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Role of C*issus quadrangularis* in Bone Fracture and Osteoporosis- A Review

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KEYWORDS

Osteoporosis, *Cissus quadrangularis*, Bone health, Fracture healing, Patent, Marketed products

ABSTRACT:

Osteoporosis is a skeletal disorder causing bone mass reduction and deterioration, increasing fracture risk. Treatments include supplementation, Hormone Replacement Therapy (HRT), and bisphosphonates. HRT can decrease hip and spine fracture risk when administered correctly, but can also cause thromboembolism, withdrawal bleeding, and breast cancer. Alternative therapies like bisphosphonates may also be effective. Given the limitations and side effects of these therapies, there arises a pressing need to explore alternative options to prevent and treat osteoporosis while promoting improved bone health. The growing interest in herbal medicines has arisen from their perceived safety compared to chemically synthesized drugs. Hence, there exists a need for an effective compound of *Cissus quadrangularis* Linn (CQL) that specifically can exhibit the desired attributes, including the prevention and treatment of illnesses and diseases associated with bone health, complemented by the influence of effective fracture healing through its anabolic steroid properties. *Cissus quadrangularis* contains various active compounds, including flavonoids, steroids, and triterpenes. These compounds are responsible for numerous health benefits, such as the flavonoids in CQL, which have anti-inflammatory and antioxidant properties for treating various conditions, including pain, arthritis, and asthma. *Cissus quadrangularis* has garnered attention in scientific research for its potential role in managing obesity and related metabolic disorders. This article reviews *Cissus quadrangularis* Ayurvedic usage, Patents on CQL for bone health and osteoporosis, CQL Marketed Products, Chemical Constituents of CQL in Bone healing, Osteoblasts and osteoporosis and Preclinical and clinical studies of CQL in Osteoporosis and Bone fractures.

1. Introduction

Cissus quadrangularis (Linn), commonly referred to as "Hadjod," has a history of traditional use in India for promoting the healing of fractures. This perennial plant belongs to the Vitaceae family and is a climber throughout India, primarily in tropical regions. In Sanskrit, it is called by the name "Vajravalli." At the same time, in Hindi, it is known as "Hadjod," in Marathi, "Kandvel" in Punjabi, "Haddjor," "Hadbhanga" in oria, "Vedhari" in Gujarati, in Tamil "Perandi," for Telugu "Nalleru," and in English, it's referred as "Veldgrap" or "Edible Stemmed Vine [1]." CQL popularity stems from its exceptional healing properties, making it a key component in various traditional medicinal practices across India. Its impressive adaptability and effectiveness have made it a cherished botanical resource in the region. CQL thrives in warm tropical climates and is typically propagated through stem cutting during June and July. This versatile plant is also known by various other names such as "Adamant creeper," "Square stalked vine," "veldt grape," "devil's backbone," "asthisamharaka," "pirandai," "Sannalam," "Nalleru," "Vajravelli," and "Mangara valli." Its natural habitat includes India, Bangladesh, Sri Lanka, Africa, and Southeast Asia, and it is exported to Brazil and the southern United States for its medicinal uses [2] . CQL contains various active compounds, including flavonoids, steroids, and triterpenes. These compounds are responsible for numerous health benefits, such as the flavonoids in *Cissus quadrangularis*, which have anti-inflammatory and antioxidant properties for treating

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various conditions, including pain, arthritis, and asthma [3]. The steroids in the CQL promote bone growth and healing, an option for fractures and other bone injuries [4] . The triterpenes in CQL have been shown to lower cholesterol and blood sugar levels for people with diabetes and high cholesterol [5] . CQL can be formulated in many forms, such as capsules, powders, and teas. *Cissus quadrangularis*, with its distinctive growth characteristics, is a remarkable botanical specimen. Typically, it reaches a height of 1.5 meters, making it an easily identifiable climber. Its branches are notable for their quadrangular cross-section, featuring internodes measuring approximately 8 to 10 cm long and 1.2 to 1.5 cm wide. The branches also display a rugged and leathery edge along each angle, adding to its unique appearance [6] . The leaves of CQL are equally intriguing. They are trilobed, serrated edges, and their width spans 2 to 5 cm. The tendrils emerge from the opposite side of the nodes on the branches, aiding it in climbing and anchoring itself. Adding to its aesthetic appeal, CQL produces racemes of delicate flowers. These blooms come in varying hues of white, yellowish, or greenish, lending a touch of elegance to the plant. Furthermore, as the berries mature, they undergo a striking transformation, turning into a vibrant shade of red [7]. This captivating combination of growth patterns and visual elements contributes to *Cissus quadrangularis*'s unique botanical profile.

