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REVIEW

Exploring the Role of *Cissus quadrangularis* in Osteoporosis Management

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Abstract: *Cissus quadrangularis* (CQ) is a Vitaceae-derived medicinal plant rich in flavonoids, phytosterols, triterpenoids, vitamins, and bone-relevant minerals, conferring combined antioxidant, anti-inflammatory, phytoestrogenic, and osteoanabolic properties that modulate key pathways involved in bone remodeling. This narrative review aims to synthesize preclinical and clinical evidence on CQ as a potential adjunct in osteoporosis management. Preclinical studies demonstrate that CQ enhances osteoblast differentiation, collagen and matrix deposition, and mineralization, while inhibiting osteoclastogenesis and inflammatory osteoclastogenic cytokines, leading to improved bone microarchitecture, bone mineral density, and callus formation in fracture and estrogen-deficiency models. CQ phytobioactives have also been successfully integrated into advanced biomaterials, exosome-like vesicles, and self-emulsifying drug delivery systems, improving bioavailability, osseointegration, and regenerative performance in critical-sized defects and implant models. Clinical data, although limited and heterogeneous, consistently indicate that CQ accelerates fracture healing, reduces bone pain, and increases functional recovery in maxillofacial and mandibular fractures, with favorable effects on serum calcium, alkaline phosphatase, and osteopontin expression and without major safety concerns based on available short-term data. In postmenopausal osteopenia, randomized trials show that 24-week oral CQ stabilizes bone turnover markers and delays bone loss, albeit without short-term gains in bone mineral density. CQ thus emerges as a multi-target, generally well-tolerated candidate for integrative osteoporosis care, particularly for early bone loss (i.e., osteopenia), fracture healing, and osteoprotection during antiresorptive drug holidays (i.e., temporary suspension of bisphosphonate therapy, particularly in the context of dental procedures). However, the absence of standardized formulations, small sample sizes, short follow-ups, and lack of head-to-head comparisons with standard anti-osteoporotic therapies currently available underscore the need for long-term, multicenter randomized controlled studies using bioavailable, well-characterized CQ preparations.

Keywords: bisphosphonates, bone mineral density, *Cissus*, osteoporosis, review

Introduction

Osteoporosis (OP) is a significant global health concern affecting over 200 million individuals, particularly postmenopausal women and the elderly. It is characterized by reduced bone mineral density (BMD) and deterioration of bone tissue microarchitecture, leading to an increased risk of fractures that can cause substantial morbidity and diminished quality of life (QoL).[1] The condition results in physical limitations in activities of daily living (ADLs) and consequent increased healthcare costs, making effective treatment strategies imperative.[2] A multitude of pharmacological therapies are now available for OP management, including bisphosphonates, selective estrogen receptor modulators (SERMs), denosumab, teriparatide, and romosozumab.[3] These medications serve distinct roles; for example, bisphosphonates and SERMs primarily act as antiresorptive agents, while teriparatide and romosozumab function as anabolic therapies.[4] Despite the efficacy of these treatments in enhancing BMD and reducing fracture risk, adherence and compliance remain significant challenges due to associated side effects and financial burdens. Studies have indicated that while drugs such as romosozumab demonstrate superior fracture risk reduction compared to traditional bisphosphonates, concerns about

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adverse events like cardiovascular complications and the cost of these newer therapies influence patient acceptance.[5] It is noteworthy that cost-effectiveness analyses indicate that while agents like romosozumab and denosumab yield better clinical outcomes, they also represent a considerable expense, complicating decisions related to long-term management of OP.[6] Furthermore, transitioning patients between therapies poses additional challenges. For instance, pharmaceutical strategies such as suspending bisphosphonates in conjunction with dental procedures can complicate treatment regimens and necessitate therapeutic windows to minimize adverse effects during a transition period.[7] This is particularly critical for patients with a history of osteoporotic fractures, who comprise a substantial demographic that may face heightened risk factors during treatment adjustments.[8] The clinical implications of these suspensions and the need for careful management highlight the intricate balance required in optimizing therapeutic outcomes while ensuring patient safety and adherence.

In this context, the necessity for potential alternative treatments becomes paramount.

This need is further amplified by documented patient preferences: epidemiological surveys have consistently reported that many patients under treatment for OP use some form of complementary and alternative medicine, with herbal preparations, vitamin supplements, and relaxation techniques being the most frequently reported modalities.[9] Poor long-term adherence to conventional anti-osteoporotic pharmacotherapy, driven by gastrointestinal intolerance, fear of rare but serious adverse events such as osteonecrosis of the jaw or atypical femoral fracture, and the financial burden of long-term treatment, further motivates patients to seek plant-derived adjuncts perceived as safer and more aligned with a holistic approach to skeletal health.[10] Throughout history, medicinal plants have served as remedies for diverse pathological conditions.[11] *Cissus quadrangularis* (CQ - a.k.a. *Veldt grape, Winged Treebine*, or *Adamant Creeper* - Figure 1), predominantly found in regions such as America, Australia, India, Sri Lanka, Java, Southeast Asia, and Africa, is a well-known medicinal plant belonging to the Vitaceae family.

