

Review

Medicinal properties of plants from the genus *Cissus*: A review

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Traditional medicine has been practiced in different parts of the world from time immemorial. Even now it is heavily relied on by native people. Moreover, a quarter of the allopathic medications are based on compounds isolated from natural products. With increase in drug recalls resulting from severe side-effects, the pharmaceutical industry also is interested in finding new drugs from natural sources with fewer or no side-effects. Recently, these traditional medicines are receiving more scientific support which helps in not only authenticating the use of these medicines for treatment but also understanding the mechanism of action of these drugs. We started with testing one species of *Cissus*, *Cissus quadrangularis*, for its bone protective properties and found that many species from this genus have been reported to have medicinal properties for treating various ailments. In this review, we have compiled all the information related to the medicinal use of the different species from this genus. We used Pubmed and OVID as our major source for the literature collection and also used cross-references from the papers.

Key words: Genus *Cissus*, medicinal properties, obesity, gastrointestinal tract, bone, diabetes, *Cissus quadrangularis*, *Cissus sycoides*.

INTRODUCTION

Many cultures around the world still rely heavily on traditional medicines, though about 38% of American adults use alternative medicines (Barnes et al., 2008). People take alternative or complementary medicines mainly to avoid the side effects, and some others who have tried allopathic medicines but did not get relief from the ailment. The drug discovery industry is equally dependent on natural products for new medicines (Newman and Cragg, 2007) mainly because existing therapies exhibit many side effects that results in the recall of drugs, bringing huge losses to the

pharmaceutical industries. Therefore, there is interest in identifying plants or groups of plants that are used in traditional medicines around the world. However, scientific backing authenticates the proper use of these plants and also removes any medicines that may cause more harm than good to patients. It is encouraging to see that recently, many Researchers are interested in giving scientific authentication and explanation to the activity of plants used in traditional medicine around the world.

One such group of plants that is used in all the continents and is implicated to treat different ailments is plants belonging to the genus '*Cissus*'. It belongs to the Vitaceae family which includes the common fruit- grapes (*Vitis vinifera*) and the medicinal properties of resveratrol, an active ingredient in grapes, are well established. It is anti-diabetic (Szkudelski and Szkudelska, 2011), anti-neurogenerative diseases (Sun et al., 2010), anti-cancer (Athar et al., 2009), protects from cardiovascular disease (Bertelli and Das, 2009), increases longevity (Das et al., 2010), to name a few. For detailed information please

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ABBREVIATIONS: **CQ**, *Cissus quadrangularis*; **MAPK**, mitogen activated protein kinase; **CS**, *Cissus sycoides*; **IGF**, Insulin-like growth factor; **NF- κ B**, nuclear factor kappa B.

refer to the Resveratrol and Health Issue in the Annals of New York Academy of Sciences (2011). We searched the literature using Pubmed and OVID (Ovid MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register) and compiled this review on the medicinal properties of the different species from the genus *Cissus*.

PLANTS FROM THE GENUS *CISSUS*

The genus *Cissus* consists of about 350 species of which, at least, a dozen is used globally in traditional medicine to treat different ailments (Table 1). In Australia, Bush Medicine Practitioners use *C. hypoglauca* to treat sore throat (Lassak and McCarthy, 1997). Many cultures in Asia, both East and West Asia, have used locally available species of *Cissus* to treat several medical problems. In China and the far East, *C. assamica*, is used as anti-snake venom as it decreases endothelin-1 and sarafotoxin 6b (Yang et al., 1998), while in South east Asia including the Indian subcontinent and Sri Lanka, *Cissus quadrangularis* is used for fracture healing (Udupa and Prasad, 1962) and as an anti-obesity agent (Oben et al., 2006). In West Asia, *Cissus hamaderoensis*, is reported to inhibit angiotensin converting enzyme (ACE), neutral endopeptidase (NGP) and aminopeptidase N (APN) (Oleski et al., 2006) as well as have anti-viral properties (Mothana et al., 2006). Several countries in Africa use different species of *Cissus* in their traditional medicinal practices: Cameroon traditional medicine uses *C. aralioides* as anti-microbial and toxicological agent against microorganisms of the gastrointestinal and urogenital tracts (Assob et al., 2011). Alcoholic extracts of a Gabonese medicinal plant – *C. debilis* - showed anti-proliferative activity on human CaCo-2 cells (Line-Edwige et al., 2009). In Nigeria, a few species like *Cissus populnea*, *Cissus ibuensis* and *C. quadrangularis* are used in their native medicine. Methanolic extracts of *C. populnea* increased proliferation of sertoli cells TM4 in *in vitro* studies (Osibote et al., 2011) but not in humans treated for 72 days (Ojekale et al., 2006). In addition, it has anti sickling and anti-bacterial properties (Kone et al., 2004; Moody et al., 2003) as well as to treat trypanosomiasis (Atawodi et al., 2002). Most importantly, *C. populnea* had no adverse side effects after long term administration to Rabbits (Ojekale et al., 2007). While *C. ibuensis* is used to treat gastrointestinal problems (Irvine, 1961), rheumatism and arthritis (Dalzeil, 1958). In Congo, *Cissus rubiginosa*, is used as anti-dysentery and anti-diarrhoea agent (Otshudi et al., 2000). *Cissus rotundifolia* from Africa and Asia shows anti-diabetic (Onyechi et al., 1998) as well as anti parasitic properties (Alzoreky and Nakahara, 2003). In the Caribbean islands of Trinidad and Tobago, *C. verticillata* is used as an anti-diabetic agent and to treat urinary problems (Lans, 2006). Moving