2. MORPHOLOGY

This climbing herb, known for its tenacity, exhibits many intriguing botanical features. Its tendrils are straightforward and are positioned opposite to the leaves during the plant's early stages, gradually shedding leaves as they mature. The leaves can be either simple or lobed, with shapes ranging from cordate, broadly ovate to reniform. Their margins are typically serrate or dentate, and in some instances, they may manifest as trifoliate and devoid of any hair, displaying a smooth texture. The petite greenish-white flowers, which are bisexual and tetramerous, are arranged in umbellate cymes, mirroring the leaves' opposite arrangement. The calyx forms a cup-like structure around the base of the flowers. When it comes to the fruit, it takes on the appearance of globose or obovoid fleshy berries, noted for their succulence yet characterized by their intense acridness. These berries transition in color from dark purple to black and house a single seed, which can be either ellipsoid or pyriform in shape. The stem of this herb is quite distinctive, boasting a buff hue with hints of green and branches dichotomously, adopting a sub-angular form. The stem is devoid of hair, presenting a fibrous and smooth texture.

3. AYURVEDIC USAGE:

Within Ayurvedic medicine, CQL has a longstanding reputation as a versatile remedy for various health concerns. Its multifaceted applications span a spectrum of therapeutic purposes. In Ayurveda, it is advocated as an alternative remedy, addressing many health issues. Moreover, it serves as an anthelmintic, effectively combating parasitic infections that afflict individuals in different regions. Beyond its anthelmintic properties, CQL has the property of dyspeptic and digestive aid, facilitating the proper functioning of the digestive system and alleviating discomfort associated with indigestion [8]. As a tonic, it bestows a sense of overall well-being and vitality when incorporated into wellness regimens. This plant is used as an analgesic in Ayurvedic treatments, particularly for managing eye and ear ailments, where its properties are harnessed to alleviate pain and discomfort. It further extends its therapeutic utility to address conditions like irregular menstruation and asthma, where it is administered to help manage and alleviate symptoms [9]. CQL has garnered attention in scientific research for its potential role in managing obesity and related metabolic disorders. Studies have highlighted its effectiveness, suggesting it may contribute to weight management efforts [10].Additionally, its antioxidant properties have been demonstrated in its ability to scavenge free radicals, which are implicated in various health issues [11] .In the contemporary context, formulations often feature CQL extracts in combination with other active ingredients. These formulations are primarily designed to assist in managing overweight and obesity and the complications that can arise from these conditions, such as metabolic syndrome (syndrome X) [12]. This dynamic blend of traditional wisdom and modern science underscores the enduring significance of CQL in natural health remedies.

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4. PATENTS ON CQL BASED ON BONE HEALTH AND OSTEOPOROSIS

There are currently two patents filed for CQ over bone disorders or for fracture treatments, which are as follows.

a. Patent 1:

Villoo Morawala Patell, holding the patent with patent publication number US 2009/0280,196A1 dated November 12, 2009, is credited as the inventor. This patent is titled "Utilization of CQL Plant Extracts and the Extraction Procedure for Addressing Osteoporosis." The patent pertains to deriving extracts from the entire CQL plant. The invention encompasses both the methods and compositions designed to prevent, treat, or manage conditions such as osteoporosis and related disorders, including bone loss, fractures, osteoporosis induced by glucocorticoids, Paget's osteoarthritis, peri-prosthetic, and illness osteolysis, cartilage deterioration, and defective osteogenesis, and similar ailments. The patent encompasses the administration of prophylactic and therapeutic doses of the CQL plant or its extracts to individuals requiring such treatment, predominantly targeting human subjects. The compositions may consist of single extracts or combinations thereof. Furthermore, the patent extends to extracts derived from various parts of the CQL plant, their preparation, medications containing these extracts, and their application in the production of medicines [13].

b. Patent 2:

Lal Hingorani, Vijay Thawani, and Brian Cortes are responsible for inventing and holding a patent with the publication number US 2005/0048,141A1. This patent, titled " Use of the plant CQL or its extracts for osteohealth including prevention or mitigation of degenerative disease, fracture healing, and anabolic increase in osteo tissues," was granted on March 3, 2005. The innovation described herein pertains to extracting substances from the CQL plant. The invention encompasses formulations and techniques for preventing, treating, or managing conditions like osteoporosis, bone loss, fractures, osteoporosis brought on by glucocorticoids, Paget's osteoarthritis, peri-prosthetic and illness osteolysis, cartilage deterioration, and defective osteogenesis, and related ailments. It involves administering the CQL plant or its extract compositions, which may consist of a single extract or any suitable one. Additionally, the invention covers extracts from various parts of the CQL plant, the creation of these extracts, the pharmaceuticals containing them, and their application in medicinal product development [14].