CQ exhibits a unique bone-joining ability, earning it the Sanskrit name Asthisandhan and the Hindi name Hadjod, both of which literally translate to "bone setter".[12] Although not very widespread in the Western world, CQ is widely utilized in Eastern medicine, primarily for the treatment of bone fractures and as an analgesic. CQ extracts have been reported to contain a wide variety of bioactive compounds, including alkaloids, phytoestrogenic steroids, calcium, resveratrol, piceatannol, Parthenocissus, ascorbic acid, carotene, flavonoids, vitamins, enzymes, nicotinic acid, tyrosine, triterpenoids (including β-sitosterol, δ-amyrin, and ketosteroid).[13] Amongst the various medicinal properties (e.g., anti-inflammatory, antioxidant, antimicrobial, antiobesity, antinociceptive, anticonvulsant, and antidiabetic effects), anti-osteoporotic ones are the most studied and demonstrated for CQ.[14,15] Notably, unlike currently approved pharmacological agents, which are classified as either predominantly antiresorptive (e.g., bisphosphonates, denosumab) or predominantly osteoanabolic (e.g., teriparatide, romosozumab), CQ appears to confer both antiresorptive and osteoanabolic effects simultaneously within a single phytocomplex.

From a regulatory perspective, CQ is available in several jurisdictions as an over-the-counter dietary supplement or traditional herbal preparation, with regulatory classification varying by country and no harmonized EU-level authorization currently in place.

This narrative review aims to report a qualitative synthesis of the current literature on CQ in OP management, focusing on its mechanisms, efficacy, safety, and research gaps, with the goal of exploring the possibility and the opportunity to integrate CQ in some clinical scenarios of OP management.

Phytochemical Composition and Mechanisms of Action

CQ extracts are rich in various phytochemicals and minerals relevant to bone health. The bone protective potential of CQ is highlighted by various phytochemicals that support two complementary ways to improve bone homeostasis: anabolic stimulation of osteoblast differentiation and mineralization, and antiresorptive suppression of osteoclastogenesis.

CQ contains flavonoids such as quercetin, kaempferol, daidzein, and quercitrin, as well as polyphenols like resveratrol and piceatannol.[16] These compounds possess significant antioxidant and anti-inflammatory activities, which contribute to their beneficial effects on bone metabolism.[17] Flavonoids including quercetin, kaempferol, and daidzein have been

Figure 1 *Cissus quadrangularis* plant.

demonstrated to enhance osteoblast differentiation, inhibit osteoclastogenesis, and regulate signaling pathways involved in bone remodeling, such as the mitogen-activated protein kinase (MAPK), receptor activator of nuclear factor-κB and its ligand (RANK/RANKL), osteoprotegerin (OPG), and estrogen receptor pathways.[18] Quercetin and kaempferol, in particular, promote osteogenic activity, while daidzein acts as a phytoestrogen with anti-resorptive effects.[19] Phytosterols, particularly β-sitosterol, have high concentration in CQ extracts. CQ also features ketosteroids (anabolic or phytoestrogenic steroidal substances). These compounds may participate in modulating lipid metabolism and exhibit estrogenic action relevant for bone metabolism.[20] CQ "triterpenoid" fraction, which includes δ-amyrin and δ-amyrone, among other alkaloids, appears to contribute to the plant's antioxidant and anti-inflammatory properties and may further support bone regenerative effects.[21] Vitamins are also well represented. CQ is a natural source of vitamin C (i.e., ascorbic acid), vitamin A (i.e., carotene), and provides a significant content of minerals such as calcium, phosphorus, zinc, iron, magnesium, and strontium. These are all relevant nutrients for bone formation and mineralization.[22]

CQ offers a dual approach to managing OP by both enhancing bone formation (i.e., osteogenesis) and inhibiting excessive bone resorption. The management of oxidative stress is vital, given that excessive free radical generation and compromised antioxidant defenses contribute to the onset of age-related diseases, including metabolic bone disorders and bone mass reduction.[23] Flavonoids are integral to this action by providing antioxidant and anti-inflammatory capacity, effectively alleviating cellular oxidative stress which otherwise impairs bone remodeling and precipitates bone mass decline.[24] Specifically, flavonoids suppress pro-inflammatory osteoclastogenic cytokines, including interleukin 1β (IL-

Table 1 Main Cissus Quadrangularis Components and Mechanisms of Action

Class of Compound	Specific Constituents	Relevant Mechanism of Action on Bone Health
Flavonoids & Polyphenols	Quercetin, Kaempferol, Daidzein, Quercitrin, Resveratrol, Piceatannol	Significant antioxidant and anti-inflammatory activities. Enhanced osteoblast differentiation and inhibited osteoclastogenesis.[16] Regulated signaling pathways (e.g., MAPK, RANK/RANKL/OPG) involved in bone remodeling.[18] Quercetin and Isorhamnetin suppress the NF-κB pathway, modulating inflammatory gene expression.[26] Daidzein acts as a phytoestrogen with anti-resorptive effects.[19]
Steroidal Compounds & Phytosterols	Ketosteroids, β-sitosterol	Exhibit estrogenic action relevant for bone metabolism, particularly in modulating lipid metabolism.[20] Modulate bone remodeling by stimulating osteoblasts via estrogen receptors.
Triterpenoids	δ-amyrin, δ-amyrone, Triterpenoids	Contribute to the plant's antioxidant and anti-inflammatory properties.[21] Promote the synthesis and deposition of collagen and mucopolysaccharides, essential elements for matrix mineralization and repair.[28,29]
Minerals	Calcium, Phosphorus, Zinc, Iron, Magnesium, Strontium	Provide foundational mineral elements, accelerating matrix biomineralization.[22] High natural content of calcium and phosphorus contributes to observed enhancement of BMD.[31]
Vitamins	Vitamin C (Ascorbic acid), Vitamin A (Carotene), Nicotinic acid	Relevant nutrients for bone formation and mineralization. Vitamin C is essential for collagen synthesis.[22]

