

## ANTI-OSTEOPOROTIC AND BONE-HEALING POTENTIAL OF *CISSUS QUADRANGULARIS*: A REVIEW

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### ABSTRACT

*Cissus quadrangularis* is a medicinal plant with a wide range of traditional uses as an Ayurvedic herb for the treatment of fractures and musculoskeletal problems. Recent research has emphasised the evaluation of the therapeutic potential of the plant by conducting human clinical trials. This review aims to provide an overview of the current evidence of the use of *Cissus quadrangularis* in maintaining bone health, particularly with respect to biomarkers, fractures, and osteoporosis. Clinical and biomarker studies of *Cissus quadrangularis* supplementation have demonstrated an increase in the level of parathyroid hormone (PTH) in the serum, indicating a possible stimulatory effect of the plant on bone remodelling. However, there is no change in the levels of calcium, phosphorus, and alkaline phosphatase, indicating that the plant is safe with

respect to mineral metabolism. Clinical studies of patients with fractures, especially mandible and facial fractures, have demonstrated a reduction in pain, swelling, and inflammation, as well as faster radiographic healing and early callus formation. Furthermore, placebo-controlled studies on postmenopausal women with osteopenia indicate that *Cissus quadrangularis* may assist in the slowing down of bone loss, as observed after about 24 weeks. However, the increase in bone mineral density was not significantly observed, as the studies were limited in duration and had small subject pools. It can be concluded that, based on the current evidence, *Cissus quadrangularis* exhibits promising effects on bone healing and fracture healing, and more clinical studies are warranted.

**KEYWORDS:** *Cissus quadrangularis*; Bone healing; Osteoporosis; Fracture healing; Parathyroid hormone; Bone mineral density; Osteogenesis.

## INTRODUCTION

Osteoporosis is a metabolic bone disease characterised by low bone density, deterioration of bone microstructure, and increased bone fragility, thus increasing the risk of bone fractures. Osteoporosis is considered one of the major health challenges affecting postmenopausal women due to estrogen deficiency, as well as elderly individuals due to age-related bone loss. The bone physiology of osteoporotic patients is characterised by a disbalance between bone resorption and bone formation, where bone resorption is greater than bone formation, thus leading to bone loss. Various risk factors, such as genetic factors, nutritional factors, sedentary lifestyle, smoking, and long-term use of corticosteroids, have been implicated in the development of osteoporotic bone disease. Current pharmacological agents, such as bisphosphonates, hormone replacement therapy, selective estrogen receptor modulators, and calcitonin, have shown efficacy in the prevention of bone fractures. However, these agents have shown adverse effects, such as gastrointestinal disturbances, osteonecrosis of the jaw, cardiovascular disease, and long-term use of these agents, thus limiting their use. This has led to a search for alternative agents, especially those derived naturally. Traditional uses on phytochemistry *Cissus quadrangularis*, a medicinal plant used in traditional medicine, is found to have drawn considerable attention due to its bone-healing activity. Traditionally, this plant is used to enhance bone healing, increase bone strength, and reduce the time required to heal bone fractures. Recently, various studies have validated its pharmacological activities, which provide evidence for its use in treating osteoporotic patients.<sup>[6]</sup>

## Phytochemistry

The therapeutic potential of *Cissus quadrangularis* has been attributed to its rich phytochemical content. *Cissus quadrangularis* has been found to contain a variety of bioactive compounds such as ketosteroids, flavonoids, triterpenoids, and phytosterols, which play an important role in bone metabolism and regeneration.<sup>[10]</sup> Ketosteroids have been found to exert an anabolic effect on bone tissue, which results in an increase in osteoblastic activity, thereby promoting bone formation. Flavonoids such as quercetin and kaempferol have antioxidant properties, which help to reduce oxidative stress, a major factor responsible for bone loss in patients with osteoporosis.<sup>[11]</sup>



*Cissus quadrangularis* has also been found to contain essential minerals such as calcium and phosphorus, which are essential for bone mineralization and structural integrity. In addition to this, *Cissus quadrangularis* has also been found to contain ascorbic acid, which plays an important role in collagen synthesis, an essential component of the bone matrix.<sup>[12]</sup> Phytosterols such as  $\beta$ -sitosterol also exert an anti-inflammatory effect, which plays an important role in bone regeneration.

