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Review article

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Review on efficacy of *Cissus quadrangularis* Linn. in the treatment of arthritis

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ABSTRACT

The succulent medicinal plant *Cissus quadrangularis* L. belongs to the genus Vitaceae. It's fleshy in nature, a cactus. It is also known as *Vitis quadrangularis*. It is used in Ayurveda as Pachana (digestive aid), Sara (constipation relief), Athiyuk (bone strengthening), Vrushya (Aphrodisiac), etc. It is used to relieve gastritis in Unani. The powdered root is specifically used in the treatment of bone fractures and the entire plant is used in the treatment of asthma. The powder's normal dosage is 30-40 grains. In Southern India, leaves and young shoots are usually taken with curry. In Chennai, in a closed vessel, young shoots of the plant are dried, ground, burnt to ashes. In dyspepsia, indigestion, and some gastrointestinal problems, these ashes are treated. In gastrointestinal therapies, leaves and young shoots are also known to be potent substitutes. Stem juice is lowered into the ear in the otorrhoea and into the epistaxis of the nose. There are many therapeutical applications for the herb. In the ancient Ayurvedic literature, the herb is prescribed as a general tonic and analgesic, with particular curing properties for bone fracture. Helminthiasis, anorexia, dyspepsia, colic, flatulence, skin disorders, leprosy, hemorrhage, epilepsy, convulsions, haemoptysis, cancers, chronic ulcers, swelling are believed to be beneficial throughout the herb. Scientists have made attempts to test the potency of the plant by scientific biological screening following numerous folk statements for the cure of different diseases. Some important pharmacological activities of the herb, such as antioxidant, free radical scavenging, anti microbial, anti bacterial, bone healing, anti ulcer, analgesic, anti inflammatory and diuretic, were disclosed in the literature scrutiny. In this study, it is possible to determine the future application of the plant in pharmaceuticals or as an agricultural resource. The present analysis is an effort to illustrate phytochemicals, diverse common applications and *Cissus quadrangularis* L. pharmacological reports.

Keywords: *Cissus quadrangularis* L., Osteoarthritis, Bone healing, Convulsion, Haemoptysis, Tumors, Chronic ulcers.

INTRODUCTION

Cissus quadrangularis (Linn) Is commonly used in India by average income population to facilitate fracture healing and is known as "Hadjod." It is also called the Wall of the *Vitis quadrangularis*. It belongs to the Vitaceae family. It is a popular perennial climber which, especially in tropical regions, is distributed throughout India. The plant is widely known in Sanskrit as Vajravalli, Marathi as Kandvel, Punjabi as Haddjor, Oriya as Haddhanga, Gujarati as Vedhari, Tamil as Perandi, Telugu as Nalleru and Veldgrap as Edible Stemmed Vine in English. It needs a warm tropical climate and is propagated in June and July by stem cuttings. It is a climbing herb, a simple tendril, and having opposite the branches.

The morphology of the leaves shows or lobed leaves, cordate, narrowly ovate or reniform, serrate, dentate, often 3-foliolate and glabrous. Small, greenish white, bisexual, tetramerous flowers, opposite to the leaves, in umbellate cymes. Calyx has the shape of a cup. Fleshy berries, succulent, very acrid, dark purple to black, one seeded, fruit globose or obovoid; seeds ellipsoid or pyriform. The stem is greenish-colored buff, dichotomously branched, sub-angular, glabrous, fibrous and smooth. [1,2]. Hyperglycemia, mediated by diabetes, raises the risk of bone osteoporosis and other pathological complications. Owing to the inactivation and death of pancreatic beta cells, bone loss during type I diabetes mellitus is caused by lack of insulin. In exchange, this is accompanied by increased blood glucose that induces osmotic shock, altered proliferation, and mediated bone cell apoptosis with decreased bone remodeling. In the Indian subcontinents, *Cissus quadrangularis* Linn. (Vitaceae family) commonly referred to as Hadjod is well known for its anti-resorptive and bone healing properties. *Cissus quadrangularis* (CQ) has been very well shown for estrogen deficient osteoporosis because of its osteogenic activity. [3,4]

Uses of *Cissus quadrangularis*

In particular, *Cissus quadrangularis* is used to treat the following conditions: haemorrhoids, obesity, allergies, asthma, bone loss, gout, diabetes, high cholesterol. While CQ has been shown to help treat some of these conditions, there is either a lack of research on some of its uses or no benefits have been shown. For example, one study of 570 individuals showed that CQ was no more effective at mitigating haemorrhoid symptoms than placebo.