1β), IL-6, and Tumor Necrosis Factor α (TNF-α), while elevating anti-osteoclastogenic signals.[15,25] Quercetin and isorhamnetin can modulate inflammatory cell activity and the transcription of pro-inflammatory genes, notably by suppressing the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway.[26] CQ extract has shown potential in protecting osteogenic cells, such as MC3T3-E1 cells, from hydrogen peroxide-induced oxidative damage, supporting its role in cellular defense and bone maintenance.[27] Concurrently, the triterpenes and alkaloids in CQ promote the synthesis and deposition of collagen and mucopolysaccharides, essential elements for matrix mineralization and repair.[28,29] Additionally, CQ inhibits gene expression of key cytokines and matrix metalloproteinases, thus alleviating inflammatory responses at the cellular level.[28] Phytosterols and steroidal compounds exhibit phytoestrogenic activity, modulating the bone remodeling process by stimulating osteoblasts via estrogen receptors and contributing to anti-resorptive potential.[30] Lastly, the high natural content of calcium and phosphorus in CQ provides the foundational mineral elements, accelerating matrix biomineralization and contributing to the observed enhancement of BMD and mechanical strength through the upregulation of MAPK-dependent alkaline phosphatase activity in osteoblasts.[31] This multifaceted phytochemical profile ultimately supports improved osteoblast differentiation and mineralization, while inhibiting RANKL-induced osteoclastogenesis and reducing bone loss. Table 1 summarizes main CQ's components and mechanisms of action.

Preclinical Evidence

The robust anti-osteoporotic potential of CQ has been comprehensively validated across diverse preclinical platforms, revealing critical mechanisms underpinning its dual-action capacity.[32] Beyond stimulating the upregulation of osteogenic markers like Runx2 and Alkaline Phosphatase (ALP) demonstrated in in vitro studies,[33] the pro-osteogenic activity of CQ extends to innovative regenerative applications. For instance, exosome-like nanovesicles isolated from CQ callus tissue actively induce osteogenic lineage commitment in human mesenchymal stem cells (hMSCs) and myoblast (C2C12) cells.[34] These CQ exosomes significantly enhance ALP activity and mineralization (assessed through Alizarin Red staining) in hMSCs, surpassing levels achieved by positive control media after 14 and 21 days, respectively. Furthermore, extracts obtained using ethyl acetate (0.3 mg/mL) demonstrated superior efficacy in promoting the maturation of bone marrow mesenchymal stem cells (BM-MSCs) by increasing ALP gene expression three times compared to positive controls.[35] In complex tissue engineering, CQ phytobioactives integrated into nano-hydroxyapatite ceramic nano-cement enhanced neo-bone formation in a critical-sized tibial defect model in vivo, yielding

significantly higher volumes of mineralized tissue and volumetric bone formation compared to non-functionalized cement.[27] This optimized bioactive fraction, rich in polyphenols and flavonoids, concomitantly provided protection against cellular oxidative stress while promoting cellular proliferation and migration in vitro. The translational relevance is further supported by evidence from a rabbit model, where a novel CQ Chitosan Hydrogel coating on titanium implants significantly improved osseointegration, showing higher new bone formation and increased Implant Stability Quotient and Removal Torque Quotient values at 12 weeks.[36] Crucially, the anti-resorptive capacity of CQ is robustly demonstrated in models simulating postmenopausal osteoporosis.[15] In ovariectomized mice, oral CQ attenuated inflammatory bone loss, resulting in a significant reduction in bone resorption markers, such as Howship's lacunae in femoral cortical areas. Micro-computed tomography confirmed that CQ dramatically enhanced bone microarchitecture, significantly improving parameters like volumetric bone formation, trabecular thickness, and connectivity density in the fifth lumbar vertebra region and femur, while reducing destructive indices. This protection seems to be partially mediated through an osteoimmunological effect: CQ regulates the host immune system by significantly increasing anti-osteoclastogenic immune cells [e.g. lymphocytes T helper1 (Th1), Th2, Regulatory T cells (Tregs), and Regulatory B cells (Bregs)] and concurrently lowering osteoclastogenic Th17 cells in lymphoid organs.[15] This results in a favorable shift in the serum cytokine balance, characterized by increased anti-osteoclastogenic cytokines [e.g. Interferon-gamma (IFN-γ), IL-4, and IL-10] and decreased pro-inflammatory osteoclastogenic cytokines (e.g., TNF-α, IL-6, and IL-17). The preclinical evaluation of CQ extends beyond generalized OP models into specialized regenerative medicine, tissue engineering, and pharmaceutical formulation optimization. For guided bone regeneration applications, a composite biomaterial incorporating CQ extract within a gelatin/pectin polymeric matrix reinforced by β-tricalcium phosphate (β-TCP) demonstrated substantial in vitro osteogenic expression, achieving 168.0% and 188.0% upregulation for Runt-related transcription factor 2 (RUNx2) and Osteocalcin (OCN) respectively, positioning it as a potent biomaterial for bone tissue repair.[30] Furthermore, CQ's efficacy in complex tissue restoration is highlighted in models of periodontal regeneration, where scaffolds composed of hyaluronic acid (HA) doped with ovine tendon extracellular matrix (ECM) and CQ extract showed maximum proliferation and tenogenic activity of mesenchymal stem cells in vitro, confirming its utility beyond purely osseous tissue.[37] This regenerative capacity was mirrored in a zebrafish caudal fin amputation model, employed to mimic periodontal bone regeneration criteria, where composite scaffolds containing CQ, carrageenan, tendon ECM, and silver tricalcium phosphate (Ag-TCP) exhibited superior regeneration characterized by organized tissue regrowth, enhanced collagen deposition, and reduced inflammatory responses compared to control groups.[38] In published fracture healing models, the use of alcoholic CQ extracts (alone or combined with *Cryptolepis buchanani* and *Sardinella longiceps*) in Wistar rats effectively restored bone strength and reduced the repair period by supplying rich phytochemicals that elevate serum calcium levels.[16] Lastly, in inflammatory models such as monosodium iodoacetate (MIA)-induced osteoarthritis (OA) in rats, CQ extract mitigates knee joint damage, reduces subchondral bone erosion, and preserves cartilage integrity by suppressing the mRNA expression of key inflammatory mediators (i.e., inducible nitric oxide synthase, Cyclooxygenase-2, 5-Lipoxygenase) and Matrix Metalloproteinases, thereby preventing extracellular matrix degradation.[32] Collectively, these preclinical findings strongly support CQ's versatility as an effective dual-action agent that promotes osteogenesis and facilitates complex tissue repair, justifying its integration into next-generation regenerative materials and improved delivery platforms. Table 2 summarizes main findings from preclinical studies assessing CQ potential.

