Herbal Medicines Journal **2022; 7(2):68-74**
DOI: 10.22087/hmj.v7i2.895 **ISSN:** 2538-2144

Review Article

Phytochemical and Pharmacological Investigation of *Cissus quadrangularis* L.

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Received: 11.07.2021; Accepted: 03.03.2022

Abstract

Traditional system of medicine practiced since time immemorial has emerged as an alternative for modern medicine as it is economical, nature-based and without side effects. Medicinal plant *Cissus quadrangularis* L. has been used in the Indian system of traditional medicine due to its easier propagation and availability. The phytochemical composition of the plant mainly consists of flavonoids, alkaloids, glycosides, steroids, saponins, tannins, triterpenes, benzenoids, phenols, and total protein. The stem is the most important part of the plant with various therapeutic properties. The plant exhibits anti-arthritis, anti-inflammatory, anti-cancer, antioxidant, antidiabetic, anti-obesity, anti-microbial, anti-hemorrhoidal, anthelmintic, and other pharmacological properties. The plant has traditionally been used in the treatment of broken bones, rheumatic pains, bowel infections, burns, wounds, eye disorders, menstrual disorders, boils, asthma, gastritis, piles hemorrhoids, anemia, and indigestion. This systematic review documented the phytochemical composition of various plant parts along with evaluating research articles for designing the pharmacological application of the plant and its use in drug industries.

Keywords: *Cissus quadrangularis*, Phytochemical, Pharmacological, Traditional medicine

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Please cite this article as: Pandey S, Parmar Sh, Shukla M, Sharma V, Dwivedi A, Pandey A, Mishra M. Phytochemical and Pharmacological Investigation of *Cissus quadrangularis* L. Herb. Med. J. 2022;7(2):68-74.

Introduction

Cissus quadrangularis L., commonly known as 'Veld grape' and locally called 'Hadjod', is an important member of the family Vitaceae which is a large deciduous, succulent, rambling perennial shrub present throughout tropical Africa, the Arabian Peninsula, Indian subcontinent, Thailand, Myanmar, Philippines, and Indonesia.

Plant formulations have been used in traditional, and alternative medicine in almost all parts of the world. Traditional medicines is common in developing countries due to its approachability and affordability, whereas in developed countries, it is consumed as an alternative of chemical drugs (1). Phytochemical and pharmacological activities of various medicinal plants are available in the literature (2-9). Therefore, this study has been attempted to collect information on phytochemical and pharmacological activities of the plant for signifying its medicinal value and

significance in the pharmaceutical industries.

Plant Profile

This plant is generally 3 m long. The stems are quadrangular, long, glabrous, fleshy, constricted at nodes and deep green in color. The young branches are sharply winged or angular bearing simple and long tendrils. Its leaves are deciduous, simple, with obtuse apex, denticulate, 3-lobed, size 2-5 x 2-5 cm, spinulose-crenate margin, ovate-subreniform or suborbicular, truncate base, thick-coriaceous, occuring only on the nodes, and petiole are 1 cm long. The plant bears umbellate cymes inflorescence. The flowers are small, present in the form of clusters, peduncled and green or yellow in colors. The calyx are reddish, cup-shaped, tetra-lobed, and 2 mm long. Petals are 4 in number, ovate, acute, oblong, hooked at apex, having tetra lobed disk, greenish-yellow and 2.5 mm long. Stamens are 4 in number with introrse anthers, yellow in color and filaments are 2 cm in length. Ovary bilocular, 1 mm long, 2-celled, each cell having 2 ovules. The style is short, disk tetralobed, and yellow in color. Its fruits are berry red, 7 mm, globose, and seeds are solitary, smooth and black in color. The plant flowers in the month of June–July (10,11).

Phytochemical Composition

The phytochemical analysis of the plant contributes to the isolation of bioactive compounds which in turn is helpful in the discovery of new drugs with potentiality to combat diseases (12-15).

Qualitative analysis of the aerial part of the plant shows the presence of carbohydrate, tannin, phenol, alkaloids, phytosterol, saponin, fixed oil and fats, and flavonoids (16). This plant also contains carbohydrate, µ-sitosterol, ascorbic acid, free amino acids, and gums and mucilage (17). The quantitative analysis of the aerial parts of the plant exhibited a good percentage of glycosides, terpenoids, calcium salt, Vitamin C, and alkaloids (16, 18).

Phytochemical Composition of the Stem

The NMR and mass spectral data analyses isolated 55 compounds from fresh stems mainly 14 benzenoids, 9 steroids, 11 triterpenes, 5 tocopherols, 4 flavonoids, 2 tannins, 2 benzoquinones, 5 chlorophylls, and 3 other compounds. Among these compounds, 1,2-bis-(5-γ-tocopheryl) ethane was isolated for the first time (19).

