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Role of *Cissus quadrangularis* in bone loss pathologies

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Abstract

Cissus quadrangularis (CQ) is a well-known medicinal plant from Vitaceae family. It shows various pharmacological activities such as, anti-inflammatory, antioxidant, anti-osteoporotic, antimicrobial, antiobesity, antinociceptive, anticonvulsant, antigluco-corticoid, and antidiabetic activity. Among these, bone healing and anti-osteoporotic properties are the most studied and demonstrated across multiple pre-clinical and clinical studies.

Bone loss is a condition which must be treated with proper medication at its early stages for faster recovery and to maintain quality of life. Bone loss may be due to impaired remodeling or bone fracture or due to pathological conditions like osteoporosis. Current management strategies include most of the synthetic agents that need to be administered for long durations and associated with several adverse effects. Hence there is a need for supportive herbal treatment options which can reduce or prevent bone loss with minimal safety concerns. CQ enhances bone formation and reduces bone resorption process to maintain bone remodeling and bone homeostasis through various mechanisms. With an increasing number of studies and publications on this subject, the exact role played by CQ in the management of bone loss is getting clearer. This narrative review provides a summary of the mechanisms of action of CQ extract as demonstrated across various *in-vitro*, animal model and clinical studies.

Keywords: Bone resorption, osteoporosis, fracture healing, anti-osteoclastogenic, osteoblastogenesis

Introduction

Since ancient times, medicinal plants have been used as remedies for various pathological conditions. *Cissus quadrangularis* (CQ) is one such well-known medicinal plant from Vitaceae family. Veldt Grape, Winged Treebine and Devil's Backbone are some common names of CQ. Due to its bone joining ability, CQ is also known as Asthisandhan in Sanskrit and Hadjod in Hindi which literally translates to 'bone setter'. The stem and leaves of CQ are the parts which are used in medicine. It mainly occurs in America, Australia, India, Sri Lanka, Java, Southeast Asia, and Africa^[1-5].

CQ is commonly used in Ayurvedic and Siddha systems of medicines, mostly as a general tonic, for bone fracture healing and as an analgesic. Besides these, CQ further shows various pharmacological activities such as, anti-inflammatory, antioxidant, anti-osteoporotic, antimicrobial, antiobesity, antinociceptive, anticonvulsant, antigluco-corticoid, and antidiabetic activity^[6, 7, 8, 2]. Traditionally, CQ is used in the management of a wide range of disease conditions such as gastritis, bone fractures, osteoporosis, skin infections, heart disease, cancer, constipations, eye diseases, piles, anemia, ulcer, asthma, menstrual disturbances, burns and scurvy^[4, 5]. From various analytical studies CQ extracts were reported to contain numerous bioactive compounds such as alkaloids, phytoestrogenic steroids, calcium, resveratrol, piceatannol, pallidol, *Parthenocissus, quadrangularis*, ascorbic acid, carotene, flavonoids (quercetin), vitamins, enzymes, nicotinic acid, tyrosine, triterpenoids, β -sitosterol, δ -amyrin, δ -amyrone and ketosteroid^[1, 3, 4]. Amongst the various medicinal properties, bone healing and anti-osteoporotic properties are the most studied and demonstrated properties of CQ.

Bone fracture is a common injury and one that is associated with the burden of higher treatment costs, decreased social productivity and individual disability. There is an increased incidence of trauma and life-threatening bone fractures due to increased access to motorized transportation and advanced mechanical machinery. Approximately 5 to 10% of fractured bones end in nonunion and/or incomplete healing.