Advanced and Innovative Delivery Systems

The therapeutic potential of CQ in managing bone loss is fundamentally constrained by low aqueous solubility of several phytoconstituents, which limits dissolution in gastrointestinal fluids and reduces the fraction available for absorption. In addition, first-pass intestinal and hepatic metabolism can further reduce systemic exposure, leading to inconsistent plasma levels and therapeutic responses.[39,40] The administration begins with ingestion, where CQ preparations are exposed to gastric pH, enzymes and mechanical mixing. Many plant secondary metabolites are unstable or undergo degradation or transformation in gastric juice, and co-ingested food can modify gastric emptying and complex with phytochemicals, thereby influencing subsequent bioavailability.[41] Absorption becomes critical once CQ constituents reach the small intestine, which is the main site for uptake of most orally administered drugs and phytochemicals. The

Table 2 Main Findings from Preclinical Studies Assessing Cissus Quadrangularis Potential

Authors, Year	Sample Size	Condition	Intervention	Key Findings	Outcome Measures	Adverse Events
Archita Gupta et al, 2023[27]	30 male Wistar rats (divided into 4 groups)	Critical-sized bone defect model	Nano-hydroxyapatite ceramic nano-cement functionalized with optimized CQ phytobioactives (MF); controls: nano-cement alone, nano-cement + BMP + zoledronic acid	CQ phytobioactives enhanced bone formation with increased mineralized bone volume, fractional bone volume (BV/TV%), calcium deposition, proliferation, migration, reduced oxidative stress	Bone mineral density (DEXA), micro-CT bone volume and fractional bone volume, histology (H&E, Masson's trichrome, Picrosirius red), biochemical markers, cell viability, ALP activity, calcium deposition, cell migration assays	No AE observed in rats; histology showed no toxicity; normal hematological parameters
Treasa Richa Roy et al, 2024[36]	12 male New Zealand white rabbits (24 implants: 12 test, 12 control)	Not disease: Biocompatibility/ osseointegration model	3% chitosan-CQ hydrogel –coated titanium implant vs. uncoated commercially pure Ti implant (control), in femur and tibia	At 12 weeks, CQChH-coated implants showed significantly higher stability, removal torque, and new bone formation with robust osteoblast activity vs. controls; at 6 weeks differences were not significant	ISQ (Implant Stability Quotient), RTQ (Removal Torque Quotient), histopathology (H&E and Masson trichrome staining for new bone)	No AE or toxicity observed, animals survived to endpoint, well tolerated
Yean-Jung Choi et al, 2025[32]	60 male Sprague-Dawley rats (6 groups, 10 rats each)	Osteoarthritis (MIA-induced)	Oral CQ extract (CQE) at 30, 50, 100 mg/kg body weight/day for 5 weeks; control groups include Normal control, OA control, and MSM (150 mg/kg) positive control	CQE significantly reduced knee joint damage, subchondral bone erosion; increased bone volume and trabecular structure; preserved cartilage integrity; suppressed inflammatory mediators, pro-inflammatory cytokines, and MMPs mRNA expression	Micro-CT: bone surface/bone volume ratio, bone volume fraction, trabecular number/ thickness; Histology (H&E, safranin O); Immunofluorescence for COL2A1, aggrecan; mRNA RT-PCR for inflammatory enzymes, cytokines, MMPs	No reported AE or toxicity observed during study
Lele Liao et al, 2023[30]	hBMSCs (human bone marrow mesenchymal stem cells)	Bone tissue regeneration (in vitro model)	β-tricalcium phosphate (β-TCP) combined with gelatin (Gel) and pectin (Pec) polymers loaded with *Cissus quadrangularis* (CQ) extract	The β-TCP/Gel-Pec/CQ composite supports good cell viability (92%), enhances mesenchymal stem cell proliferation, and significantly upregulates osteogenic differentiation markers RUNx2 and OCN (168% and 188% expression)	Cell viability (MTT assay), gene expression (RT-PCR for RUNx2, OCN, VEGF), microscopy (SEM, TEM)	No toxicity or adverse effects observed in vitro
Ritu Gupta et al, 2023[34]	Human mesenchymal stem cells (hMSCs) and mouse myoblast (C2C12) cells	Osteogenic differentiation	Exosome-like nanovesicles isolated from callus tissue culture of *Cissus quadrangularis* (CQ exosomes)	CQ exosomes significantly internalized by hMSCs; enhanced proliferation, differentiation measured by alkaline phosphatase activity; protected against oxidative stress; induced wound healing through enhanced cell migration	Internalization assay, oxidative stress viability, wound scratch assay, proliferation (resazurin), ALP activity, alizarin red staining for mineralization	No AE reported in vitro
Zaffar Azam et al, 2023[15]	18 female Balb/c mice (3 groups, n=6 per group)	Postmenopausal osteoporosis (estrogen deficiency)	Oral *Cissus quadrangularis* crude extract 500 mg/kg/day for 45 days in ovariectomized (Ovx) mice	CQ suppressed RANKL-induced osteoclastogenesis and osteoclast activity dose-dependently; improved bone microarchitecture and mineral density in Ovx mice; increased anti-osteoclastogenic immune cells (Th1, Th2, Tregs, Bregs) while reducing pro-osteoclastogenic Th17 cells; increasing IFN-γ, IL-4, IL-10 and decreasing TNF-α, IL-6, IL-17	Osteoclastogenesis assays (TRAP staining), F-actin ring formation; μ-CT bone structural analysis; flow cytometry for immune cell populations; serum cytokine levels by ELISA; histology	No adverse events or cytotoxicity observed in vitro or in vivo

