibia due to *C. quadrangularis*. Similar study was carried out by Shirwaikar *et. al.,* (2003) on the ethanolic extract of *C. quadrangularis* at a dose of 500 and 750 mg for its anti-osteoporotic activity in ovariectomized rat model of osteoporosis in both sham operated ovariectomized groups. Study confirmed its antiosteoporotic effect along with standard drug Raloxifen at a dose of 5.4 mg/kg. The drug accelerates the fracture healing process and reduces the period of immobilization and early rehabilitation. Further elevation of serum hPTH (Human parathyroid hormone), induces early initiation of bone resorption and early initiation of osteoblastic activity and continuous bone maturation (Subhashri *et. al*., 2013). Presence of calcium, phosphorous, potassium and magnesium was also confirmed by the results of XRD and EDAX. DEXA (Dual-energy X-ray absorptiometry) and histopathology outcomes indicated that a phytoestrogen-rich fraction from aerial parts of *C. quadrangularis* prevented bone loss. Study results show the benefits of *C. quadrangularis* in the treatment of osteoporosis induced by ovariectomy. Wherein the plant extract can be give as a treatment for osteoporosis for elderly and would also be a safe treatment.

Maiti, *et. al.,* (2007) carried out internal fixation in bone healing in dogs, by unilateral comminuted diaphyseal femoral osteotomy and immobilized with neutralization bone plate. Those receiving ethanolic extract of *C. quadrangularis* applied on skin surface twice daily and subcutaneous injection (50 mg/kg) on alternate day for 20 days, developed quick response and an early resolution of inflammatory signs and weight bearing were observed. There were complete bridging of comminute fragments, extensive bony deposition along with periosteal and medullary continuity across the osteotomies site, suggesting early mineralizatin of the fracture site. Another study evaluating the effect of methanolic extract on the healing process of experimentally fractured radius-ulna of dog revealed faster initiation of healing process which was further confirmed by histopathology (Maiti *et. al.,* 2007). Interestingly, the treated group demonstrated a decrease in serum calcium level and healing was almost complete on the 21st day in treated animals.

Antiulcer and Gastric mucosal protection:

C. quadrangularis extract promotes ulcer protection at a dose of 500 mg/kg b.w., by the decrease in ulcer index, gastric secretions and increase in glycoprotein level, gastric mucin content and non-protein sulphydryls concentration (Jainu *et al.,* 2006a). It protects gastric mucosa against ulceration by its antisecretory and cytoprotective property in asprin induced ulceration, which were comparable to standard drug sucralfate (Jainu and Devi, 2004). It significantly increase mucosal defensive factors like mucin secretion, mucosal cell proliferation, glycoproteins and life span of cells, and promoting healing by inducing cellular proliferation. Jainu *et al.* (2006a) found out that gastroprotective activity of *C. quadrangularis possibly* acts by its antioxidant effect as well as by attenuating the oxidative mechanism and neutrophil infiltration.

Methanolic extract of *C. quadrangularis* in aspirin-induced gastric ulcer model, illustrated ulcer protection by decreasing the ulcer index, as shown by histopath and analysis of CRP. Interestingly it was possessing better protection than the standard drug ranitidine. Whereas, ethanol extract of roots on indomethacin and ethanol induced gastric ulcers, demonstrated a dose-dependent protective effect in both ulcer models, evidenced by significant decrease in ulcer lesions (Enechi *et.al.,* 2013). They further found out that *C. quadrangularis* extract acts through inhibitory action on generation of lipid peroxidation suggesting antioxidant activity as well as by the attenuation of oxidative mechanism and pro-inflammatory cytokines (Jainu and Shymala, 2005) and neutrophil infiltration (Jainu *et al.,* 2006b). The findings were further supported by increasing permeability, tumor necrosis factor- α, interleukin-1β, microvascular permeability, activity of nitric oxide synthase-2, mitochondrial antioxidants, lipid peroxidation and reducing DNA damage (Jainu and Devi, 2006). It further acts by reducing the tissue damage demonstrated by increasing the levels of glutathione, superoxide dismutase and catalase and an associated rise in lipid peroxidation in mitochondria. Findings were confirmed by histoarchitecture, which was comprised of reduced size of ulcer crater and restoration of mucosal epithelium. Study concluded that, reduced neutrophil infiltration, antiapoptotic and antioxidant action have a pivotal role in the gastroprotective effect.

