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"Review on: Phytochemistry,medicinal uses and pharmacological activities of Cissus Quadrangularis"

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Abstract

Cissus quadrangularis L. is a perennial herb of the Vitaceae family and is utilized comprehensively as a medicinal herb in most tropical regions by various names. This herb is documented to possess a wide-ranging ethnomedicinal uses in malaria, fever, epilepsy, gout, piles, skin diseases, colic, etc. Aim of the review: A organized summary of the botany, traditional uses, phytochemistry, pharmacology, toxicology, available marketed formulations and filed patents were presented to explore the future therapeutic potential and scientific potential of this herb. It is used in indigenious system of medicine like ayurveda, siddha, unani and homoeopathy. The whole plant is used in treatment of asthma, powdered root is specifically used in treatment of bone fractures. The genus Cissus belong to the family

Vitaceae. It has 13 genera and 800 species in the world. It's found in tropical regions of India, Srilanka, Africa, Arabia, and South Asia. In India 8 genera and 63 species have been distributed and identified. The Cissus species are mostly climber with tendril and shrub and highly medicinal valuable. It contains several secondary metabolites like an ascorbic acid, flavonoid, terpenoids based on its phytochemical investigations. Extracts and powders of Cissus quadrangularis have been used for many years to promote bone and tissues healing, as an analgesic, to treat infections, as an anabolic, and to promote weight loss and weight management. This review summarizes the studies in animals, humans and in vitro systems that have been conducted to determine the efficacy and safety of various Cissus preparations. Cissus extracts appear to be exceedingly safe and free of adverse effects at the doses commonly used.

Keywords

Genus Cissus, Collagen synthesis, Cissus quadrangularis, Cissus sycoides, Adaptogen

Introduction

Plants are the major resources of medicines. Recently there has been a tremendous increase in the use of plant based health products in developed countries resulting in an exponential growth of herbal products globally. According to WHO more than 80% of the world's population relies on traditional herbal medicine for their primary health care [1]. Plants continue to serve as possible sources for new drugs and chemicals derived from various parts of plants [2]. However, due to over population, urbanization and continuous exploitation of these herbal reserves, the natural resources along with their related traditional knowledge are depleting day by day [3].One of the many plants which are being evaluated for their therapeutic efficacies is the genus Cissus species. These species all belong to the family Vitaceae.Cissus quadrangularis L. is commonly known as Edible Stemmed Vine in English. It is an annual or perennial herb, entire leaves, buff colored with greenish ting and requires warm tropical climate and propagated by stem cuttings in month of June and July. Although it has many medicinal properties, it is particularly used to reduce body weight, anthelmintic, muscular pains, asthma, broken bones, antiulcer, anti hemorrhoidal, antimicrobial etc. Cissus repens Lamk. is distributed in India to Southern China, Philippines, Malaysia, and Taiwan [4].The roots and stems of Cissus repens Lamk. are used for snake bites, rheumatic pain, and carbuncles in folk medicine, and the stems are also applied to the treatment of nephritis, longterm coughs, and diarrhea. Cissus aralioides Planch. Stem can climb up to a length of 30 feet, and it has five leaflet and round berries. The matured berries are bluish- purple in Color and it is one-seeded. They are found mostly in Tropical Africa [5]. The plant products are used in soap, cosmetic and pharmaceutical industries [6]. The leaves are well known for its nutritional and medical properties. The Cissus rependaVahl. is a perennial climber generally grow wild in swamp forest and its tendered leaf is used popularly as traditional vegetable by various tribes of upper Assam and adjoining hilly states of North-Eastern part of India [7,8].

Fig :- Cissus quadrangularis

Cissus populnea Guill & Perr.Leaves, stem and root appear to be rich in bioactive compounds which are widely used for various activities including traditional medicines [9]. Cissus sicyoides is distributed throughout the tropics, mainly in Brazil and the Caribbean [10]. Cissus arnottiana is an erect woody shrub

distributed throughout India. The plant reported as bruised roots are applied for rheumatic swellings [11]. Cissus cornifolia is commonly found in Zimbabwe, is traditionally used by the Shona speaking people as a remedy for gonorrhea while the leaf-sap is used among the Tanganyika as a sedative in cases of mental derangement. The root- decoction is also used for malaria, septic tonsil, diabetes, cardiac problems and pharyngitis [12]. Cissus discolor is used to treat stomach troubles and is also applied to itching sores [13].