Balaji Ganesh S et al, 2024[37]	Not explicitly specified (multiple in vitro assays)	Periodontal regeneration (tendon/ligament tissue regeneration model)	Hydrogel scaffolds of hyaluronic acid (HA), HA + CQ, HA + tendon extracellular matrix, HA + CQ + tendon ECM	CQ addition to HA scaffold significantly increased tenogenic potential; higher stem cell proliferation and differentiation with HA+CQ+Tendon group; improved scaffold morphology and mechanical properties; hydrogels showed low swelling and cell viability >68%	SEM morphology, swelling ratio, MTT cell viability, cell differentiation by microscopy, Sirius red staining for tenogenesis	No AE observed in vitro
Eriani et al, 2023[35]	3 rats, 3 groups (triplicates)	Osteoporosis-related bone cell maturation	CQ methanol or ethyl acetate extracts at 0.3 mg/mL in DMEM culture	Ethyl acetate extract significantly increased alkaline phosphatase (ALP) gene expression 3-fold vs positive control (osteoblast basal growth medium); methanol extract decreased ALP six-fold; MSC morphology and surface markers (CD73, CD105 positive; CD34, CD45 negative) confirmed; RT-qPCR validated with <5% CV	MSC morphology, osteoblast differentiation markers (ALP gene expression), PCR for surface markers	No AE reported in vitro
Ganesh SB et al, 2025[38]	6 zebrafish / group (5 groups total)	Periodontal bone regeneration (mimicked by fin amputation)	Scaffolds: CQ, carrageenan, tendon ECM, with silver hydroxyapatite (Group 3) or silver tricalcium phosphate (Group 4); Controls: PERIO COL-GTR (Group 1), scaffold without bioceramic (Group 2)	Group 4 showed superior fin regeneration with well-defined bifurcation and structural restoration; increased osteoblast activity, matrix deposition, organized epithelial layer; regulated inflammatory response and vascularization; enhanced collagen deposition; significantly higher growth vs. controls.	Microscopic fin growth, histological analysis (H&E staining), FTIR and UV-Vis spectroscopy	No AE or toxicity mentioned
Ramachandran et al, 2021[16]	36 Wistar rats divided into 6 groups	Bone fracture healing	Ethanol extracts of CQ, Cryptolepis buchanani, Sardinella longiceps, alone or combined	Increased serum calcium and femur bone thickness; Xray and histology showed complete bone bridging bone healing; combination extract most effective	Serum calcium, X-ray radiography, histopathology of kidney, liver, brain	No AE reported, confirmed organ safety

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intestinal epithelium constitutes a selective barrier; limited passive diffusion, active efflux and variable permeability for different CQ components can substantially restrict the amount entering the portal circulation.[42] After crossing the intestinal barrier and entering the systemic circulation, CQ constituents undergo distribution to tissues, which represents the distribution phase. Plasma protein binding, tissue affinity for bone, and competition with concomitant drugs or nutrients for transporters and binding sites can all modulate effective concentrations at skeletal targets and thereby the anti-osteoporotic potential of CQ.[43]

Achieving enhanced bioavailability of CQ's active constituents is thus essential to guarantee adequate outcomes. Addressing this pharmacological challenge, advanced delivery approaches, such as the Self-Emulsifying Drug Delivery System (CQ-SEDDS), have been successfully developed to facilitate absorption by forming nano-emulsions upon dispersion in the gastrointestinal tract.[44] Preclinical testing of this system in an osteoporotic rat model demonstrated that CQ-SEDDS resulted in approximately 76% enhancement in the bioavailability of active CQ markers, effectively reducing variability. This improved kinetic profile directly translated to enhanced therapeutic efficacy in ovariectomized rats, yielding greater BMD gains compared to crude extracts. Moreover, innovative localized delivery systems, such as CQ-loaded polyhedral oligomeric silsesquioxane-reinforced chitosan-based bilayer sponges, are being designed for tissue engineering applications.[22] These bilayer systems, designed to mimic skin tissue structure, successfully encapsulated CQ extract and provided a controlled release profile of up to 78%−80% cumulative release over 4 days, demonstrating antibacterial activity and inducing cell proliferation and collagen deposition in vitro. Therefore, modifying the delivery system from traditional crude forms, which carry associated risks of high dosage and limited efficacy, to novel carriers, whether for systemic absorption or sustained local delivery, is critical for unlocking CQ's full multi-target synergistic osteoprotective potential for clinical application.

