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Review Article

Cissus quadrangularis L - Its Botany, Chemistry and Medicinal Importance: A Review

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ABSTRACT

Herbs are known as a natural source of medicines as well as other commercial products and have gained attention for many reasons such as low price, no side effects, solutions for chronic diseases and many preventive approaches, etc. Out of 2, 50,000 higher plant species, 80,000 species are medicinal important plants. *Cissus quadrangularis* L. is one of the important medicinal plants, belonging to family Vitaceae and common name is 'Hadjod'. It is a succulent plant found in warm tropical areas. The plant is well known in Ayurveda for its bone fracture healing properties. The literature survey revealed that the plant has some pharmacological properties such as free radical scavenging, anti microbial, anti bacterial, antioxidant, bone healing, anti ulcer, anti inflammatory, analgesic and diuretic properties. The plant extract is also useful in skin diseases, epilepsy, tumors, chronic ulcers, swellings, hemorrhage helminthiasis, anorexia, etc. The present review is an effort to focus on the medicinal importance of *C. quadrangular is*, its Botany, phytoconstituents and pharmacological reports.

Key words: *Cissus quadrangularis* L, pharmacological, phytoconstituents

INTRODUCTION

For the past several years plants have been important source of medicines, agriculture, food, health care, pharmaceuticals, etc. As a possible basis of alternative and effective drugs, medicinal plants have gained increased importance. According to World Health Organization (WHO), nearly 80 per cent of the people in developing countries consume traditional medicines for nourishing health and gaining strength. Trivedi *et al.,* (2006) have reported that in entire world around 20,000 to 35,000 species of plants are used in pharmaceuticals, neutraceuticals, cosmetics and as medicines. Many traditional herbal therapies have originated from the medicinal properties of different plant species. In pharmaceuticals, the essential component of both research and development are medicinal plants.

WHO estimated that in each year about one fourth of the 500 million prescriptions given in US mention plant extracts or active ingredients obtained from plants. The chemical constituents present in *Heliotropium indicum, Taxus brevi* act as antitumour, *Centella asiatica, Boerhaavia diffusa* act as diuretic and *Siphonichilus natalensis* act as anti-malarial. (Malik *et al.,* 2012).

Sales of medicinal plants in the world**:** According to Phytopharm Consulting, in 1996 the global sales of herbal products was US $ 14 billion and demand for herbal products has been steadily increasing at the rate of 10-15 % per annum touching around US $ 62 billion. The main herbal product markets are primarily in Europe, France, Asia, North America and Japan which constitute around 63% of world herbal product market. Highest *per capita* consumption of botanical medicines is in Japan. In world market, China occupies the top position in the export of traditional medicines and 400,000 tones of medicinal plants are imported in Europe annually with an average market value of US $1 billion from Africa and Asia. According to the report of Export- Import Bank of India the Global market of medicinal plants was around US $ 60 billion and continues to increase with the growth rate of 7% (Natesh, 2001).

The accurate calculation of the value and volume of herbal plants trade from India is quiet arduous but an estimate refers that the medicinal plants trade in India might be touching approximately Rs 5.5 billion. Since the past few years herbal medicines have increased tendency for consumption particularly with the standardization and development of herbal medicines (Malik *et al.,* 2008).

Table 1. Total sales of herbal products 1999 to 2010 and also % increase/decrease annually.