Fracture healing is a complicated cellular process. Post-surgical, prescription of supportive medication for early recovery is an important aspect of fracture treatment [9]. Osteoporosis is a metabolic skeletal disorder leading to increased risk of fractures due to reduced bone strength. Typically, it's an age-related disease characterized by compromised bone density and bone quality. Osteoporosis is more frequent in women than men due to postmenopausal estrogen deficiency induced bone loss. Current management strategies include selective estrogen receptor modulators like raloxifen and droloxifen, estrogens in hormone replacement therapy, bisphosphonates, and calcitonin. These all are synthetic agents that need to be administered for long durations and associated with side effects such as increased risk of endometrial and breast cancer, hypercalcemia, hypercalciuria, breast tenderness and thromboembolic events [5, 10]. Hence there is need of supportive herbal treatment options which can reduce or prevent bone loss with minimal side effects. CQ has been used in traditional medicine for a long time. The therapeutic use of CQ is also supported by scientific studies leading to better understanding of the mechanism of actions. In this review, mechanisms of action of CQ extract in preventing bone loss, associated with bone fractures and osteoporosis, identified across various pre-clinical and clinical studies have been summarized.

Bone physiology and bone loss pathologies

Bone is a dynamic tissue which continuously undergoes modeling and remodeling cycles. In modeling, bone formation and bone resorption occur independently at distinct sites. Bone remodeling is the process of renewal of old and damaged bones, which helps to maintain skeletal integrity by concomitant bone resorption and bone formation at a distinct site. The equilibrium between bone resorption and bone formation has a crucial role in bone homeostasis. Osteoporosis is the pathological condition resulting from the impaired remodeling process, where bone resorption get favored over bone formation [10]. Unbalanced bone remodeling also leads to conditions like micro-architectural deterioration of bone, bone loss, and ultimately fractures [11]. Mainly three types of cells involved in remodeling process - osteoclasts (bone resorbing), osteoblasts (bone forming) and osteocytes (former osteoblasts that have become trapped in the bone matrix).

Hardness and rigidity of bone is the output of bone mineralization process, which is regulated by osteoblasts. Mesenchymal stem cells (MSCs) proliferate and differentiate forming osteoblasts by the process known as osteoblastogenesis. Runt-related transcription factor 2 (RUNX2) is the master regulator of osteogenesis and regulates the expression of osteoblast marker genes including osterix, collagen I, alkaline phosphatase, bone sialoproteins, osteopontin and osteocalcin. Bone morphogenic proteins (BMP), transforming growth factor beta (TGF- β) and insulin-like growth factor (IGF) are signaling molecules which upregulate the expression of transcription factor, RUNX2 via mitogen activated protein kinases (MAPK) pathway. Wnt proteins also pass signals for RUNX2 transcription via Wnt / β -catenin signaling pathway. RUNX2 further helps to proliferate MSCs into mature osteoblasts. In this process alkaline phosphatase (ALP) activity get increased and hence ALP acts as a biomarker of osteoblastogenesis [12].

Osteoblasts regulate the mineralization process by synthesizing the organic matrix. About 90% of the organic bone matrix, or osteoid is made up of type I collagen secreted

with osteoblast formation in the beginning of osteogenesis. Active osteoblasts begin to produce large amounts of ALP, a phosphate-splitting enzyme that is released into the osteoid to initiate the deposition of minerals. After mineralization, the complete bone becomes hard and rigid [3].

Nuclear factor-kB (NF - kB) signaling pathway plays an important role in bone homeostasis. Three major components of this pathway are- Receptor activator of nuclear factor-kB (RANK), its ligand RANKL and its decoy receptor osteoprotegerin (OPG). Osteocytes, which are mature osteoblasts that get entrapped in bone matrix, send signals to osteoblasts for bone resorption leading to the secretion of RANKL, which activates monocytes to form osteoclasts via NF- kB signaling pathway. RANKL activates the RANK receptor present on the surface of monocytes and promotes its differentiation to form osteoclast, which ultimately leads to increased bone resorption. Whereas binding with OPG suppresses the RANK and inhibits osteoclastogenesis. [10, 12] Estrogen inhibits bone resorption by increasing OPG level, hence, estrogen deficiency leads to increased level of RANKL leading to increased bone resorption. Estrogen, also responsible for producing transforming growth factor beta (TGF β), which inhibits osteoclast differentiation and facilitates osteoclast apoptosis, which also gets inhibited due to estrogen deficiency. In women, mostly after menopause, bone resorption increases due to estrogen deficiency which leads to post-menopausal osteoporosis [13].