Available Clinical Evidence

Clinical evidence supporting the use of CQ in managing bone loss pathologies is still in development. Available data primarily validates CQ traditional application in acute trauma, while emerging data investigates its potential in chronic conditions. Systematic reviews of randomized controlled trials (RCTs) focusing on bone fractures have demonstrated that CQ provides a measurable benefit, specifically by significantly reducing bone pain scores compared to placebo.[45] An open-label RCT evaluating a combination product including CQ in patients with maxillofacial fractures reported a promising osteoanabolic effect characterized by early pain relief, supporting the acceleration of healing and restoration of functional outcomes.[46] This capacity to accelerate repair is further supported by observations that CQ treatment improves new bone formation in patients undergoing dental implant placement in atrophic ridges.[47] The pilot RCT by Brahmkshatriya et al evaluated the osteogenic efficacy of CQ in patients with maxillofacial fractures, comprising 9 subjects (8 male, 1 female, aged 20–63) who underwent open reduction and internal fixation.[48] Over 45 days, those receiving CQ capsules (500 mg thrice a day for 6 weeks) showed greater reductions in pain, swelling, and fragment mobility, with accelerated bone healing as evidenced by earlier periosteal reaction and callus formation on CT scans at day 21 and complete bone deposition by day 45, compared to controls receiving standard care alone. Additionally, CQ recipients had significantly increased serum calcium and phosphorus levels, and the supplement was well tolerated with no reported side effects. Mohammad et al too examined the comparative effectiveness of *Ocimum sanctum*, CQ, and placebo for mandibular fracture healing in 29 patients.[49] Patients treated with CQ (3.5 g of 80% alcoholic extract powder thrice a day) demonstrated significantly improved fracture healing evidenced by shortened immobilization time, increased serum calcium, and enhanced alkaline phosphatase levels, reflecting active bone formation. Additionally, the CQ group showed the greatest increase in bite force, good radiographic healing, and favorable hematinic and hypoglycemic effects, all without reported adverse events. Singh et al evaluated the osteogenic activity of CQ in 60 patients with mandibular fractures (age 20–35), allocated to receive either CQ capsules or placebo.[50] Patients in the CQ group (300 mg per capsule, 2 capsules BID) demonstrated superior clinical and radiological fracture healing, with marked reductions in pain, swelling, and mobility at fracture sites and greater increases in bite force relative to controls. Biochemical analyses revealed significantly elevated serum calcium and alkaline phosphatase levels in the CQ group, alongside sustained and significant osteopontin expression, particularly within CD4+ T cell populations, at all sampled time points (0, 4,

6 weeks), correlating with early callus formation, neovascularization, and enhanced bone remodeling. No adverse effects were reported, supporting both efficacy and safety of CQ as an adjunct in osteogenic therapy for fractures.

Beyond acute repair, clinical investigations have explored CQ in chronic degenerative conditions such as bone loss in postmenopausal women. A study administering oral CQ for 24 weeks to postmenopausal women with osteopenia revealed a significant delaying effect on bone loss, indicated by a measurable reduction in bone turnover markers, suggesting a slower overall bone remodeling rate. Crucially, however, this short-term intervention did not result in a significant change in BMD at any measured site compared to the placebo group.[51] A similar, pivotal, RCT involving 108 postmenopausal women with osteopenia assessed CQ at oral doses of 1.2 and 1.6 g/day for 24 weeks, focusing on BMD and bone turnover markers as primary endpoints.[52] Although BMD changes at the lumbar spine, femoral neck, and total hip sites did not significantly differ from placebo over the 24-week period, CQ supplementation notably stabilized the bone remodeling process, as shown by stable serum C-telopeptide of type 1 collagen and a significant reduction in procollagen type 1 amino-terminal propeptide compared to the continuous increase seen with placebo. These effects, while moderate, were achieved without an increased incidence of adverse events, indicating a favorable safety profile in the studied population.

Despite these positive indications in acute fracture repair and encouraging early results in bone loss and related musculoskeletal diseases, there is still a critical need for comprehensive, high-quality, long-term RCTs to conclusively validate CQ's efficacy and establish optimal dosing for the chronic management of OP. Table 3 summarizes main findings from clinical studies assessing CQ potential.

Clinical Implications and Limitations

The clinical implication of CQ as an anti-osteoporotic agent is rapidly transitioning from traditional medicine to evidence-based acceptance, driven by its unique pharmacological profile. The core therapeutic advantage of CQ lies in its dual mechanism of action, distinguishing it from many conventional monopathway pharmaceutical interventions, as it effectively acts both by stimulating osteoblasts (enhancing osteogenesis) and inhibiting osteoclasts (reducing resorption).[13,33,36] The potential for CQ to be included in integrative OP management, especially as a potential alternative in selected conditions or in low-resource settings, is affirmed by emerging clinical data, such as the discussed recent RCTs demonstrating a delaying effect on bone loss in postmenopausal women, evidenced by a reduction in bone turnover markers.[51,52] This application is highly favorable given that CQ is consistently demonstrated to be safe and devoid of major toxicity in preclinical models, presenting fewer associated risks compared to synthetic agents.[53] Crucially, the historical challenge of poor oral bioavailability of CQ's active constituents is now showing potential to be mitigated by modern pharmaceutical technology.[22,44] Advanced delivery modalities like the SEDDS may help in overcoming this bioavailability barrier, showing a substantial 76% enhancement in the bioavailability of active markers in preclinical studies, a pharmacokinetic leap that promises superior clinical efficacy by ensuring adequate systemic exposure. However, the existing clinical evidence presents limitations, notably small clinical sample sizes and short follow-up durations (typically ≤6 months), coupled with a pervasive lack of standardized extraction protocols that hinders replicability.[45,51] Furthermore, there remains a critical absence of head-to-head trials comparing CQ against established standard OP drugs.

