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A Review on the Promising Role of Cissus quadrangularis in Bone Fracture Healing

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Abstract:

Since olden times, humans have used plants as a natural source of treatments and therapies. Herbalremedies are popular due to their widespread applications and low risk of side effects. Currently, it is clear that there is a growing emphasis on plant research, and an enormous amount of evidence has been gathered to indicate the immense potential of medicinal plants used in various traditional systems. Every major ancient civilization in the globe has its own traditional methods for treating mental and physical illnesses. *Cissus quadrangularis* extract is one such natural remedy that is popular throughout the Indian subcontinent. It is a succulent herbaceous plant and belongs to the member of the Vitaceae family. It is commonly seen in the hottest parts of India, and is widely known as "Hadjod" in India, which is used to strengthen bones. Its roots and stems are particularlyuseful in repairing bone fractures. Bone fractures are a serious public health concern and a large financial burden worldwide, particularly among people with osteoporosis. Interesting pharmacological and nutritional properties found in the stem of *Cissus quadrangularis* support the maintenance of bone health. *Cissus quadrangularis* powder and extracts have long been used as an anabolic and analgesic, to cure infections, stimulate bone and tissue recovery, and aid in weight loss and management. The use of *Cissus* as an anti-osteoporotic and to improve bone fracture recovery has been validated by both animal and in vitro experiments. *Cissus quadrangularis* is also widely used in traditional medicinal systems for its antibacterial, antifungal, antioxidant, anthelmintic, anti-hemorrhoidal, and analgesic activities. This extract has already been used to create and analyze several dosage forms; however, the most difficult challenge is identifying which dosage forms are stable, effective, and acceptable to patients.

Keywords: Hadjod, *Cissus quadrangularis*, Fracture healing, Fractures, Bone regeneration, Phytoconstituents, Pharmacological activity, Formulation.

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1 Introduction:

Bone fractures are a common and often dangerous medical condition worldwide. They affect people in different anatomical regions and people of different ages and genders because, they can result in absences from work, low productivity, disability, poor quality of life, death, and expensive medical bills, fractures place a heavy cost on people, families, communities, and healthcare systems(Wu et al., 2021).

For decades, traditional medicine, especially plant-based therapies have drawn interest due to its ability to speed up the healing of fractures. One such plant that has been traditionally utilized for bone-related illnesses such as bone fractures and joint injuries is *Cissus quadrangularis*, sometimes referred to as "Hadjod" in India. The perennial plant *Cissus quadrangularis* belongs to the Vitaceae family. It is indigenous to Bangladesh, Sri Lanka, and India. It can also be found in Southeast Asia and Africa. Brazil and the southern United States are the two countries that import it. *Cissus quadrangularis* is a 1.5 m tall plant with branches that have quadrangular sections and internodes that are 1.2 to 1.5 cm broad and 8 to 10 cm long. There's a leathery edge at each angle. At the nodes are the 2 to 5 cm broad-toothed trilobed leaves(Siddiqua et al., 2017). Each node has a tendril coming out of the side that faces it and little white, yellowish, or greenish flower racemes with globular, red-ripe berries(Frank et al., 1995). Its various restorative properties, including wound healing, antioxidant activity, and antibacterial activity, highlight its historical relevance in ancient medical systems like Ayurveda and Unani. Its traditional applications in Ayurvedic medicine include aiding in digestion, strengthening bones, and having aphrodisiac properties. In the Unani system, it is used to cure gastritis and bone fractures. Different components of the plant have been used medicinally by different cultures; for example, dried shoots have been used to treat digestive ailments, powdered roots for fractures, and stem juice for problems with the ears and nose. While recent studies have broadened its medicinal potential to include treating malaria, fever, epilepsy, gout, piles, and skin problems, with a particular focus to its anti-osteoporotic qualities. Modern scientific study has confirmed its usefulness in bone regeneration. *Cissus quadrangularis'* extensive ethnopharmacological significance highlights its everlasting worth as a medicinal plant, connecting conventional knowledge with modern scientific confirmation and presenting it as a flexible botanical resource with significant therapeutic potential. The traditional uses of *Cissus quadrangularis* that have been described and the patent applications for its medicinal qualities provide more evidence of its historical use. This deep historical context has aided in the investigation of the herb's possible uses in the future as well as its scientific relevance (Mishra et al., 2010). Fractures may be costly to one's health and finances. The majority of modern methods for treating bone fractures include allopathic measures, such as immobilization, surgical fixation, and bone grafting. Despite their effectiveness, these methods have certain side effects, which include immunological responses, dermatological issues, and surgical risks. Furthermore, the need for innovative treatment models is highlighted by the financial cost and healthcare consequences related to fractures. In view of this, it becomes even more important to investigate alternative remedies. Renowned for its customary application in bone regeneration, *Cissus quadrangularis* has become a ray of hope within the field of therapy. Using its pharmacological abilities and traditional knowledge, the plant can improve fracture healing, reduce related morbidities, and promote overall health. This review aims to clarify the clinical effectiveness and mechanisms of action of *Cissus quadrangularis* in order to provide insight into its potential therapeutic use in the repair of bone fractures.

1.1 Table 1: Vernacular names of *Cissus Quadrangularis* (Siddiqua et al., 2017):

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
Malayalam	Cannalamparanta, Peranta
Marathi	Horjora, Harsankar, Kandavel, Nalllar

Tamil	Piranti, Vajjravalli
Telugu	Nalleru, Nelleratiga, Vajravalli
Oriya	Hadavhanga
Urdu	Harjora, Hadsankal

1.2 Table 2: Taxonomy of *Cissus quadrangularis* (Siddiqua et al., 2017) :

Kingdom	Plantae
Subkingdom	Tracheobionta
Super division	spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Vitales
Family	Vitaceae
Genus	*Cissus*
Species	*quadrangularis*

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2 Phytoconstituents present in the plant:

Cissus quadrangularis has a very diverse chemical composition where various items like lipids, triterpenoids, steroids, stilbenes, and flavonoids are contained in it. Among the active compounds are iridoid picroside 1; besides there have been recently discovered 6-O-[2,3-dimethoxy]-trans-cinnamoyl catalpol and 6-O-meta-methoxy-benzoyl catalpol. Noteworthy there are also quadrangularin A; pallidol; quercitin; quercitrin;b-sitosterol as well as b-sitosterol glycoside (G. Singh et al., 2007). Additionally, it is important to note that *Cissus quadrangularis* has a broad spectrum of components like vitamins and phytosterols which are responsible for its pharmacological actions, these not only help in healing bones but also act as anti-inflammatory agents with antioxidant effects. Most noticeable among them are ketosterones, beta-sitosterol, calcium, vitamin C, phosphorus, vitamin A, and steroidal compounds due to their significance in bone health improvement as well as the acceleration of fracture repair processes. Consequently, promotes collagen synthesis together with connective tissue regeneration accelerators, immune system enhancers, and bone formers. This promotes bone repair and speeds up the healing of fractures. This wide variety of bioactive components emphasizes the value of *Cissus quadrangularis* in both conventional medicine and contemporary pharmacology, as well as its promise as a natural treatment for conditions relating to the bones (Sanyal et al., 2005) (Oben et al., 2007).