Inflammation can also be the cause of increased bone loss via manipulation of RANKL signaling by pro inflammatory cytokines. T helper-17 (Th17) subset of CD4 + cells promote osteoclastogenesis by the secretion of interleukin - 17 (IL-17) that stimulates RANKL expression. IL-17 increases inflammation and the production of inflammatory cytokines interleukin - 6 (IL-6) and tumor necrosis factor (TNF) which also tends to increase RANKL expression. On the other hand, regulatory T (Treg) cells show anti-osteoclastogenic function by inhibiting expression of various inflammatory cytokines [10].

Actions of CQ in bone loss pathologies

The mechanisms of action of CQ extract have been evaluated through various *in vitro* and animal studies. Some of the important mechanisms are discussed further. These have been summarized in Table 1.

A few cell line studies have demonstrated that CQ upregulates the expression of transcription factor RUNX2 via MAPK pathway which enhances the expression of ALP, collagen I, osteopontin and osteocalcin. In a study with bone marrow mesenchymal stem cell culture, treatment with CQ ethanol (CQ-E) extract, a higher rate of proliferation and differentiation of MSCs into ALP-positive osteoblasts was observed. CQ treatment also enhanced extracellular matrix calcification, which supports bone mineralization process [3]. Another experiment demonstrating similar results was conducted on murine osteoblastic cells, treated with CQ-E extract. Results showed a significant increase in the extent of mineralization nodules and ALP activity. Increased ALP activity and mineralization are markers of RUNX2 transcription, which further induces osteoblastogenesis. [14] These findings (enhanced ALP activity and mineralization) were also observed when CQ hexane fraction (CQ-H) was used in a study with osteoblast cell culture [15]. A comparative study between CQ-H and CQ dichloromethane fraction (CQ-D) on mouse pre-osteoblast cell line reported CQ-H as more effective extract showing early and enhanced mineralization.

Based on the study results, it was proposed that CQ may act via Wnt/ β -catenin signaling pathway which upregulates RUNX2 and expression of marker genes including collagen I, osterix, osteocalcin and osteopontin [12].

Multiple animal studies also reported osteoblastogenic potential of CQ via expression of ALP activity and mineralization process. In three different studies, ovariectomized female rats were treated with CQ to see its efficacy on bone structure. Results showed increased levels of serum ALP with enhanced mechanical strength, micro-architecture, and thickness of bones [16-18]. Also drastically enhanced alkaline phosphatase and cartilage tissue formation was observed when osteotomized male-female Swiss albino rats treated with CQ [19]. Implants in Sprague-Dawley rats treated with CQ also demonstrated their osteogenic potential by enhanced osteoblast proliferation, alkaline phosphatase production, improved early bone formation and ingrowth [20].

An *in vitro* experiment of CQ-E treatment on osteoblast cell culture was conducted to evaluate DNA content, RUNX2 gene expression, intracellular reactive oxygen species (ROS) intensity, apoptosis, and matrix mineralization of osteoblasts. In this study, treatment with CQ resulted in reduction of ROS intensity, with enhanced rate of matrix mineralization, DNA content in S phase of the cell cycle, and increased RUNX2 expression were also observed. These results indicated that CQ promotes cell cycle progression in S phase by inhibiting the generation of ROS leading to enhanced cell proliferation and differentiation. Low levels of ROS have major regulatory impact on some important mechanisms like MAPK pathway, cell proliferation, cell differentiation and apoptosis which supports bone formation [21].

CQ also has anti-osteoclastogenic properties which plays a supportive role in maintaining bone homeostasis. In a study conducted to evaluate biological activities of human osteoblast cell culture when treated with CQ-E, it was observed that CQ treatment inhibited RANKL and activated OPG expression, leading to the suppression of RANK receptors on monocytes and inhibition of osteoclastogenesis. OPG and RANKL inhibit and activate osteoclastogenesis, respectively. Thus, a decrease in RANKL: OPG ratio indicates the anti-osteoclastogenic trend with CQ treatment [6]. The anti-osteoporotic activity of CQ was also demonstrated in two similar studies conducted on ovariectomized female rats treated with CQ extract. It was observed that CQ treatment increased trabecular density, the amount of osteoblast cells and decreased the amount of osteoclast cells.