The ethanolic and methanolic extracts of the stem shows the presence of steroids ,flavonoid, alkaloids, saponins, tannins, glycosides, carbohydrates, protein, amino acid, terpenoids, triterpenoids, and phenolic compounds (20-24).

The spectroscopic and chromatographical analyses isolated 9 compounds from methanol, pet-ether, ethyl acetate and chloroform fraction of the stem. Among these three compounds, viz triterpene d-amyrin acetate, stilbene glucoside trans-resveratrol-3-O-glucoside, and aliphatic acid hexadecanoic acid were reported for the first time. The other compounds isolated from these fraction include δ- amyrone, β-sitosterol, quercetin, d-amyrin, kaempferol and resveratrol (25). The spectral data analysis of methanolic stem extract reveals the presence of three compounds, i.e. lupeol, β-sitosterol, and freidalin (26). GC-MS analyses of the methanolic stem extract isolated 19 compounds major being n-Hexadecanoic acid, 2- 9,12-Octadecadienoic acid, methyl ester, furancarboxaldehyde, 5-(hydroxymethyl), 4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl), Urs -12 -en -24 -oic acid, 3 -oxo-, Methyl ester, 3,7,11,15 -Tetramethyl -2-hexadecen -1-ol (3.30), Propane, 1,1,3-triethoxy, Vitamin E, E-10-Pentadecenol, methyl ester, 2-(7-heptadecynyloxy) tetrahydro, 2H-Pyran, 2(1H) Naphthalenone, ethyl ester, Docosanoic acid, squalene, and phytol (27).

The NMR and MS spectroscopy of hexanes stem extract isolated 5 dammarane-type triterpenes. Among these 4 items were detected for the first time most importantly being esterified with palmitic acid (28). The spectroscopic analysis of the stem extract also reported three new compounds- phenolic glycoside and two lignan glycosides, along with 12 known compounds (29).

The plant extract mainly contains of steroids, flavonoids, gallic acid derivatives, iridoids, stilbenes and triterpenes (30). The GC-MS analyses of the aqueous and ethanol extract of aerial part of the plant isolated 30 compounds, mainly acid derivatives, fatty acid ester, fatty acid, hydrocarbons and alcoholic compounds The major constituents includes n-hexadecanoic acid, 9, 12, 15-octadecatrienoic acid-methyl ester (Z,Z,Z), ethan-1,1-diethoxy, Ethyl a – d – glycopyranoside, 2- formylhistamine, glycerin and octadecanoic acid, ethyl ester (31).

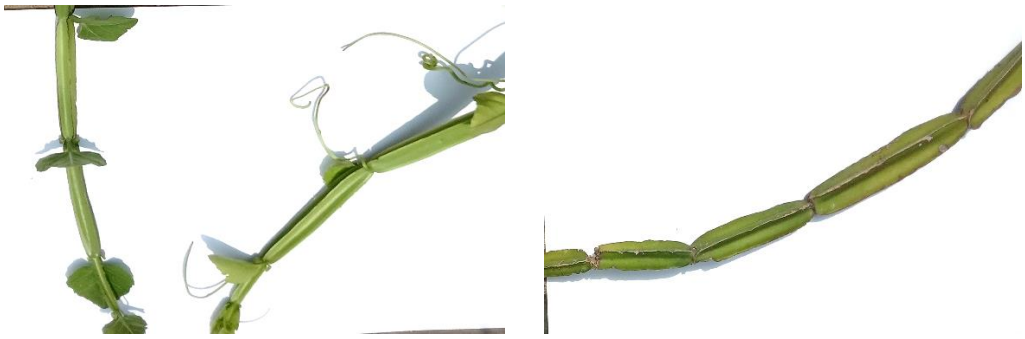

Figure 1. *Cissus quadrangularis.*

Phytochemical composition of leaves

The methanolic and ethanolic leaf extracts reveal the existence of alkaloids, flavonoids, tannins, terpenoids, saponins, proteins, carbohydrates, and phenols (22).

Spectroscopic analyses of the hexane extract of leaves isolated 5 compounds, mainly eicosyl eicosanoate, α-amyrin, tetratriacontanoic acid, tetratriacontanol and β-sitosterol (32).

GC-MS analysis of the ethanolic extract of leaves shows presence of n-hexadecanoic acid, phytol, bis (2-methylpropyl) ester, ethyl ester, 1, 2-benzenedicarboxylic acid, caffeine, hexadecanoic acid, 3-dodecanol, 3,3,11-trimethyl, dibutyl phthalate and pentane,1,1-diethoxy (33).