Numerous phytochemicals found in *Cissus quadrangularis'* ethanolic extract support the plant's potential for bone regeneration. The ethanolic extract of *Cissus quadrangularis* contains important phytochemicals such as phytosterols, triterpenoids, and flavonoids. It has been claimed that flavonoids, such as quercetin and kaempferol, have anti-inflammatory qualities and encourage the creation of new bone, which helps the body mend broken bones. *Cissus quadrangularis* contains triterpenoids that help with osteoblast development and mineralization. These are necessary for bone repair and regeneration, as it has been shown. The plant’s phytosterols also promote bone density while preventing bone loss; therefore, this gives further evidence of its role in bone healing (Kalpana, 2013). Having said that, the chemical constitution of *Cissus quadrangularis*, with its contents of calcium, triterpenoids, flavonoids, and phytosterols is a significant advantage as far as using it as a homeopathic remedy for osteoporosis and healing bones is concerned. These components work together to stimulate bone cell formation, lay down minerals in the bone, decrease inflammation, and up osteoblast function hence vital for good bone health (Kaur et al., 2021).

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2.1 Table 3: Phytoconstituents of the plant:

Sr. No.	**Phytochemical Name**	**Part of herb**	**Reference**
Alkaloids			
1.	Caffeine	Whole herb	(Eswaran et al., 2012)
2.	Quinine	Leaves	(Pandit et al., 2020)
Carotenoids			
3.	β Carotene	Stem	(Jainu & Devi, 2005)
Vitamins			
4.	Vitamin C	Stem	(Jainu & Devi, 2005)
Flavonoid and flavonoid glycosides			
5.	Quercitrin	Whole herb	(G. Singh et al., 2007)
6.	Quercetin	Whole herb	(G. Singh et al., 2007)
7.	Kaempferol	Stem	(A. Gupta & Poorani, 2008)
8.	Daidzein	Leaves	(Mukherjee et al., 2016)
Iridoids			
9.	6-O-meta-methoxybenzoyl catalpol	Whole herb	(G. Singh et al., 2007)

10.	6-O-[2,3-dimethoxy]-trans-cinnamoyl catalpol	Whole herb	(G. Singh et al., 2007)
11.	Picroside 1	Whole herb	(G. Singh et al., 2007)
Glycosides			
12.	Cardiac glycosides	Stem	(Nalavade et al., 2022)
Phenolic glycosides			
13.	Cissusic acid	Stem	(P. Kumar et al., 2019)
Steroids			
14.	β-sitosterol	Stem	(Jainu & Devi, 2005)(U. M. Shah et al., 2010)(G. Singh et al., 2007)
Terpenes and Terpenoids			
15.	24-methyl-dammara2,20,25-triene-1-one	Stem	(Pathomwichaiwat et al., 2015)
16.	24-methyl-dammara20,25-diene-3β-ylacetate	Stem	(Pathomwichaiwat et al., 2015)
17.	24-methyl-dammara20,25-diene-3β-ylstearate	Stem	(Pathomwichaiwat et al., 2015)

18.	24-methyl-dammara20,25-diene-3-one	Stem	(Pathomwichaiwat et al., 2015)
19.	24-methyl-dammara20,25-diene-3β-ylpalmitate	Stem	(Pathomwichaiwat et al., 2015)
20.	7-Oxo-Onocer-8-ene-3 β 21 α diol	Aerial parts	(Adesanya et al., 1999)(Dinan et al., 2001)(Sen & Dash, 2012)
21.	Onocer – 7 ene 3 α, 21 β diol	Aerial Parts	(Dinan et al., 2001)
22.	Friedelan-3-one	Aerial Parts	(M. M. Gupta & Verma, 1991)(Dinan et al., 2001)
23.	δ-amyrin	Stem	(Bhutani et al., 1984)
24.	δ-Amyrin acetate	Stem Roots, aerial parts	(Dinan et al., 2001)
25.	δ-Amyrone	Stem Roots, aerial parts	(Dinan et al., 2001)
26.	Taraxerol acetate	Stem	(Sen & Dash, 2012)
27.	Eugenol	Stem	
28.	Taraxerol	Stem	(Sen & Dash, 2012)
Lipid constituents and Fatty acids			

29.	7- hydroxy- 20-oxodocosanyl cyclohexane	Aerial Parts	(M. M. Gupta & Verma, 1991)
30.	4-hydroxy 2 methyltricos-2 ene -22- one	Aerial Parts	(M. M. Gupta & Verma, 1991)
31.	9-methyloctadec-9-ene	Aerial Parts	(M. M. Gupta & Verma, 1991)
32.	31 methyl tritriacotannoic acid	Stem	(M. M. Gupta & Verma, 1991)
33.	Heptadecyloctadecanoate	Aerial Parts	(M. M. Gupta & Verma, 1991)
34.	Iso-pentacosanoic acid	Aerial Parts	(M. M. Gupta & Verma, 1991)
35.	Isopentadecanoic acid	Stem	(Sen & Dash, 2012)
36.	Hexadecanoic acid	Stem	(Thakur et al., 2009)
37.	Eicosyl Eicosanoate	Leaves	(Mukherjee et al., 2016)
38.	Tetratriactanoic acid	Leaves	(Mukherjee et al., 2016)
Lignan glycosides			
39.	Cissusol	Stem	(P. Kumar et al., 2019)
40.	Cissuside	Stem	(P. Kumar et al., 2019)
Stilbene derivatives and Stilbenoid Glycoside			

41.	Trans-resveratrol-3-Oglucoside	Stem	(Thakur et al., 2009)
42.	Resveratrol	Leaves	(Adesanya et al., 1999)(M. M. Gupta & Verma, 1991)
43.	Piceatannol	Leaves	(M. M. Gupta & Verma, 1991)
44.	Quadrangularin A	Whole herb	(Adesanya et al., 1999)(G. Singh et al., 2007)
45.	Quadrangularin B	Whole herb	(Adesanya et al., 1999)(G. Singh et al., 2007)
Indane derivatives			
46.	Pallidol	Leaves	(Adesanya et al., 1999)(M. M. Gupta & Verma, 1991)(G. Singh et al., 2007)
Saponins			
47.	Saponins	Stem	(Johns et al., 1999)
Alcoholic compounds			
48.	Tetratriacotanol	Leaves	(Mukherjee et al., 2016)

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3 Pharmacological activity and therapeutic uses:

Cissus quadrangularis has a number of pharmacological properties, such as anti-inflammatory, anti-ulcer, and anti-osteoporotic effects. It also has gastroprotective activity. These are the reasons why it is used as a medicine: for healing fractures faster; control of obesity; treatment of metabolic syndrome. The antioxidant, antiulcer, anti-osteoporotic, gastroprotective, cholinergic activity, fracture healing, antibacterial, and weight loss management are among the therapeutic properties of *Cissus quadrangularis* (De la Puerta et al., 2000)(Jainu & Devi, 2006). Studies have demonstrated it's advantageous in treating osteoporosis, hemorrhoids, ulcers, and arthritis. It's packed with flavonoids, triterpenoids, and vitamin C which makes it a potent medicinal herb good for various health conditions (Mishra et al., 2010). The tribal populations of Andhra Pradesh have been using *Cissus quadrangularis* for treating several ailments among which include dysmenorrhea, piles, worm infestations, constipation, and eye troubles (Prasad et al., 2018).