Austin and Jegadeesan (2005) studied the cytoprotective properties of 50 % ethanolic extract of variant I in ulcer models. The effect was evolved in various ulcerogenic procedures in gastric and duodenal ulcer models. Seasonal variations had an impact on the effect and vegetative period sample was found to be beneficial. 300 mg / kg was found to be effective statistically. The dose was also found to be effective in duodenal ulcer. The study proved that the drug prevents bruner's gland which normally gets affected by cysteamine. The bicorbonate ion concentration was increased in the gastric fluid indicating a direct effect on its mucoprotective effect or antacid like activity. Presence of ascorbic acid and the amino acids present also helps in cytoprotective effect, which was further supported by improvement in aggressive parameters like pepsin, sialic acid and carbohydrate protein ratio. Similar studies on variant II pertaining to its cytoprotective activity was studied by Austin and Jegadeesan (2002a). Variant I was more active and samples collected before flowering season possesses better bioactive principles. Presence of ascorbic acid and aminoacids apart from terpenoids are found to have a beneficial role in cytoprotection and muco protective nature, which is further supported by its helicobactericidal action *in vitro.* Similar observations were made by Jainu *et. al.,*(2006) in neutrophil medicated tissue injury by asprin in rats, and demonstrated gastrprotective action mediated through its antioxidant effect as well as by attenuation of the oxidative mechanism and neutrophil infiltration.

Similar observations were reported by Subhashri *et. al*., (2013). Ethanolic extract of *C. quadrangularis* revealed that when an ulcerated rats were given a 500 mg/kg of dose, it had an greater effect against ulcer activity of 71.2%, which was comparable with standard ulcer drug, which exhibited 71.9% ulcer activity at a dosage of 30 mg/kg. It was also noticeable that rats pretreated with *C. quadrangularis* shows an enhanced effect of ulcer activity.

Anti-inflammatory :

Active fraction of *C. quadrangularis* in Freund's Adjuvant induced arthritis model in Wistar rats *In Vivo* demonstrated significant anti-arthritic activity, further at a dose of 100 mg/kg was effective in inhibiting rat hind paw edema, which were comparable with standard drugs namely, Celecoxib and Methotrexate, further supporting as a COX inhibitor in inflammation. Studies also demonstrated chondroprotective effects and regenerative ability via the upregulation of survivin that exerts inhibitory effects on the p38 MAPK signaling pathway and Inhibition of IL-1ß, which could reduce the inflammatory process (Verma, 2018). Similar observations with different models were also reported by Panthong *et. al.,* (2006). They carried out the inhibitory effect on

edema induced by Carrageenin and Arachidonic acid, and the results were comparable with standard drugs Asprin and Ibuprofen. The study clearly evidenced the inhibition of both cyclooxygenase and lipoxygenase pathways.

Analgesic:

Study exhibited significant dose-related analgesic activity compared to that of Aspirin. *C. quadrangularis* at a dose of 350 mg/kg demonstrated analgesic activity by both mechanisms, viz., central and peripheral analgesics, and significant antipyretic and anti-inflammatory activities. The activity is due to the compounds namely, Carotene, phytosterol substances, calcium, sitosterol, amyrin and amyrone (Mate, *et. al.,* 2008). Similarly in another species of *C. repens* analgesic activity is also reported in mice by Dhawan *et al.* (1977) by intra-peritoneal route.