Year	$ Total Sales (millions)	% Increase (-decrease)
1999	4,110	2.7
2000	4,230	2.9
2001	4,356	3.0
2002	4,238	2.7
2003	4,146	2.2
2004	4,290	3.5
2005	4,381	2.1
2006	4,561	4.1
2007	4,759	4.3
2008	4,800	0.9
2009	5,030	4.8
2010	5,200	3.3

Source: Nutrition Business Journal, nutrition business journal.com

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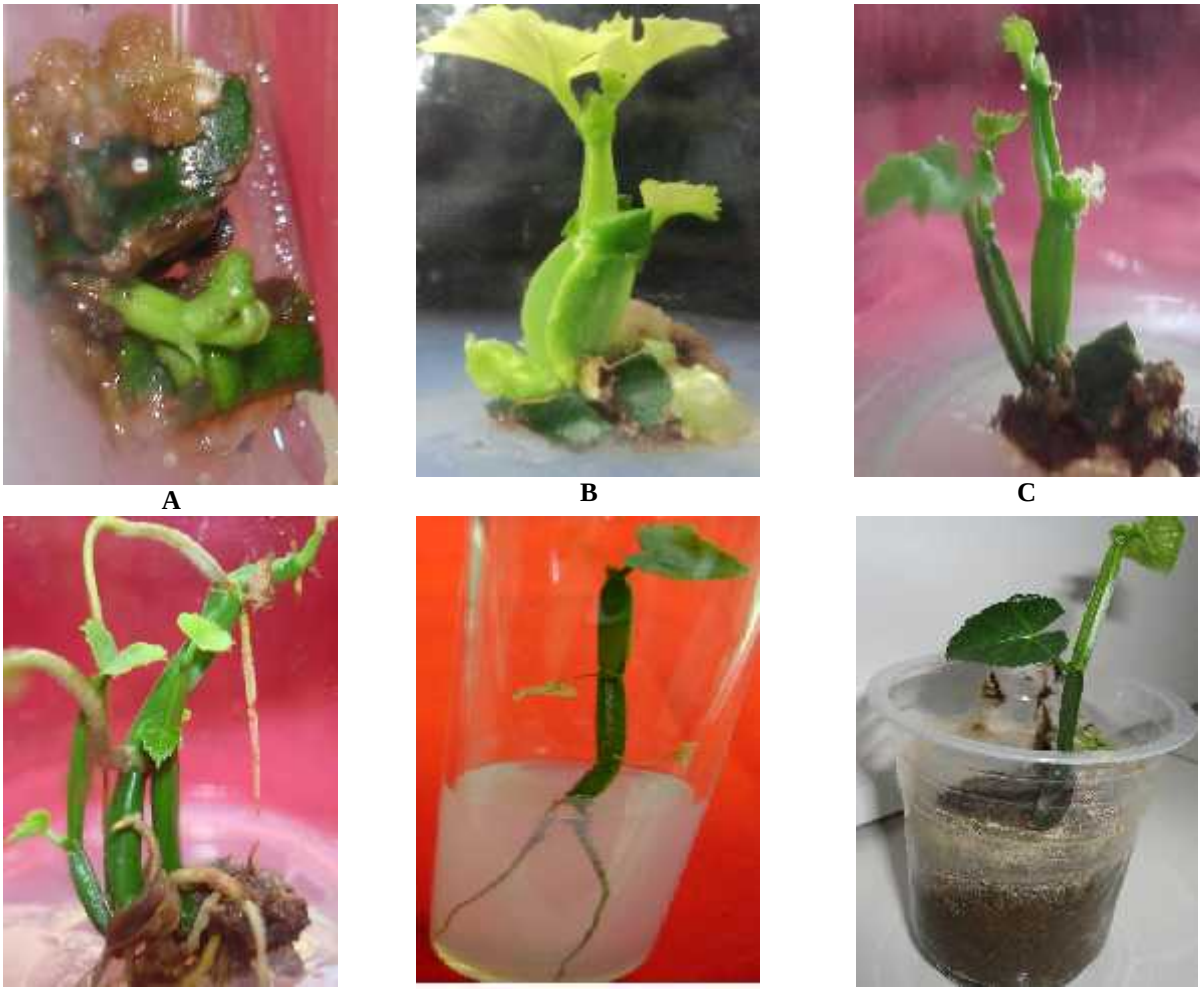
Fig.1. Left. Vegetative part of stem and leaves with tendrils, Right. Bunch of flowers and fruit