3.1 Table 4: Therapeutic activity of *Cissus quadrangularis*:

SL No	Plant Part	Therapeutic Activity and Use	Reference
1.	Stem	Anti-inflammatory properties, used in joint health support	(Siddiqua et al., 2017)
2.	Leaves	Anti-osteoporotic activity, promotes bone health	(Kaur et al., 2021)
3.	Aerial Parts	Anti-arthritic effects, supports joint function	(Lakshmanan et al., 2020)
4.	Root	Antioxidant properties, may aid in reducing oxidative stress	(A. Kumar et al., 2014)
5.	Whole Plant	Traditional use for bone fractures and ligament injuries	(Mahar et al., 2016)
6.	Bark	Wound healing properties, used in traditional medicine	(Marume et al., 2018)
7.	Seeds	Potential anti-diabetic effects, may help regulate blood sugar levels	(Lekshmi et al., 2015)

8.	Flowers	Anti-inflammatory effects, used in treating inflammatory conditions	(Srisook et al., 2011)
9.	Fruit	Digestive aid, may help with gastrointestinal issues	(Mishra et al., 2010)
10.	Stem Bark	Antimicrobial properties, used in treating infections	(Yaya Alain et al., 2015)
11.	Root Bark	Analgesic properties, may help alleviate pain	(Youyi et al., 2022)
12.	Stem	Antipyretic effects, used to reduce fever	(Vijay & Vijayvergia, 2010)
13.	Leaves	Antiulcer activity, may help protect the stomach lining	(Jainu & Devi, 2006)
14.	Aerial Parts	Adaptogenic properties, used to combat stress	(Meena et al., 2009)
15.	Stem	Hepatoprotective effects, supports liver health	(Viswanatha Swamy et al., 2010)
16.	Leaves	Anti-diarrheal properties, may help alleviate diarrhea	(Atre et al., 2022)
17.	Root	Anticancer potential, under investigation for cancer therapy	(A. Kumar et al., 2014)
18.	Whole Plant	Immunomodulatory effects, may help boost immune function	(Youyi et al., 2022)
19.	Stem Bark	Antifungal properties, used to treat fungal infections	(Santhoshkumar et al., 2012)
20.	Roots	Aphrodisiac properties, traditional use as a libido enhancer	(Bafna et al., 2021)
21.	Stem	Antidepressant effects, may help alleviate depression	(Marume et al., 2018)
22.	Leaves	Antihypertensive activity, may help regulate blood pressure	(Zhang et al., 2022)
23.	Fruit	Antioxidant-rich, supports overall health and wellness	(Vijayalakshmi et al., 2013)
24.	Stem Bark	Antivenom activity, used in traditional snakebite treatment	(Binorkar & Jani, 2012)
25.	Whole Plant	Diuretic properties, aids in promoting urine flow	(Joseph & Raj, 2011)

26.	Seeds	Antianemic effects, may help in the treatment of anemia	(Senthilvel et al., 2016)
27.	Leaves	Anticonvulsant activity, used in epilepsy management	(Moto et al., 2018)
28.	Stem	Anti-aging properties, may help reduce signs of aging	(For & Degree, 2014)
29.	Stem Bark	Antiviral effects, used in treating viral infections	(Marume et al., 2018)
30.	Root	Hypolipidemic activity, helps in lowering cholesterol levels	(A SHORINWA & EI EMENU, 2021)
31.	Whole Plant	Anti-inflammatory effects, used in treating inflammatory conditions	(Srisook et al., 2011)
32.	Stem	Antidiabetic properties, may help manage diabetes	(Srivastava et al., 2011)
33.	Leaves	Antispasmodic effects, helps alleviate muscle spasms	(Pharmacy, 2013)
34.	Flowers	Sedative properties, aids in promoting relaxation	(Edewor-Kuponiyi, 2013)
35.	Stem Bark	Antirheumatic effects, used in rheumatism treatment	(Sharadha et al., 2020)
36.	Stem	Antiemetic properties, helps alleviate nausea and vomiting	(Neamsuvan et al., 2012)
37.	Root Bark	Antiepileptic effects, used in epilepsy management	(Moto et al., 2018)
38.	Leaves	Antifertility activity, traditional contraceptive use	(Kansotiya et al., 2023)
39.	Stem	Anticoagulant properties, helps prevent blood clot formation	(Madike et al., 2020)
40.	Whole Plant	Anxiolytic effects, helps reduce anxiety and stress	(Moto et al., 2018)
41.	Stem Bark	Anti-inflammatory effects, used in treating inflammatory conditions	(S. Shamina et al., 2022)
42.	Stem	Antihistaminic properties, helps alleviate allergy symptoms	(Loganathan, 2021)
43.	Leaves	Antifungal activity, used in fungal infection treatment	(Of et al., 2023)

44.	Stem Bark	Antimicrobial effects, used in microbial infection treatment	(Marume et al., 2018)
45.	Root	Antipyretic activity, helps reduce fever	(Vijay & Vijayvergia, 2010)
46.	Whole Plant	Antiasthmatic effects, aids in asthma management	(Mahant, 2021)
47.	Stem	Anticatarrhal properties, helps relieve respiratory congestion	(Stephen & Suresh, 2015)
48.	Leaves	Antileukemic effects, under investigation for leukemia therapy	(Parimala et al., 2017)
49.	Stem Bark	Antihyperglycemic effects, helps regulate blood sugar levels	(Lekshmi et al., 2015)
50.	Leaves	Antimutagenic properties, may help prevent DNA damage	(Parimala et al., 2017)