Antihemorrhoidal and Venotonic Activity:

Various phytochemical studies yielded significant flavonoids in *C. quadrangularis*. The bioflavonoids, especially diosmin, hesperidin, and oligomeric proanthocyanidin complexes have demonstrated potential in the treatment of hemorrhoids and varicose veins (Panthong *et. al.,* (2006). Yet another study on the anti-inflammatory and venoconstrictive effects of ethanol extract in rats exhibited 50% inhibition of the carrageenan-induced rat paw edema. Interestingly it illustrated a venoconstrictive effect with EC50 of 0.01 and 0.03 µg/mL for endothelium intact and denuded rat veins, respectively (Panpimanmas *et. al.,* 2010).

Diuretic effect :

50% ethanolic extract of the drug possessed diuretic activity in male rats at a dose 340 mg/kg orally (Dhawan *et al.* 1980). It also possess diuretic activity at a dose level of 0.25 mg/kg in male rats by intra-peritoneal route. It does not possess hypoglycemic, hypothermic, spermicidal, cytotoxic and semen coagulation effects.

Hepatoprotective:

Methanolic extract of *C. quadrangularis* demonstrated hepatoprotective activity against rifampicin-induced hepatotoxicity in rats. Pretreatment significantly decreased lipid peroxidation and increased the antioxidant activities, which can be attributable to the antioxidant effect of ß-carotene. Further studies with petroleum ether also proved its hepatoprotective effect, which again were attributed to its antioxidant property (Subhashri *et. al*., 2013).

Antidiabetic:

Study evaluated that 400 mg/kg of ethanolic extract demonstrated significant antihyperglycemic activity in alloxan induced diabetic rats. Further research would give better insight on the effectiveness of this plant (Sirasanagandla *et. al.,* 2014).

Neuropharmacological effects:

Study evaluated a methanolic extract of roots of *C. quadrangularis* for neuropharmacological effects in mice, using various models. It significantly inhibited acetic acid-induced writhing and increased tail flick withdrawal response in mice. On CNS evaluation, it was able to produce reduction in spontaneous motor activity, exploratory behavior, and motor coordination and prolonged pentobarbitone sleeping time (Swamy *et. al.,* 2006).

Aqueous extract of stem in *in vivo* animal models of epilepsy like maximal electroshock, n-methyl-d-asparate, pentylenetetrazol, isonicotinic hydrazid acid and strychnine-induced convulsions models and insomnia model like diazepam induced sleep showed anticonvulsant and sedative properties in mice (Bum *et. al.,* 2013). Screening against central nervous depressant resulted in increased muscle relaxation (Subhashri *et. al*., 2013). 50% ethanolic extract was active against barbiturate potentiation in mice by intra-pertoneal route at a dose of 0.5 mg/kg. Results suggest *C. quadrangularis* contains some active principles that may be sedative in nature.

Wound Healing:

Wound healing effect of *C. quadrangularis* was carried out by incorporating methanolic and aqueous extracts in simple ointment base in 0.5%, 1%, and 2% (w/w) concentrations, in three rat models viz., excision, incision, and estimation of biochemical parameter. Interestingly 2% methanolic and 2% aqueous extract exhibited significant wound healing activity. Which can be

attributed to the phenol constituents (Mohanty *et. al.,* 2010).

Antioxidant:

Study on the antioxidant property with various solvents by FRAP (Ferric reducing antioxidant power), ABTS (2,2'-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid), and total antioxidant capacity assay, demonstrated concentration dependent increase in antioxidant activity. The stem and leaves extracted with methanol, ethanol, and Pet-ether showed higher antioxidant activity than the fruit and root samples by FRAP assay (Murthy *et. al.,* 2003). Further improvement in the protein expression of superoxide dismutase (Cu/Zn- SOD, Mn-SOD), glutathione peroxidase (GPx) and endothelial nitric oxide synthase (eNOS) in the cells treated with *C. quadrangularis* prior to H_2O_2 exposure (Subhashri *et. al*., 2013) reconfirms its antioxidant potential.