A **B** **C**

D **E** **F**

Fig.2. Cissus quadrangularis L. (A) Single shoot formation from nodal segment on BAP-4 mg L^{-1} with adenine sulphate-8 mg L^{-1} after 15 days of inoculation (B) Regeneration of shoots from nodal segment on BAP-2 mg L^{-1} with Kn-2 mg L^{-1} after 35 days (C) Regeneration of shoots from nodal segment on BAP-2 mg L^{-1} after 60 days of inoculation. (D) Multiple shoot regeneration on 2,4-D- 1 mg L^{-1} after 90 days of inoculation (E) rooted shoots 25 days after inoculation (F) acclimatized plants after 40 days.(After Garg and Malik, 2012)

Herbal therapies attract people globally because of several rational motives such as low pricing, solutions for chronic diseases and disorders, no side effects, time tested remedies, etc.

Phytometabolites from Medicinal Plants: Phytometabolites are the compounds synthesized by

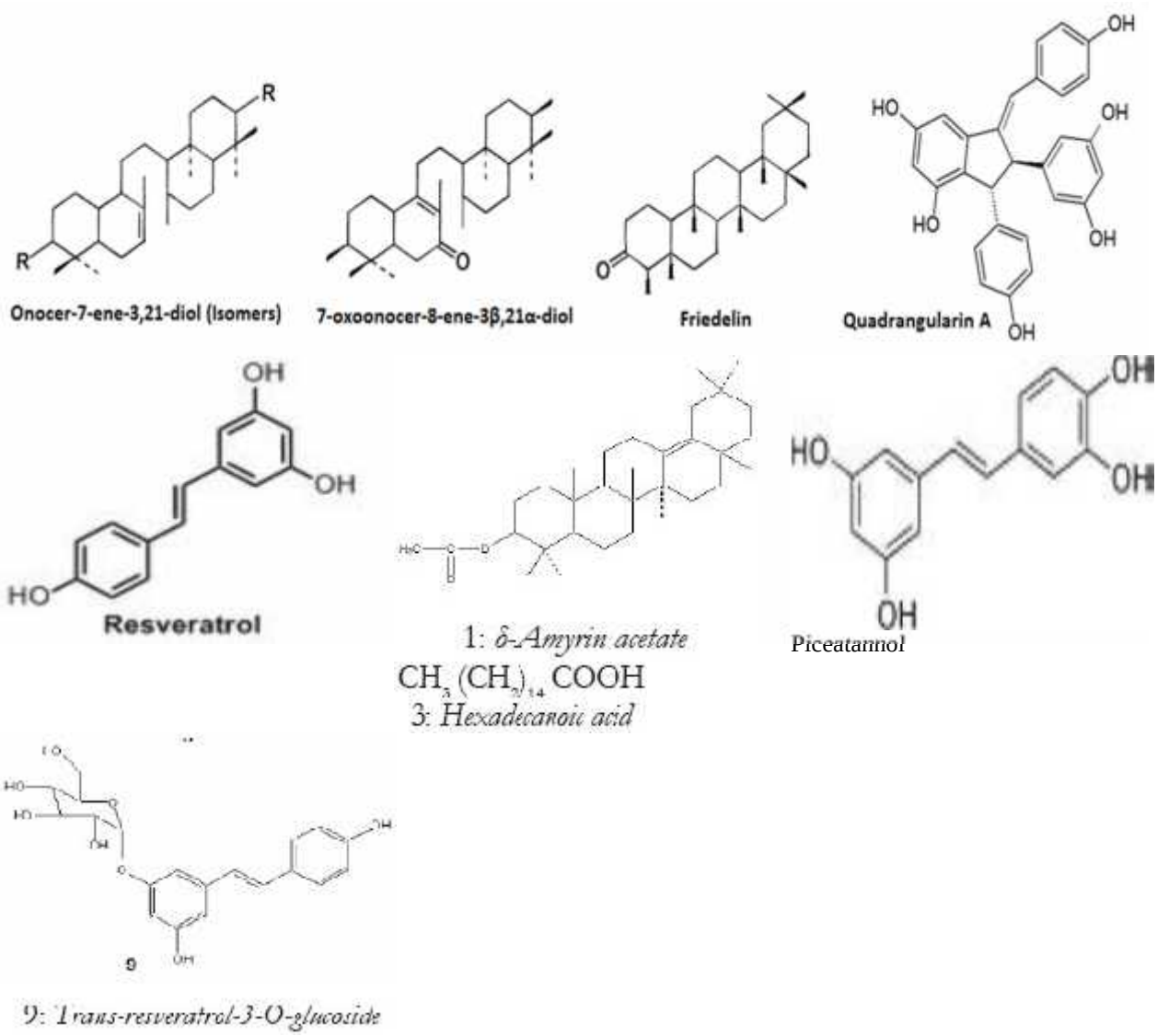


Fig. 3. Chemical structure of compound isolated from Cissus.

plants, which may be primary and secondary in nature. Primary phytometabolites are produced to fulfill basic requirements whereas secondary phytometabolites are mainly produced for self-defense comprising alkaloids, phenolics, lignins, essentials oils, steroids, tannins, etc.

There are three large classes of secondary metabolites described in plants:

- Nitrogen containing compounds
- Terpenoids
- Phenolics

In vitro production of secondary metabolites can be accomplished through plant cell culture. Various reports describing the production of different secondary metabolites like alkaloids, anthocyanins, coumarins, carotenoids, terpenoids, steroidal