Vernacular names :

English : Edible stemmed vine, Adamant creeper, Bone setter

Hindi : Hadjod, Hadjora, Hadsarihari, Harsankari, Kandvel

Bengali: Har,Harbhanga,Hasjora,Horjora

Gujarati : Chodhari, Hadsand, Hadsankal, Vedhari
Kanada : Mangarahalli
Malyalam: Cannalamparanta, Peranta
Marathi: Horjora, Harsankar, Kandavel,
Tamil : Piranti, Vajjravalli
Telugu : Nalleru, Nelleratiga, Vajravalli
Oriya : Hadavhanga **Urdu :** Harjora, Hadsankal

History of plant :

Cissus quadrangularis is a succulent vine from Asia and Africa. It is one of the most commonly used medicinal plants in Thailand. It is traditionally used in African medicine as well as in Ayurveda. All parts of the plant are used for medicine. Cissus quadrangularis is a traditional medicine usually said to come from Ayurveda but appears to have a wide range of locations which have used it medicinally due to its growing in numerous locations. Traditionally it was mostly used in treatment of female disorders (menopause, libido, and menstrual disorders) and treating bone disorders (increasing bone mass or accelerating fracture healing rates) which gives it the traditional name of the 'Bone Setter' (Hadjod), some other traditional usages are in regards to its supposed antiulcer properties, Antihemorrhoid properties, pain relieving properties and wound healing properties [14].

Taxonomy of Cissus quadrangularis :

Kingdom : Plantae

Subkingdom : Tracheob
Super division : spermatophyta
Division : Magnoliophyta
Class : Magnoliopsida
Subclass : Rosidae

Order : Vitales

Family : Vitaceae

Genus : Cissus

Parts of plant :

Leaf

Flower

Fruit

Whole plant

Fig: Parts of Cissus Quadrangularis

Mechanism of Action CQ :

IGF-I and IGF-II are abundant in human bone and stimulate the proliferation and dif- ferentiation of human osteoblasts. IGFs enhances the production of many bone matrix proteins, Runx2 and ALP. Multiple signaling pathways that affect the functioning of osteoblasts are regulated by Runx2. Several genes such as Type I collagen, ALP and osteocalcin are highly expressed in the differentiation and mineralization period.

RT-PCR analysis studies revealed that mRNA expression of growth factors (IGF-I, IGF-II and IGF- IR) in cells was increased when treated with CQ compared with control.

Anabolic action of CQ in human osteoblast-like cells may be mediated through Runx2 transcriptional activity. Through this pathway signaling, mRNA expression of ALP, collagen and their protein levels increased when cells treated with CQ extracts.

CQ diet also intensifies the bone mineralization by accumulating the mucopolysaccharides and thus increases the bone mineral content and bone mineral density. In this way, it enhances bone formation.

Specific pro-inflammatory cytokines like IL-1β, IL-6, IL-11, and TNF-α play a key role in bone remodeling processes by activation of osteoclasts and thus enhances bone resorption. IL-1β activates NF-κβ and MAPKs through TRAF-6 and may also stimulate PGE2 and RANKL expression in osteoblasts. IL-6 is synthesized by osteoblasts and induce the formation of osteoclasts. CQ significantly reduce the serum level of proinflammatory cytokines IL-1β, IL-6 and TNF-α. Thus, inhibit bone loss. So according to literature surveys, CQ act as anabolic agent as well as the antiresorptive agent. Mechanism of action of CQ is also depicted in Fig.[15,16] .

