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Osteogenic Potential of Cissus Quadrangularis: A Systematic Review

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Abstract

Research shows that Cissus quadrangularis extracts can promote osteoblast proliferation, enhance collagen synthesis, and influence key signalling pathways like the Wnt/β-catenin pathway, which is vital for bone growth and remodelling. These findings suggest that Cissus quadrangularis could be an effective natural treatment for osteoporosis, bone fractures, and other skeletal disorders. A comprehensive search strategy was developed to systematically review the osteogenic potential of Cissus quadrangularis. Relevant studies were identified through searches of PubMed/MEDLINE, EMBASE, Cochrane Library, Scopus, Web of Science, and Google Scholar, using key terms such as "Cissus quadrangularis," "osteogenesis," "bone healing," and "bone regeneration." Boolean operators were employed to refine the search. Inclusion criteria focused on in vitro, in vivo, and clinical studies exploring the plant's role in bone health, while studies unrelated to osteogenesis or without original data were excluded. Titles, abstracts, and full texts were screened for relevance, followed by data extraction and quality assessment using appropriate tools. The strategy aimed to ensure comprehensive coverage of the available literature, minimizing bias and including diverse sources. A comprehensive search identified 975 articles. After excluding studies involving other plant extracts or review articles, the final selection included 8 cell line studies, 2 animal studies, and 5 clinical studies. The selected studies were analysed thoroughly. The systematic review underscores the osteogenic potential of Cissus quadrangularis, highlighting its ability to enhance bone formation and osseointegration based on cell line, animal, and clinical studies. While promising, the review also points out limitations, including a lack of high-quality clinical trials and challenges in conducting meta-analyses due to varied study designs and methodologies.

Keywords*: Bone Healing, Bone Regeneration, Cissus quadrangularis, Natural Bone Treatment, Osteoblast, Osteogenesis.*

Introduction

Traditional medicines, particularly those derived from plant sources, have gained considerable traction in recent years due to their extensive therapeutic potential and historical significance in various cultures [1]. The reliance on plant-based remedies has not

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only persisted but has exponentially increased as modern science continues to validate and explore the medicinal properties of these natural resources. According to the World Health Organization (WHO), over 80% of the global population relies on traditional medicines for their primary healthcare needs, with a significant proportion of these remedies being plant-based [2]. This global trend underscores the critical role of medicinal plants in healthcare systems, particularly in regions where access to conventional medicine may be limited. In India, the use of natural resources in medicine is deeply rooted in cultural practices and traditional healing systems. It is estimated that approximately 70% of modern pharmaceutical drugs in the country have origins in natural compounds, either directly derived from plants or developed from prototypes of plant-based molecules [3-5]. The rich biodiversity of India's flora has made it a significant contributor to the discovery and development of medicinal compounds, with numerous plants being the source of therapeutic agents that serve as the basis for modern drugs. Among these, *Cissus quadrangularis* stands out as a particularly important medicinal herb. *Cissus quadrangularis*, a perennial vine from the Vitaceae family, is renowned in traditional Indian medicine, particularly within the context of Ayurveda and folk medicine, for its bone-healing properties. Commonly referred to as "Hadjod" or "Bone Setter," this plant has been a cornerstone in traditional treatments, especially in the Puttur region, which is famous for its unique bone-setting practices [6]. It is widely used for treating bone fractures, dislocations, and other musculoskeletal disorders, a practice that has been passed down through generations. The plant’s popularity in these treatments is attributed to its reputed ability to accelerate bone healing, reduce pain, and improve joint function. The surge in global interest in alternative and complementary medicine has driven scientific research into the osteogenic potential of Cissus quadrangularis. Preclinical studies have provided promising evidence of its efficacy in promoting bone formation, enhancing bone mineral density, and supporting overall bone health. The plant's therapeutic effects are believed to stem from its rich phytochemical profile, which includes a variety of bioactive compounds such as flavonoids, triterpenoids, and phytosterols. These compounds are known for their anti-inflammatory, antioxidant, and anabolic properties, which collectively contribute to the bone-healing process [7-10]. Research indicates that extracts of Cissus quadrangularis can stimulate osteoblast proliferation, the cells responsible for bone formation, and enhance collagen synthesis, a critical component of bone matrix. Moreover, the plant’s bioactive compounds have been shown to modulate key signalling pathways involved in bone regeneration, such as the Wnt/β-catenin pathway, which plays a crucial role in bone growth and remodelling. These mechanisms suggest that Cissus quadrangularis could be a potent natural remedy for conditions like osteoporosis, bone fractures, and other skeletal disorders [11, 12]. Despite these encouraging findings, the scientific community recognizes the need for a more comprehensive synthesis of the existing evidence. While individual studies have highlighted the osteogenic potential of Cissus quadrangularis, there remains a gap in the literature regarding the consistency of these findings, the quality of the research, and the clinical relevance of the results.