alkaloids, flavones, tannins, sterols, saponins, and numerous others have been attained (Sampat, 2013). The production of secondary metabolites in cells can be increased through various methods such as growth of differentiated cells, biotransformation and elicitation (Marwaha and Arora, 2003; Kumar, 2003). Zenk *et al.*, (1978) for the first time reported the successful establishment of the cell lines which were capable of producing high yields of secondary compounds in cell suspension culture. One of recent organ culture systems employed for large scale production of secondary metabolites is given by Kaur and Malik, (2009) in which formation of hairy root cultures by genetic transformation of plant tissues by bacterium *Agrobacterium rhizogenes* has been discussed. In a more recent review Kaur and Eisenstein (2011) have discussed herbal medicines prospects for economic oppurtunities and wellness. They have also emphasized raising of root culture in the production of secondary metabolites.

Correlation between Phytomedicine Markets and Resource Based Species**:** Development of medicinal plant markets are providing better opportunities for the herbal industry and increased utilization of resources. As the demands of consumer increase, a general threat to the plant resources also enhances. Unfortunately, plant specific resources are continuously depleting in order to meet the ample demands of the consumers and industries.

Very few medicinal plant species are being cultivated and

Table 2. Chemical compounds with their molecular formulae and molecular weight isolated from the stem of *Cissus* (Adopted from Kumar *et al.*, 2012)