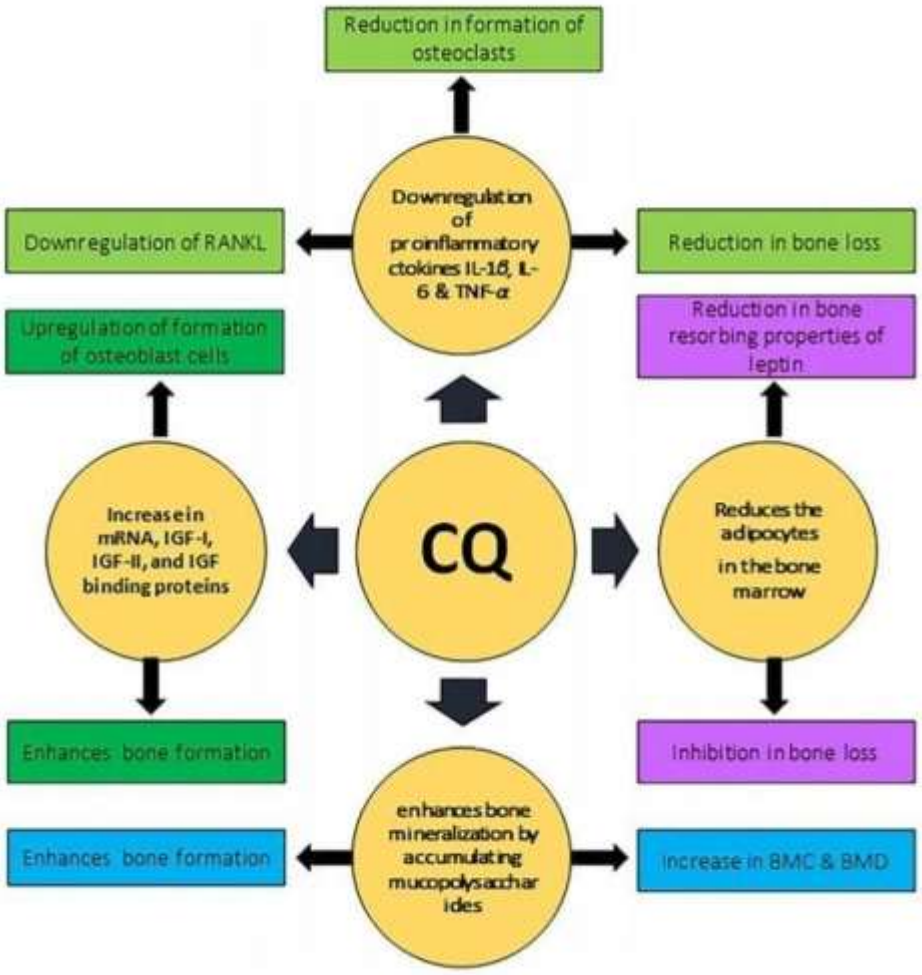

Fig : Mechanism of Action or Possible Different Route of CQ

Medicinal use of CQ :

Traditional uses :

It is used to cure diseases like Asthibhagana (dislocation of joints), Agnimandhya (digestive insufficiency), Ajeerna (indigestion), Arsha (Piles), Krimi (Worm infestation), Vatarakta (Gout), Firanga (syphilis), Updanshya (chanchroid), Raktasrava (blood-letting), Pradara (menorrhagia) [17].

Therapeutic Uses :

It is useful in the treatment of Arsha (Piles), Asthibhagna (Bone fracture), Krimi (Worm infestation), Netraroga (Diseases of the eye), Shwasa (Asthma), Urustambha (Stiffness in thigh muscles), and Vrana (Ulcer) [17].

Traditional uses :

In Ayurveda :

- Asthiyuk -strengthens bones.
- Sara -induces mobility, causes diarrheoa, purgation, relieves constipation
- Krumighna -Relieves worm infestation, useful in infected wounds
- Amaghna -Relieves ama – a product of indigestion and altered metabolism.
- Vrushya -aphrodisiac, improves vigor
- Pachana - Digestive, relieves Ama Dosha
- Pittala -Increases Pitta Dosha

It is used in the treatment of obesity, gout, syphilis, Veneral diseases, leucorrhea, worm infestation, anorexia, diabetes, peptic ulcer, haemorrhoids and high cholesterol. It is also used as a body building supplement. In North eastern states of India, its stem is used as a vegetable. In Siddha system of medicine, it is used for healing bone fracture, piles, as an anti-aging herb, in Asthma, cough and gonorrhoea [18].

In Unani :

Cissus quadrangularis is a plant found in hotter parts of India. Powdered root is used as a specific for the fractures of the bones, with the same effects as plasters externally. Dose of the powder is 30-40 grains. “Leaves and young shoots are frequently taken with curry in Southern India. In Madras, young shoots of the plant are dried and powdered, are burnt to ashes in a closed vessel and administered in dyspepsia and

indigestion" and certain bowel complaints. Leaves and young shoots are also considered as powerful alternatives. Juice of stem is dropped into the ear in otorrhoea and into the nose in epistaxis. It has also a reputation in scurvy and in irregular menstruation. Stem beaten into a paste is used to treat asthma [19].