5. MARKETED PRODUCTS [15]:

Various brands offer a range of products, including tablets, capsules, powders, and drops, containing CQL or Hadjod, each with its unique composition and recommended dosage for specific purposes.

a. **Tablets**:

Himalaya Pvt. Ltd. produces "Hadjod" tablets, containing 450 mg of Hadjod (CQL), designed to accelerate fracture healing, promote bone restoration, and support joint wellness. H & C Herbal Ingredients Experts offer "Hadjod" tablets with 450 mg of Hadjod (CQL) to strengthen bones, enhance joint health, and reduce swelling. Genius Nature Herbs Pvt. Ltd. manufactures "Genius Herb's CQL" tablets, primarily for weight loss in 2000 mg or 3000 mg doses. Maxcure Nutravedic Ltd. produces "Walktall" tablets containing 500 mg of vitamin K, calcium carbonate, and CQL. These tablets are used for joint pain and inflammation, especially in osteoarthritis cases. Zenonz International presents "Zenonz Hadjod" tablets, consisting of 500 mg of CQL prepared from the stem, with benefits including improved mobility, accelerated fracture healing, and support for bodybuilding.Tregen Pharmaceutical Pvt. Ltd. offers "Nopore-750" tablets containing 100 mg or 750 mg of CQL standardized to saponins from Moringa oleifera and ketosterones extract. These tablets are designed for osteoporosis, fractures, and joint relief.

b. Capsules:

“Bixa Botanical” offers "Hadjod" capsules with 450 mg of Cissus/Hadjod extract, enriched with 2.5% 3-Keto steroids, to promote more rapid healing of bone, serve as a mineral tonic for bone, support blood clot and ulcer healing. “Primeforce” provides "Cissus extracts" capsules, Ketosterones, and 1000 mg of CQL extract (root and stems), supporting weight control, joint health, and enhanced bone fracture recovery. “Maxgars” produces "Cissus extract" capsules, containing an entire aerial extract of 1000 mg of CQ herbs with 3-ketosterone, intended for healing bone fracture, relief

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from weight loss, and joint discomfort. “Best Source Nutrition Products” presents capsules with 350 mg of CQL extract (stem) standardized to 5% Ketosterone, designed to enhance bone health, provide joint strengthening, and aid tissue healing.“ Quality Supplements and Vitamins, Inc.” offers "Strum’s Intensive Bone Formula" capsules, as a dietary supplement, has CQL (aerial section extract - 10% ketosterones), DimaCal®, vitamin D, vitamin k, silica, zinc, boron, magnesium, and 300 mg of potassium citrate. “Tonga Pharmaceutical” provides "CQL plus capsules," combining extracts of CQL along with 500 mg of selenium, chromium, soy, and B vitamins. Targeting inflammation reduction, pain relief, joint wellness, growth of bone tissue, and treatment of menstrual disorders. “Greencross Health Innovation” offers "Vitagreen Hadjod" capsules with 500 mg of CQL extract to increase bone mineral density and assist in osteoporosis management. “Sage Care” produces "Herbo Natural Hadjodh (CQL) Extract Capsule" containing 500 mg of CQL extract for bone strength and osteoporosis support. Hawaiian Herbals offers "Hawaiian Herbal CQL Capsules" with 500 mg of CQL extract, addressing inflammation and pain reduction, joint health, bone tissue development, and conditions affecting women such as menopause problems and low libido“ Akumentis Healthcare Ltd.” presents "Bindbone CQL Ashvagandha" capsules, combining CQL (750 mg) with Ashvagandha (100 mg), promoting joint soothing, flexibility, and improves joint and cartilage health. “Sigmek Nutriscience” offers "Nutramagik Cissus & Boswellia" capsules containing Boswellia serrata with CQL extracts (500 mg and 250 mg, respectively), which minimize pain and inflammation, defend against free radical damage, and promote bone and joint health.“TVS Biotech” provides "TVS Biotech Cissus Capsules" with 475 mg of CQL extract, specifically intended for bone fracture care.

c. Powders:

“Sinhal Herbs” offers "CQL (Hathjod)" powder in 3 gm doses, promoting improved joint support, connective tissue, and bone health healing. “Himalaya” presents "Hadjod powder" with 3 gm doses for skeletal and joint health and offers antidiabetic therapeutic purposes. “Bixa Botanical” offers "Hadjod prepared from roots of CQL" powder, which supports bone healing and improved cartilage health. It is also helpful in blood clot ailments, healing ulcers, anti-inflammation, and promoting weight loss and a healthy metabolism.

d. Drops:

“Hawaiian Herbal CQ” offers "CQ plus" drops containing 500 mg of CQL extract, with benefits including inflammation reduction, pain relief, joint health promotion, and bone tissue support. “Hawaiian Herb” provides "CQ Drops" with an Extract of CQL (10 drops), offering similar advantages for inflammation and pain reduction, joint health support, growth of bone tissue, and assistance in managing menopause and other female problems and libido.