The combined action of all these bioactive compounds makes *Cissus quadrangularis* a potent agent in promoting bone healing and treating patients with osteoporosis.

### **Mechanism of Action**

The anti-osteoporotic activity of *Cissus quadrangularis* is exerted through various biological activities, thus rendering it a multi-target drug. One such mechanism is the induction of osteoblastic proliferation and differentiation. Osteoblasts are bone-forming cells, and their increased activity leads to increased bone matrix deposition. Various studies have demonstrated that *Cissus quadrangularis* upregulates alkaline phosphatase activity, which is a marker of bone formation.

Another mechanism is the inhibition of osteoclastogenesis, where osteoclasts are bone-resorbing cells, and their increased activity leads to bone loss. *Cissus quadrangularis* inhibits the RANKL signalling pathway, thus inhibiting osteoclast differentiation and activity.

Another significant mechanism is its antioxidant activity, where flavonoids and phenolic compounds present in the plant have shown potent antioxidant activity by scavenging ROS, which is known to cause bone resorption and damage to bone cells. Its anti-inflammatory

activity is also one of the major reasons for its anti-osteoporotic activity, thus preventing bone loss by inhibiting pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$ .

*Cissus quadrangularis* is also known to have phytoestrogenic activity, which is helpful in postmenopausal osteoporotic patients.

### **Proposed Mechanisms of *Cissus quadrangularis***

- Stimulates osteoblast activity → bone formation
- Increases collagen synthesis → stronger bone structure
- Promotes mineralisation and callus formation
- Has phytoestrogenic activity → useful in menopause
- Reduces inflammatory mediators → reduces pain and swelling
- Has antioxidant activity → prevents degradation of bone tissue

### **Preclinical Evidence**

Several preclinical studies have generated significant evidence for the anti-osteoporotic and bone-healing properties of *Cissus quadrangularis*. Animal studies, especially in ovariectomized rats, have been widely used as an experimental model for simulating human postmenopausal osteoporosis. Studies have shown that the administration of *Cissus quadrangularis* extract in these animal models resulted in a significant increase in bone mineral density as well as bone microarchitecture.<sup>[16]</sup>

In studies using fracture healing models, *Cissus quadrangularis* plant extract has also demonstrated its ability to accelerate the bone fracture healing process by increasing callus formation and mineral deposition in the fracture site. Studies have also shown an increase in the biomechanical strength of the bone, indicating stronger and more resilient bone formation.

In biochemical studies using these models, increased serum levels of calcium and phosphorus have been noted along with increased levels of alkaline phosphatase, which indicates increased bone formation.

### **Clinical Evidence**

Clinical studies conducted to evaluate the effectiveness of *Cissus quadrangularis* in human subjects are scarce but promising. Various clinical studies have shown the potential of the herb in the healing of fractures. Accelerated healing of fractures has been observed in