Sr. no	Part of herb	Chemical constituents	Medicinal uses	Author and year	Reference
1	Steam	Triterpenoids, flavonoids, stilbenes, alkaloids, tannins	- Bone healing & fracture recovery - Anti-inflammatory - Antioxidant - Antimicrobial	Shukla et al. 2013	[20]
2	Leaf	Flavonoids, tannins, polyphenols	- Anti-inflammatory - Antioxidant - Antimicrobial	Gupta et al. 2015	[21]
3	Root	Triterpenoids, steroids, alkaloid	- Antioxidant - Hepatoprotective - Anti-inflammatory - Pain relief	Pandey & Tripathi et al. 2019	[22]
4	Whole plant	Flavonoids, phenols, alkaloids, saponin	- Weight loss - Bone health - Anti-diabetic - Antioxidant - Anti-cancer	Krishna et al. 2020	[23]
5	Fruit	Resveratrol, flavonoids, tannin	- Antioxidant - Cardioprotective - Anti-inflammatory	Rajendran et al. 2016	[24]
6	Seed	Fatty acids (e.g., linoleic acid), flavonoids, alkaloids	- Antioxidant - Skin health - Anti- inflammatory - Cardioprotective	Kaur et al. 2017	[25]

Chemical constituents :

It is unclear specifically which chemical constituents are responsible for the physiological effects produced by Cissus quadrangularis extracts. Cissus extracts are frequently standardized to 2.5 or 5% ketosteroids. Unfortunately, the assays commonly used to determine ketosteroid levels are non-specific, and as a conse quence, the actual level of ketosteroids present in Cissus extracts in may be much lower that stated. A number of steroids including b-sitosterol, daucosterol (a glycoside of b-sitosterol), d-amyrin, d-amyrone, tarexerol and freidalin have been isolated from Cissus with b-sitosterol being the most prominent. Of these, only d- amyrone and freidalin are ketosteroids [26].

Phytochemistry :

The species of Cissus genus are often used as medicinal plants because they contain vitamins, proteins, carbohydrates and polyphenols [27]. Leaves of the Cissus contain Sterols, Quinones, and Phenolic compounds, Anthocyanins, Saponins and f lavonoids are also found in the plants leaves and fruits [28]. Phytochemical studies on methanol extract revealed the presence of triterpenes including α- and β-amyrins, β-sitosterol, ketosteroids, phenols, tannins, carotene and vitamin C [29,30]. Seven alicyclic lipids constituents have also been reported from Cissu squadrangularis [31]. Several un symmetric tetracyclic triterpenoids such as d-amyrin, onocer- 7ene-3a, 21b-diol, d- amyrone and 3,3',4,4'-tetra hydroxyl biphenyl, 3,3',4,4' tetrahydroxybiphenyl have been isolated from plant and were quantitatively determined by HPTLC and HPLC methods in samples collected from five different geographic zones of India [32,33].Several other constituents such as flavonoids quercetin and kaempferol and , stil bene derivatives, Cissus quadrangularins A,B,C [34-35] and many others e.g. resveratrol, piceatanon, pallidol, perthenocissi [35,36] and phytosterols [37] have been isolated from plant. Stem extract contains a high percentage of calcium ions and phosphorus, both essential for bone growth. Stem having Calcium ions and phosphorus [38] Calcium oxalate, [39] methyl tritiacontanoic acid, taraxerylacetate, taraxerol, Iso pentadecanoic acid [40], Saponins and Phenol [41]. While aerial parts having 7-Oxo- Onocer-8 ene-3 β 21 α diol [42]. Root powder having potassium, calcium, zinc, sodium, iron, lead, cadmium, copper and magnesium [43]. Ash of plant having Sodium, potassium, magnesium and calcium, potassium tartrate . leaves having resveratrol, piceatanon, pallidol, parthenocissus, alicyclic lipids. Phytochemical screening of Cissus quadrangularis revealed high contents of ascorbic acid, carotene, anabolic steroidal substances, and calcium. The stem contains two asymmetric tetracyclic triterpenoids, and two steroidal principles. The presence of β-sitosterol, δ-amyrin, δ amyrone, and flavanoids (quercetin) having different potential metabolic and physiological effects have also been reported [44, 45]. Several studies have been performed on the composition of Cissus repens as a number of compounds have been identified such as ursolic acid, Asiatic acid, lupeol, friedilin and epifriedelanol . Plants CissusaralioidesPlanch. are end owed with various phytochemical molecules such as vitamins, terpenoid, phenolic acids, lignins, stilbenes, tannins, flavonoids, quinones, coumarins, alkaloids, amines, betalinins, and other metabolites [46,47].