4 Prevalence of bone fractures:

In 2019, the global prevalence of bone fractures was estimated to be 455 million cases, with an age-standardized prevalence rate of 5614.3 per 100,000 people. With a 70.1% rise since 1990, the frequency was greater in men than in women. Age, gender, and geographic location are some of the variables that affect the frequency of fractures. For example, in 2019 age-specific incidence rates in the 20–24 age group to the 40–44 age group were more than 50% higher in males than in girls. Fracture incidence is highly influenced by age and gender. The elderly, especially those 95 years of age and above, have the greatest rates, and in certain age groups, males have greater rates than females due to hazardous behaviors and occupational risks. Comprehending these demographic trends is essential for developing focused preventive measures. Fractures are frequently caused by falls, car accidents, and mechanical pressures; violence and terrorism have little effect. Mitigating the prevalence of fractures, especially in males, and enhancing general preventive and treatment strategies require targeted interventions such as workplace safety regulations, sports injury prevention, and violence prevention initiatives. By age-standardized prevalence rate, Australasia, Central Europe, and Eastern Europe were the top three areas. The data did not specifically include lifestyle issues. Age-standardized fracture incidence rates have significantly decreased worldwide during the past three decades, despite an increase in absolute counts brought on by aging and population expansion. Anatomical areas with persistently greater fracture prevalence rates include the patella, tibia, fibula, ankle, femur (not including the femoral neck), hand, wrist, or distal hand portions. Global age-standardized rates of fracture incidence, prevalence, and years lived with disability (YLDs) declined little between 1990 and 2019. However, due to population expansion and aging, the absolute counts of incident cases, prevalent cases, and YLDs grew significantly. The greater rates of fractures in men than in women across all age groups, with differing patterns in various age groups, and the disproportionately high risk of fractures in the elderly are among the factors leading to the increase in the absolute counts of fractures. The financial burden, time away from work, reduced productivity, disability, worse quality of life, and high healthcare expenditures related to fractures all contribute to the burden of fractures (Wu et al., 2021).

Based on a review of 223 case records, the incidence of bone fractures in Jorhat was found to be more common in men (86.5%) than in women (13.5%), with a male-to-female ratio of 6.4:1. Between the ages of 21 and 30, the greatest frequency of fractures (39.9%) was seen. Of the documented injuries, mandibular fractures made up 19.3%; dental and soft tissue injuries made up 30.5% and 30.9%, respectively. The most common cause of injuries was automobile accidents (67.7%), which were followed by assault trauma (27.8%) and falls (4.48%). Anatomical fractures most frequently occurred in the mandibular body (24%), symphysis (22%), and para-symphysis (18%) (Goswami & Talukdar, 2022)**.** Important information is revealed by the frequency of bone fractures in the population under study that fall under the purview of road traffic accidents (RTAs). In a population of 100,000, the frequency of RTAs was 39.04, accompanied by injury rates of 55.60 and fatality rates of 5.48 per 100,000. There were 463 RTAs in all, with 659 injuries (91%) and 65 fatalities (9%). The average age of those impacted was thirty-one, with a male-to-female ratio of 7.13:1, and 73% of victims were in the 15–44 age range. 35 RTAs per 100 kilometers and 7 RTAs per 1000 cars annually were reported as accident rates. All RTAs were single-vehicle accidents, with automobiles (17%) and motorbikes (19%) making up 42% of the total. Furthermore, pedestrians were involved in 24% of accidents and collisions accounted for 34% of all accidents. The study also showed seasonal patterns, with a slight increase in RTAs in December and January, which specifically resulted in more injuries. The majority of drivers (89%) were between the ages of 15 and 44; 15% did not have a license, and 19% had drunk alcohol the day before they drove. The head and neck (mean AIS 2.2), followed by the chest and abdomen, were the most seriously afflicted body areas, with the head and neck (66%), upper limb (44%), and lower limb (41%), being the most often impacted (Bhuyan & Ahmed, 2013).

These findings highlight the critical need for enhanced treatment and prevention plans. In order to improve both individual well-being and public health outcomes, we may work toward a future where the burden of fractures is greatly decreased by prioritizing research and putting comprehensive strategies into practice.

5 Existing treatments and their side effects:

Conventional methods for bone healing usually combine immobilization, surgical fixation, bone replacement or grafts, and pharmaceutical medications. Using casts, braces, or splints to immobilize a fracture helps limit mobility and stabilize the fracture, maintaining stability and alignment and promoting the body's natural healing process (Boyd et al., 2009)**.** When a fracture is unstable or hard to immobilize, surgery is required to stabilize and align the broken bone pieces for the best possible healing outcome. Metal plates, screws, rods, or external fixators are used in this procedure. When bone healing is impeded, other options for treatment may be used, such as synthetic replacements, autografts from the patient's body, or allografts from donors. Because of their osteogenic, osteoinductive, or osteoconductive qualities, these grafts promote the healing process by acting as scaffolds for the production of new bone. A customized approach to fracture care is ensured by the consideration of several aspects, including fracture type, site, patient age, general health, and surgeon skill, in making the decision of therapy (Roberts & Rosenbaum, 2012). Pharmacological therapies frequently involve the use of analgesics and anti-inflammatory medications to relieve pain, together with calcium, vitamin D and other minerals that are vital for healthy bones as supplements (Perna et al., 2020).

Ayurvedic medicine uses a variety of herbs and formulas to help heal bone fractures. Among the frequently used remedies is ashwagandha (Withania somnifera), which is known for its reviving and bolstering properties, which help to strengthen the musculoskeletal system and promote bone healing (Qayoom et al., 2020)**.** Resin from the Mukul myrrh tree, guggulu (Commiphora mukul), is prized for its analgesic and anti-inflammatory properties. It is reported to support bone regeneration processes and reduce associated pain and inflammation. (Khan et al., 2012)**.** Arjuna is a heartwood extract from Terminalia arjuna, which has been traditionally highly regarded for its cardioprotective properties (Karthikeyan et al., 2003) is acknowledged in Ayurveda as capable of strengthening bones and encouraging the growth of new bone tissues (Suguna et al., 2017)**.** Shallaki (Boswellia serrata), also known as Indian frankincense, is prized for its analgesic and anti-inflammatory properties as it is said that it can aid in reducing pain and swelling of fractures (Sharma et al., 2010)**.** Additionally, *Cissus quadrangularis* (Asthi shrankhala) which is a creeper frequently utilized in Ayurveda for the treatment of diseases relating to bones, is thought to quicken healing of fractures by increasing collagen formation and bone mineralization improvement. (HU et al., 2006). By combining these therapies a holistic approach is taken to promote the healing of bone fractures showcasing the traditional wisdom and versatility of Ayurvedic healing practices (Abd Jalil et al., 2012). There are few obvious similarities between *Cissus quadrangularis* and conventional remedies even though there are promising data that supports the plants effectiveness, in bone healing. Preliminary studies suggest that *Cissus quadrangularis* could reduce pain and swelling, speed up fracture recovery, and improve the outcomes. However further research is needed to validate these findings and explain the mechanisms underlying their advantages, which may involve carefully planned clinical studies.