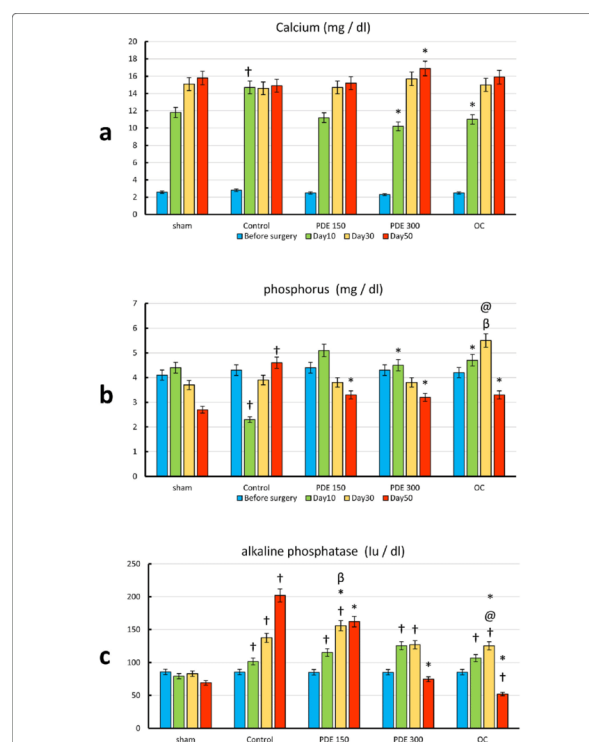
patients receiving *Cissus quadrangularis* supplementation compared to the control group.<sup>[18]</sup> Patients receiving the herb extract experienced less pain and swelling and faster healing of the fractures, especially in the case of mandibular and long bone fractures.,

The effectiveness of the herb has also been tested for the management of osteoporosis. Various clinical studies conducted among postmenopausal women have shown the potential of the herb in the management of bone loss. Clinical trials have shown improvements in bone turnover and bone loss in patients receiving the herb supplementation. However, the effectiveness of the herb in improving bone density has been inconsistent.

### Key Clinical Outcomes of *Cissus quadrangularis*

- Raises serum parathyroid hormone (PTH) levels, which may trigger bone formation
- Does not significantly alter calcium, phosphorus, and ALP levels, making it safe for mineral metabolism
- Reduces pain, oedema, and inflammation in the case of fractures
- Enhances the rate of bone fracture healing and callus formation
- Demonstrates potential in retarding bone loss in postmenopausal females
- Enhances functional recovery and mobility
- Exhibits anti-inflammatory, antioxidant, and osteogenic potential

### HUMAN CLINICAL EVIDENCE FOR *CISSUS QUADRANGULARIS*



### Biomarker and Clinical Studies

The assessment of *Cissus quadrangularis* in human subjects using biochemical and clinical biomarkers is an emerging field. A recent systematic review and meta-analysis of human studies on *Cissus quadrangularis* have yielded important but limited information about its physiological impacts in humans. Among the most prominent features in the analysis is the increase in serum parathyroid hormone levels following *Cissus quadrangularis* administration.

Parathyroid hormone is an important hormone in the endocrine system that is involved in the homeostasis of calcium and phosphate. This hormone is essential in the integrity and health of bone tissue. The increase in parathyroid hormone may be an indication that *Cissus quadrangularis* is involved in bone remodelling through the promotion of bone growth and repair, as suggested by the anabolic effect in bone tissue.

Notably, despite the increase in PTH levels, there were no significant changes in the levels of serum calcium, phosphorus, and ALP. This is an interesting observation because it suggests that the administration of *C. quadrangularis* does not result in any imbalance in the levels of minerals in the body. This indicates that the mechanism of the drug may not be related to the regulation of bone metabolism in a general sense. The mechanism may be localised and may even result in the enhancement of bone metabolism without interfering with the general biochemical status of the body.

Moreover, it is a known fact that the plant *C. quadrangularis* contains a number of bioactive compounds like ascorbic acid (vitamin C), carotenoids, calcium, and anabolic steroids. These compounds play a very important role in the synthesis of collagen and the formation of osteoid and bone.

### Fracture Healing Trials

Study type	Population	Outcomes	Result
Biomarker Study	Adults	PTH levels	Increased
Biomarker Study	Adults	Calcium ALP	No Change
Fracture Trails	Mandible fractures	Healing Time	Reduced
Fracture trails	Patients	Pain & Swelling	Decreased
Osteoporosis Trail	Postmenopausal woman	BMD	Slight improvement
Osteoporosis Trail	Osteopenia	Bone loss	Slowed

One of the most researched aspects of *Cissus quadrangularis* is its efficacy in accelerating fracture healing, which has been conducted on humans. Traditionally, this herb is known by names such as 'Hadjod' or 'Bone Setter' and is used to cure bone fractures and injuries. Recent clinical trials have shown promise in confirming these claims using scientific methods.