The Health Benefits of *Cissus quadrangularis*

A folk medicine *Cissus quadrangularis* has used for bone/ joint wellbeing and weight loss that has long been used.

Bone Health

Cissus quadrangularis showed benefit in osteoporosis prevention, a report published in *La Clinica Terapeutica* in 2011 indicates. The study examined mice given either as the drug raloxifene for osteoporosis or a mixture of raloxifene and a CQ extract. Although there were no substantial differences in blood calcium levels after one-month, cortical bone (the strong outer part of the bone) and trabecular bone (the 'spongy' inner bone) rats given raloxifene and CQ extract had higher rises than those given raloxifene alone. In a similar research published in the *Journal of Cellular Biochemistry*, scientists stated that increased osteoblast development occurred in human bone cells exposed to CQ in the test tube (the cells accountable for formation of new bone).

Traditional Uses

The roots and branches are most effective in the healing bone fracture. The stem is bitter; and administered internally and topically to broken bones also used in back and spine complaints. For muscle pains, a stem paste is helpful. The plant use has been reported in Ayurveda for osteoarthritis, rheumatoid arthritis, and osteoporosis therapy. For the prevention of scurvy, menstrual problems, otorrhoea and epistaxis, the stem juice of the plant is used. For the treatment of gonorrhoea, the use of sap with tamarind was documented in East Africa. To encourage the flow of milk, the herb is fed to cattle. Plant ash is useful as a supplement for baking powder. [5].

Therapeutic Uses

Traditionally used to treat gastritis, bone breaks, skin lesions, constipation, eye diseases, piles, anemia, asthma, prolonged menstruation, burns and wounds, the stout, and fleshy quadrangular stem is used. Strong alternatives are the leaves and young shoots. In the treatment of hemorrhoids and some bowel infections, powder is given. In scurvy and erratic menstruation, stem juice is helpful, whereas in asthma, the stem paste boiled in lime water is given. *Cissus quadrangularis* Linn. has strong antimicrobial, anti-ulcer, antioxidant, anti-osteoporotic, gastroprotective, cholinergic and beneficial impact on cardiovascular disorders and fracture healing properties. [6]

Uses for the cracks of the limbs

Ayurvedic medicines with Lakshadi Guggul component *Cissus*: commonly used in the treatment of bone-related diseases and fracture recovery in Ayurvedic. Panchajeeraka Gudam Zeotone Soft Gel Capsule: An important Ayurvedic drug for post-natal treatment, suitable for digestive and respiratory diseases. It's given in the form of herbal jam [7]. A plant found in hotter areas of India is *Cissus*

quadrangularis in Unani. The powdered root is used for the cracks of the limbs, and has the same results as the exterior plasters. The powder dosage is 30-40 grains. "In Southern India, leaves and young shoots are usually taken with curry. Young shoots of the plant are dried and powdered in mortar, burned to ashes in a closed vessel and administered for dyspepsia indigestion and bowel complaints. Often, leaves and young shoots are known as good alternatives. Stem juice is lowered into the ear in the otorrhoea and into the epistaxis of the nose. It also has a reputation for scurvy and uneven menstruation. To cure asthma, a stem pounded into a paste is used. Somachic storage of stem prepared by boiling it in lime water is helpful [8].