5.1 Table 5: Various Approaches to Bone Fracture Healing:

Treatment	**Explanation**	**Side Effects**
Allopathic Approaches		
Immobilization	Involves the use of braces, splints, or casts to restrict movement, promoting stability and alignment of fractured bone pieces (Boyd et al., 2009).	• Skin problems such as pressure sores or dermatitis (Ekanayake et al., 2023) • Muscle atrophy (Appell, 1990) • Joint stiffness (Akeson et al., 1987)

Surgical Fixation	Utilizes metal plates, screws, rods, or external fixators to stabilize the bone and ensure proper alignment during healing (Roberts & Rosenbaum, 2012).	• Infection (Metsemakers et al., 2018) • Bleeding (Malyavko et al., 2022) • Nerve damage (Antoniadis et al., 2014) • Complications related to anesthesia (Friscia et al., 2017) • Allergic reactions or irritation at implant site (Pacheco, 2019)
Bone Grafts/Substitutes	Involves the use of grafts or substitutes such as allografts, autografts, or synthetic alternatives to accelerate bone healing (Roberts & Rosenbaum, 2012).	• Infection at graft site (Fischer et al., 2013) • Rejection of graft material (Kadiyala & Ganapathy, 2019) • Surgical complications (e.g., bleeding, nerve damage) (Lobb et al., 2019)
Ayurvedic Perspectives		
Herbal Medicines	Ayurvedic herbs and formulations aimed at promoting bone fracture repair, including Ashwagandha, Guggulu, Arjuna, Shallaki, and AsthiShrinkhala (Qayoom et al., 2020)(Khan et al., 2012)(Karthikeyan et al., 2003)(Suguna et al., 2017)(Sharma et al., 2010)(HU et al., 2006)(Abd Jalil et al., 2012).	• Gastrointestinal upset (P. Singh et al., 2020) • Interactions with other medications (Sprague et al., 2007)

Alternative Approaches		
Traditional Chinese Medicine	Utilizes herbs, acupuncture, and other techniques to enhance bone healing, employing medicinal herbs like Astragalus membranaceus, Curculigoorchioides, and Epimedium grandiflorum (Abd Jalil et al., 2012).	• Gastrointestinal upset (Du et al., 2016)
Homeopathy	Offers remedies such as Symphytum officinale and Calcareaphosphorica to support bone healing and alleviate fracture-related pain (Abd Jalil et al., 2012).	• Aggravation of symptoms (Stub et al., 2022)
Nutritional Supplements	Provides essential nutrients like calcium, vitamin D, and magnesium vital for bone health, aiding in fracture healing when taken orally or applied topically (Abd Jalil et al., 2012).	• Toxicity symptoms (e.g., hypercalcemia)(Karpouzos et al., 2017) • Interactions with other medications (Ilich & Kerstetter, 2013)
Physical Therapy	Involves exercises, stretches, and manual therapy to increase range of motion, strength, and flexibility near the fracture site, expediting recovery and preventing issues like muscle atrophy	• Exacerbation of pain or further injury (Ripamonti & Fulfaro, 2000) • Muscle or joint stiffness (McClure et al., 1994)

	and joint stiffness (Buza III & Einhorn, 2016).	

6 Effectiveness of *Cissus quadrangularis* in Bone Fracture Healing:

6.1 Traditional use of the plant for bone healing:

Powdered roots and stem paste of *Cissus quadrangularis* are specially administered topically and given orally for shattered bones in traditional uses for bone regeneration. Tribes and traditional healers utilize this plant for bone fractures because they think it has fracture-healing powers (Prasad et al., 2018).

6.2 Mechanism of the plant in bone healing:

Notably, *Cissus quadrangularis* has anti-osteoporotic qualities and the ability to speed up fracture healing, suggesting that it may be used as an adjuvant in fracture treatment plans. Compounds like onocer ne 3b 21a die (C3)H5202, onocer ne 7-ene-3a21b-diol (C30H5202), B-sitosterol, d-amyrin and d-amyrone, which are known to promote osteoblast activity and aid in the early stages of fracture repair processes, are among the rich phytochemical profile of this plant. Moreover, *Cissus quadrangularis* improves bone composition by adding vital components like collagen, calcium, and phosphorus to the chemical composition of bones. Fracture healing is further accelerated by its capacity to promote the proliferation of mesenchymal cells, such as fibroblasts, osteoblasts, and chondroblasts. Elevated levels of alkaline phosphatase in samples treated with *Cissus quadrangularis* highlight the compound's function in accelerating the production of calluses and the mineralization of bones (Potu, Rao, et al., 2009)**.** In addition to its direct effects on bone, *Cissus quadrangularis* has analgesic qualities and is a good source of calcium, carotene A, and anabolic steroidal substances, all of which add to its overall capacity to support skeletal health. *Cissus quadrangularis* shows promise as a natural resource for preventing and promoting bone diseases and healing through its pharmacological and nutritional properties. This suggests a potential direction for future research and treatment approaches pertaining to bone-related conditions (Roy et al., 2023). Accelerated bone regeneration results from *Cissus quadrangularis*' enhancement of osteoblast development and mineralization. Furthermore, it regulates a number of cytokines and growth factors related to bone repair. By stimulating the early regeneration of connective tissues involved in healing and encouraging speedier mineralization of the callus, *Cissus quadrangularis* promotes bone regeneration and the repair of fractures (UDUPA & PRASAD, 1964a)(UDUPA & PRASAD, 1964b). Rats administered *Cissus quadrangularis* showed full restoration of normal bone composition and faster bone repair than controls. Additionally, it shortens the fracture healing process by around 10 to 14 days throughout the fibroblastic, collagen, and osteochondritis phases. The normalization of collagen and mucopolysaccharide levels in bones is accelerated by *Cissus quadrangularis*, according to histological and histochemical data (Mishra et al., 2010).

Research has demonstrated that *Cissus quadrangularis* promotes bone health by enhancing some elements of the IGF system in human osteoblast-like cells. *Cissus quadrangularis*' anti-osteoporotic properties are further supported by the discovery that it increases the osteoblast-like cells differentiation, proliferation, and mineralization (Muthusami et al., 2011)**.** *Cissus quadrangularis* may also be used as a natural treatment for osteoporosis because it has been demonstrated to have an anti-osteoporotic impact via a variety of routes and mechanisms (Banu et al., 2012). These processes include the activation of the phytoestrogen-rich fraction in preserving bone density, the stimulation of osteoblast-like cell activities, and the promotion of bone health through the IGF system (Kaur et al., 2021).