This systematic review seeks to address these gaps by critically evaluating and consolidating the available scientific literature on Cissus quadrangularis. By systematically reviewing in vitro (laboratory), in vivo (animal), and clinical studies, this review aims to provide a detailed understanding of the plant’s mechanisms of action, its efficacy in promoting bone health, and its potential

application in modern medicine. Through this comprehensive analysis, the review will offer insights into the potential of Cissus quadrangularis as an alternative or complementary therapy for bone-related disorders, and guide future research to further explore and validate its therapeutic benefits.

Material and Methods

Structured Question

Is cissus quadrangularis having the osteogenic potential to be effective in treating healing bone fractures?

PIO (Population, Intervention, Outcomes)

P- Patient undergoing treatment of healing bone fractures

I- Application of Cissus plant extracts

Outcomes- Bone formation and Osteogenesis

Search Strategy

This systematic and thorough search strategy was designed to ensure that the review would comprehensively cover the osteogenic potential of Cissus quadrangularis, offering a reliable and evidence-based conclusion on its efficacy and applications in bone health. A comprehensive and methodologically rigorous search strategy was employed to identify all relevant studies, both published and unpublished, to review the osteogenic potential of *Cissus quadrangularis* systematically. The strategy was designed to ensure a thorough coverage of the available literature, minimizing the risk of bias and ensuring the inclusion of diverse sources of evidence.

Databases Searched

The following electronic databases were searched to gather relevant studies:

PubMed/MEDLINE: For biomedical literature, focusing on peer-reviewed articles related to the pharmacological and therapeutic aspects of Cissus quadrangularis.

EMBASE: To capture studies from a wide range of biomedical journals, including those not indexed in PubMed.

Cochrane Library: To include systematic reviews, clinical trials, and other high-quality studies related to osteogenic agents and natural products.

Scopus: For broad coverage of scientific articles, including those in the fields of pharmacology, medicinal plants, and osteogenesis.

Web of Science: To capture interdisciplinary research and citation analysis of key studies.

Google Scholar: To identify grey literature, theses, conference papers, and other sources that might not be indexed in traditional databases.

Search Terms and Keywords

The search strategy was constructed using a combination of Medical Subject Headings (MeSH) terms, keywords, and phrases that were relevant to both the plant and its osteogenic potential. The main search terms included: Cissus quadrangularis, Osteogenesis, Bone healing, Bone regeneration, Bone fractures, Bone density, Phytochemicals, Herbal medicine, and Traditional medicine.

Boolean operators (AND, OR, NOT) were used to combine these PIO terms effectively like

("Cissus quadrangularis" OR "Hadjod") AND ("Osteogenesis" OR "Bone healing" OR "Bone regeneration"), ("Cissus quadrangularis" AND "Phytochemicals") AND ("Bone density" OR "Bone fractures").

Inclusion and Exclusion Criteria

The search was refined using specific inclusion and exclusion criteria to ensure the relevance and quality of the studies included in the review.

Inclusion Criteria

1. Studies investigating the osteogenic potential of Cissus quadrangularis.

2. In vitro (laboratory-based), in vivo (animal-based), and clinical studies.
3. Articles published in peer-reviewed journals.
4. Studies published in English.
5. Studies that specifically explored the mechanisms of bone healing, bone density enhancement, or fracture healing associated with Cissus quadrangularis.