Effect on adjuvant induced arthritis

In both formaldehyde-induced and adjuvant-induced arthritis, *Cissus quadrangularis* hydroalcoholic extract (CQHE) inhibited joint swelling in a dose-dependent manner. TNF-, oxidative stress, and synovial expression of inflammatory and angiogenesis markers were all decreased by CQHE therapy. Chronic administration of CQHE did not induce any physiological or pathological changes in normal rats in a subacute toxicity sample. [9]

In vivo Studies on Antiarthritic Activity

At a dosage of 100 mg/kg body weight, the Active Fraction of *Cissus quadrangularis* (AFCQ) was found to be more effective than the standard drugs celecoxib and methotrexate in inhibiting rat paw edema. The findings revealed that AFCQ has a strong anti-arthritis effect in CFA (cystic fibrosis-related arthropathy) induced arthritis. Histopathology and radiography were used to examine the results.[10]

Effect on osteoarthritis

In a research of the effectiveness of *Cissus quadrangularis* Linn. on the prevention and treatment of osteoporosis was found to alleviate joint pain, swelling, and tenderness despite causing side effects on humans. At the conclusion of the treatment, 60 % of cases of joint pain in groups B and C were relieved, 50 % in group A and the decrease of joint pain was highly substantial in groups A, B, and C (p0.0001). 80 % reduction in symptom of joint swelling in group C, 15% reduction in group A, and 5% reduction in group B, which is very important in group A and group B (p0.001), and highly significant in group C (p0.0001). Tenderness symptom 'C' was reduced in 90% of cases, 'A' in 85% of cases, and 'B' in 10% of cases. When comparing classes, the difference in tenderness is statistically significant (p0.0001). [11]

In vitro anti-arthritis activity

Invitro anti-arthritis activity was observed in both Methanolic Extract of *C. quadrangularis* (MECQ) and Aqueous Extract of *C. quadrangularis* (AECQ) In comparison to AECQ, the MECQ had a strong anti-arthritis effect. The existence of phenolic acid, flavonoid (leuteotin), and sitosterol in the chemical profile may explain the activity. The findings indicate that *C. quadrangularis* Linn. may be used as a potent anti-arthritis in a number of applications. [12].

Anti-arthritis properties of Stem Powder

In the Alloxan-induced model in rats, the stem powder demonstrated promising anti-arthritis activity at dose levels of 300mg/kg body weight. Glycoside 2.34 (g/100g), anabolic steroidal substances, and calcium are all abundant in Hadjod. The stem powder also contains a high concentration of minerals (mg/100g dry matter): calcium (33.3 mg/100g dry matter) (mg), The preliminary physico-phytochemical study of stem powder yielded intriguing findings, which were highlighted and discussed. The current study found that hadjod stem powder could be used to treat inflammation and arthritis, confirming the traditional use of medicinal plants. [13]

In silico Antig out, arthritis activities

The inhibitory activity of xanthine oxidase, proteinase enzyme, protein denaturation, and membrane stabilisation of ethanolic and aqueous extracts of *Cissus quadrangularis* stem in vitro was assessed. Study by, ethanolic extract had stronger anti-arthritis activity in vitro. In the LIGPLOT study, three key components, Pentadecanoic acid, 14-methyl,-methyl ester, 10-Octadecenoic acid, methyl ester, 4-one,2-(3,4-dihydroxyphenyl)-2,3-dihydro-3,5,7-trihydroxy, showed stronger antagonistic activity based on docking score. These three ligands may be established further as a potential anti-gouty arthritis drug. [14]

Bone Turnover activity

C. quadrangularis has been studied for its bone-protective properties and to determine the mechanism by which it benefits bone [15]. Because of decreased inflammation and regulation via the bone morphogenetic protein and Wnt-related integration site (Wnt) signaling pathways, it had preserved the microarchitecture of the long bones from ovariectomy-induced bone loss. The findings suggested that the plant could be used to treat postmenopausal osteoporosis with no side effects. The thickness of both cortical and trabecular bone was substantially increased by a petroleum ether extract of *C. quadrangularis*, indicating the plant's

powerful anti-osteoporotic function. Furthermore, the extract decreased bone loss as demonstrated by femur weight gain, as well as osteoclastic activity, allowing for bone formation [16, 17]. In addition, the percentage of total ossified cartilage (bone) in pups was higher, implying that maternal administration of *C. quadrangularis* petroleum ether extract during pregnancy can stimulate foetal bone growth during the intrauterine developmental period [18]. In another study, ethanol extract showed substantial restorative development, including mineralization and well-distributed osteocytes, as well as full recovery of normal bone features. [19].