Phytochemical composition of fruits and roots

The methanolic and ethanolic fruit extracts show the presence of alkaloids, tannins, proteins, carbohydrates, and phenols, and they are also found in root extract terpenoids, and saponins. The ethanolic fruit extract shows the maximum amount of tannin, phenol and total protein (22).

Pharmacological Activities

Anti-Osteoarthritic Activity

The plant stem powder at 300mg/kg body weight exhibited an effective anti-arthritic activity in the alloxan-induced animal model (18).The plant exhibited the healing potentiality of fracture jaw bones as 500 mg capsule of the plant was administered three times a day for 6 weeks that reduced pain, fragment mobility, and swelling but increased serum phosphorus and serum calcium of maxillofacial fractured bone (34). The phytochemicals present in the plant extract of *C. quadrangularis* and *Butea* monosperma can act as osteogenic substances with potentiality in altering cell signaling and metabolic pathways and can be mixed with sulphonated poly (aryl ether ketone) sponges as porous scaffolds used as important factors during the delivery of bone growth (35).

The ethanolic extract of the stem with 25 bioactive compounds is potentially able to manage osteoarthritic in mono-sodium iodoacetate-induced osteoarthritic in animal models and was found comparable with standard drug naproxen (36). The plant extract expresses significant anti- rheumatic disorders activities reducing the detrimental effect of cytokine interleukin-1β (IL-1β), which causes cell toxicity, and affects cell growth and proliferation. The plant extract controls gene expression of IL-1β and matrix metalloproteinases, responsible for cartilage and bone destruction, and also inhibits p38 MAPK (mitogen-activated protein kinase) signaling pathway, which aggravates irregular expression of gene survivin, an important factor of cell growth in humans. Moreover, certain in vivo studies reported the enhancement of cartilage tissue formation and alkaline phosphatase in plant extract-treated animal model (37).

The hydroalcoholic extract of the plant exhibits anti-arthritic activity and when tested on formaldehyde-induced and adjuvant induced arthritis in rats, inhibits joint swelling. The treatment also decreases oxidative stress, serum TNF-α level, and synovial expression of angiogenesis and inflammatory marker. Even in sub-acute toxicity condition, the extract does not show any impact on physiological and pathological mechanisms

in animal models (38). On the contrary, some other studies reported that 3-ketosteroids could serve as active phytochemical compounds present in the plant extract promoting bone health that generally does not have any biological effect on bone health promoting activities. Hence, further research should be conducted on the isolation of biologically active principles in plants that contribute to bone formation and health (39).

Anti-inflammatory Activities

The methanolic extract of the plant has potentiality in inhibiting arachidonic acid metabolism by controlling edema formation in ears in ethyl phenylpropiolate induced, as well as paw edema induced by both arachidonic acid and carrageenin in rat models (40).

The ethyl acetate extract of stem shows anti-inflammatory activity in Lipopolysaccharide (LPS) induced nitric oxide formation in RAW (Ralph, rAschke, Watson) 264.7 macrophage cells by suppressing mRNA and protein expression of nitric oxide synthase (iNOS) and p65 NF-κB nuclear translocation. The extract induces heme oxygenase-1 (HO-1) gene expression and inhibits nitric oxide formation by producing zinc protoporphyrin IX (ZnPP), a HO-1 inhibitor (41). The fresh stem extract contains a bioactive compound betulinic acid, which shows a significant inhibition of superoxide anion, and the same compound along with another bioactive compound pheophytin-a helps inhibit elastase release, initiating neutrophils activation in response to macrophage activator *N*-formyl-L-methionyl-phenylalanine/cytochalasin B (fMLP/CB) during inflammatory reactions in humans (19).

Antidiabetic Activities

The ethanolic extract of the plant is capable of preventing diabetic nephropathy in high-fat diet/streptozotocin induced diabetes in rats. The extract regularizes insulin resistance, creatinine level, and lipid profile. Moreover, it restores albuminuria, creatinine clearance, and glomerular filtration rate and brings in level SIRT1 and DNMT1 expression caused by a high fat diet. The extract shows safety against renal inflammation and oxidative damage and protection from renal fibrosis by repressing TGFβ, col1/3 and Smad2/3expression in animal models (42). The ethanolic extract of leaves exhibit anti-hyperglyceamic activity with a remarkable reduction in the serum glucose, prevents decrease in the body weight, and increases the entrance of glucose against alloxan-induced diabetes in rats (43).