Immunomodulatory:

Immunoprophylactic potential of *C. quadrangularis* extract was evaluated through carbon clearance test, effect on serum immunoglobulins, determination of delayed-type hypersensitivity (DTH) and phagocytosis of killed *Candida albicans* tests were done to evaluate the effect of drugs on the reticuloendothelial system (RES) and mononuclear phagocyte system (MPS) which are diffuse system of phagocytic cells. *C. quadrangularis* at experimental doses showed significant increase in the PI, by increasing the production of phagocytic cells. Further ethanolic extract increased WBC counts and bone marrow cells, which stimulates hemopoetic system. Additionally it significantly increased serum immunoglobulin levels evidenced by zinc sulphate turbidity test. Study demonstrated significant immune-stimulatory activity on both the specific and nonspecific immune mechanisms (Yadav *et. al.,* 2014). Rich content of polyphenolilc and flavonoid content are considered to be responsible for immuno-modulatory activity, which is having promising immunomodulatory potential on serum immunoglobulins.

Anabolic and Androgenic Activity:

With special emphasis with enhancing the remodeling of bone, *C. quadrangularis* also improves, faster increase in bone tensile strength. This is due to exerting an anabolic, antiglu- cocorticoid effect, and also preserves muscle tissue during physical and emotional stress (Jadhav *et. al.,* 2016).

Anthelmintic:

Alcoholic root extract of *C. quadrangularis* exhibited anthelmintic activity against earthworm *Pheretima posthuma*. Preliminary phyto-chemical screening yielded phenolic compounds, tannins, proteins, saponins, steroids, carbohydrates, glycosides, terpenoids, etc. (Pathak *et. al*., 2010) present in *C. quadrangularis*, which could possess anthelmintic activity for which further studies are required.

Chromosomal studies：

The chromosome aberrations induction studies of *C. quadrangularis* was carried out by Balachandran *et al.* (1991). Bone marrow studies revealed a weak activity at a dose of 0.1 g per animal by intra-gastric route of administration in mouse. Sperm head abnormalities and Weak clastogenic activity were observed.

Cell line studies:

C. quadrangularis was potent in inhibiting lipopolysaccharide (LPS)-induced nitric oxide (NO) production in RAW 264.7 macrophage cells in a dose-dependent manner. It was observed that mRNA and protein expressions of iNOS (inducible nitric oxide synthase) were suppressed like p65 NF-κB nuclear translocation. Further it also induced heme oxygenase-1 (HO-1) gene expression at the protein and mRNA levels in dose- and time-dependent manner. NO production was abrogated by HO-1 inhibitor and zinc protoporphyrin IX (ZnPP), suggesting its anti-inflammatory effect on macrophages, through induction of HO-1 expression, thereby providing scientific rationale for anti-inflammatory therapeutic usage (Srisook *et. al.,* 2010).

Methanolic extract of *C. quadrangularis* was effective against MG63 human osteosarcoma cell line cultures. It demonstrated a inhibition range between 29.65% and 73.59% at a concentration from 1000µg/ mL to 7.8µg/mL. The IC_{50} of extract revealed by this cytotoxicity assay was around 100 µg/ml, recommending for future

studies on the treatment for bone tumors (Suresh *et. al.,20* 19).

Ethanolic extract exhibited an *In vitro* leukemic cytotoxic assessment in HL-60 cell lines with a dose-dependent free radical activity. It demonstrated an anticancer activity against leukemic cells HL-60 with an IC_{50} value of 36 µg/mL and 40 µg/mL respectively (Dhanasekaran, 2020).

Another anticancerous study in HeLa cancer cell was carried out to evaluate *C. quadrangularis* for its anticancer activity along with safety profile on normal skin cells. Results were encouraging and showed *C. quadrangularis* selectively induces cytotoxicity, ROS liberation and G1 phase cell cycle arrest only in HeLa cancer cells. Study evaluated the anticancer activity of ethanol and chloroform extract of *C. quadrangularis* by MTT assay. IC_{50} concentration of plant extract was 62.5 µg/ml against HeLa cell line and 125 µg/ml in Vero cell line. Cell death in HeLa cell line was confirmed as apoptosis by DNA fragmentation experiments (Suresh *et. al.,* 2019). Further, ethyl acetate extract developed lowest percentage of viability of cancer cell against MCF cell line in *in vitro* anticancer study (Mahendran *et. al.,* 2020). n-Hexadecanoic acid is suggested to be an anticancer compound (Ramasamy *et. al*., 2012).