Exclusion Criteria

1. Studies not involving Cissus quadrangularis.
2. Studies not related to bone health or osteogenesis.
3. Review articles, opinion pieces, or editorials without original data.
4. Articles published in languages other than English.
5. Studies with insufficient methodological detail or unclear outcomes.

Screening and Selection Process

1. Title and Abstract Screening: Initially, the titles and abstracts of all retrieved articles were screened for relevance based on the inclusion and exclusion criteria.
2. Full-Text Review: Studies that passed the initial screening underwent a full-text review to confirm eligibility. Two independent reviewers assessed the full texts, and discrepancies were resolved through discussion or consultation with a third reviewer.
3. Data Extraction: Relevant data, including study design, sample size, interventions, outcomes, and key findings, were systematically extracted using a standardized data extraction form.

Quality Assessment

The quality of the included studies was assessed using appropriate tools:

1. In vitro and in vivo studies: Evaluated for methodological rigour, including sample size, experimental controls, and reproducibility.
2. Clinical studies: Assessed using the Cochrane Risk of Bias tool or similar criteria to evaluate randomization, blinding, and outcome reporting.

Data Synthesis

Data from the selected studies were synthesized to provide a comprehensive overview of the osteogenic potential of Cissus quadrangularis. Narrative synthesis was used for studies that were not suitable for meta-analysis due to heterogeneity in study designs, outcomes, or methodologies.

Results

This systematic review included all the cell line studies, animal studies, and clinical studies revealing the Osteogenic potential of Cissus quadrangularis. The articles searched through Pubmed Central National Library of Medicine(MEDLINE/PubMed), Google Scholar, Cochrane, and Hand search resulted in a total of 975 articles, out of which 400 articles were excluded research articles involving different plant extracts, duplicate articles, 575 articles were screened by title and abstract, further filtered by excluding 553 articles, among those, 268 articles were excluded as they were general review and systematic review articles, 170 articles were removed due to their title and abstract were found irrelevant, 115 articles were found combination of Cissus and other plant extracts, finally conclude that there were 8 cell line studies two animal studies and five clinical studies found. This can be clearly explained from the PRISMA Flow chart diagram (Fig1). The data were extracted from the selected studies and analysed (Tables 1-5).