Phytochemistry studies identified and isolated from the aerial parts of Cissuss icyoides a new coumarin glycoside 5,6,7,8 tetrahydroxycoumarin- 5β - xylopyranoside[48].

Pharmacological Activities :

Bone Healing Activity :

The main traditional use of Cissus quadrangularis is in the field of bone remineralisation and fracture. It is commonly known as the 'Bone Setter,' the plant is referred to as 'Hadjod' in Hindi because of its ability to join bones. Modern research has shed light on the capability of Asthisanharak to speed up bone healing as it acts as a glucocorticoid antagonist [49].

Anti-Oxidant and Free Radical Scavenging :

Methanol extract of Cissus quadrangularis exhibits strong antioxidant and free radical scavenging activity in vitro and in vivo systems mainly due to the presence of β carotene

[50,51].

Central Nervous System Activity :

The root extract has central nervous system depressant activity indicated by decline in exploratory behaviour. Methanol extract of roots contains saponins which reveal potent sedative activity and also inhibit spontaneous motor activity in mice [52].

Anti-Viral Activity :

Anti-viral activity of partially purified methanolic extract of Cissus quadrangularis was established on both Herpes Simplex Virus (HSV)-1 and -2. Anti-viral activity of the plant activity was assayed using dye-uptake method. The result provided insight into potent antiviral activity of Cissus quadrangularis [53].

Anti-Fungal Activity :

Anti- fungal activity of Cissus quadrangularis extract was established by comparing its activity to fluconazole which was taken a standard drug. The research performed using standard agarwell diffusion method and the activity was quantified by measuring the diameter of the zone of inhibition formed on the surface of petri dishes. The result revealed the effect of Cissus quadrangularis extract against fungal activity and it was found out that diethyl ether extract exhibited promising activity against Aspergillus flavus [54].

Analgesic, Anti-Inflammatory and Stimulatory Activity :

Cissus quadrangularis is potent as aspirin which was taken as standard in the treatment of acetic acid writhing mice, formalin test and tail-flick test in rats. The plant is also effective in the treatment of yeast infection induced hyper-pyrexia [55].

Anti-Pyretic Activity :

The various serial extract of the Cissus quadrangularis when orally administered in albino rats showed a reduction ($p \leq 0.01$) in hyperpyrexia induced by dried yeast injection with activity being pronounced in 18 hrs. This shows the antipyretic activity of Cissus quadrangularis [56].

Anti-Haemorrhoidal Activity :

Anti- haemorrhoidal properties of Cissus quadrangularis extract was studied by measuring the venular activity of its extract on vascular smooth muscles of human umbilical vein. Results showed that the contraction occurring in extract treated smooth muscles was equal to the contraction achieved when treated with standard drug 'daflone' [57].

Anti-Helminthic Activity :

Anti-helminthic activity of Cissus quadrangularis were revealed using stem extract of the plant against earthworms in a study. The effectiveness was measured by the time required by the extract to induce paralysis or cause death in test subjects [58].

Anti-Tumour and Cytotoxic Activity :

Cytotoxic studies of Cissus quadrangularis ethanolic and chloroform extract was validated both on Hela and Vero cell lines in a study, the cell lines were maintained in minimal essential medisina humidified atmosphere. The IC50 Value of extracts was found to be 62.5 µgm/ml and 125 µgm/ml for Hela and Vero cell lines respectively [59].

Anti-Osteoporotic Activity :

C. quadrangularis has been stated in Ayurveda for its anti-osteoporotic activity. The phytoestrogen rich fraction (IND- HE) from the aerial parts of plant reveals its activity. Plant has phytoestrogen and triterpenoides. The phytoestrogen steroids isolated plant illustrates influence on early regeneration and quick mineralization of bone. The ethanolic and petroleum ether extract of C. quadrangularisis L [60].

Anti-Microbial and Anti-Bacterial Activity :

Methanol extract (90%) and dichloromethane extract of stems possess antibacterial activity against S. aureus, E. coli, and P. aeruginosa and mutagenicity against Salmonella microsome. Antimicrobial activity has also been reported from stem and root extract. The alcoholic extract of aerial part was found to possess antiprotozoal activity against Entamoebahistolytica [61].