6. CHEMICAL CONSTITUENTS

The analysis of phytochemical components within CQL has unveiled a rich composition, emphasizing its significance in various nutritional and therapeutic contexts. Among the notable constituents, the plant has a substantial level of ascorbic acid (vitamin C), carotene (a precursor to vitamin A), and anabolic steroidal compounds. In particular, the stem of CQL stands out as a reservoir of valuable bioactive compounds. Researchers have identified two distinct asymmetric tetracyclic triterpenoids from the stem, which contribute to the plant's diverse chemical profile. Additionally, two steroidal principles have been isolated from this plant part, further enriching its phytochemical repertoire. B-sitosterol, δ-amyrin, δ-amyrone, and flavonoids (such as quercetin) have been isolated among the identified components. These compounds hold great promise because of their potential to influence many metabolic and physiological processes within the human body. For instance, β-sitosterol has garnered attention for its potential in managing cholesterol levels and supporting heart health. δ-amyrin and δ-amyrone have anti-inflammatory and analgesic properties, offering prospects for pain management and alleviating inflammatory conditions. The diverse phytochemical profile of *Cissus quadrangularis*, encompassing vitamins, steroidal substances, and other bioactive compounds, influences its multifaceted potential in nutrition, traditional medicine, and pharmaceutical applications. Further research into these compounds' specific mechanisms and therapeutic potential is warranted to unlock the full spectrum of benefits this

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plant can offer to human health and well-being [16,17] . Figure 1 shows the chemical constituents of *Cissus quadrangularis*. Phytochemical investigations conducted on the methanol extract of CQL have unveiled a rich array of seven alicyclic lipid constituents, which includes d-amyrin, onocer-7-ene-3a, 21b-diol, d-amyrone, and 3,3',4,4'-tetrahydroxy biphenyl, which were successfully isolated and quantitatively analyzed using HPTLC and HPLC techniques. This analysis was performed on samples collected from diverse geographic zones across India. Furthermore, a diverse range of compounds has been isolated from *Cissus quadrangularis*. It includes flavonoids like quercetin and kaempferol and stilbene derivatives such as quadrangularins A, B, and C. Additionally, this remarkable plant has identified and extracted the phytosterols resveratrol, piceatanon, pallidol, perthenocissi, and others. Interestingly, the stem extract of CQL stands out for its high content of essential minerals, specifically calcium ions and phosphorus. These minerals are pivotal in supporting bone growth, making CQL a valuable natural source for bone health. In summary, the phytochemical profile of CQL is diverse and impressive, encompassing triterpenes, lipids, flavonoids, stilbene derivatives, and essential minerals. These findings critically establish the plant's potential as a valuable resource for various health-related applications, particularly bone health [6].

7. CQ in Bone healing, Osteoblasts, and osteoporosis

a. Biology of Bone remodeling

Orchestration of such as Vitamin D, growth hormone (GH), parathyroid hormone (PTH), and regional signaling via cytokines and growth factors are all examples of the influential role of bone remodeling even after completing skeletal growth. This remodeling process is termed fundamental multicellular units found at certain locations on the surface of bones. They are executed by two essential cell types: osteoclasts (engaged in bone production) and osteoblasts (bone resorption) (Tolstoi 2004, Manolagas and Weinstein 1999). Both osteocytes and osteoclasts originate from precursor cells found in the development and activation of these cells in the bone marrow. Bone marrow-produced cytokines and growth factors which, are influenced by mechanical stimulation and systemic variables [18]. The balance between regulatory and metabolic processes is crucial for the bone remodeling process signals and cellular activities. When the ability to deactivate osteoclasts or active osteoblasts is compromised, it can result in a net loss of bone mass, potentially leading to osteoporosis. Additionally, bone remodeling serves several vital functions beyond maintaining skeletal integrity. It helps repair micro-damage to bones incurred from everyday activities [19] and supports the mineral homeostasis of the body by regulating calcium and phosphate levels. Moreover, this dynamic process facilitates the release of growth factors stored within the bone matrix, contributing to tissue repair and regeneration in various contexts, such as injury healing. Furthermore, the balance of bone remodeling is influenced by numerous factors, including hormonal changes, aging, and lifestyle choices like diet and physical activity. Hormonal fluctuations, especially in postmenopausal women, can disrupt this equilibrium, leading to accelerated bone loss and an increased risk of osteoporosis. Therefore, understanding and managing the intricate mechanisms of bone remodeling is crucial for maintaining skeletal health.