S.No.	Name of the chemical compound	Molecular formula	Molecular weight
1	n – Hexadecanoic acid	$C_{16}H_{32}O_2$	256
2	9, 12, 15 – Octadecatrienoic acid methyl ester (Z, Z, Z)	$C_{19}H_{32}O_2$	292
3	Ethan -1,1- diethoxy	$C_6H_{14}O_2$	118
4	Tetradecanoic acid, ethyl ester	$C_{16}H_{32}O_2$	256
5	9, 12, Octadecadienoic acid, methyl ester (E, E)	$C_{19}H_{34}O_2$	
6	Butanedioic acid - 2, 3 – bis (acetyloxy), (R, R*, R*)	$C_8H_{10}O_8$	234
7	Ethyl a – d – glycopyranoside	$C_8H_{16}O_6$	208
8	13 - Tetradece – 11 – yn – 1 – ol	$C_{14}H_{24}O$	208
9	Glycerin	$C_3H_8O_3$	92
10	Tetradecanoic acid	$C_{14}H_{28}O_2$	228
11	Benzene – 1, 2, 4 - trimethyl	C_9H_{12}	120
12	Formylhistamine	$C_6H_9N_3O$	139
13	Phytol	$C_{20}H_{40}O$	296
14	Glycerin	$C_3H_8O_3$	92
15	2 – Cyclopenten – 1 – one, 2 – hydroxyl	$C_5H_6O_2$	98
16	Undecanoic acid	$C_{11}H_{22}O_2$	186
17	Octadecanoic acid, ethyl ester	$C_{20}H_{40}O_2$	312
18	DL – 3, 4 – Dimethy – 3, 4 – hexane diol	$C_8H_{18}O_2$	146
19	Hexanedioic acid, mono 2- ethylhexyl) ester	$C_{14}H_{26}O_4$	258
20	4H–Pyran–4–one, 2, 3 - dihydro– 3, 5 – dihydroxy – 6 - methyl	$C_6H_8O_4$	144
21	DL – 3, 4 – Dimethyl – 3, 4 – hexane diol	$C_8H_{18}O_2$	146
22	1, E – 11, Z – 13 – Octadecatriene	$C_{18}H_{32}$	248
23	Benzene – 1 – ethyl – 3 – methyl	C_9H_{12}	120
24	2 – Furancarboxaladehyde, 5 – hydroxyl methyl)	$C_6H_6O_3$	126
25	n - Decanoic acid	$C_{10}H_{20}O_2$	172
26	Asarone	$C_{12}H_{16}O_3$	208
27	1, 3, 8 – P – Menthatrien	$C_{10}H_{14}$	134
28	Phenol– 4 – (3– hydroxyl–1–Propenyl) – 2 - methoxy	$C_{10}H_{12}O_3$	180
29	Nonanoic acid, 5 – methyl, ethyl ester	$C_{12}H_{24}O_2$	200
30	1, 2, 3 – Propanetriol, monoaceta	$C_5H_{10}O_4$	134
31	Benzene – 1 – ethyl 2,4 - dimethyl	$C_{10}H_{14}$	134
32	Nonanol	$C_9H_{18}O$	142
33	Benzene – 1 - methlethyl	C_9H_{12}	120
34	D –Glycero – d – tallo - heptose	$C_7H_{14}O_7$	210
35	Dacanoic acid, octyl ester	$C_{18}H_{36}O_2$	284
36	Hexadecanoic acid, ethyl ester	$C_{18}H_{34}O_2$	282
37	Oleic acid	$C_{18}H_{34}O_2$	282
38	Linoleic acid ethyl ester	$C_{20}H_{26}O_2$	308

rest are wild populations subjected to rigorous harvesting from phyto-diversity rich areas. All parts of the plant (leaves, flowers, fruits, seeds, roots) are used for preparing plant based drugs and in some instances even young (immature) parts are being harvested. Moreover, numerous other factors such as expansion of land for agricultural purposes, dwindling forests, over exploitation of resource, grazing, etc have increased the demand on wild population of medicinal plant species. In this situation biotechnological tools are handy and significant for multiplication and their genetic improvement through *in vitro* regeneration and genetic transformation.

Botany:

Classification

Kingdom: Plantae or green plants

Subkingdom: Tracheobionta: Vascular plants

Table3. shows the Human Effect Matrix of *Cissus quadrangularis* (Source- www.amazon.com)