Clinical trials conducted on patients suffering from mandibular, maxillofacial, and long bone fractures have shown that *C. quadrangularis* supplementation resulted in a significant reduction of pain, oedema, and tenderness, compared to those not taking the supplement. This could be due to its anti-inflammatory and analgesic activities, which may be mediated by the suppression of prostaglandins, histamine, and cytokines, all of which are pro-inflammatory mediators. Safety and Side Effects:

The results of the radiographic investigations of the trials conducted with *C. quadrangularis* have consistently demonstrated an accelerated rate of fracture healing, as evidenced by early callus formation, mineralization, and bridging of fracture gaps. The results of some of the trials also demonstrated a reduction of 2-3 weeks in the period required for the union of fractures, as observed by radiological investigations. This is a clear indicator of an accelerated rate of fracture healing.

The histopathological investigations of the effects of *C. quadrangularis* supplementation also demonstrated an increase in the following:

- The proliferation and differentiation of osteoblasts
- The formation of collagen matrices
- The development of angiogenesis

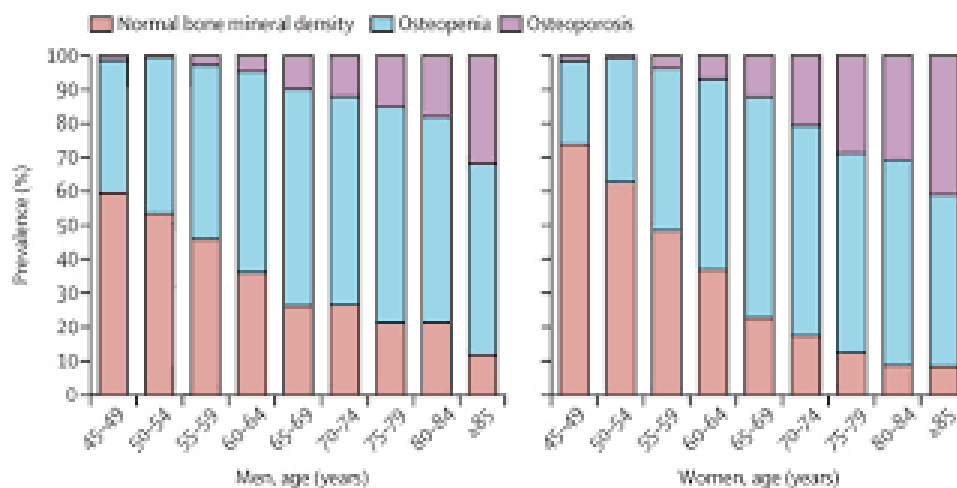
These are the essential steps for effective bone regeneration. The presence of ketosteroids and flavonoids in the plant is believed to account for the observed effects by stimulating the osteoblasts and ensuring an adequate blood supply to the injured areas.

The results of the supplementation with *C. quadrangularis* also demonstrated an accelerated rate of functional recovery, as evidenced by improved locomotion. This is a clear indicator of the clinical importance of the supplementation, as it helps in the prevention of complications arising from immobilisation.

- Despite these promising results, some limitations need to be kept in mind:
- Most studies have not followed proper blinding and randomisation methods
- Sample size is relatively small in most cases
- Types and methods of fractures vary in different studies
- Standardisation in dosage forms is lacking in most cases

Thus, in spite of promising evidence for the use and efficacy of *C. quadrangularis* in fracture healing in accordance with traditional use, more multicentric, double-blind randomized studies need to be conducted to prove its efficacy and lay guidelines for its use.

### Osteoporosis in Humans



The use of *Cissus quadrangularis* in the management of osteoporosis, especially in postmenopausal women, is an area that has attracted much interest in recent times. Osteoporosis is characterised by low bone mass and microstructural deterioration of bone tissue, leading to an increased risk of bone fractures.,

A placebo-controlled human clinical trial aimed at assessing the impact of *Cissus quadrangularis* supplementation in postmenopausal women diagnosed with osteopenia resulted in a decrease in bone loss after approximately 24 weeks. This indicates that the plant may have a protective role in bone health and may potentially delay the progression of osteopenia to osteoporosis.