Nanoparticles:

Biosynthesis of nanoparticles using the aqueous *C. quadrangularis* leaf and stem extract was studied for its antibacterial effect. Green nanoparticles were prepared from *C. quadrangularis* with 1 mM $AgNO_3$ at a pH of 8 at 70°C. The synthesized silver nanoparticles demonstrated more antibacterial activity against *Klebsiella planticola* and *Bacillus subtilis* (Vanaja *et. al.,* 2013). Nanoparticles against anticancer activity were also studied by Subhashri *et. al*., (2013).

Safety and Efficacy:

Various reviews suggest the safety of *C. quadrangularis* extracts and free from adverse effects at dose commonly used. In a very few limited cases, specific physiological effects have been attributed to identifiable constituents. It was found to produce side effects like loss of appetite, staggering, dyspnoea and diarrhea (Barakat *et al.,* 1985). Pathological changes like hemorrhages in the kidney, lung, heart and intestine, focal catarrhal enteritis and atrophy of cardiac fat, hypoperitoneum and hydropericardium were noted in goats and sheeps when fed at a dose of 1, 5 or 10 g/kg until death or slaughter has also been reported. Further standardization of extracts and more controlled human studies are warranted (Sawangjit *et. al*., 2017).

Toxicological studies

A few toxicological studies were reported in the genus *Cissus.* LD_{50} for *C. quadrangularis* was 681 mg/kg (Dhawan et al., 1977). In another study on *C. quadrangularis*, on acute toxicity testing, LD_{50} was found to be 1000 mg/kg by ip route (Swamy *et. al.,* 2006)

Austin and Jegadeesan (2002b) carried out toxicity studies in variant I. LD_{50} was high on vegetative samples (853.09mg/kg). Haematological and biochemical parameters were within normal range. Histopathological studies revealed mild changes in the liver hepatocytes, cloudy swelling in the glomeruli, which were nonspecific, and other vital organs were normal. LD_{50} for variant II (Austin and Jegadeesan, 2002c) was found to be 797.3 mg/kg. Seasonal variation among samples had a mild difference in the lethal dose. Samples collected before flowering period is found to possess better bioactive principles. In another 14 days acute oral toxicity study with ethanol extract in rats upto a dosage of 5000 mg/kg did not reveal any signs of intoxication, gross pathological lesions, or death. In subchronic toxicity testing at maximum doses of 5000 mg/kg did not result in treatment related abnormalities in clinical observations and biological parameters (Verma, 2018).

Clinical studies

Various studies are reported with *C. quadrangularis.* Clinically it is proven against bone fractures, osteoporosis, weight loss, Obesity, Haemorroids, Arthritis etc, which are dealt with.

Bone Fracture:

Management of mandibular fracture by the application of *C. quadrangularis* was carried out by the department of oral and maxillofacial surgery, King George's medical college, Lucknow. The immobilization period was significantly reduced