b. Osteoporosis's aetiology

Even though several risk factors have been identified as contributors to the development of osteoporosis, influencing factors like Caucasian ethnicity, advancing age, being female, a history of fractures, drunkenness, and smoking are precise etiology of this osteoporosis [20]. Nevertheless, various hypotheses have been proposed to elucidate its underlying causes. Some of these theories pertain to cellular aging of bone cells, and lifestyle elements (particularly Exercise, diet, and declining vitamin D metabolism are other factors associated with aging [24]. According to the theory, aging results in reduced vitamin D metabolism. Activated vitamin D plays a central role as a signaling molecule in regulating calcium absorption in the intestines. Consequently, reduced vitamin D metabolism results in decreased intestinal calcium absorption, triggering parathyroid hormone (PTH) signaling through the endocrine system [21]. This signaling prompts the withdrawal of calcium derived from bones. As time goes on, this ongoing extraction leads to bone mass decreasing due to the loss of calcium from the bones, eventually resulting in osteoporosis. Osteoporosis is a systemic skeletal disorder characterized by a reduction in bone mass and the

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deterioration of bone tissue's microarchitecture, resulting in increased bone fragility and susceptibility to fractures. It primarily stems from insufficient bone tissue, often known as low bone mass or poor bone density. The diminishing structure and bone density frailty render bones vulnerable to fracturing even from minimal stress [22] . The low bone mass density commonly escalates with advancing age. As an individual ages, especially in middle and old age demographics, this condition becomes a progressively significant contributor to painful fractures and associated complications such as deformities, decreased mobility, and, in severe cases, mortality. The most prominent complications of osteoporosis include hip, spine, and Colle's fractures. Severe osteoporosis significantly diminishes the quality of life, primarily due to pain, physical deformities, restricted mobility, and the constant fear of experiencing additional fractures. Following fracture healing, the physical limitations endured by individuals can further worsen their overall quality of life. Other therapeutic approaches encompass Supplemental calcium, Hormone Replacement Therapy (HRT) for postmenopausal osteoporosis, and alternative therapies such as bisphosphonates[23]. Utilizing calcium supplements during clinical studies examining the effectiveness of calcium and vitamin D supplementation has yielded inconsistent results [24] . When administered at an adequate dosage, hip and spine fracture risk can be decreased with hormone replacement therapy (HRT). Still, the advantages are countered by adverse consequences such as thromboembolism, withdrawal bleeding, and breast cancer [25]. Figure 2 shows the Colle's distal radial fracture [26] and Figure 3 shows the Macroscopic feature of osteoporotic vertebra with collapse and trabecular thinning [27]. Bisphosphonates, another treatment option, is often associated with drawbacks, including esophagitis, diarrhea, and constipation. Given the limitations and side effects of these therapies, there arises a pressing need to explore alternative options to prevent and treat osteoporosis while promoting improved bone health. The growing interest in herbal medicines has arisen from their perceived safety compared to chemically synthesized drugs. India has a rich tradition of utilizing various Ayurvedic remedies for many years. One such natural remedy within the realm of Ayurveda is *Cissus quadrangularis*, an indigenous plant medicine native to India. Hence, there exists a need for an effective compound of *Cissus quadrangularis*, which can exhibit the desired attributes, including the prevention and treatment of illnesses and diseases associated with bone health, complemented by the influence of effective fracture healing through its anabolic steroid properties, figure 4 illustrate the mechanism of *Cissus quadrangularis*.

Figure 1:Colle's distal radial fracture **[25]**

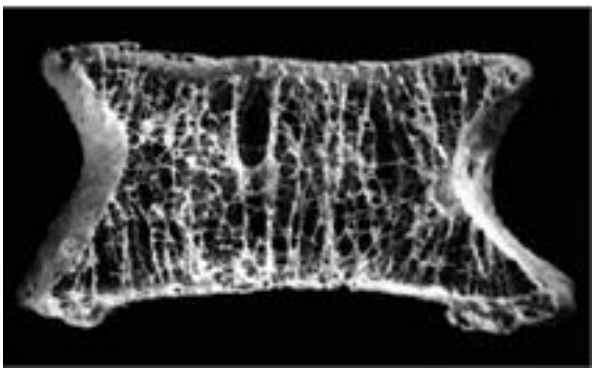

Figure 2:Macroscopic feature of osteoporotic vertebra with collapse and trabecular thinning [26]

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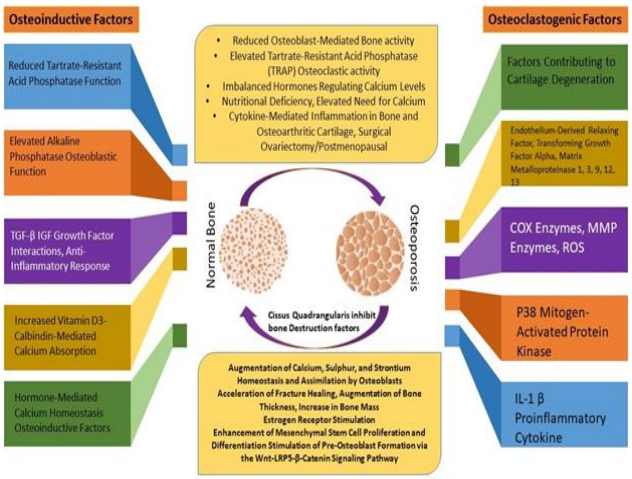