Although the plant may have beneficial properties in the management of bone health as indicated by the reduction in bone loss in women with osteopenia, bone mineral density

assessment in this study failed to demonstrate any significant difference in comparison to placebo-treated groups. This may be attributed to the following reasons

- The process of bone remodeling is a gradual process.
- Variability in bone density in the subjects.
- Small sample size.
- Variability in the absorption rate of the drug.

Besides its impact on bone density, other benefits associated with the use of *C. quadrangularis* include an improvement in muscle strength, physical performance, as well as overall body composition. This is particularly important in elderly patients, as it can help reduce the incidence of falls, which often results in fractures.

The phytoestrogenic and antioxidant properties of *C. quadrangularis* can also help in alleviating some of the effects of osteoporosis in postmenopausal women. This is due to the fact that it has estrogen-like activity, which can help mitigate the effects of hormonal imbalances that lead to excessive bone loss. Moreover, it can also help reduce oxidative stress, which has been implicated as a contributing factor to bone resorption.

However, it is important to note that there is currently insufficient evidence to support the use of *C. quadrangularis* as a treatment for osteoporosis. Instead, it can be considered as a supplement to other forms of treatment, such as calcium, vitamin D, as well as bisphosphonates.

- Future studies on this plant should include:
- Long-term studies involving a larger population
- Standardization of dosage regimens
- Assessment of fracture risk reduction
- Comparison to other forms of treatment for osteoporosis

### **Safety and Toxicity**

*Cissus quadrangularis* is generally considered safe as a medicinal plant when administered in recommended doses for therapy based on both preclinical and clinical evidence. Acute and subacute toxicity studies were conducted in various animal models that showed that *Cissus quadrangularis* extracts administered in both lower and relatively higher doses did not exhibit significant toxicological effects on various vital organs such as the liver, kidneys, and heart.<sup>[21]</sup> Histopathological examination also did not reveal significant alterations in the

structural integrity of organs in this study. Moreover, various biochemical markers such as liver and renal functions were within normal limits in this study. Good tolerability in humans has also been noted in clinical investigations into *Cissus quadrangularis* formulations. In most cases, subjects have not shown significant adverse effects, and only minor complaints such as gastrointestinal disorders, nausea, and headache have been noted in a few cases.<sup>[12]</sup> Thus, it may be safely used as a long-term adjuvant therapy in bone disorders. Moreover, antioxidants such as flavonoids and vitamin C may also be responsible for its protective action against oxidative stress-induced injuries and may be beneficial in this regard.

However, some limitations need to be taken into consideration in this regard. Firstly, long-term safety in humans has not been sufficiently studied, and there is a need for more well-controlled clinical trials to evaluate its long-term toxicity in a large number of subjects<sup>[18]</sup> Inconsistency in its phytochemical composition due to geographical location and extraction methods may also be a point of concern in this regard.<sup>[22]</sup> Moreover, its potential to cause drug-herb interactions has not been sufficiently studied. Its effect on calcium and hormonal metabolism may require caution in its use in combination with anti-osteoporotic agents, corticosteroids, and hormonal therapy.

Another major issue is the absence of standard dosing recommendations. Various preparations may have different levels of active ingredients. This may impact the efficacy and safety of the herb. Therefore, the development of a standard extract form and dosing regimen is critical for its clinical application.

The herb has an acceptable safety profile based on the current data. There is low toxicity and good tolerance. However, the herb needs extensive long-term toxicity studies and the assessment of its potential for interacting with drugs for its safe and effective use in contemporary medicine.