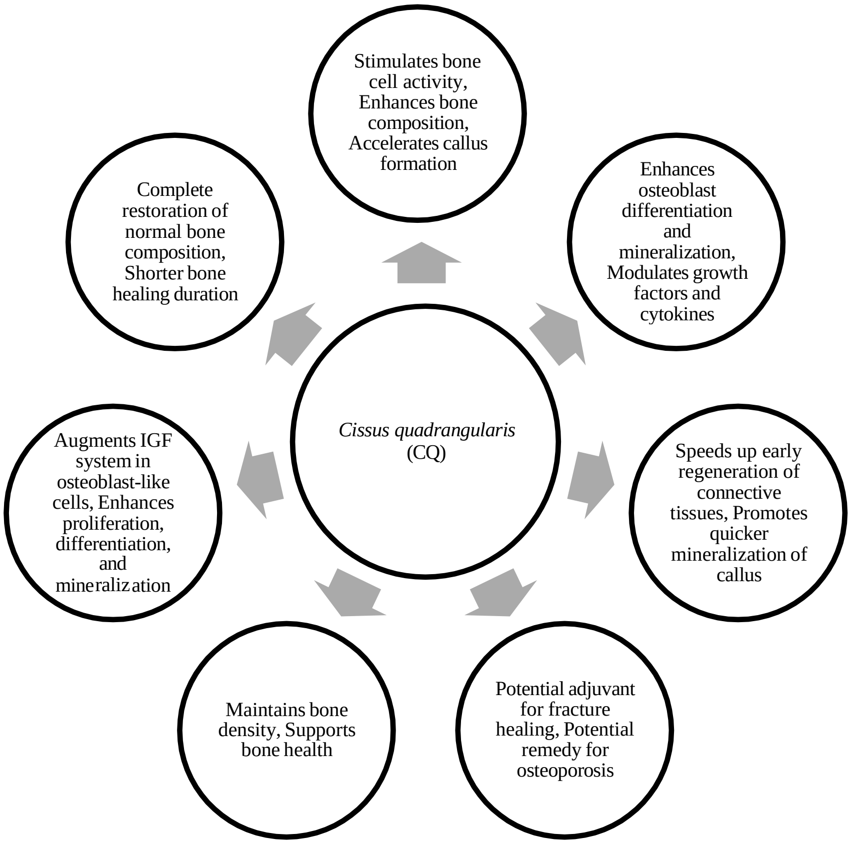

Fig: Mechanism of action or possible different routes of *Cissus quadrangularis*

7 Preclinical trials:

Pre-clinical studies conducted before have delivered promising outcomes from experiments on animals that were aimed to uncover possibilities of *Cissus quadrangularis* (CQ) ability to enhance bone fracture recovery while also shedding light on its therapeutic potential. A study demonstrated CQ's ability to accelerate fracture healing, while another study highlighted its Anti-oesteoporotic effects of CQ on ovariectomized rats. These studies collectively emphasize CQ's potential in promoting fracture healing and preventing osteoporosis, providing a solid foundation for further exploration in human subjects. The findings highlight the significance of CQ as a potential candidate for enhancing bone health and fracture recovery (Azam et al., 2023). Some studies include investigations on the biochemical and Ca45 effects of CQ in fracture healing, the use of phosphorus 32 in studying CQ's effects on fractures, and the acceleration of fracture healing by CQ. Additionally, CQ has been reported to enhance biomineralization through the up-regulation of MAPK-dependent alkaline phosphatase activity in osteoblasts (Potu, Bhat, et al., 2009). Promising outcomes have been observed in pre-clinical investigations examining the effect of *Cissus quadrangularis* (CQ) on fracture healing in animal models. These studies have demonstrated that CQ treatment can lead to faster initiation of the healing process, accelerated bone formation, and improved healing outcomes compared to control groups. Additionally, Udupa and Prasad conducted studies showing that CQ treatment resulted in a decrease in serum calcium levels to a greater extent than control groups, indicating enhanced mobilization of calcium in the formation of callus and faster healing. Overall, pre-clinical studies have consistently shown that *Cissus quadrangularis* has a positive impact on fracture healing in animal models, suggesting its potential as a therapeutic agent for promoting bone repair and regeneration (Deka et al., 1994).

The following table lists some similar pre-clinical trials that are currently being reviewed which demonstrate the beneficial effects of *Cissus quadrangularis* in the repair of bone fractures:

7.1 Table 6:

Study title	**Conditions**	**Model**	**Interventions**	**Main Findings**	**Reference**
Evidence-based assessment of antiosteoporotic activity of petroleum-ether extract of *Cissus quadrangularis* Linn. on ovariectomy-	Postmenopausal osteoporosis	Ovariectomized rat model	CQ treatment (500 mg/kg)	Reduction in bone loss evidenced by weight gain in femur compared to OVX control group. Reduced osteoclastic activity indicated by TRAP staining and facilitated bone formation assessed by ALP staining in femur sections.	(Potu, Rao, et al., 2009)

induced osteoporosis.				CQ treatment is effective on both enzymes, suggesting potential for prevention and treatment of postmenopausal osteoporosis.	
Cissus quadrangularis plant extract enhances the development of cortical bone and trabeculae in the fetal femur.	Intrauterine growth of trabeculae	Rat model	CQ treatment (750 mg/kg)	Increased thickness of cortical bone at mid-shaft level and individual trabeculae compared to control rats. Enhanced bone formation during fetal growth by CQ is attributed to its rich content of calcium, phosphorus, and phytoestrogenic properties.	(B. Kumar et al., 2007)
Cissus quadrangularis (Hadjod) Inhibits RANKL-Induced Osteoclastogenesis and Augments Bone Health in an Estrogen-Deficient Preclinical Model of Osteoporosis Via Modulating the Host Osteoimmune System	Inflammatory bone loss under estrogen-deficient conditions	Mouse model (ex vivo and in vivo)	CQ treatment (dose-dependent)	Ex vivo: CQ suppresses RANKL-induced osteoclastogenesis and inhibits osteoclast functional activity in a dose-dependent manner in mouse BMCs. In vivo: CQ administration improves bone health and preserves bone micro-architecture by raising the proportion of anti-osteoclastogenic immune cells (Th1, Th2, Tregs, Bregs) and lowering	(Azam et al., 2023)

				osteoclastogenic Th17 cells in bone marrow, lymph nodes, Peyer's patches, and spleen. Serum cytokine analysis supports the osteoprotective and immunoporotic potential of CQ, showing increased levels of anti-osteoclastogenic cytokines (IFN- , IL-4, IL-10) and decreased levels of osteoclastogenic cytokines (TNF- , IL-6, IL-17).	
Petroleum ether extract of *Cissus quadrangularis* (Linn.) enhances bone marrow mesenchymal stem cell proliferation and facilitates osteoblastogenesis	Control media and osteogenic media supplemented with CQ extract	In vitro MSC culture	CQ treatment (100, 200, 300 µg/mL)	CQ enhances MSCs differentiation into ALP-positive osteoblasts and increases extracellular matrix calcification. Higher proliferation rate observed with 300 µg/mL CQ treatment. MSCs grown in osteogenic media containing CQ exhibit higher proliferation, differentiation, and	(Potu, Bhat, et al., 2009)