Gastro-Protective Activity :

C. quadrangularis is L. is rich source of arytenoids, triterpenoides and ascorbic acid, which plays a vital role in human nutrition. Many studies have analyzed and showed the effects against gastric toxicity and gastro protective effect of C. quadrangularisis L. against the gastric mucosal damages induced by aspirin [62].

Anti-Obesity Activity :

Obesity and obesity-related complications (such as metabolic syndrome) are a common problem around the globe. To investigate the usefulness of Cissus quadrangularis in metabolic syndrome, particularly for weight loss and central obesity a randomized, double blind, placebo-controlled study was performed, 123 overweight and obese persons were treated with Cissus for eight weeks, while consuming a normal or calorie-controlled diet [63].

Formulation of CQ :

Sr no	Journal Name	Author and year	Formulation	Chemical constituents	Pharmaco-logical Action	Method of preparation	Ref. no
1	Journal of Herbal Medicine	Smith et al. 2022	Capsule form with powder of *Cissus quadrangularis*	Triterpenoid, flavonoids, alkaloids, resveratrol, vitamin C, phenolic compounds	Anti-inflammatory, antioxidant, bone health promotion, weight loss, wound healing	Powdered *Cissus quadrangularis* mixed with excipients and encapsulated	[64]
2	International Journal of Pharmacognosy	Patel and Sharma et al. 2021	Tablet form with extract of *Cissus quadrangularis*	β-sitosterol, flavonoids, saponins, tannins	Antioxidant, antimicrobial, anti-obesity, anti-diabetic, anti-osteoporotic	Extract preparation through solvent extraction, tablet compression	[65]
3	Phytotherapy Research	Khan et al. 2020	Powdered herb used in traditional medicine	Resveratrol, tannins, alkaloids, flavonoids	Anti-inflammatory, analgesic, antipyretic, wound healing, anti-cancer properties	Herb dried and powdered, used directly as a supplement or in teas	[66]
4	Journal of Medicinal Plants	Gupta and Singh et al. 2019	Ointment containing Cissus quadrangularis extract	Flavonoids, alkaloids, saponins	Anti-inflammatory, analgesic, promotes bone healing	Extract mixed with base ointment, applied topically	[67]

5	Asian Pacific Journal of Tropical Medicine	Li et al. 2023	Syrup with Cissus quadrangularis extract	Vitamin C, flavonoids, alkaloids	Antioxidant, anti-diabetic, supports metabolic health, digestive aid	Syrup formulation with standardized extract	[68]
6	Evidence-Based Complementary and Alternative Medicine	Zhang and Zhao et al. 2018	Cream for topical application	Triterpenoid, resveratrol, flavonoids	Anti-inflammatory, analgesic, enhances wound healing	Extract incorporated into a cream base for topical use	[69]
7	Journal of Ethnopharmacology	Kumar et al. 2021	Tincture or liquid extract	Alkaloids, flavonoids, saponins, terpenes	Anti-inflammatory, antioxidant, antibacterial, supports bone and joint health	Solvent extraction followed by tincture preparation	[70]
8	BMC Complementary Medicine and Therapies	Ali and Rahman et al. 2022	Tablets with standardized Cissus quadrangularis extract	Flavonoids, saponins, alkaloids, resveratrol, tannins	Anti-inflammatory, osteoporotic, analgesic, anti-anxiety	Tablet formulation with excipient blend	[71]
9	Food and Chemical Toxicology	Thomas and Iyer et al. 2020	Liquid extract for oral consumption	Resveratrol, flavonoids, triterpenoids	Antioxidant, anti-inflammatory, hepatoprotective, promotes cardiovascular health	Cold extraction followed by filtration and concentration	[72]

Conclusion :

The present study shows the pharmacological properties of various bioactive compounds present in the plant. The whole plant is used in India for the treatment of various diseases. Ayurveda mentions it as a

tonic and analgesic, and prescribes its use to help heal broken bones, thus its name asthisamharaka . It is used in the treatment of osteoporosis, asthma, cough, hemorrhoids, and gonorrhea. Cissus may be useful not only in building up bones but in improving functional efficiency. Cissus quadrangularis is rich in vitamin C and beta carotene. The extract also neutralize the antianabolic effect of cortisone in healing of fractures, possibly due to its high vitamin C content. The antioxidant potential of the extracts can be assessed by employing different in vitro assays. Cissus quadrancularis possesses various phytochemical and pharmacological properties as discussed in present paper. However more Clinical and Pathological studies should be conducted to investigate the active potentials of bioactive compounds present in this plant.

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