on to the mainland of South America, in Brazil, *Cissus sycooides* is commonly used as vegetal insulin (Salgado et al., 2009). Of these reports, the most studied are *C. quadrangularis* for obesity, fracture healing and bone diseases and *C. sycooides* as an anti-diabetic agent. We have compiled all the related reports for these two species in this review with an attempt to determine the possibility of using these plants and plant compounds as therapeutic agents to treat or prevent obesity, bone related disease and diabetes.

Cissus quadrangularis (CQ)

C. quadrangularis (CQ) is promoted as a weight loss agent. CQ by itself or in formulations like Cylaris and CORE and in the combination with *Irvingia gabonensis* reduced body weight (Hasani- Ranjbar et al., 2009; Oben et al., 2006; Oben et al., 2007; Oben et al., 2008). In addition to weight reduction, CQ also reduced blood glucose levels and serum lipids (Oben et al., 2006). It also alleviated insulin resistance and scavenged free radicals (Chidambaram and Carni, 2010). Antioxidant and antimicrobial activity (Chidambara et al., 2003) are also reported with CQ consumption. CQ shows gastroprotective (Jainu and Devi, 2004, 2005, 2006; Jainu et al., 2006) and hepatoprotective properties (Viswanatha et al., 2010), as well as suppresses chronic ulcers (Jainu and Mohan, 2008; Jainu et al., 2010). CQ is also reported to reduce hemorrhoids (Panthong et al., 2007), however this claim is controversial (Panpimanmas et al., 2011). CQ also demonstrates anti-inflammatory and analgesic properties (Panthong et al., 2007; Vijay and Vijayvergia, 2010). In rats, CQ reduced edema of the ears and paws. In addition, CQ also shows anti-tumor activity (Nalini et al., 2011).

In Ayurvedic medicine, the extract of CQ is used to enhance bone fracture healings. In the 1960's several studies using animal models have shown that CQ increased the fracture healing process, by accumulation of mucopolysaccharides at the site of bone fracture and also hastened the calcification process (Udupa et al., 1961; Singh and Udupa, 1962) and increased the tensile strength of the bone in rats (Udupa and Prasad, 1964a,b). There was enhanced fracture healing in dogs after intramuscular injections of aqueous of CQ (Chopra et al., 1975, 1976). Ethanol and petroleum extracts of CQ completely restored the biomechanical properties and structure of the bone in rats (Shirwaikar et al., 2003; Potu et al., 2010, 2011). Petroleum extracts also reduced Trap activity and increased alkaline phosphatase activity, histochemically, in ovariectomized rats (Potu et al., 2009). Even fetal bone development was stimulated when pregnant rats were given this extract (Potu et al., 2008).

In *in vitro* studies using a couple of cell lines, there is evidence that CQ may be of benefit to the bone. Bone

Table 1. List of different species of *Cissus* genus used in medicine.