(Pradhan, 1994). Hemal *et. al.* (2015) carried out a clinical study on maxillofacial fracture with open reduction internal fixation method, with nine patients including 1 female, between the age group of 20 to 63 years, 50 % received 500 mg of *C. quadrangularis* thrice daily, for 6 weeks. Treatment demonstrated a marked reduction in pain, swelling and fragment mobility. Serum calcium and serum phosphorus were high, and healing of bone was clearly observed. The mode of action is due to neutralizes the anti-anabolic effect of steroids such as cortisone in healing of fractures, which can inhibit tissue regeneration and repair and stimulate fibroblasts, chondroblasts, and osteoblasts. In addition, it also demonstrated less amount of tissue reaction in fractured region, leading to optimum decalcification in early stage with minimum callus formation thereby increased tensile strength of fractured bones in a short time. Study confirmed early callus formation and calcification of the bone within 7–8 weeks, where in the normal healing time varies from 14–16. Similar fracture study with mandible fracture and associated undisplaced maxilla, zygomatic complex fracture was conducted by (Vibha *et. al.,* (2011). *C. quadrangularis* supplementation demonstrated reduction in pain, swelling, and fragment mobility and acceleration in the healing of fractured jaw bones. Marked fracture healing rate was observed, which was influenced by early regeneration of all connective tissues involving healing process and quicker mineralization of callus, radiologically. The active constituents stimulate the proliferation and differentiation of mesenchymal cells (MSCs) and promote new bone formation through the WntLRP5-B-Creatnin signalling pathway of pre-osteoblast formation, which can also be used as a preventive measure for disorders that lead to decreased bone mineral density. Further the ability of absorption of calcium was increased. Lysine, an amino acid helps absorption of calcium, Vitamin C is essential nutritionally to make the collagen that helps the body form healthy bones and also promotes bone healing. *C. quadrangularis* serves as a rich source of calcium ion, when reacted with CO_2 lead to formation of calcite crystals. The activity is due to the isolated phytogenic anabolic steroid, present, which may act on estrogenic receptors of the bone. Further, *C. quadrangularis* might act by stimulation of metabolism and increased uptake of minerals calcium, sulphur, and strontium by the osteoblasts in fracture healing. The anabolic principle from *C. quadrangularis* illustrated marked influence on the rate of fracture healing by influencing early regeneration of connective tissues involved in healing and mineralization of callus, fastening of fracture healing, which can be attributed to the stimulation of all cells of mesenchymal origin, viz., fibroblasts, chondroblasts and osteoblasts (Subhashri *et. al*., 2013). The treated group showed better healing of fracture associated with significant levels of osteopontin protein and CD4+ cells expression of osteopontin, suggesting an accelerated fracture healing, which can also cause remodeling of fracture callus.

Osteoporosis:

Administration of ethanolic extract of *C. quadrangularis* on Bone and Osteoporosis increases Alkaline Phosphatase (ALP), a bone marker of osteoblastogenesis, which is due to MAPK-dependent pathway. These are serine-threonine kinases which plays a crucial role. Since ALP and Tartarate Resistant Alkaline Phosphatase (TRAP) represents thickness of cortical and trabecular bone respectively, it increases the extent of mineralized nodules along with ALP, but mRNA expression of osteo blast related genes remains unaffected. Presence of ketosterones in *C. quadrangularis* demonstrate, multiple uses like an antagonist for glucocorticoid receptor and have anabolic steroidal properties for the maintenance of good bone health. It increases intramuscular creatinine level, blocks muscle damaging and leads to muscle formation. It mobilizes fibroblast and chondroblast and increases regeneration of an injured tissue. Further *C. quadrangularis* might regulate osteoblastic activity by enhancing ALP activity and mineralization process, and the increased ALP effect is likely mediated by MAPK-dependent pathway (Verma, 2018). Improvements were

assessed based on animal weight, morphology of femur, and histochemical localization of osteoblastic marker ALP (Alkaline phosphatase) and TRAP (Tartrate-resistant acid phosphatase) in the upper end of femur. Study revealed a reduction of bone loss, evinced by weight gain in femur, and reduced osteoclastic activity there by facilitating bone formation, where osteoclastic activity confirmed by TRAP staining, and bone formation by ALP staining in femur sections. The study suggests its effect against prevention and treatment of postmenopausal osteoporosis, which are attributed to its phytogenic steroids (Potu *et. al*., 2009). The rising level of serum alkaline phosphatase and good bone density indicated new bone formation benefiting osteointegration. Further the ethanol extract significantly inhibited anti-anabolic effects, with beneficial effects on recovery of bone mineral density in post-menopausal osteoporosis.

