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REVIEW ARTICALE

PHYTOCHEMICAL-INFUSED SCAFFOLDS: THE ROLE OF CISSUS QUADRANGULARIS IN ADVANCING BONE TISSUE ENGINEERING: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Cissus Quandrangularis has been used in traditional medicine for centuries for its repair of bone fractures, joint health, osteoporosis prevention, antibacterial, analgesic, anti-inflammatory, antioxidant properties. When this herb is mixed in modern day research of bone engineering, the greater demand of bone grafts and graft failure can be met. Therefore this study aimed to assess the effect of Cissus quandrangularis infused scaffolds in bone regeneration in various cell cultures.

Materials and Methods: Last 10 year published english articles from pubmed, scopus, web of science etc were searched for inclusion in the review. Original invitro research investigating the effect of Cissus Quandrangularis based scaffolds on Cell cultures were included. Data extraction was done by two authors and risk of bias was determined by QUIN guidelines

Results: After the data was extracted, 12 studies out of the 51 that were assessed were included. Ten of the twelve research that were included used human cell cultures, while the other two used murine cell lines. Alkaline phosphatase activity was the primary test employed in the included trials for bone regeneration. Nine of the twelve studies that were included employed this.Alkaline phosphatase activity (ALP activity) is a biochemical assay that can be used to detect the enzyme alkaline phosphatase, which is involved in dephosphorylation reactions.

Conclusion: The bone regenerative potential of Cissus quadrangularis-infused scaffolds using both animal and human cell cultures is proved by all the 12 studies with positive results. This avoids the biological complications of allografts and autografts.

Keywords: Cissus quandrangularis; Bone regeneration; Scaffold; Osteoblast activity, Murine Cell line

INTRODUCTION

Bone tissue engineering is an exciting and evolving field that tackles the complex challenges of bone loss and repair. Bone tissue engineering (BTE) seeks to restore bone that has been lost due to trauma, illness, infection, tumors, or genetic conditions by employing advanced treatment and augmentation methods. These interventions are designed to address disruptions in normal biomechanics caused by such losses[1]. The greater demand for bone-grafts with intrinsic osteoinductivity is still a significant confrontation for clinicians.This area blends biology, materials science, and engineering to create innovative solutions for regenerating bone tissue. At the heart of this field are scaffolds—three-dimensional frameworks designed to mimic the natural extracellular matrix and support the growth of new bone tissue [2].

When it comes to bone grafting treatments, bone replacement scaffolds are in great demand as substitutes for autografts and allografts. It makes sense that choosing the right materials for the scaffold is essential since it will support the defect location and promote osteogenesis, or the growth of new bone [3]. Calcium phosphates (CaPs) are considered highly promising for bone replacement due to their chemical similarity to the inorganic component of bone. Among them, β-tricalcium phosphate (βTCP, Ca3(PO4)2) has gained significant attention for its biocompatibility, bioactivity, and biodegradability. Additionally, 3D-printed scaffolds with custom-designed porosity have been employed to more accurately replicate the complex hierarchical structure of natural bone, particularly in the cancellous (spongy) regions. [4].

Recently, integrating phytochemicals into these scaffolds has shown promise for improving their effectiveness. Among these natural substances, Cissus quadrangularis, a plant with a rich history in traditional medicine, has emerged as a particularly interesting candidate for advancing bone tissue engineering [5].

Cissus quadrangularis (CQ), a member of the Vitaceae family, also commonly known as veldt grape and devil's backbone. It has been used in traditional medicine for centuries to treat fractures and promote bone health.Other names for Cissus quadrangularis (CQ) include devil's backbone and veldt grape [6]. With quadrangular-sectioned branches that have internodes that are 8–10 cm (3–4 inch) long and 1.2–1.5 cm (0.5–0.6 inch) wide, the plant can grow up to a height of 1.5 m (4.9 ft). These species are indigenous to Arabia and tropical Asia. In conventional medicine, it is used for the repair of bone fractures, joint health, osteoporosis prevention, antibacterial, analgesic, anti-inflammatory, antioxidant, and tissue protection [7].