Consequently, defining the exact colocation of CQ in the OP general picture across multiple clinical scenarios necessitates future research, specifically demanding large-scale, multi-center RCTs using standardized, bioavailable CQ formulations, alongside long-term safety and efficacy studies and specialized combination therapy studies with conventional anti-osteoporotic agents. However, some hypotheses related to the current CQ picture can be made. Considering CQ capacity to accelerate bone injury repair by directly affecting callus formation and contributing to accelerated mineralization due to its calcium content and given its dual action (i.e., stimulating osteogenesis and inhibiting osteoclastogenesis) and its safety profile, CQ appears as an option for patients unwilling or unable to take bisphosphonates or other therapies, which often carry side effects such as osteonecrosis of the jaw or hypercalcemia.[54,55] Furthermore, CQ is a potential therapeutic agent for patients with osteopenia or for individuals (such as men under 50 or premenopausal women) with risk factors that do not meet the indications for bisphosphonates.[56] CQ can also be used in more complex settings: for patients who, despite being treated with antiresorptives (such as bisphosphonates), show

Table 3 Main Findings from Clinical Studies Assessing Cissus Quadrangularis Potential

Authors, Year	Sample Size Sex	Age: Mean	Type of Disease	Intervention	Key Findings	Follow-Up	Outcome Measures	Adverse Events
Sindhu Priya R et al, 2024[51]	60 Female (postmenopausal)	Not explicitly stated	Osteopenia	Oral administration of CQ (dose not specified)	CQ delayed bone loss, reduced bone turnover markers; no change in BMD after 24 weeks	24 weeks	BMD, bone turnover markers, pain level questionnaires	No AE reported
Gigi PG et al, 2023[46]	24 (3 groups) Both sexes (mostly male)	18-60 years	Maxillofacial fractures	Group 1: Control (ORIF only); Group 2: Tablet Reunion (CQ 500 mg + *Dalbergia sissoo* 400 mg) twice daily orally; Group 3: Teriparatide SC injection	Both treatments showed accelerated fracture healing; Teriparatide group showed highest anterior and posterior bite force recovery; Tablet Reunion showed early pain relief; increased serum ALP in Teriparatide group indicating osteoanabolic effect	12 weeks	Pain scale (NRS), fracture site mobility, anterior/ posterior bite force, serum calcium, PTH, ALP, radiographic assessment	No significant AE; 2 patients reported nausea with Tablet Reunion; no complications with teriparatide
Brahmkshatriya Hret al, 2015[48]	9 patients (Cissus: 5, Control: 4) 8 male, 1 female	20-63 years	Maxillofacial fractures (mandible, maxilla)	CQ 500 mg capsule TID × 6 weeks (Group 1); Control (no CQ, Group 2); all with ORIF, antibiotics, and analgesics	CQ group had reduced pain, swelling, mobility, faster bone healing, higher serum calcium and phosphorus vs control; earlier periosteal reaction and callus on CT (day 21), complete bone deposition by day 45 in CQ group	45 days	Pain (VAS), swelling (measurement), fragment mobility, serum calcium/ phosphorus, 2D-CT	None reported; CQ well tolerated orally
Mohammad S et al, 2014[49]	29 patients Group A: Ocimum sanctum, Group B: CQ Group C: Placebo control 27 male, 2 female	20-40 years	Mandibular fractures (most common site: angle, followed by canine region)	Group A: Ocimum sanctum 1 tsp QID (25 g 6-hourly); Group B: CQ 1 tsp TID (3.5 g 8-hourly); Group C: Placebo 1 tsp TID. 80% alcoholic extract powder.	Period of immobilization lowest in Group A (Ocimum) followed by Group B (CQ); significant increase in alkaline phosphatase and serum Ca in Group B; maximum tensile strength (bite force) in Group B; good Xray healing in CQ group	8-15 weeks,	Time of immobilization, hemoglobin, serum calcium, serum phosphate, alkaline phosphatase, blood sugar, urea, bite force (kp), radiographs	None reported; transient blood urea elevation
Singh N et al, 2013[50]	60 patients Group 1: 30 CQ-treated; Group 2: 30 placebo controls	20-35 years	Mandibular fractures	Group 1: CQ capsules (300 mg) 2 capsules BID; Group 2: Placebo (starch powder) 2 capsules BID Double-blind design.	CQ group showed better Xray healing; significant expression of osteopontin protein and CD4+ T cells; that remained elevated through all time points (0, 4, and 6 weeks), sustained early callus formation, neovascularization, and bone remodeling.	8 weeks	Pain, swelling, mobility at fracture site, bite force, OPG Xray, serum Ca, serum phosphates, serum alkaline phosphatase, osteopontin expression	No AE reported in the study
Benjawan S et al, 2022[52]	134 enrolled, Placebo: 36, CQ 1.2 g/day: 34 CQ 1.6 g/day: 38) Women	Mean ~56 years	Osteopenia in postmenopausal women	Orally administered dried CQ stem powder in capsules (CQ 1.2 g/day or 1.6 g/day) vs placebo for 24 weeks	CQ significantly slowed bone turnover reducing P1NP and stabilized CTX vs placebo. Unchanged BMD compared to placebo after 24 weeks	24 weeks	BMD, serum CTX, serum P1NP, safety labs	CQ well tolerated; mild GI upset in all groups

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worsening densitometry without fractures, CQ could be used as an adjunct. These indications also make it an attractive alternative for patients who must suspend antiresorptive therapy for dental treatments (a period known as a "drug holiday"), providing osteoprotective support without the risks associated with conventional medications.[57]

Table 4 summarizes CQ potential clinical indications.