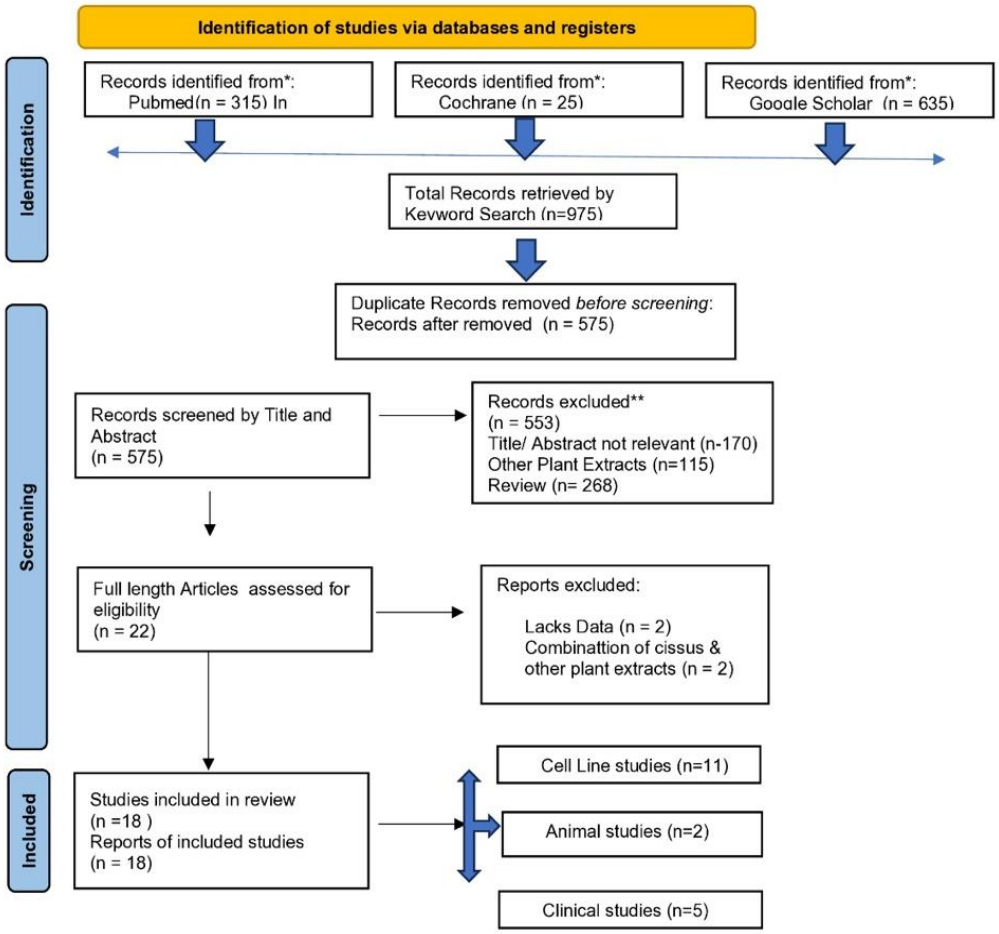

Fig 1. PRISMA Flow Chart for Selection of Studies

Table 1. Characteristics of the Included Studies-Cell Line Studies

S.No	Author & year	Cell line	Outcome
1.	Parisuthiman et al,2009[12]	MC3T3-E1	CQ enhanced Osteoblastic Activity and ALP activity by MAPK-dependent pathway.
2.	Potu et al, 2009[13]	n=30	CQ can stimulate osteoblastogenesis, an effective preventive measure in osteoporotic bone disorders.
3.	Muthusami et al, 2011[14]	NA	Concluded that CQ showed positive regulation on the cell proliferation, differentiation, and matrix mineralization of human osteoblast-like SaOS-2 cells
4.	Siddiqui et al, 2015[15]	NA	CQ extract revealed concentration-dependent biphasic effects, which would contribute notably to future assessment of pre-clinical efficacy and safety studies.

5.	Parvathi et al, 2017[16]	NA	PLLA Fibers with CQ results have a good osteogenic potential without any osteogenic medium, enhancing the possibility of using it as a biomaterial for bone regeneration.
6.	Tasadduq et al, 2017[17]	MC3T3-E1	It has been evidenced that Cissus quadrangularis induces bone formation and dose-dependent effects, also CQ-E has a lot of osteogenic potential to be used to treat fractures and in the prevention and treatment of osteoporosis.
7.	Toor et al, 2019[18]	MC3T3-E1	CQ-H has the highest osteogenic potential and is not cytotoxic So it can be a promising medicine in the treatment of osteoporosis.
8.	Toor et al, 2019[19]	MC3T3-E1 (Subclone 4)	This study concluded that CQ-EA and CQ-B have good proliferation and osteogenic properties. However, CQ-EA has more potent osteogenic potential than CQ-B at low concentrations.
9.	Ruangsuriya et al, 2020[20]	MG-63	CQ enriched with both quercetin and rutin has biphasic effects that activate the molecules that participated in bone formation and the molecules inhibiting bone resorption may be developed as antiosteoporotic therapeutic agents in future.
10.	Nair et al, 2021[21]	n=5	Bioactive constituents in HE and WE extracts were found to be promising in bone tissue regeneration procedures.
11.	Liao et al,2023[22]	hBMSC	The physicochemical characterizations and cell viability experiments indicate that the β-TCP/Gel-Pec composite loaded with CQ has the potential to be used as a biomaterial for bone tissue regeneration and repair.

Table 2. Cell Line Studies

Author and Year	**Study Design**	**Level of Evidence**
Parisuthiman et al, 2009[12]	Cell line study	V
Potu et al, 2009[13]	Cell line study	V
Muthusami et al, 2011[14]	Cell line study	V
Siddiqui et al, 2015[15]	Cell line study	V
Tasadduq et al, 2017[16]	Cell line study	V
Parvathi et al, 2017[17]	Cell line study	V
Toor et al, 2019[18]	Cell line study	V
Toor et al, 2019[19]	Cell line study	V
Ruangsuriya et al, 2020[20]	Cell line study	V
Nair et al, 2021[21]	Cell line study	V
Liao et al, 2022[22]	Cell line study	V