Effect	Scientific consensus(%)	Comments
Hemorrhoids	100	Although some traditional usage of the herb suggests otherwise, limited (accessible) human data does not support a role for *Cissus* in the treatment of hemhorroids
Weight	100	There may be a small weight loss associated with 300 mg *Cissus* (2.5% ketosteroids) which was seen alongside a reduction in appetite in obese persons; no known direct fat
Total Cholesterol	100	Reductions in total cholesterol not overly remarkable relative to placebo and confounded with weight loss which occurred with *Cissus*
Triglycerides	100	Reduction in triglycerides is not overly potent and occurred alongside weight loss, which was likely a confounding factor.
Plasma Serotonin	100	Increase in plasma serotonin was significant (30-39%) and fairly noteworthy, deserves more research.
Creatinine	100	An increase in creatinine has been noted alongside weight loss; practical significance of this information is not known.
Lipid Peroxidation	100	A minor reduction in lipid peroxidation has been seen in serum associated with weight loss; uncertain significance.
Bone Healing Rate	100	More evidence is required, as the one study noting that *Cissus* was ineffective in isolation noted that combination therapy with *Cissus* and calcium was quite effective
Pain	100	Joint pain appears to be reduced following supplementation of *Cissus*, and while the magnitude is not remarkable (respectable, but comparable to other supplements) it seems
Functionality in Elderly or Injured	100	An increase in the function of the joint appears to occur alongside reductions in perceived pain and soreness when *Cissus* treats athletic joint pain; one of the few options
Heart Rate	100	No significant influence on heart rate when taken over the course of eight weeks.
Blood Pressure	100	In otherwise healthy athletic men, there is no significant influence of supplementation over eight weeks on blood pressure

Super division: Spermatophyta: Seed bearing plants
Division: Angiosperm (Flowering Plants)
Class: Dicotyledoneae: Dicots; Angiosperms; Flowering plants;
Subclass: Rosidae
Order: Rhamnales

Plant description: *Cissus quadrangularis* (Fam:Vitaceae) commonly known as "Hadjod", found on the lower slopes of the Western Ghats and dry areas of Arabia, Africa, India, Sri Lanka, Malaysia and Thailand (Udupa *et al.,* 1970) and commonaly used as a food item in Southern India (Chidambaram *et al*., 2003) and Sri Lanka (Arya *et al*., 2009). In Ayurvedic System of medicine, stem of *C.quadrangularis* Linn. is very important part of the plant and used in piles, bone fracture, pain in joints, swelling, scurvy, gout, asthma, scurvy, disease of ear and nose-bleeding (Nagani *et al.,* 2011).

C. quadrangularis is a succulent shrubby climber. Stems is 4-angled, jointed at nodes, internodes are 8 to 10 cm long and 1.2 to 1.5 cm wide. Leaves are simple, lamina ovate or reniform, ±5 cm wide, crenate-serrate (Panda, 2004; The Wealth of India,) 2005; Fig.1 Left. Three morpho-variants of *C. quadrangularis* have been reported on the basis of stem morphology; square-stem, round-stem and flat-stem and known as variant I, II and III respectively (Kumar *et al*., 2012).

Flowering and hence fruit formation is rare (Fig. 1, right).

Mode of propagation: *C.quadrangularis* is a vegetativaly propagated plant because the seeds are not viable and flowering and seed formation are very rare in *C. quadrangularis.* Because of its constant use in medicines, scientific studies and food and lack of conservation strategies have caused its significant depletion, and now it is being threatened (Garg *et al.,* 2012). The *in vivo* rate of vegetative propagation of this plant through stem cuttings

is meager. Therefore, for the conservation of this medicinal plant, the *in vitro* clonal propagation technique provides a promising method of propagation. With the help of tissue culture techniques, Sharma *et al.,* (2011) have succeeded in establishing callus tissue of this plant

Fig 4. Different formulations based on Cissus available in the market.

but failed to develop a protocol for plantlet formation. Later on, Garg and Malik (2012) developed a standardised protocol for *in vitro* propagation of *C. quadrangularis* which is easy and reproducible. The plantlet formation were formed from nodal segments through axillary bud proliferation in which 6- benzylaminopurine (2 mg L^{-1}) was added to MS medium and then the regenerated shoots were rooted on MS basal medium without auxins.