However, a clinical dosing or timing guideline has not yet been standardized, and therapy should be personalized according to the single patient condition. Based on current clinical evidence, clinical administration has varied significantly, depending on the study's focus and the formulation utilized.[45] For the purpose of accelerating bone fracture healing, CQ has been clinically administered at a high range, with systematic reviews noting clinical use ranging from 1.2 to 10 g/day for 4–12 weeks.[45,58] Specific pilot studies administered one capsule of CQ (500 mg) thrice a day for 6 weeks (total 1500 mg/day).[48] For chronic bone loss conditions, such as osteopenia in postmenopausal women, CQ was administered orally for 24 weeks, a period which, at the time of publication, represented the longest continuous oral CQ administration reported to date.[52] Doses evaluated in this trial were 1.2 g/day and 1.6 g/day, with the 1.6 g/day dose showing a promising effect in delaying bone loss by significantly reducing bone turnover markers. This lack of standardization in both dosage and administration time represents an actual limitation. Moreover, studies frequently employ different dosage forms and extraction procedures, which makes direct comparison of clinical effects challenging. Lastly, the majority of current clinical trials are of short duration, often lasting six months or less, and limited data exist on the long-term safety required for the chronic management of osteoporosis. Therefore, future research must focus on conducting large-scale, long-term randomized controlled trials (RCTs) to conclusively validate the efficacy, establish the optimal dose, and define the appropriate duration of therapy for CQ.

An additional topic that deserves discussion is CQ economic accessibility. Conventional pharmacological agents approved for OP management carry substantial direct costs, with annual per-patient expenditures ranging from approximately US$458-$1,874 for oral bisphosphonates to US$1,838 for denosumab and up to US$22,156 for teriparatide, placing a considerable financial burden on both patients and healthcare systems. In contrast, CQ is currently marketed in

Table 4 Cissus Quadrangularis Potential Clinical Indications

Potential Clinical Indication	Rationale and Suggested Use
Acute Bone Injury Repair *(e.g., fractures, maxillofacial reconstruction, dental implant procedures)*	CQ has the capacity to accelerate bone injury repair by directly affecting callus formation and promoting accelerated mineralization.[29] CQ restores bone strength and reduces the repair period.[27] CQ enhances biomineralization through the upregulation of MAPK-dependent ALP activity in osteoblasts.[16]
Alternative Therapy for Patients with Contraindications to bisphosphonates	CQ exhibits a dual mechanism (stimulating osteogenesis and inhibiting osteoclastogenesis) and a good safety profile.[15] This makes CQ an option for patients who are unwilling or unable to take bisphosphonates or other conventional anti-resorptive therapies.[33]
Management of Early Bone Loss (Osteopenia)	CQ is a potential therapeutic agent for patients with osteopenia or young individuals (such as men under 50 or premenopausal women) with risk factors that do not meet the indications for standard anti-resorptive drugs.[49] Clinical trials suggest that oral CQ has a delaying effect on bone loss in postmenopausal women with osteopenia.[52]
Support During "Drug Holiday"	CQ is a potential alternative for patients who must suspend antiresorptive therapy for dental treatments (a period known as a "drug holiday"). This provides osteoprotective support during the pause, without the risk of conventional side effects like osteonecrosis of the jaw.[13]
Adjunct Therapy for Sub-Optimal Response	• For patients who, despite being treated with antiresorptives, show worsening BMD without fractures, CQ could be added. • Studies indicate that the co-delivery of CQ synergistically elevates the osteogenic effect of synthetic molecules like Bone Morphogenetic Proteins and zoledronate, suggesting a potential strategy to reduce the doses of synthetic molecules.[27]

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most jurisdictions as a dietary supplement or herbal/nutraceutical product rather than a licensed pharmaceutical drug, and is therefore available without prescription at substantially lower cost, with commercially available standardized extracts retailing at approximately US$13–$40 per month for clinically evaluated dose ranges.[59,60] However, CQ is typically not reimbursed by public or private insurance systems, and the wide variability in extraction protocols and phytochemical standardization across commercial preparations introduces significant uncertainty regarding therapeutic equivalence with formulations used in clinical trials. Until high-bioavailability, standardized CQ formulations receive formal regulatory approval and undergo health technology assessment, any cost-effectiveness conclusion remains premature.

Conclusion

The comprehensive data accumulated across centuries of traditional use and modern investigation strongly establishes the promising osteoprotective potential of CQ. Its distinction from conventional pharmaceuticals lies in its dual mechanism of action (i.e., simultaneously promoting osteogenesis by stimulating osteoblasts and inhibiting bone resorption by suppressing osteoclasts). Robust preclinical studies consistently confirm this activity, demonstrating enhanced callus formation, improvements in bone microarchitecture and BMD, and the suppression of inflammatory bone loss in estrogen-deficient models. Emerging human evidence supports its clinical relevance, particularly its measurable benefit in reducing bone pain scores associated with fractures and its role in delaying bone loss among postmenopausal women with osteopenia.

This therapeutic relevance is significantly amplified by continuous advancements in delivery technology, with pharmacokinetic improvements that translate to enhanced efficacy.

Given its safety profile and multi-target action, CQ is positioned not as a replacement for established pharmacotherapy but as a valuable adjunct in comprehensive OP management. This role is particularly relevant for managing early bone loss (osteopenia) or serving as osteoprotective support during patient-specific scenarios, such as when antiresorptive therapies must be suspended for dental treatments ("drug holiday"). However, the current evidence is insufficient to recommend CQ as monotherapy for established OP due to many limitations, including small sample sizes and short follow-up durations (≤6 months), coupled with a persistent lack of standardized extraction protocols. Therefore, a definitive clinical conclusion requires larger-scale, multi-center RCTs utilizing standardized, high-bioavailability CQ formulations, along with long-term safety assessments and studies exploring its synergistic potential in combination therapy with established anti-osteoporotic agents.

Disclosure

The authors report no conflicts of interest in this work.

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