### **Future Perspectives**

The rise in osteoporosis and other bone-related disorders worldwide has led to a greater need for safe and cost-effective agents that have a positive impact on multiple targets and are derived from a natural source. In this regard, *Cissus quadrangularis* has shown promise as a potential candidate; however, its journey from traditional medicine to evidence-based medicine is a long and arduous one that requires extensive and systematic research in various areas. One such area that requires attention is the standardization of plant extracts. The

phytochemical content of *Cissus quadrangularis* may vary due to differences in origin, environmental conditions, and extraction methods, which may affect its efficacy and safety profile. Thus, it is important to have a standardized extract with a definite concentration of active compounds such as ketosteroids and flavonoids.

Another area of importance is the identification and isolation of bioactive compounds that have osteogenic activity. Even though various bioactive compounds have already been reported, their precise molecular structure, including their synergistic effects, is not clearly understood. Advanced techniques such as high-performance liquid chromatography, mass spectrometry, and nuclear magnetic resonance spectroscopy can be effectively employed to study these bioactive compounds. In addition, molecular docking techniques can help us understand their interaction with critical targets that have implications in bone metabolism, such as RANKL, osteoprotegerin, and estrogen receptors.

Another area of importance is the application of novel drug delivery systems (NDDS) that have immense potential to increase the efficacy of *Cissus quadrangularis*. Various conventional formulations have shown low bioavailability and poor absorption of active compounds. Advanced techniques such as nanoparticles, liposomes, nanoemulsions, and polymer-based carriers have shown immense potential to increase their bioavailability. Bone-targeting drug delivery systems, such as hydroxyapatite-binding carriers, have shown immense potential to increase their efficacy.

The integration of artificial intelligence and computational biology in drug discovery and development may expedite the discovery of potential targets and optimize formulation techniques. Such models may use large amounts of data to predict pharmacokinetics, toxicity, and interactions between drugs and herbs, thereby reducing the cost and time involved in the drug development process.

Even though *Cissus quadrangularis* has shown promising results in preclinical trials, it is important to conduct large-scale well-designed RCTs to prove its efficacy and safety in humans. Currently, most clinical trials have shown limitations due to small sample sizes and short study durations. In future, well-designed methodologies such as placebo control and long-term study design must be incorporated into clinical trials to assess *Cissus quadrangularis* efficacy and safety in humans by measuring outcome measures such as bone mineral density and fracture risk reduction and biochemical markers in bone turnover.

Additionally, research should also aim at the evaluation of the pharmacokinetic and pharmacodynamic profiles of the extracts of *Cissus quadrangularis*. This will help in the optimization of the dosing regimen and the improvement of the therapeutic outcome. The herb-drug interaction potential of the herb should also be investigated, especially in patients taking conventional anti-osteoporotic drugs.

Another area of interest for the herb is its potential application in the field of regenerative medicine and bone tissue engineering. The potential of the herb in the stimulation of the differentiation of osteoblasts and the synthesis of collagen has shown its application in biomaterials and bone grafts. The incorporation of the active ingredients of the herb into biodegradable scaffolds may help in the regeneration of bone in critical-sized bone defects.

With regard to the commercialization of the herb and its products, the development of quality control standards and guidelines is important. This is because the regulatory bodies require well-documented evidence of the safety and efficacy of the herb and its products.

However, while *Cissus quadrangularis* possesses tremendous potential as a natural therapeutic drug for treating osteoporosis and bone healing, it is only by undertaking multidisciplinary research in pharmacology, biotechnology, nanotechnology, and clinical sciences that it will be able to reach its true potential and be incorporated into modern healthcare systems as a scientifically accepted treatment option in the future.

## RESULT AND DISCUSSION

Preclinical and early clinical evidence supports *C. quadrangularis* as a potential anti-osteoporotic and bone-healing herbal agent. Biological mechanisms include immunomodulation, osteoblast stimulation, osteoclast inhibition, and antioxidant activity. Nevertheless, the quality of human evidence is variable, and future research must prioritize standardized extract preparations, defined dosing, and larger randomized controlled trials to establish efficacy and safety profiles.