				calcification rates compared to control cells.	
Effect of *Cissus quadrangularis* in accelerating healing process of experimentally fractured radius-ulna of dog: a preliminary study	Experimental fracture of radius-ulna	Dog model	CQ treatment	CQ-treated animals exhibited faster initiation of the healing process compared to control animals on radiological and histopathological examinations. The treated group showed a greater decrease in serum calcium level compared to controls. Healing was almost complete by the 21st day of fracture in the treated animals, while it remained incomplete in the control group. No significant alteration of serum calcium level was observed by the 21st day of fracture in either group.	(Deka et al., 1994)
Potential of *Cissus qudrangularis* transdermal patch for fracture healing	Critical-sized bone defects	Male Wister rats weighing 250-350 g	Transdermal patch containing ethanolic	The transdermal patch was developed and studied for various parameters including thickness,	(A. Kumar et al., 2018)

			extract of *Cissus quadrangularis*	moisture content, SEM analysis, drug content, in-vitro drug release, and in-vivo animal activity. Fractures were induced in male Wister rats, and the formulated patch was applied to the fractured bone and immobilized with silica cast. X-ray imaging showed better fracture healing potential with the silica cast containing the herbal patch compared to the control group. The study validates the potential of *Cissus quadrangularis* as a fracture healing agent.	
Evaluation of the Herb, *Cissus quadrangularis* in Accelerating the Healing Process of Femur Osteotomies in dogs	Bone healing in dogs	Dog model with unilateral comminuted diaphyseal femoral osteotomy	Internal fixation with neutralization bone plate + routine postoperative treatment (Group A) vs. Internal fixation + ethanolic	Animals in Group B showed early resolution of inflammatory signs and weight bearing compared to Group A. Accelerated bone healing with complete bridging of comminuted fragments and extensive bony deposition was observed in Group B. Union was relatively slow	(Maiti et al., 2007)

			extract of *Cissus quadrangularis* applied topically and subcutaneously (Group B)	and incomplete on day 60 in Group A (control). Conclusion: *Cissus quadrangularis* accelerated fracture healing.	
Evaluation of clinical efficacy of *Cissus quadrangularis* in pain management and bone healing after implant placement–a pilot study	Pain management and bone healing after implant placement	Prospective Randomized Control Study	*Cissus quadrangularis* (Study group) vs. routine antibiotics (Control group) after implant placement	Patients were divided into Study and Control groups receiving implants. The study group received *Cissus quadrangularis* while the control group received routine antibiotics. Pain assessed using VAS at 3rd, 5th day, and after one week. Swelling categorized as mild, moderate, or severe. Serum alkaline phosphatase levels recorded pre-operatively and at 4th and 8th week post-operatively. Densitometric analysis of Orthopantomogram for bone density around implants. Results showed minimal pain and swelling and more bone healing in	(D. N. Shah et al., 2015)

				the study group compared to the control group. Study group showed increased serum alkaline phosphatase levels and improved bone density around implants compared to control group, indicating new bone formation and osteointegration.	
Effect of *Cissus quadrangularis* on Fracture Healing in Laboratory Animal	Fracture healing in artificially induced fractured rabbits	Experimental Study, 15 rabbits divided into groups A, B, and C	Application of *Cissus quadrangularis* paste via close reduction (Group B) and open reduction (Group C) methods; Group A served as control	Both treated groups (B and C) showed lower serum calcium levels than the control group after 24 hours of fracture, which normalized by day 14. Fracture healing commenced more rapidly in the treated groups, with complete bridging of discontinuity by osseous callus on day 7 and complete effacing of fracture line on day 14. No anomalousness, clinical deviations, or alteration of serum calcium levels were observed on day 14 in treated animals, suggesting the applicability of *Cissus*	(Zahan et al., 2022)

				quadrangularis paste in fracture management.	
Antiosteoporotic effect of ethanol extract of *Cissus quadrangularis* Linn. on ovariectomized rat	Ovariectomized rat model of osteoporosis	Experimental Study, Healthy female albino rats divided into five groups	Oral treatment with ethanol extract of *Cissus quadrangularis* at doses of 500 and 750 mg/kg/day	Biomechanical, biochemical, and histopathological parameters assessed	(Shirwaikar et al., 2003)

8 Clinical trials:

The effectiveness and safety of *Cissus quadrangularis* on humans have been measured through clinical trials. Such tests offer important information regarding its effectiveness, optimal dosages, and treatment durations.

A clinical study evaluated the effect of *Cissus quadrangularis L.* on the healing process of a fractured metatarsus bone. The study used both stem paste and oral solution formulations of CQ as treatment options. Promisingly, positive healing outcomes were observed after 21 days of treatment, indicating the significant potential of *Cissus quadrangularis L.* in biomedical applications related to bone fracture healing. The findings not only shed light on the effectiveness of CQ but also provide valuable insights into optimal dosages and treatment durations, increasing the understanding of this natural remedy's therapeutic efficacy in orthopedic situations. These outcomes open the door to more research and the incorporation of Cissus quadrangularis into clinical practice; thereby, providing a hopeful way forward for developing treatments of bone fracture medicines (Mahar et al., 2016).

The following table includes a list of comparable clinical trials that have demonstrated the beneficial effects of *Cissus quadrangularis* in the repair of bone fractures:

8.1 Table 7:

Study title	**Conditions**	**Model**	**Interventions**	**Main Findings**	**Reference**
Cultivation and Biomedical Application of *Cissus quadrangularis* L. in Bone Fracture	Accidentally fractured metatarsus bone	Human case study on a 52-year-old man	Stem paste administration (twice a day) and oral solution (10% solution, 10ml once a day)	Positive X-ray observation of bone healing process after 21 days of treatment. Almost complete healing was observed by the twenty-first day of fracture in the treated bone. Biomedical application of *Cissus quadrangularis* in bone healing is recommended.	(Mahar et al., 2016)
Efficacy and Safety of *Cissus quadrangularis* L. in Clinical Use: A Systematic Review and Metaanalysis of Randomized Controlled Trials	Systematic Review	1108 patients from 9 studies	*Cissus quadrangularis* and combination products	Effects of *Cissus* on hemorrhoid symptoms were not different from comparators, but significant effects were observed on bone pain. Combination products containing *Cissus* showed superiority in reducing body weight,	(Roy et al., 2023)

				low-density lipoprotein, triglyceride, total cholesterol, and fasting blood sugar compared to placebo. No serious adverse effects were reported. Quality of evidence ranged from low to high based on GRADE assessment, with high quality for hemorrhoids and body weight reduction, and low quality for bone fractures. Conclusion: *Cissus* had benefits for bone fractures and obesity/overweight when used in combination products, but high-quality studies are still needed.	
Clinical evaluation of *Cissus quadrangularis* as osteogenic agent in maxillofacial fracture: A pilot study	Maxillofacial fracture	Patients undergoing open reduction internal fixation for maxillofacial fractures	Group 1: C. quadrangularis capsule (500 mg) thrice a day for 6 weeks, Group 2 (Control): No	- Pain, swelling, and fragment mobility were lower in Group 1, - Higher levels of serum calcium and serum phosphorus in Group 1, - Accelerated healing of bone was observed in	(Brahmkshatriya et al., 2015)