Figure 3:Possible Mechanisms Behind Antiosteoporotic Activity of CQL

c. CQL IN BONE FRACTURE:

CQL elicits a minimal tissue response in the fractured area, facilitating optimal decalcification in the initial stages of the healing process with limited callus formation. As a result, the increase in calcium is precisely calibrated to bridge the two fractured bone segments, expediting their remodeling [28] . This accelerated calcification process and earlier remodeling contribute to the swift recovery observed in animals treated with Cissus. Furthermore, Cissus demonstrates the capacity to substantially enhance the Tensile strength of broken bones, reaching approximately 90% of their typical strength within six weeks [1] . CQL is vital in augmenting collagen, mucopolysaccharides, calcium, phosphorus, and other elements while improving their functional efficiency. Mucopolysaccharides are pivotal in the healing process as they supply essential components for repair. Therefore, during the early phases of bone, higher buildup of these compounds during fracture healing leads to a more rapid healing rate. The expeditious use of these raw materials further accelerates the healing process. CQL promotes mucopolysaccharide buildup and expedites mucopolysaccharide removal, vanishing from the fractured area, coinciding with accelerated calcification and forming a more robust callus [29]. CQL contains substantial calcium, vitamin C, beta-carotene, anabolic steroids, and other nutrients. These steroid anabolic drug compounds derived from CQL notably accelerate the early regeneration of all connective tissue to impact the pace of fracture repair tissues originating from mesenchymal sources [30] . These tissues encompass fibroblasts, chondroblasts, and osteoblasts, all integral to the callus's rapid callus mineralization and healing. Cissus has a particularly pronounced influence on osteoblastic growth, surpassing its effects on other cellular responses. The multifaceted properties of CQL extend beyond its influence on fracture healing. It significantly impacts bone health and regeneration by orchestrating a symphony of cellular processes. This herbal remedy expedites the deposition of essential minerals like calcium and phosphorus within the fractured region. It promotes the synthesis of crucial connective tissue components such as collagen and mucopolysaccharides [7] .Furthermore, Cissus's high vitamin C and carotene A content contributes to its antioxidant capabilities, protecting bone tissues from oxidative stress and potentially mitigating the risk of bone-related degenerative disorders like osteoporosis. Its anabolic steroidal substances play a pivotal role in stimulating the proliferation and maturation of bone-forming cells (osteoblasts), ensuring the efficient repair and strengthening of fractured bones. Figure 5 shows the image of bone healing [31]. Therefore, CQL emerges as a potent natural remedy that accelerates fracture healing and enhances overall bone health, offering a holistic approach to skeletal well-being. Its potential implications in preventing and treating other health-related conditions warrant further exploration and investigation.

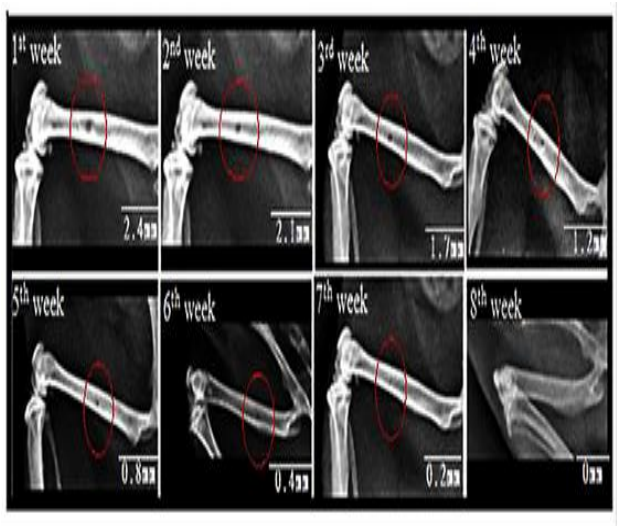

Figure 4: *Cissus quadrangularis* Bone Healing Activity [31]

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d. Preclinical and clinical studies of CQ in Osteoporosis and Bone fractures