The osteoblastogenic and anti-osteoclastogenic potential of CQ increased the number of osteoblasts and decreased osteoclasts leading to the enhanced bone formation and reduced bone resorption promoting bone growth which maintains bone homeostasis and inhibits osteoporosis [22, 23].

CQ also acts via modulation of inflammation, wherein it prevents bone loss by the inhibition of osteoclastogenic cytokines. Several pro-inflammatory cytokines like tumor necrosis factor alpha (TNF- α), IL-1, IL-6, and IL-11 activate osteoclasts leading to increased bone resorption. IL-1 enhances the expression of RANKL in osteoblasts via activation of NF- κ B and MAPKs. IL-6 also stimulates the formation of osteoclasts promoting bone loss. A study was conducted on ovariectomized mice to evaluate the effect of CQ treatment on cytokine induced bone loss. The results of this study clearly showed that CQ reduces ovariectomy (OVX) induced bone loss primarily by downregulating proinflammatory cytokines that are often increased after ovariectomy [7]. CQ administration regulates the cytokine balance even under estrogen-deficient conditions and thus enhances bone health. Under estrogen deficient conditions, proinflammatory cytokines play pivotal role in bone remodeling. Th17 cells secrete osteoclastogenic cytokines IL-6, IL-17, TNF- α whereas T helper 1 (Th1), T helper 2 (Th2), Tregs, and regulatory B cells (Bregs), secrete anti-osteoclastogenic cytokines IFN- γ , IL-4, and IL-10. CQ significantly decreases the levels of osteoclastogenic cytokines like IL-17, IL-6, and TNF- α along with significantly increasing the levels of anti-osteoclastogenic cytokines like IL-10, IL-4, and interferon gamma (IFN- γ). This was demonstrated by a study conducted on ovariectomized rats treated with CQ extract to elucidate the effect of CQ under estrogen-deficient conditions. It was observed that CQ decreased both pain and swelling along with accelerating the healing of fractured jaws. CQ significantly reduced differentiation and functional activity of osteoclasts and improved bone mass by enhancing the microarchitecture. [2] A study was conducted on human Osteoblast like Sarcoma Osteogenic (SaOS-2) cells treated with CQ-E to evaluate the effects of CQ on the regulation of insulin like growth factor (IGF) system components. Study results revealed increased levels of IGF-I, IGF-II and insulin like growth factor binding protein (IGFBP-3). CQ upregulates the m-RNA expression of IGFs, which act as mitogenic and differentiative factors for bone cells through an autocrine/paracrine mechanism [24].

Table 1: Mechanisms of *Cissus quadrangularis* action on bone and their evidence

Action	Mechanism	Evidence
Osteoblastogenic	Upregulation of RUNX2 expression, resulting in increased osteoblastogenesis via MAPK and Wnt/ β -catenin signaling pathways.	<ul style="list-style-type: none"> In bone marrow MSCs cell culture and murine osteoblastic cell line \Rightarrow \uparrow ALP levels, \uparrow proliferation and differentiation of MSCs, \uparrow RUNX2 expression [3, 12, 14, 15] In ovariectomized, osteotomized and implant operated rats \Rightarrow \uparrow serum ALP levels, \uparrow mechanical strength, \uparrow micro-architecture, \uparrow thickness of bones, \uparrow cartilage tissue formation, \uparrow osteoblast proliferation, \uparrow bone formation [16-20]
Bone mineralization	Deposition of calcium salts in the extracellular matrix by differentiated osteoblasts.	<ul style="list-style-type: none"> In bone marrow MSCs cell culture and murine osteoblastic cell line \Rightarrow \uparrow extracellular matrix calcification, \uparrow mineralization nodules, \uparrow Collagen I, \uparrow levels of osterix, osteocalcin and osteopontin [3, 12, 14, 15].
Bone formation	Inhibition of ROS generation leading to cell cycle progression in S phase, enhanced cell proliferation and differentiation which supports bone formation.	<ul style="list-style-type: none"> In primary culture of rat osteoblasts \Rightarrow \downarrow ROS intensity, \uparrow matrix mineralization, \uparrow DNA content in S phase of the cell cycle, and \uparrow Runx2 expression [21]
Anti-osteoclastogenic	Downregulation of RANKL and increase in OPG levels leading to inhibition of osteoclastogenesis which	<ul style="list-style-type: none"> In human osteoblast cell line \Rightarrow \uparrow expression of OPG, \downarrow