Phytochemistry: The plant contains potassium, calcium, zinc, sodium, iron, lead, cadmium, copper, calcium oxalate and magnesium. Other constituents of the plant are resveratrol, piceatannol, pallidol, parthenocissin (Oben *et al.,* 2006). The phytochemical analysis of *C. quadrangularis* revealed the presence of some additional compounds such as taraxeryl acetate, taraxerol, iso-pentadecanoic acid, phenol, tannin, α-amyrin and β-sitosterol. It also contains 31 methyl tritiacontanoic acid and 7 -Oxo onocer-8-ene-3, 21- diol. *C.quadrangularis* is a very good source of vitamin C and beta- carotene (Fig. 3 and Table 2). For greater details a reference may be made to a recent paper by Kumar *et al.,* (2012).

Medicinal importance of *Cissus quadrangularis;*

Traditional Uses: The plant is very much known in Ayurveda for the treatment of rheumatoid arthritis, osteoporosis, osteoarthritis (Paulsen *et al.,* 2000), scurvy, menstrual disorders, epistaxis (Anonymous, 1999). In East Africa it is used with tamarind for the tratment of gonorrhoea (Burkill *et al.,* 2000). A stem paste is useful in burns, wounds, bites of poisonous insects and for saddle sores of camels and horses (Sharma *et al.,* 2001). The stem of *C. quadrangularis* is used for the treatment of gastritis, constipation, eye diseases, piles and anemia. Useful in stomachic when preserve is made with stem and lime water.

Pharmacological Uses-

In Neurology-

GABAergic Neurotransmission-The methanol extract of whole plant of *C. quadrangularis* acts a low binding affinity to the $GABA_A$ benzodiazepine site. (Bah *et al*., 2007).

Sedation-Oral intake of *C.quadrangularis* reduces the sleep tendency and enhaces the $GABA_A$ signalling.

Convulsion- Based on priliminary evidences, this plant shows anticonvulsion properties (Kumar *et al*., 2010).

Analgesia- Drug aspirin (300 mg/kg) is more effective in the late phase of pain and *C. quadrangularis* (10-40 mg/kg) is more effective in reducing pain. (Kumar *et al*., 2010).

Cardiovascular Health-

Endothelium- The extract of *C.quadrangularis* reduces the hydrogen peroxide mediated oxidative damage which increases the antioxidative enzymes in the endothelium cells and this is because of two minor components of *Cissus*, Resveratrol and Quercetin (Sapsrithong *et al*., 2012).

Bone and Joint Health-

Osteoblasts- The extract of *C.quadrangularis* can stimulate osteoblastic proliferation and differentiation and may effect the promotion of mesenchymal stem cells to osteoblasts. The production of osteoblasts are related to 6′-O-trans-cinnamoyl-catalpol which is present in *C.quadrangularis* (Muthusami *et al*., 2011).

Fractures- *C. quadrangularis* is well-known in traditional medicine for healing bones. According to the surveys of traditional medicine usage it is commanly used for bone setting purpose (Upadhya *et al*., 2012).

Bone Loss- The ether extract of *C. quadrangularis* in rat, fully prevents the losses of bone strength and bone thickness (Potu *et al*., 2010). It increases the inflammatory cytokines and IL-1β which preserves corticol and calcellous bone mineral density and thickness (Potu *et al*., 2011).

Relation with Hormones

Estrogen- The ethanolic extract of *C. quadrangularis* seems to have estrogenic properties by increasing the serum estrogen rather than directly acting on estrogen receptors (Aswar *et al.*, 2012).

Cortisol- *C. quadrangularis* reduces the catabolic effect by inhibiting the receptor which shows the potential role as a glucocorticoid antagonist (Chopra *et al.*, 1976).

Testosterone- Due to the capability of *C. quadrangularis* to act as a glucocorticoid antagonist, it has been projected to have anabolic/androgenic activity.