In a study by Deka et al. 1994, the impact of the methanolic extract of CQL on the healing process of experimentally fractured radius-ulna bones in dogs was thoroughly investigated. The animals treated with CQ exhibited a notably accelerated initiation of the healing process when compared to the control group, as confirmed through radiological and histopathological assessments. The serum calcium levels in both groups experienced a decline by the 11th day following the fracture. However, the treated group showed a more substantial reduction in serum calcium levels than the control group. Radiographic evidence indicated an early periosteal reaction and bony dissolution in the treated group, signifying a swifter healing process. No significant alterations in serum calcium levels were observed in either group on post-fracture. The greater decrease in serum calcium levels within the treated group may be attributed to the faster healing process, which necessitates increased calcium mobilization in callus formation. Histopathological examination further corroborated the accelerated initiation of healing, characterized by heightened osteoblastic activity on the 11th day post-fracture and bony trabeculae on the 21st day following the fracture in the treated group [32]. Linn as a supplementary treatment alongside a unilateral diaphyseal femoral osteotomy was performed in dogs as an internal fixation for bone healing surgically done wherein an ethanolic extract of CQL was topically applied to the skin surface twice daily. Additionally, subcutaneous injections of this extract, administered at 50 mg per kilogram of body weight, were administered every other day for 20 days following the surgery. It resulted in an expedited bone healing process characterized by completely bridging comminuted bone fragments. Extensive deposition of new bone tissue was observed, along with the establishment of both the periosteum and medulla across the location of the osteotomies in the treated animals. In contrast, the bone healing process in the control group progressed relatively slow, thus ensuring the potential benefits of incorporating CQL extract as a supplement to fixation, promoting accelerated and robust bone healing, and providing valuable insights for future research and clinical applications [33]. Through morphometric analysis, it was determined that the proportion of ossified cartilage (bone) relative to the total length in offspring born to dams treated with CQL petroleum ether extract was significantly higher (P 0.001) compared to the control group, indicating that maternal administration of CQL petroleum ether extract during pregnancy promotes fetal bone growth during the critical intra-uterine developmental phase The impact of the extract of petroleum-ether derived from CQL on an osteoporotic rat model established through ovariectomy unveiled that the CQ petroleum-ether extract played a pivotal role in mitigating bone loss, observed by the increase in femur weight. CQ contributed to a reduction in osteoclastic activity, ultimately fostering bone formation. This osteoclastic activity was corroborated through tartrate-resistant acid phosphatase (TRAP) staining, while bone formation was assessed using alkaline phosphatase (ALP) staining on sections of the femur. The intensity of color exhibited by Tartrate resistant acid phosphatase (TRAP) and alkaline phosphatase (ALP) enzymes in the images confirmed that the CQ exerted a beneficial influence on both those enzymes, underlining its potential as a promising candidate for the prevention and treatment of postmenopausal osteoporosis. These findings offer valuable insights into the therapeutic prospects of CQL in addressing bone health concerns associated with postmenopausal conditions [34] . Researchers examined the effects of CQL petroleum ether extract on multiple aspects of mesenchymal stem cells from bone marrow behavior. Combined effects of osteogenic media and CQL on these cellular processes on the proliferation rate of these stem cells, their differentiation into osteoblasts (a process known as osteoblastogenesis), and the calcification of the extracellular matrix revealed that the petroleum ether extract of CQL played a significant role in promoting the distinction between bone increasing calcification and transforming marrow mesenchymal stem cells into ALP-positive osteoblasts of the extracellular matrix. CQ boosted the pace of the stem cells' growth compared to control cells [35] . Phytoestrogen-rich fraction (IND-HE), extracted from the aerial parts of CQL, on ovariectomy-induced osteoporosis in rats yielded statistically significant enhancements in bone thickness, density, and bone hardness. Furthermore, these treatments led to a marked increase in serum estradiol levels and elevated levels of serum vitamin D3 and serum calcium compared to the control group. Conversely, alkaline phosphatase

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levels were notably reduced following treatment with IND-HE and estrogen. These findings provided substantial evidence to support the assertion that the phytoestrogen-rich fraction, IND-HE, possesses robust antiosteoporotic properties. This research insists on the potential of CQL as a valuable resource in developing therapeutic interventions for combating osteoporosis, particularly in the context of hormone-related bone loss [36]. The anti-osteoporotic potential of the ethanol extract derived from CQL was evaluated in an ovariectomized rat model. The ethanol extract's impact was evaluated through a comprehensive assessment encompassing biomechanical, biochemical, and histopathological parameters. The results demonstrated a discernible and beneficial antiosteoporotic effect attributable to the ethanol extract of CQL [37] .