			supplementary medication	Group 1 on day 21 compared to the control group	
Osteogenic potential of *Cissus quadrangularis* assessed with osteopontin expression	Mandible fracture healing	60 patients with mandible fractures, aged 20-35 years	Administration of *Cissus quadrangularis* capsules to Group 1, while Group 2 served as control	Clinical and radiological analysis suggested better healing of fractures in Group 1 (CQ group). Western blot analysis and flow cytometry showed significant levels of osteopontin protein expression and CD4+ T cells expressing osteopontin, respectively, in Group 1. Conclusion: CQ accelerates fracture healing and promotes early remodeling of fracture callus.	(N. Singh et al., 2013)
Evaluation of osteogenic potential of *Cissus quadrangularis* on mandibular alveolar ridge distraction	Alveolar distraction for implant installation	20 patients with atrophic ridge undergoing alveolar distraction	Administration of *Cissus quadrangularis* or placebo during consolidation period after alveolar distraction	Faster bone formation and maturation were observed in *Cissus quadrangularis* group compared to the placebo group. Increased bone density in the distracted area and around the implant in *Cissus quadrangularis* group.	(Altaweel et al., 2021)

				Significantly less bone loss was reported in the *Cissus quadrangularis* group compared to the placebo group.	

9 Available formulations in the market:

Cissus quadrangularis extracts have antibacterial, anti-inflammatory and antioxidant properties that make them useful in a variety of dosage forms. Studies assessing the plant extract's efficacy against Candida albicans have demonstrated its antimicrobial qualities. (Jabamalai et al., 2010) When *Cissus quadrangularis* extract is put into various dosage forms, such as ointments, creams, capsules and oral liquids, it may effectively and steadily supply these advantageous features to patients (Rohit R. Eklare, 2024). For the most part, *Cissus quadrangularis* extract tablets (marketed under the "Hadjod" brand) have been successful in treating fractures (Brahmkshatriya et al., 2015)**.** Additionally, research has indicated that transdermal patches containing *Cissus quadrangularis* extract may be a promising alternative to targeted delivery for the purpose of accelerating the healing of fractures. Further investigation is required to fully understand the therapeutic potential of these formulations since they offer a multitude of options that allow specific techniques to be used during the bone-settling process (A. Kumar et al., 2018).

Ayurvedic formulations for *Cissus quadrangularis* are different from regular ones because they are based on the traditional literary and regulatory norms concerning their composition and production methods. Churna (powder), taila (oil), lepa (plaster), kashayam (decoction) and bhasma (involving heating and divine intervention) contain these Ayurvedic drugs' natural ingredients (Martínez Pérez, 2012)(Tdcl et al., 2020)**.** However, the conventional formulations of *Cissus quadrangularis* used by pharmaceutical companies may differ in composition even though they use similar formulae. When combined with *Cissus quadrangularis*, innovative drug delivery techniques offer several advantages, such as safety, efficacy, and patient adherence due to the facilitation of site-specific release, which enhances pharmaceutical performance. Improved *Cissus quadrangularis* therapeutic benefits can be achieved by using transdermal patches and nanoparticles (Panda et al., 2023) which allow for controlled as well as extended release. Moreover, these new delivery systems compensate for deficiencies in traditional formulations like poor bioavailability and high frequency of administration. In summary, the combination of new drug delivery methods with *Cissus quadrangularis* in Ayurvedic formulations affords an opportunity to enhance its safety profile through improved drug release while still maintaining patient adherence levels (Kaur et al., 2021).

10 Future prospective:

Cissus quadrangularis has a rich history of traditional usage in controlling many ailments; its potential for use in bone fracture repair looks promising. Many studies have demonstrated that, while being well known for its anti-osteoporotic action, *Cissus quadrangularis* has broad therapeutic promise for a variety of conditions, including anti-inflammatory, analgesic, and anti-cancer properties. With more than 46 known compounds, including flavonoids and alkaloids, that account for its wide range of pharmacological effects, this plant offers a great deal of potential for more research and the extraction of new phytochemicals. In order to completely comprehend the plant's medicinal potential, future studies should fill in the gaps in the literature by examining the plant's particular sections, such as its fruits and flowers, and by using a wider variety of extracts. Furthermore, thorough clinical trials are required to confirm its preclinical pharmacological potential, especially in the healing of bone fractures, for which there is insufficient clinical data despite the drug's usage in a variety of marketed formulations (Bafna et al., 2021).

To fully understand the effect of *Cissus quadrangularis* on the caliber of regenerated bones, more investigation is needed. Moreover, conventional excipients make up the bulk of those used in its commercial formulations. Furthermore, there was a lack of pharmacokinetic studies on produced formulations in the literature. It is necessary to confirm the pharmacokinetic and pharmacodynamic characteristics of created formulations. Because of this, we will soon have the chance and freedom to choose the excipients and formulation technique required to develop a special *Cissus quadrangularis* formulation that will improve its pharmacokinetic and pharmacodynamic properties in line with the demands of the patient's body (Kaur et al., 2021). The herb *Cissus quadrangularis* shows great potential in the treatment of diabetes. When *Cissus quadrangularis* is used as a reducing agent during the manufacture of silver nanoparticles (CqNps), strong anti-diabetic effects are shown that are on par with conventional medications.

Exploring nano-formulations offers great opportunities for future anti-diabetic therapeutics by using the well-established function of *Cissus quadrangularis* in folk medicine for diabetes and other illnesses (Sai Nivetha et al., 2022).

Applications for *Cissus quadrangularis* in bone healing might include orthopedic surgery and osteoporosis. Large-scale clinical studies, formulation optimization, and investigating the product's synergistic benefits with traditional therapies should be the main areas of future study. Its therapeutic potential can also be better understood by looking at its molecular processes.

11 Conclusion:

Cissus quadrangularis seems as a viable substitute treatment for the repair of bone fractures. Its historic usage in bone-related illnesses is backed by pre-clinical and clinical studies about its bioactive ingredients and mechanism of action. Although more investigation is required to completely comprehend its modes of action and maximize its therapeutic use, the current research offers a solid basis for contemplating *Cissus quadrangularis* as a beneficial natural substitute in the field of bone regeneration and fracture repair. However, further investigation, encompassing extensive clinical studies, is vital to ascertain its efficacy, ideal doses, and enduring safety. While considering this as an alternate treatment for bone fractures in patients, those in the medical field must be aware of both its possible advantages and disadvantages.

As a result, *Cissus quadrangularis* a very good option in the treatment of bone fractures. It may be a very helpful supplement for repairing fractures because of its all-natural makeup and capacity to reduce pain and swelling while increasing stability and accelerating the repair of bones. This herbal remedy may offer a solution to reduce the financial and personal expenses that bone fractures impose on patients and healthcare systems, as well as accelerate healing and enhance patient comfort.

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