Inflammation and Immunology: The ethyl acetate extract of *C. quadrangularis* possesses antioxidant compounds which activates HO-1 which then suppresses inflammation, But *C. quadrangularis* also contains tannin like structures which when tested *in vitro*, are potent COX inhibitors which shows that it also have anti-inflammatory effects (Srisook *et al.* , 2011: Bhujade *et al.* , 2012).

Interactions with Organs

Stomach- The methanolic extract of *C. quadrangularis* seems to have proton pump inhibitory (PPI) properties (Yadav *et al.*, 2012). *In vitro*, water extracts of *Cissus quadrangularis* appear to have antibacterial properties against *Helicobacter pylori* Austin *et al.*, 2003)

Liver- The methanolic extract of *C. quadrangularis* reduces the liver damage done by rifampicin but there is no influence on liver enzymes, lipid peroxidation (Chidambaram *et al.*, 2010).

Anti microbial and antibacterial activity : The 90% methanol extract of stems own antibacterial activity against *E. coli*, *S. aureus*, and *P. aeruginosa* and mutagenicity against *Salmonella microsome (*Luseba *et al.*,2007).The stem and root extract possesses antimicrobial activity (Murthy *et al.*, 2003). The alcoholic extract of upper part of plant was found to possess antiprotozoal activity against *Entamoeba histolytica* (Rajpal *et al.*, 2005).

Formulations of *Cissus*: The formulations based on *Cissus* are available in different forms e.g. dry powder, syrup and capsules to be administered for different ailments. These are manufactured by large number of companies under different brands. These include Amazon, GN labs, USP Labs, Primaforce, etc. USP Labs make number of claims about the origins of its product, suggesting that auxiliary benefits to the primary indications of fat loss and anabolic assistance such as the relieving of muscle and tendon pain, as well as appetite suppression, were discovered through feedback from its users. While the company may well have been overjoyed to learn of the additional applications its customers were finding for Super Cissus Rx, the ancient Ayurvedic tradition has offered such herbal wisdom on *Cissus* through the ages. Nevertheless, user experiences involving the anti-inflammatory and analgesic effects of Super Cissus Rx have become predominant among the growing body of community testimonies, and customers seem overwhelmingly satisfied. Super Cissus is sold in 750 mg capsules; Mega *Cissus* contains 400 mg per pill, and Primaforce's caps contain 1000mg. As a result, Super Cissus can be described as one of the most mild options for intake, and for this reason it scores high points among the majority of users.

Use of *Cissus quadrangularis* may support weight-loss efforts, according to a small study published in *Lipids in Health and Disease* in 2008. For the study, researchers assigned 72 obese or overweight people to 10 weeks of treatment with a placebo, *Cissus quadrangularis*, or a combination of *Cissus quadrangularis* and ***Irvingia gabonensis***.

Compared to the placebo group, those assigned to *Cissus quadrangularis* showed significantly greater improvements in a number of factors (including body weight, waist size, and cholesterol levels). However, those given the combination of *Cissus quadrangularis* and *Irvingia gabonensis* appeared to experience the greatest improvements.

In a 2007 study published in the same journal, researchers found that *Cissus quadrangularis* was more effective than a placebo in promoting weight loss, reducing blood sugar levels, and improving cardiovascular risk factors in obese and overweight people. The study involved 168 overweight and obese adults, 153 of whom completed the study.

CONCLUSION

From decades plants are used as traditional medicines in different parts of the world and believed to be safe for human use. So these plants deserve modern scientific analyses such as phytochemical studies, toxicology, biological examination on model animals and the role of isolated phytochemicals and their clinical trials. A comprehensive study on *C. quadrangularis* reveals that it has a potential as a bone protective agent and many other diseases. More interesting fact is that *Cissus* shows minimum side effects on human consumption even at high doses. Overall *Cissus* has very high medicinal properties but it requires details in the mechanisms by which the phytochemical principles act and need to be assessed the action of molecular mechanism. More evidences will completely elaborate the potential of *Cissus quadrangularis*.

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