The efficacy of *C. quadrangularis* in promoting osteoblast differentiation of murine pre-osteoblast cell lines was investigated by Tasadduq et al. [20]. The ethanolic extract promoted osteoblast differentiation, as evidenced by a significant increase in alkaline phosphatase activity, an early osteoblast marker. Toor, et al. [21] investigated the osteogenic potential of *Cissus*, and found that an ethanolic extract of the plant improved fracture healing and early callus remodeling. The effect of hexane and dichloromethane fractions on the differentiation and mineralization of a mouse pre-osteoblast cell line was also investigated. [22].

The treatment of human osteoblastic SaOS-2 cells with *C. quadrangularis* increased DNA synthesis, suggesting increased cell proliferation [23]. The anabolic effects of *C. quadrangularis* ethanolic extract in human osteoblast-like cells are mediated by increased mRNA and protein expression of Runx2, a key transcription factor involved in the regulation of bone matrix protein, according to the report. *C. quadrangularis* was studied for its osteogenic potential on mandibular fracture recovery, and the plant was found to help reduce pain, swelling, and fracture mobility, as well as speed up the healing of fracture jaw bones. [24].

Anti-inflammatory activity

Panthong, et al. [25] determined the anti-inflammatory activity of *C. quadrangularis*, which is linked to luteolin and -sitosterol. Similarly, at 50 mg/kg dose level, methanolic root extract of *C. quadrangularis* showed potent activity. [26]. In RAW 264.7 macrophage cells, ethyl acetate extract of *C. quadrangularis* inhibited lipopolysaccharide-induced nitric oxide production in a dose-dependent manner [27]. The extract also inhibited inducible nitric oxide synthase mRNA and protein expression, as well as p65 NF-B nuclear translocation. Further research revealed that the extract alone induced heme oxygenase-1 gene expression in a dose- and time-dependent manner at the protein and mRNA levels. Similarly, the plant's acetone extract inhibited cyclooxygenase and 5-lipoxygenase, with IC50 values

of 7 g/ml, 0.4 g/ml, and 20 g/ml, respectively, for cyclooxygenase-1, cyclooxygenase-2, and 5-lipoxygenase. It also had anti-inflammatory properties in the RAW 264.7 cell line, with an IC50 of 65 g/ml. Furthermore, the extract inhibited proinflammatory mediators such as inducible nitric oxide synthase, TNF, nuclear factor E2 p45-related factor 2 translocation and upregulation of Heme oxygenase-1 [28]. The administration of *C. quadrangularis* extract significantly decreased aspirin-induced gastric lesions, which was followed by an increase in uric acid, antioxidative enzymes, SH groups, and a substantial decrease in lipid peroxidase, TNF-alpha, myeloperoxidase, and xanthine oxidase activities [29]. Kanwar et al. [30] confirmed the anti-inflammatory and cartilage-regenerative effects of *C. quadrangularis*, as well as its mechanism of action involving matrix metalloproteinase inhibition and reactive oxygen species. The plant's hydroalcoholic extract decreased serum TNF-, oxidative stress, and synovial expression of inflammatory and angiogenesis markers.[31].

How to use *Cissus quadrangularis*

Cissus quadrangularis stem is fried with ghee in Ayurvedic preparations and administered with milk for the prevention of wound healing, fractures and osteoarthritis. Processed in sesame oil, the *Cissus quadrangularis* stem is very helpful for the care of Sandhivata. Chutney is made with coconut in Tamil Nadu and eaten as a side dish to enhance immunity. Traditional healers use their paste in Kerala to add it to broken or displaced joints. The soup is often served to quicken the process of bone healing. The stems of the plant are consumed as a pickle in Southern India to reinforce the bones and to restore epithelial cell loss in the event of any injury. [13]