	ultimately reduces bone resorption.	expression of RANKL, ↓ RANKL:OPG ratio ^[6] .
Ant-osteoporotic	Increase in formation of osteoblasts and decrease in osteoclasts, leading to the enhanced bone formation and reduced bone resorption inhibiting osteoporotic bone loss.	<ul style="list-style-type: none"> ▪ In ovariectomized rats ⇒ ↑ trabecular density, ↑ osteoblast cells and ↓ osteoclast cells ^[22, 23]
Anti-inflammatory	Maintenance of bone homeostasis by decreasing osteoclastogenic and anti-osteoclastogenic cytokines under inflammatory and estrogen-deficient conditions.	<ul style="list-style-type: none"> ▪ In ovariectomized rats ⇒ ↓ Th17 cells and pro inflammatory cytokines like TNF-α, IL-1, IL-6, and IL-11. ▪ ↑ Th1, Th2, Tregs, and Bregs cells and anti-osteoclastogenic cytokines IFN-γ, IL-4, and IL-10 ^[2, 7]
Bone remodeling	Increased m-RNA expression of IGFs, which act as mitogenic and differentiative factors for bone cells through an autocrine/paracrine mechanism.	<ul style="list-style-type: none"> ▪ In human osteoblast like Sarcoma Osteogenic (SaOS-2) cell culture ⇒ ↑ m-RNA expression of IGF -I, IGF-II, IGF-IR. ^[24]

RUNX2 = Runt-related transcription factor 2, MSC = Mesenchymal Stem Cells, ALP = Alkaline Phosphatase, MAPK = Mitogen Activated Protein Kinase, ROS = Reactive Oxygen Species, RANKL = Receptor activator of nuclear factor- κ B ligand, OPG = Osteoprotegerin, Th = T helper cell, TNF = Tumor necrosis factor, IL = Interleukin, Tregs = Regulatory T cells, Bregs = Regulatory B cells, IFN = Interferon, IGF = Insulin like growth factor, IGF-IR = Insulin like growth factor - I receptor

Clinical evidence

There are multiple clinical studies that demonstrate the therapeutic benefit of CQ in bone loss conditions. One such study was conducted in 29 male subjects who experienced chronic joint pain because of strenuous exercise. A daily dose of 3200 mg of CQ was given over 8 weeks. Assessment was conducted based on pre- and post-intervention Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. A significant improvement was noted from pre- to post-intervention ^[25]. In another study which evaluated the healing potential of CQ, 5 out of 9 subjects with maxillofacial fracture were administered with CQ 500 mg thrice a day for 6 weeks. Pain, swelling, and fragment mobility were lower in CQ treated group. Further, serum calcium and serum phosphorus levels were higher, and healing of bone was clearly visible ^[26]. Another prospective, randomized, controlled pilot study conducted on 6 patients with missing teeth requiring replacement with fixed prosthesis. Half of the subjects were treated with 500 mg/day CQ for 50 days post-surgery. Results showed reduced pain, swelling and increased levels of serum ALP in those treated with CQ. These results indicated accelerated new bone formation after surgery with CQ treatment ^[27].