Table 3. Animal Studies

Author and Year	Study Design	Level of Evidence
Robertson et al, 2020[23] (in vitro and in vivo)	Randomized Controlled clinical trial	II
Azam et al, 2022[24] (in vitro and in vivo)	Randomized Controlled clinical trial	II

Table 4. Clinical Studies

Author and Year	Study Design	Level of Evidence
Singh et al, 2013[25]	Randomized controlled trial	II
Brahmakshatriya et al, 2015[26]	Non-randomized clinical trial	III
Managutti et al, 2015[27]	Prospective randomized control trial	II
Nayak et al, 2020[28]	Randomized controlled clinical trial	II
Altaweel et al, 2021[29]	Randomized controlled clinical trial	II

Table 5. Risk of Bias in Clinical Studies

S.no	Author and Year	Randomization	Allocation concealment	Assessor blinding	Dropouts	Risk of bias
1.	Singh et al, 2013[25]	Yes	Yes	Yes	No	Low
2.	Brahmakshatriya et al, 2015[26]	Yes	Yes	Yes	No	Low
3.	Managutti et al, 2015[27]	Yes	No	No	No	Moderate
4.	Nayak et al, 2020[28]	Yes	No	Yes	No	Moderate
5.	Altaweel et al, 2021[29]	Yes	No	Yes	No	Moderate

Discussion

The findings of this systematic review provide a comprehensive evaluation of the osteogenic potential of Cissus quadrangularis, a plant traditionally recognized for its bone-healing properties. By synthesizing evidence from cell line studies, animal models, and clinical trials, this review sheds light on the mechanisms through which Cissus quadrangularis may contribute to bone formation and osseointegration. Despite the promising outcomes observed across various experimental settings, the current body of literature reveals gaps and limitations, particularly in the context of clinical evidence. The discussion will critically analyze the strengths and weaknesses of the available studies, explore the biological plausibility of Cissus quadrangularis as an osteogenic agent, and identify areas where further research is needed to solidify its role in bone health and

therapeutic applications. In the cell line studies summarized in Table 1, researchers employed various cell lines derived from rat calvaria and human osteosarcoma cells to investigate the osteogenic potential of Cissus quadrangularis (CQ). Potu et al demonstrated that Cissus quadrangularis (CQ) exhibited significant osteoblastic activity using bone marrow mesenchymal cells derived from the bones of Wistar rats [13]. In a related study, Muthusami et al used human osteoblast-like SaOS-2 cells to assess the cell differentiation and matrix mineralization potential of CQ extracts, finding that CQ effectively promoted osteoblastic activity [14]. The Other cell line Studies by Parisuthiman et al [12], Tasadduq et al [16], and Toor et al [18, 19] utilized the MC3T3-E1 cell line (murine osteoblastic cells) and found that CQ extracts enhanced osteoblastic activity, as evidenced by increased ALP activity and results from the MTT assay. Ruangsuriya et al[20]. employed the MG-63 cell line and concluded that CQ, when combined with quercetin and rutin, exhibited biphasic effects [20]. This combination not only stimulated the molecules involved in bone formation but also activated those that inhibit bone resorption. Similarly, Nair et al. assessed the osteoblastic potential of CQ using ALP activity and the MTT assay, but instead of murine cells, they utilized human osteosarcoma cells [21].