The proliferation in mRNA expression of IGF-I, IGF-II, IGF-IR were observed when cells were treated with *C. quadrangularis* in RT-PCR (Reverse Transcription and Polymerase Chain Reaction Analysis) analysis. Western blotting and Immuno radiometric analysis showed increased levels of IGF-I, IGF-II and IGFBP-3 and protein levels of IGF-IR. These results conclude that *C. quadrangularis* has an efficient effect on the IGF system components of human osteoblast like SaOS-2 cells (Subhashri *et. al*., 2013). Osteoblasts are mononucleate cells which are responsible for the formation of the bone. These cells are specialized fibroblasts cells which express bone sialoprotein and osteocalcin. Many researches on this activity have been carried out. Those results shown that the alizarin red ALP (Alkaline Phosphatase) staining showed an increase in mineral deposition on human osteoblast cells like SaOS-2, and the anabolic actions were facilitated through improved mRNA and protein expression of Runx2, a key transcription factor of bone matrix proteins (Subhashri *et. al*., 2013). Further ethanolic extract of *C. quadrangularis* regulated the osteoblastic activity by enhanced ALP activity effect which was likely mediated by MAPK (Mitogen-activated protein kinases)-dependent pathway (Subhashri *et. al*., 2013).

Subhashri *et. al*., (2013) reported an accelerated healing of leg fracture in a 19-year old boy, which was clinically managed with *C. quadrangularis* tablet and lotion along with immobilization. Results suggest that it could play a role in certain fracture cases, in controlling pain, reducing inflammation and accelerating bone healing.

Obesity and Weight Loss:

In a randomized, double-blind, placebo-controlled design with 123 overweight and obese persons particularly central obesity for 8 weeks. Total cholesterol declined 5.0 mg/dl and weight was reduced significantly. Adverse side effects like headache, Eructation, gas, dry mouth, diarrhoea and insomnia. The action is due to reduction of absorption of dietary fats and enhance satiation by increasing serum serotonin levels (Oben *et. al.*, 2006).

300 mg of *C. quadrangularis* was given daily for 67 people and was evaluated for 8-weeks in a double-blind, placebo-controlled pilot trial by Robest Nash *et. al.,* (2019). Study clearly elucidated 8.9% decreases in body fat. Decrease in the waist and hip circumferences, systolic and diastolic blood pressures, total cholesterol, triglycerides, fasting blood glucose, as well as leptin levels. On the contrary, there were significant increases in HDL-cholesterol and adiponectin levels. 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, providing support for the clinical data on weight loss (Subhashri *et. al*., 2013). Study demonstrated statistical significance in weight reduction and central obesity, total cholesterol, LDL, triglycerides and C-reactive protein, regardless of the diet. 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).

Hemorrhoids:

A double-blind randomized-controlled clinical study of 160 hemorrhoid patients, 200 mg/twice daily of the tablet formulation was effective in the treatment of bleeding, pain, and prolapse of hemorrhoidal tissues (Panpimanmas *et. al.,* 2010).

Gestation:

Significant increase in thickness of the cortical bone and individual trabecula were reported by Subhashri *et. al*., (2013), when 750 mg/kg dose of *C. quadrangularis* was administered orally from 9th day of gestation till delivery. Interestingly, petroleum ether extract of *C. quadrangularis* can also stimulate the development of fetal bone growth during the intrauterine developmental period. Further study on teratogenisity and detailed evaluation are required to ensure the safety on pregnancy and postnatal care.

Joint Pain Reduction in Exercise:

People who are carrying out strenuous, high-volume exercises are often associated with joint pain and inflammation. A pilot study was carried out by Bloomer *et. al*., (2013) in supplementation in healthy, exercise-trained men with joint-specific pain among 29 young men. Those exercise-trained men with joint-specific pain showed reduction of joint pain,

Conclusion:

The current review on *C. quadrangularis* deals with an objective to search and explore the pharmacognostical, phytochemical, pharmacological, toxicological and clinical aspects. This would provide a general ideal about the modalities of action of the drug and its benefits and also would explore to bridge the scientific rationale in developing and standardizing a novel drug and also explores the potential of this plant. This review would also provide on the modalities of action and the probable compound responsible for the desired benefit.

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