S/N	Species	Location	Common name	Medicinal property	References
1	<i>C. araloides</i>	Cameroon	Kindamina	Anti-microbial	Assob et al. (2011)
2	<i>C. assamica</i>	China, India, Cambodia, Bhutan, Nepal, Thailand		Anti-snake venom	Yang et al. (1998)
3	<i>C. debilis</i>	Cameroon		Anti-cell proliferation	Line-Edwige et al. (2009)
4	<i>C. hamaderoensis</i>	Yemen		Anti-viral, anti ACE, NGP and APN	Oleski et al. (2006)
5	<i>C. hypoglauca</i>	Australia	Jungle grape, Water vine, five leaf water vine	Sore-throat	Lassack (1997)
6	<i>C. ibuensis</i>	Nigeria (Africa), Niger, Ghana		Rheumatism, arthritis, Gastrointestinal tract	Dalzeil (1958) and Irvine (1961)
7	<i>C. populnea</i>	Nigeria (Africa)	Food gum, Ager, Okoho	Increase proliferation of sertoli cells	Osibote et al. (2011)
8	<i>C. quadrangularis</i>	India, Sri Lanka (Asia)	Veldt grape	Fracture healing, increases bone strength, protects bone from postmenopausal bone loss	Udupa and Prasad (1962; 1964)
9	<i>C. rotundifolia</i>	Africa, South America	Arabian wax Cissus, Peruvian grape Ivy	Anti-parasitic, anti-diabetic	Onyechi et al. (1998) and Alzoreky and Nakamura (2003)
10	<i>C. rubiginosa</i>	Congo		Anti dysentery, anti diarrhoea	Otshudi et al. (2000)
11	<i>C. sicyoides</i>	Brazil (South America)	Princess vine, curtain ivy, millionaire vine	Anti-diabetic, diuretic, anti-inflammatory, anti-convulsant, anxiolyte	Salgado et al. (2009)
12	<i>C. verticillata</i>	Trinidad and Tobago (Caribbean)		Anti-cholesterol, anti-diabetic	Lans (2006)

marrow mesenchymal stem cells showed that petroleum ether extracts of CQ stimulated osteoblastogenesis (Potu et al., 2009). Murine osteoblastic cells exhibited MAPK dependent increase of alkaline phosphatase after treatment with ethanol extracts of CQ (Parisuthiman et al., 2009). Rat calvarial cells treated with compound isolated from CQ showed increased mineralization (Kumar et al., 2010). SaOS₂ cells, when treated with ethanolic extracts of CQ increased mRNA and proteins related to the bone formation pathway and IGF-I, IGF-II and IGF binding protein

(Muthusami et al., 2011a, b).

CQ can influence bone by several mechanisms. At the fracture site, it increases mucopolysaccharides and mineral that is deposited during the bone formation phase. In addition, it also reduces bone resorption, maybe by inhibiting the activation of NF- κ B (Srisook et al., 2010), at the endocortical surface and protects the trabecular microarchitecture in the long bones. CQ is also anti-inflammatory (Panthong et al., 2007), so it may reduce the formation of pro-inflammatory cytokines that stimulate bone

resorption, thereby reducing bone loss. It may also act as an estrogen receptor agonist as the Friedlin rich fraction of CQ increases estrogen in rats (Aswar et al., 2010).

***Cissus sicyoides* (CS)**

As mentioned earlier, in Brazil, *C. sicyoides* (CS) has shown several health benefits. Extract of this plant is used to treat diabetes, rheumatism, epilepsy and stroke. *Ex vivo* experiments on aortic

rings of guinea pigs showed that the aqueous extracts of shade dried leaves from this plant, enhanced entry of extracellular calcium into cells and recycled internal calcium deposits in the endoplasmic reticulum (Garcia et al., 1997). It is also reported to have anti-oxolytic and anti-convulsant properties on mice (Almeida et al., 2009). Crude hydroalcoholic extract had sedative effects and reduced anxiety levels. Flavanoids, linalool and α -tocopherol present in the leaves of this plant may be responsible for these activities (Almeida et al., 2009). CS also has anti-inflammatory properties. In mice, there was significant reduction of edema in the ears and paws after treatment with CS (Garcia et al., 2000). Flavanoids, stilbenes and some other compounds isolated from CS inhibit the release of β -hexosaminidase in rat basophilic leukemia cells (Xu et al., 2009). Methanolic extracts of CS also showed anti-allergy properties in *in vitro* (Quilez et al., 2004). Anti-mitotic activity of CS was reported in HEp-2 cells (Saenz et al., 2000). It can also reduce gastric ulcers in rodents (Paula et al., 2008).