Several clinical trials, studying the effect of CQ administration on fracture healing, have been published. In a randomized, placebo-controlled clinical trial, half of subjects with bone fracture were treated with CQ. Assessment was done to evaluate the effective remedial therapy to accelerate bone healing for early rehabilitation. In the CQ-treated group, early onset of fracture healing or osteoblastogenesis lead to early recovery as compared to placebo group. Also, increased serum parathyroid hormone (PTH) levels were observed with CQ treatment, which is known to enhance bone healing ^[28]. In another such comparative study, 100 subjects admitted for various fractures were evaluated, with half of subjects receiving CQ treatment and half without CQ. It was observed that the time required for immobilization process was shorter in CQ treated group. CQ accelerated the bone healing process by reducing pain and swelling. Hence, duration of treatment was observed to be less in CQ-treated group as compared to control group ^[29].

Facial fractures are also very critical types of fractures for bone healing. A couple of trials were conducted to evaluate the effect of CQ administration in such fractures. In one study, 60 patients with mandible fracture were included in a randomized, double blind, placebo-controlled trial. Assessments were performed to measure levels of expression of osteopontin protein, which is one of the biomarkers of osteoblastogenesis. CQ treatment group showed significant

levels of expression of osteopontin and CD4 + T cells expressing osteopontin. These results demonstrate accelerated bone formation and reduction in recovery time after CQ administration ^[30]. Another study was conducted to assess the effect of CQ in the recovery of implant patients. Twenty patients with atrophic ridge treated by alveolar distraction were equally distributed in CQ treatment group and placebo group. Radiographic evaluation was done to assess bone density and volume after distraction, along with density and bone loss around the implant. These assessments showed that bone formation and maturation of CQ-treated group were faster. Also, a significant increase in bone density around implant and in distracted area was observed in CQ group. CQ, thus not only enhanced the rate of new bone formation, but also bone density to withstand the biomechanical requirements of implant placement in a shorter time ^[31].

Multiple case studies have also been published in various fracture conditions to evaluate the effect of CQ on fracture healing. In a 26-year-old male with Bennett's fracture, treatment with oral dosage of CQ along with calcium was provided for six weeks from surgery. Pain, swelling and amount of callus formed were assessed for the study. Pain and swelling were completely reduced within a week of surgery. A united fracture with good amount of callus formation was observed in X-ray performed at 6th week of surgery ^[32]. Another report of a 78-year-old female with Colles's fracture in left hand, who underwent closed reduction and then treated with CQ and calcium supplement for 30 days, showed gradual reduction of pain and swelling which were completely absent after 30 days. Accelerated bone healing was observed in X-rays performed on 15th and 30th day ^[33]. In yet another report, a 19-year-old male subject with leg fracture was operated to introduce tibia plate and was treated with oral tablet administration as well as topical application of CQ lotion on the inflamed area. After 7-10 days of treatment there was significantly reduced pain and swelling with fast healing of fracture ^[34].

In postmenopausal women, bone loss is more frequent due to estrogen deficiency. This bone loss may lead to pathological conditions like osteoporosis and become more prone to fractures. CQ prevents such bone loss even in estrogen-deficient conditions. These effects of CQ were demonstrated by a placebo-controlled, randomized study on 134 postmenopausal women having Osteopenia. Bone mineral density (BMD) and bone turnover markers like type 1 collagen were assessed in this study. Oral administration of CQ has shown promising effects on delaying bone loss as compared to placebo group ^[35].

Conclusion

Bone loss is a condition which must be treated with proper medication at its early stages for faster recovery and to maintain quality of life. Bone loss may be due to impaired remodeling or bone fracture or due to pathological conditions like osteoporosis. CQ has been used since ancient times to accelerate bone healing process. CQ shows osteoblastogenic activities to produce osteoblast cells which enhances bone formation process; whereas anti-osteoclastogenic properties of CQ reduce osteoclast cells and prevent bone resorption. Hence CQ treatment leads to early onset of callus formation with faster recovery in bone fracture, CQ maintains bone homeostasis and ultimately reduces or prevents bone loss in osteoporosis. CQ inhibits proinflammatory cytokines to enhance bone health and reduces pain and swelling leading to early recovery. CQ is a safer herbal medicine without any major safety concerns and can be used as a supportive treatment option for early recovery in conditions associated with bone loss.

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