In order to verify the ability of the plant in the cure of different ailments, pharmacological uses following the folk and conventional uses of the plant have been scientifically studied in the animal model. Antioxidant and free radical scavenging activity The *Cissus quadrangularis* methanol extract exhibits high antioxidant and free radical scavenging activity largely due to the presence of β -carotene in vitro and in vivo processes. [14,15] *Anti-microbial and anti-bacterial activity.* The methanol extract (90%) and the dichloromethane stem extract have anti-bacterial activity against *S. Hey*, *aureus*, *E. coli*, and *P. aeruginosa*, with *Salmonella microsoma* mutagenicity. [16] Stem and root extract antimicrobial activity has also been reported.[14] The aerial portion of the alcoholic extract was shown to have antiprotozoal activity against *Entamoebahistolytica*. Alcoholic stem extract displayed action against *E. coli*. Methanol and whole

plant dichloromethane extracts were tested for *in vitro* anti plasmodial action. Bone healing operation internally and intramuscularly, paste of the alcoholic extract of the plant allowed quick healing of fracture in albino rats. Ethanol extract (95 percent) improves the growth of fetal femur cortical bone and trabeculae, which can be correlated with a rich content of calcium, phosphorus and phytoestrogenic steroids and has been shown to affect early recovery and accelerated mineralization of the healing mechanism of bone fracture. Ethanol extract (95 %) of the whole plant has anti osteoporotic function in the ovariectomized rat model.[17]

Relevance and importance

Osteoarthritis causes chronic joint pain that can last for years. However, many therapies that have major effects, such as muscle strengthening or aerobic exercise, are often only used for a brief period of time by people (weeks). It's commonly referred to as a "wear and tear" condition. However, osteoarthritis affects the whole joint, not just the cartilage. It induces bone changes and the connective tissues that keep the joint together and connect muscle to bone to deteriorate. Fatigue, poor sleep, anxiety, depression, social alienation, job loss, financial difficulties, and a general decrease in quality of life are all common symptoms of osteoarthritis. So it is very much essential to put forward a new medicinal plant towards its effect on arthritis to explore a new arthritis medicine for the eradication of Osteoarthritis.

CRITICAL DISCUSSION

The review work has illustrated the different methods used already for the assessment of *Cissus quadrangularis* anti osteoarthritis property. The different method includes adjuvant induced arthritis, effect on osteoarthritis patients, *In vitro* anti-arthritis activity, *in vitro* and *in silico* arthritic activities, ovariectomy-induced osteoporosis, murine pre

osteoblast cell line MC3T3-E1 induced model, mineralization potential of murine pre-osteoblast cell line MC3T3-E1, proliferation, differentiation and matrix mineralization of human osteoblast like SaOS-2 cells model, osteogenic agents in mandibular fracture model, osteogenic agent in maxillofacial fracture model. Comparison of the above model with the same extract and finding the most similar and reliable result producing methods could be identified and published as a standard method for the evaluation of medicinal plants against osteoarthritis.

CONCLUSION

The detailed screening of literature available on *Cissus quadrangularis* revealed a curious fact that while the plant is a popular remedy for a variety of diseases and a variety of formulations have been marketed, little attempt has been made by scientific screening to check its purity, consistency, and efficacy. The isolated concepts of *Cissus quadrangularis* need to be clinically tested in future experiments using various laboratory animal models and clinical studies to clarify the molecular mechanism of action in the search for the lead molecule from natural resources. In the world's great ancient cultures, common recipes for the treatment of physical and mental illnesses exist. It is important to note that the *Cissus quadrangularis* plant root and stem extracts have medicinal potency and are considered to have antioxidant, antimicrobial function, and are routinely used to speed up the healing process of bone fracture. For its beneficial medicinal uses, the plant is known as a versatile medicinal plant in both Ayurvedic and modern drug production fields. It is a very rich supply of some minerals that are essential for the human body to function properly. The focus was laid in the present description on the phytochemical constituents and pharmacological function of the *Cissus quadrangularis* Linn. plant.