In these cell line studies, the commonly assessed microbiological parameters included ALP activity, MTT assay, RT-PCR assay, and mRNA expression analysis. Notably, the MTT assay was utilized in studies by Parisuthiman et al [12]., Potu et al [13], Tasadduq et al [17] and Siddiqui et al [15] to evaluate cell proliferation rates, with findings indicating that Cissus quadrangularis (CQ) significantly enhanced proliferation compared to control group cells. Similarly, in the study by Toor et al [18, 19], the MTT assay was employed to measure the metabolic activity of cells, while the BrdU assay was used to assess cell proliferation, both confirming results consistent with other studies that CQ supports increased cell proliferation. Additionally, only a few studies, including those by Muthusami et al [14], Toor et al [18, 19], and Liao et al [22] conducted RT-PCR expression analysis, all of which concluded that CQ demonstrated strong osteogenic expression. Regarding the animal studies summarized in Table 2, only two relevant studies were identified in the literature, both of which incorporated both in vivo and in vitro approaches. Robertson et al conducted an animal study utilizing 3D-printed scaffolds coated with polydopamine and CQ extract [23]. They concluded that these implants performed better in promoting early bone formation and growth compared to pure β-tricalcium phosphate scaffolds, though the study had a moderate risk of bias due to the lack of allocation and blinding. Similarly, Azam et al [24] conducted a study combining both ex vivo and in vivo approaches, concluding that CQ offers osteoprotective benefits in postmenopausal osteoporotic conditions, likely mediated through a distinctive cellular and immunological mechanism [24]. According to the Oxford Centre for Evidence-Based Medicine, eight cell line studies provided level V evidence, while two animal studies and five clinical studies offered level II evidence.

By the CONSORT guidelines, four key factors were considered in assessing the risk of bias: 1) blinding of the assessor, 2) allocation concealment, 3) randomization, and 4) dropouts. Among the five clinical studies evaluated (Table 3), randomization was consistently implemented across all studies. However, allocation concealment was only observed in two studies, conducted by Singh et al [25] and Brahmakshatriya et al [26] and was not followed in the remaining studies. Notably, one clinical study by Managutti et a [27]. Exhibited a moderate risk of bias due to the absence of both allocation concealment and assessor blinding. In contrast, the other

four clinical studies were determined to have a low risk of bias. Importantly, none of the studies included in this systematic review reported any dropouts.

Among those five clinical studies, Both Singh et al [25] and Nayak et al [28] conducted the study in patients with mandibular fracture cases, whereas Brahmakshatriya et al [26] involved the patients with maxillofacial fractures. Altaweel et al [29] conducted the clinical trial in patients with atrophic posterior mandibles, In contrast to all of the above, the only one clinical pilot study by Mangutti et al [27], was conducted in patients with partially edentulous where the dental implants were placed and analyzed the level of Oseointegration after orally treated with Cissus quadrangularis. All these studies in common evaluated the clinical parameters like Pain score by VAS, Serum alkaline phosphatase , Serum Calcium and Serum Phosphorus level etc and concluded with the results that Cissus quadrangularis is a Good Oseteogenic agent and promotes excellent bone formation. This systematic review comprehensively included cell line studies, animal studies, and clinical studies that demonstrated the osteogenic potential of Cissus quadrangularis, particularly in promoting bone osseointegration. Additionally, clinical trials on Cissus quadrangularis are limited, with those included in this review showing a moderate to low risk of bias. Notably, among the clinical studies, only one involved a relatively large sample size of sixty patients, while others had smaller cohorts.

The limited number of studies specifically investigating the effects of Cissus quadrangularis on bone osseointegration posed challenges in conducting a meta-analysis, particularly due to the variation in statistical reporting in cell line studies and the scarcity of robust clinical trials. To better understand and validate the osteogenic effects of Cissus quadrangularis, future research should focus on well-designed clinical studies with larger sample sizes, extended follow-up periods, and lower risk of bias. These improvements would facilitate more definitive conclusions and enable meta-analytical approaches to assess the plant's efficacy in bone health.

Despite these limitations, the findings support the traditional use of Cissus quadrangularis and provide a strong foundation for future research. To fully establish its efficacy and therapeutic potential, more rigorous clinical studies with larger sample sizes, long-term follow-up, and standardized outcome measures are needed. Such studies would not only strengthen the evidence base but also pave the way for the integration of Cissus quadrangularis into modern therapeutic practices for bone health and regeneration.

Conclusion

The systematic review highlights the promising osteogenic potential of Cissus quadrangularis, a medicinal plant traditionally used for bone healing. Evidence from cell line studies, animal models, and clinical trials suggests that Cissus quadrangularis may enhance bone formation, promote bone osseointegration, and serve as a valuable adjunct in the treatment of bone-related disorders. However, the review also underscores the limitations in the current body of research, particularly the scarcity of high-quality clinical trials and the challenges in conducting meta-analyses due to varying study designs and statistical methods.

Conflict of Interest

The authors declare no conflicts of interest

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