The ethyl acetate fraction of stem expresses significant antidiabetic activity increasing blood glucose, liver toxicity markers, inflammatory markers, lipid peroxidation products and HbA1c along with reducing antioxidant enzyme activities. The stem fraction further increases mRNA expressions of IL-6, TNF-α, and NF-κB in adipose tissue and also restores histopathological changes in liver and pancreas in nicotinamide/streptozotocin-induced diabetes in rats. Furthermore, it was found comparable with standard drug metformin (44). Moreover, the ethyl acetate fraction of stem at 100 mg/kg body weight decreases the blood glucose level, altering the carbohydrate-metabolizing enzymes activities by increasing pyruvate kinase (2.2-fold) and hexokinase (1.9-fold) activities, and minimizing the activity of fructose-1, 6-diphosphatase, glucose-6-phosphatase, and glycogen phosphorylase, showing a significant impact on carbohydrate metabolism in diabetes induced in animal models (45).

Anti-Obesity Activities

The ethanolic extract of plant exhibits antihyperlipidemic activities and has potentiality in decreasing phospholipids, cholesterol level, high-density lipoproteins (HDL) and triglycerides (TG) in high fat fed animal models (46). The aqueous leaf and stem extract of the plant at 300 mg decrease body fat reducing systolic and diastolic blood pressures, triglycerides, waist and hip circumferences, fasting blood glucose, total cholesterol, and leptin levels, and also increases adiponectin levels and HDL-cholesterol of humans (47).

Antioxidant Activities

The ethyl acetate extracts of both fresh and dry stem showed 61.6% and 64.8% antioxidant activity in 1,1-diphenyl-2-picrylhydrazyl system and β-carotene linoleic acid system, respectively (48). The methanol extract of the plant shows a remarkable scavenging effect on DPPH free radical, hydroxyl radical production, superoxide radical, and controlling lipid peroxide production in rat models. In order to test liver marker and antioxidant defense enzymes of the liver, animals treated with CCl_4 exhibited an increase in

alanine aminotransferase (ALT), aspartate aminotransferase (AST), malondialdehyde (MDL), alkaline phosphatase (ALP), levels and a decrease in catalase (CAT), superoxide dismutase (SOD), glutathione-*S*.-transferase (GST), glutathione peroxidase (GPx), and reduced glutathione (GSH) activities reverted by treating the animals with the methanol extracts of the plant (49). The ethanolic stem extract possesses a significant free radical scavenging of DPPH, hydrogen peroxide, nitric oxide, metal chelation, and superoxide in all cell-free models (24, 50).

Anti-Cancer Activities

The compounds *epi*-glut-5(6)-en-ol and betulinic acid present in the plant stem show anticancer activity against colon cancer (HCT-116) cell lines and non-small-cell lung carcinoma (NCI-H226) without cytotoxicity (19). The MTT colorimetric assay conducted in the dark suggests that methanolic and ethanolic extracts of the plant possess significant anticancer activities against leukemic cells HL-60 (24). A bioactive compound lupeol present in plant stems exhibited a significant melanin promotion activity and was found comparable against standard compound, 3-isobutyl-1-methylxanthine (IBMX) (26). The ethanol extracts of the stem significantly inhibit the proliferation of MCF-7 breast cancer cells in a dose-dependent manner in 24 hours (50), whereas ethyl acetate extract against breast cancer cell lines (51).

Anti-Microbial Activities

The methanolic extract of the plant also exhibit antiviral activity against herpes simplex virus HSV1 and HSV2 that causes cutaneous infections in humans, without any cytotoxicity to vero cells (20). The petroleum ether extract of the plant exhibit antibacterial activity against Gram-positive *Staphylococcus aureus* and *Bacillus cereus* and Gram-negative *Salmonella typhi* and *Escherichia coli* organisms (21). Similarly, the methanol extract of the stem exhibited antimicrobial potentiality against some avian microorganisms like *Escherichia* sp. (27). The ethanol extracts of the shoot exhibited an effective anti-bacterial activity against some pathogenic bacteria like *Escherichia coli, Pseudomonas species, Staphylococcus aureus, Bacillus subtilis,* and *Klebsiella pneumonia* (51).

Anthelmintic Activities

The stem extract of methanol shows an effective anthelmintic activity against *Pheretima posthuma* and was found comparable with drug albendazole (52). Similarly, the alcoholic root extract caused paralysis at 8.33 and death at 18.50 minutes, effective against *Pheretima posthuma* and was found comparable with drug piperazine citrate (53). The higher concentration of the methanol extract of the aerial part of the plant shows strong adulticidal activity and inhibits 88% egg hatching of ruminant parasite *Haemonchus contortus* (54).

Conclusion

In conclusion, *Cissus quadrangularis* exhibited a wide range of pharmacological activities. Further investigations are required on the mechanism of action of plant metabolites for broader therapeutic applications through repeated clinical human trials. Moreover, to develop new drug formulations for an effective phytomedicine, research on phytochemistry and the isolation of chemical compounds should be given priority.

Conflict of Interest

The authors declare that they have no conflict of interest.

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