REFERENCES

- [1]. Pioneer Herb [Internet]. Pioneerherb.com. Available from: <https://www.pioneerherb.com/>
- [2]. Rastogi RP, Mehrotra BN. 995. Compendium of Indian Medicinal Plants, Part I, Publication and information directorate. 104
- [3]. Muthusami S, Senthilkumar K, Vignesh C, Ilangovan R, Stanley J, Selvamurugan N et al. Effects of *Cissus quadrangularis* on the proliferation, differentiation and matrix mineralization of human osteoblast like SaOS-2 cells. *Journal of Cellular Biochemistry*. 2011;112(4):1035-1045.
- [4]. Banu J, Varela E, Bahadur A, Soomro R, Kazi N, Fernandes G. Inhibition of Bone Loss by *Cissus quadrangularis* in Mice: A Preliminary Report. *Journal of Osteoporosis*. 2012;2012:1-10.
- [5]. Gupta M, Nath R, Srivastava N, Shanker K, Kishor K, Bhargava K. Anti-Inflammatory and Antipyretic Activities of β -Sitosterol. *PlantaMedica*. 1980;39(06):157-163.

- [6]. Jainu M, Devi C. Potent Antiulcerogenic Activity of Methanol Extract of *Cissus quadrangularis* by Antioxidative Mechanism. *Journal of Clinical Biochemistry and Nutrition*. 2004;34(2):43-47.
- [7]. Kinghorn A. Quality Standards of Indian Medicinal Plants, Vol. 1 A. K. Gupta, Coordinator (Medicinal Plants Unit, Indian Council of Medical Research). Indian Council of Medicinal Research, Ansari Nagar, New Delhi, India. 2003. xvii + 262 pp. 20 × 27.5 cm. ISBN-0972-7213. *Journal of Natural Products*. 2004;67(4):739-740.
- [8]. Indian MateriaMedica. 8th ed. Popular Prakashan; 1976.
- [9]. Kumar R, Gupta Y, Singh S, Arunraja S. *Cissus quadrangularis* attenuates the adjuvant induced arthritis by down regulating pro-inflammatory cytokine and inhibiting angiogenesis. *Journal of Ethnopharmacology*. 2015;175:346-355.
- [10]. Bhujade A, Talmale S. In vivo Studies on Antiarthritic Activity of *Cissus quadrangularis* against Adjuvant Induced Arthritis. *Journal of Clinical & Cellular Immunology*. 2015;06(03).
- [11]. Viswanath J, Cheekavolu C, Sankaraiah S, Dixit R. Effect of *Cissus quadrangularis* Linn and zingiberofficinalerosc in osteoarthritis patients. *International Journal of Research in Medical Sciences*. 2017;5(8):3540.
- [12]. P V, M S, B S. In vitro Anti-Arthritic Activity of *Cissus quadrangularis* Stem Extract. *Asian Journal of Pharmaceutical and Clinical Research*. 2019;12(1):250.
- [13]. Sabahuddin S, Taur A, Sawate A, Kshirsagar R, Patil B. Studies on effect of artificial sweeteners on the quality of herbal beverage. *Food Science Research Journal*. 2017;8(2):286-289.
- [14]. In vitro and In silico Antigout arthritic activities of Ethanolic and Aqueous stem extracts of *Cissus quadrangularis*- A TLR2 and TLR4 Receptor approach. *Journal of Applied Pharmaceutical Science*. 2018;8(9):15-22.
- [15]. Potu B, Rao M, Nampurath G, Chamallamudi M, Prasad K, Nayak S et al. Evidence-based assessment of antiosteoporotic activity of petroleum-ether extract of *Cissus quadrangularis* Linn. ovariectomy-induced osteoporosis. *Upsala Journal of Medical Sciences*. 2009;114(3):140-148.
- [16]. Potu B, Rao M, Nampurath G, Chamallamudi M, Prasad K, Nayak S et al. Evidence-based assessment of anti osteoporotic activity of petroleum-ether extract of *Cissus quadrangularis* Linn. ovariectomy-induced osteoporosis. *Upsala Journal of Medical Sciences*. 2009;114(3):140-148.
- [17]. Potu B, Rao M, Kutty N, Bhat K, Chamallamudi M, Nayak S. Petroleum ether extract of *Cissus quadrangularis*(LINN) stimulates the growth of fetal bone during intra uterine developmental period: a morphometric analysis. *Clinics*. 2008;63(6).
- [18]. Shirwaikar A, Khan S, Malini S. Antiosteoporotic effect of ethanol extract of *Cissus quadrangularis* Linn. ovariectomized rat. *Journal of Ethnopharmacology*. 2003;89(2-3):245-250.
- [19]. Gu C, Fu L, Yuan X, Liu Z. Promoting Effect of Pinostrobin on the Proliferation, Differentiation, and Mineralization of Murine Pre-osteoblastic MC3T3-E1 Cells. *Molecules*. 2017;22(10):1735.
- [20]. Toor R, Malik S, Qamar H, Batool F, Tariq M, Nasir Z et al. Osteogenic potential of hexane and dichloromethane fraction of *Cissus quadrangularis* on murine preosteoblast cell line MC3T3-E1 (subclone 4). *Journal of Cellular Physiology*. 2019;234(12):23082-23096.
- [21]. Toor R, Tasadduq R, Adhikari A, Chaudhary M, Lian J, Stein J et al. Ethyl acetate and n-butanol fraction of *Cissus quadrangularis* promotes the mineralization potential of murine pre-osteoblast cell line MC3T3-E1 (subclone 4). *Journal of Cellular Physiology*. 2018;234(7):10300-10314.
- [22]. Muthusami S, Senthilkumar K, Vignesh C, Ilangovan R, Stanley J, Selvamurugan N et al. Effects of *Cissus quadrangularis* on the proliferation, differentiation and matrix mineralization of human osteoblast like SaOS-2 cells. *Journal of Cellular Biochemistry*. 2011;112(4):1035-1045.
- [23]. Singh V, Pal U, Mohammad S, Singh N, Dhasmana S, Singh N. Clinical evaluation of *Cissus quadrangularis* and *Moringaoleifera* and osteoseal as osteogenic agents in mandibular fracture. *National Journal of Maxillofacial Surgery*. 2011;2(2):132.
- [24]. Shah K, Brahmshatriya H, Ananthkumar G, Brahmshatriya M. Clinical evaluation of *Cissus quadrangularis* as osteogenic agent in maxillofacial fracture: A pilot study. *AYU (An International Quarterly Journal of Research in Ayurveda)*. 2015;36(2):169.
- [25]. Panthong A, Supraditaporn W, Kanjanapothi D, Taesotikul T, Reutrakul V. Analgesic, anti-inflammatory and venotonic effects of *Cissus quadrangularis* Linn. *Journal of Ethnopharmacology*. 2007;110(2):264-270.
- [26]. Shadmani A, Rizwani G. H, & Ahmed M. Potential anti-inflammatory effect of *Cissus quadrangularis* L. and *Lepedium sativum* L. along with their combination extracts. *Pakistan journal of pharmaceutical sciences*. 2018; 31(5): 2119–2122.