Perhaps the most popular use of CS is as an anti-diabetic agent. The aqueous extract of the leaves reduced blood glucose levels on Alloxan induced diabetic rats (Viana et al., 2004) in a short term (7 days) and long term (30 days) studies (Pepato et al., 2003). More evidence on the anti-diabetic properties of CS in rats is reported by Salgado (Salgado et al., 2009) in rats. Another study showed that leaf extracts of CS had anti-diabetic properties in both rats and mice (Mori et al., 2001). Among the reports that support CS as having anti-diabetic properties, there are reports that hydroalcoholic or alcoholic extracts of the leaves of CS does not show hypoglycemic effects in rats (Beltrame et al., 2001). The major difference between these studies is the use of aqueous extract of leaves vs alcoholic extracts. The aqueous extracts show hypoglycemic activity suggesting that compounds extracted in water are potent anti-diabetic agents. Interestingly, humans also consume the aqueous decoction and have shown lower glucose levels. There are several thoughts on the mechanism by which CS reduces blood glucose. As CS has anti-oxidant properties, it may reduce the oxidative stress induced by diabetes (Khalil et al., 2008). It may also increase the conversion of circulating glucose to glycogen and stored in the liver (Salgado et al., 2009) or it may inhibit gluconeogenesis (Pepato et al., 2003).

CHEMICAL CONSTITUENTS OF PLANTS FROM THE GENUS *CISSUS*

The chemical constituents of plants belonging to the genus *Cissus* are also reported. Six compounds have been isolated from *C. pteroclada* – β -sitosterol, bergenin, 11-O-galloylbergenin, 11-O-(4-hydroxy benzoyl) bergenin, gallic acid and daucosterol (Chi et al., 2011). The leaves of *C. ibuensis* contained Quercetin 3-O-

rutinoside and flavanoids after ethanol extraction and butanol fractionation (Ahmadu et al., 2010). *C. assamica* yielded 8 compounds including lupeol, n-hexacosic acid, isolariciresinol-9-O-beta-D-glucopyranoside, dauco stenin, 3,3'-dimethyl ellagic acid, β sitosterol and bergenin (Xie et al., 2009). Stilbene C glucosides were reported in *C. repens* (Wang et al., 2007). Apart from flavanoids, sterols, triterpanoids, stilbenes, iridoids and 3, 3', 4, 4' tetra hydroxybiphenyl were also isolated from *C. quadrangularis* (Deokule and Waghmare, 2004; Mehta et al., 2001; Nagani et al., 2011; Singh et al., 2007; Srivastava et al., 2011). The chemical constituents of *C. sycoides* include flavonoids, stilbenes, steroids, coumarin, triterpenes, tannins and saponins (Beltrame et al., 2002; Otshudi et al., 2000; Xu et al., 2009). *C. rheifolia* leaves have quinolizidine alkaloids, flavanoids, terpenoids (Saifah et al., 1983) and the stem wood of *C. pallida* has stilbenes, triterpenoids and steroids (Khan et al., 1986). Many of the compounds isolated from the plants belonging to the genus *Cissus* have therapeutic effects.

Flavanoids have anti-inflammatory (Yamamoto and Gaynor, 2001), anti-microbial (Cushnie and Lamb, 2005, 2011), anti-cancer (Sousa et al., 2007) and anti-diarrheal (Schuier et al., 2005) properties. Triterpenoids have been well studied for their pharmacological activities and are known to have anti-inflammatory properties and are used as anti-cancer drugs and they target the phospholipases, cyclooxygenase and lipoxygenase (Braca et al., 2010). Stilbenes also have been widely studied and can induce apoptosis and are anti-inflammatory, anti-cancer and an estrogen receptor α agonist (Rimando and Suh, 2008). Iridoids also have a broad variety of use in different disease conditions. They are hepatoprotective (Yang et al., 1983) cardioprotective, anti-microbial, hypolipidemic, hypoglycemic anti-cancer etc (Tundis et al., 2008). Therefore, plants from the genus *Cissus* may be a good source of different compounds whose therapeutic use is already established, strengthening the claim that these plants may serve as good source of medicines.

CONCLUSION

At least a dozen plants from the genus *Cissus* have been used for treating various ailments in traditional medicines in different parts of the world. A detailed investigation of the mechanism will further authenticate the use of these plants as medicines. The most widely studied plants from the *Cissus* genus are CS and CQ. With the information we have now we can safely say that CS has more potential as an anti-diabetic agent while CQ has more potential as a bone protective agent. What is more exciting is that side-effects are minimum proven by the human consumption of CS and high doses of CQ (5000 mg/kg b wt) (Jainu and Devi, 2006), in an animal model, not exhibiting any adverse side-effects. Although, further

studies are required to determine the concentration and detail the mechanisms by which they act, this group of plants may serve as a potential source for drugs to treat diabetes and bone loss and with more elaborate research may be used for treating other ailments like gastrointestinal protection and inflammation.

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