The findings of this review support the potential of *Cissus quadrangularis* as a natural treatment for managing osteoporosis and promoting fracture healing. Preclinical studies in ovariectomized rat models showed significant improvements in bone mineral density, microarchitecture, and biomechanical strength. Treated animals consistently had higher levels of bone formation markers, such as alkaline phosphatase, calcium, and phosphorus. These

results match the plant's chemical makeup, where ketosteroids boost osteoblastic activity, flavonoids lessen oxidative stress-related bone cell damage, ascorbic acid aids collagen production, and beta-sitosterol has anti-inflammatory effects. Together, these factors improve bone formation and repair.

Clinical trials on fracture healing reported quicker relief from pain, swelling, and tenderness in patients taking *Cissus quadrangularis* supplements. Radiographic evidence showed faster callus formation and fracture healing, with some studies noting a reduction of two to three weeks in healing time. In the context of osteoporosis, a placebo-controlled trial with postmenopausal women who had osteopenia showed measurable slowing of bone loss after 24 weeks of treatment. Biomarker studies also showed higher serum parathyroid hormone levels, suggesting a stimulating effect on bone remodeling. Importantly, the lack of significant changes in serum calcium, phosphorus, and alkaline phosphatase indicates that mineral balance remains stable, suggesting a favorable safety profile.

Mechanistically, *Cissus quadrangularis* has a dual role: it stimulates osteoblast formation and inhibits osteoclast formation through the RANKL signaling pathway. Its phytoestrogenic and antioxidant properties provide a solid biological foundation for the positive clinical outcomes and support its historical use in Ayurvedic medicine. However, the evidence is limited by small sample sizes, short study lengths, inconsistent extract standardization, and a lack of data on long-term safety and herb-drug interactions. Future well-designed, multi-center randomized controlled trials with standardized formulations and validated measures of bone mineral density and fracture risk reduction are needed to establish *Cissus quadrangularis* as a recognized adjunct in evidence-based bone health management.

## CONCLUSIONS

*Cissus quadrangularis* exhibits considerable promise as an effective natural drug in the management of osteoporosis and bone disorders. The traditional use of *Cissus quadrangularis* as a "bone setter" is considerably substantiated by scientific evidence. Studies have indicated that *Cissus quadrangularis* increases the rate of proliferation in osteoblasts, stimulates collagen formation, and increases mineralization, thus aiding bone formation and fracture healing [9]. Moreover, *Cissus quadrangularis* is also effective in the inhibition of bone resorption mediated by osteoclasts through the modulation of critical pathways such as RANKL.

Several preclinical studies have indicated that *Cissus quadrangularis* is effective in the promotion of bone healing in animals through accelerated callus formation and increased bone strength. Clinical studies have also indicated that *Cissus quadrangularis* supplementation is effective in reducing pain and swelling in patients with fractures. Moreover, *Cissus quadrangularis* supplementation also exhibited potential in the promotion of fracture healing in humans. Additionally, *Cissus quadrangularis* supplementation may also be effective in delaying bone loss in postmenopausal women through oral administration, as indicated by clinical studies. However, the increase in bone density is inconsistent.

Despite these encouraging results, the current clinical evidence is marred by small sample sizes and a lack of standardization in research protocols. Systematic reviews and meta-analyses of existing research on *Cissus quadrangularis* indicate that, while it possesses positive effects on bone biomarkers and fracture healing, more potent and large-scale randomized controlled trials are needed for the clinical validation of the plant.

With regard to the safety of the plant, it is noteworthy that it is well tolerated with minimal side effects, and hence, it is a candidate for long-term use as an adjunct therapy. Future research on the plant must be aimed at standardizing the extracts, characterizing the active compounds, and designing advanced drug delivery systems for better efficacy.

In conclusion, it is clear that *Cissus quadrangularis* is a promising herb that can serve as a bridge between traditional medicine and contemporary pharmacotherapy for osteoporosis and fracture healing. Future research on the plant is expected to lead to the development of a safe, effective, and acceptable drug for the treatment of osteoporosis.

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