- [27]. Srisook K, Palachot M, Mongkol N, Srisook E, Sarapusit S. Anti-inflammatory effect of ethyl acetate extract from *Cissus quadrangularis* Linn may be involved with induction of heme oxygenase-1 and suppression of NF- κ B activation. *Journal of Ethnopharmacology*. 2011;133(3):1008-1014.
- [28]. Bhujade A, Talmale S, Kumar N, Gupta G, Reddanna P, Das S et al. Evaluation of *Cissus quadrangularis* extracts as an inhibitor of COX, 5-LOX, and proinflammatory mediators. *Journal of Ethnopharmacology*. 2012;141(3):989-996.
- [29]. Jainu M, Devi C. Attenuation of Neutrophil Infiltration and Proinflammatory Cytokines by *Cissus quadrangularis*. *Journal of Herbal Pharmacotherapy*. 2005;5(3):33-42.
- [30]. Kanwar J, Kumar K, Samarasinghe R, Kanwar R, Zhou S, Arya R et al. *Cissus quadrangularis* inhibits IL-1 β ; induced inflammatory responses on chondrocytes and alleviates bone deterioration in osteotomized rats via p38 MAPK signalling. *Drug Design, Development and Therapy*. 2015;:2927.
- [31]. Kumar R, Gupta Y, Singh S, Arunraja S. *Cissus quadrangularis* attenuates the adjuvant induced arthritis by down regulating pro-inflammatory cytokine and inhibiting angiogenesis. *Journal of Ethnopharmacology*. 2015;175:346-355.