In a study conducted by Viswanath et al., the effectiveness of treatments involving CQL in combination with Zingiber officinalis Rosc in managing osteoarthritis observed a notable reduction in joint pain, joint swelling, and tenderness, with no observed risk of adverse side effects. Furthermore, the combination therapy exhibited an even more pronounced effect, with an extremely significant reduction in joint swelling and tenderness noted, which ensures these treatments' potential benefits in alleviating osteoarthritis symptoms [38] . The impact of ethanol extract derived from CQL on osteoblast differentiation and function was examined utilizing murine osteoblastic cells, which revealed that the mRNA expressions of genes associated with osteoblast function remained unaffected following treatment with CQ and resulted in an increase in alkaline phosphatase (ALP) activity and the extent of mineralized nodules in comparison to the control group. It ensures ethanolic CQL influence on osteoblastic activity by enhancing ALP activity and the mineralization process, mediated through the MAPK-dependent pathway [39] . In an early reported study by Navin et al., the fracture union and the efficacy in reducing pain and swelling in a 26-year-old male patient diagnosed with Bennett's fracture involving CQL exhibited rapid fracture union, with complete healing observed within six weeks of treatment. Subsequent radiographic evaluations following treatment confirmed a successfully united fracture with a substantial amount of callus formation, indicating a favorable outcome supporting the potential of CQL as a beneficial intervention in promoting the healing process and achieving positive clinical outcomes in cases of fractures, particularly Bennett's fractures [40] . The petroleum ether extract of CQL promotes the differentiation of these stem cells into ALP-positive osteoblasts, augments extracellular matrix calcification, and accelerates the proliferation rate of those marrow mesenchymal stem cells. Cells cultured in osteogenic media supplemented with CQL exhibited elevated rates of proliferation, differentiation, and calcification compared to control cells, which supports the therapeutic potential of CQL in supporting bone health and regeneration [34]. In an *In-vivo* study conducted on osteotomized rats, researchers investigated the regenerative effects of *Cissus quadrangularis*, *Withania somnife*ra (*W. somnifera*), and their combination therapy on bone and cartilage. Exposure of chondrocytes to interleukin-1β (IL-1β) induced significant toxicity and cell death. However, the herbal treatment effectively mitigated IL-1β-induced cell toxicity while promoting cell growth and proliferation. CQL demonstrated the inhibition of gene expression associated with cytokines and matrix metalloproteinases, which are known to exacerbate cartilage and bone degradation. In osteotomized rats, treatment with CQL led to a substantial enhancement in alkaline phosphatase activity and cartilage tissue formation compared to untreated rats. These findings highlight the potential of CQL in promoting bone and cartilage regeneration while alleviating inflammatory-induced cell toxicity [41] . The impact of CQL (CQ), a medicinal herb, was assessed concerning bone loss after ovariectomy in C57BL/6 mice, revealed no discernible alterations were observed in the bone at the tibiofibular junction across the various tested animal groups, and CQ exhibited a significant inhibitory effect on bone loss. This effect was particularly pronounced in the ovariectomized mice's cancellous and cortical bones of the femur and proximal tibia. Thus, CQL mitigates bone loss, often associated with conditions like osteoporosis. CQL holds promise as a natural intervention to counteract the adverse effects of ovariectomy on bone density and integrity [4] by specifically targeting the cancellous and cortical bone regions in the femur and proximal tibia. Primary cultures of osteoblasts were employed as a model system to investigate the influence of CQL on various osteoblast functions. The isolated compounds derived from CQL were found to have a profound impact on osteoblast

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behavior. Specifically, these compounds elicited a notable increase in osteoblast differentiation, signifying the process by which osteoblasts mature and acquire their specialized functions in bone formation. Additionally, they were observed to enhance mineralization, which is a critical step in forming mineralized bone tissue.These findings collectively indicate that CQL possesses the potential to stimulate and promote key aspects of osteoblast activity and function. This research sheds light on the valuable role that CQL may play in enhancing bone health and regeneration, particularly in the context of osteoblast-related processes [42] . The examination of the impact of the ethanolic extract derived from CQL on human osteoblast-like SaOS-2 cells encompassed various critical aspects of cell behavior. It was observed that the lactate dehydrogenase levels in the conditioned medium from CQL treated cells remained within non-toxic ranges for osteoblastic cells, ensuring their viability. Furthermore, through thymidine incorporation assay, it was discerned that Treatment for CQL markedly DNA synthesis in human osteoblastic SaOS-2 cells has enhanced indicated heightened cell proliferation, implying that the extract promotes the growth of these cells. Crucially, the ethanolic extract of CQL exerted anabolic effects on human osteoblast cells. It was achieved by enhancing Runx2, an essential transcription factor with both mRNA and protein expression. integral to the bone matrix protein modulation. These findings illuminate the mechanistic underpinnings of CQL in augmenting the increase in and osteoblastogenesis of human osteoblastic cells, contributing valuable insights into its potential therapeutic applications in bone health and regeneration [7].

8. CONCLUSION

In conclusion, it is a need for further study and treatments due to CQL efficacy in bone fracture and osteoporosis. The creation of novel formulations that combine traditional knowledge with cutting-edge research as the scientific community continues to investigate the possibilities of this natural material. The combination of ancient knowledge and contemporary scientific exploration highlights the enduring importance of CQL in natural health remedies. Consequently, there is a compelling demand for developing a potent CQL compound that can effectively address various aspects of bone health and ailments, encompassing the prevention and treatment of related diseases. This research should also investigate harnessing its anabolic steroid properties to promote efficient fracture healing. In doing so, we can unlock the full potential of CQL in enhancing overall well-being and bone health. This avenue of future research holds a great promise for improving healthcare outcomes via CQL.

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