Steroids and vitamins included in CQ have been shown to have a particular impact on the repair of bone fractures. Studies on fracture healing indicate that its unknown anabolic steroids might interact with the bone's estrogenic receptors [8]. The photochemical analysis of CQ reveals that it contains high levels of ascorbic acid, carotene, anabolic steroidal compounds, vitamin C, potassium, calcium, zinc, sodium, iron, lead, cadmium, copper, calcium oxalate, and magnesium. Notably, the stem extract of CQ comprises approximately 4% calcium and phosphorus ions by weight, which are essential for bone fracture healing [9,10].

Although the exact active ingredients of CQ extract are still unknown, it is believed that many CQ compounds exhibit synergistic effects. Since β-sitosterol and stigmasterol are precursors of anabolic steroidal compounds, they can bind to osteoblasts and encourage their development and proliferation, making their quantification crucial for treating bone fractures [11,12]. In one study, the plant's phytoestrogens may have contributed to the rise in IGF expression by regulating the effects of CQ on components of the insulinlike growth factor (IGF) system in osteoblasts, which are crucial for bone development and remodeling [13]. Therefore this review aimed to assess the effect of Cissus quandrangularis infused scaffolds in bone regeneration in various cell cultures.

MATERIAL AND METHODS

Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 Statement and the Cochrane Handbook were referenced for developing the review's protocol [14,15].

Eligibility Criteria

A PICOS criterion was created [19] to assist in developing the search strategy and choosing the inclusion criteria for the papers in the current systematic review [16].The following is the PICOS formula.

- Population (P) - Different cell culture
- Intervention (I) - Cissus Quandrangularis infused scaffolds
- Comparison (C) - Conventional or other herb based scaffolds
- Outcome (O) - Bone regeneration
- Study Design (S): Original invitro research investigating the effect of Cissus Quandrangularis based scaffolds on Cell cultures were included; Brief communications, summaries, narrative reviews, editor's letters, case reports, and case series weren't.

Only articles that were published were reviewed for this evaluation. An article's publication status or the English
translation that accompanied it determined whether or not it was reviewed.

Information Sources and Search Strategy

To find all peer-reviewed papers relevant to the issue of the review, a comprehensive search of PubMed, Google Scholar, Cochrane CENTRAL, Scopus, Web of Science, and LILACS was conducted for publications published between January 2009 and June 2024 (15 years). Complex search algorithms were developed taking into account the different vocabulary and grammatical restrictions found in each database.

The following MeSH terms were used in search strategy. Cell culture OR mesenchymal cell culture OR bone stem cell culture OR sarcoma cell line OR mesenchymal stem cell OR periodontal ligament stem cell OR bone marrow mesenchymal stem cell OR murine preosteoblast cell line OR umblical cord derived mesenchymal stem cell OR human osteosarcoma cell line OR human bone marrow mesenchymal stem cell OR human osteoblast cell line OR bony defect OR bony defects OR preosteoblast cell line OR human fetal osteoblastic cell line AND Cissus Quadrangularis OR cissus genus OR cissus herb OR pirandai OR Veld Grape OR Adamant Creeper OR Hadjod AND Nanoparticle OR tricalcium phosphate OR hydroxyapatite OR Silver nanoparticles OR graphene nanoparticles OR bioceramics AND Bone regeneration OR bone fORmation OR alkaline phosphatase activity OR osteoblast activity OR osteoblast OR osteoinductive activity OR osteoinductivity OR bone healing OR periodontal regeneration OR intrabony defect regeneration OR osteoclastogenic marker OR osteogenic marker OR regenerative bone tissue engineering OR bone tissue engineering OR osteopontin expression OR Osteogenic potential OR biomineralization. A manual search of several journals, including the Journal of Periodontics, Journal of Clinical Periodontology, Journal of Osseointegration, Journal of Indian Soceity of Periodontology, Clinical Advances in Periodontics and Journal of Periodontolgy and Implant Dentistry was also conducted (Figure 1a-d).

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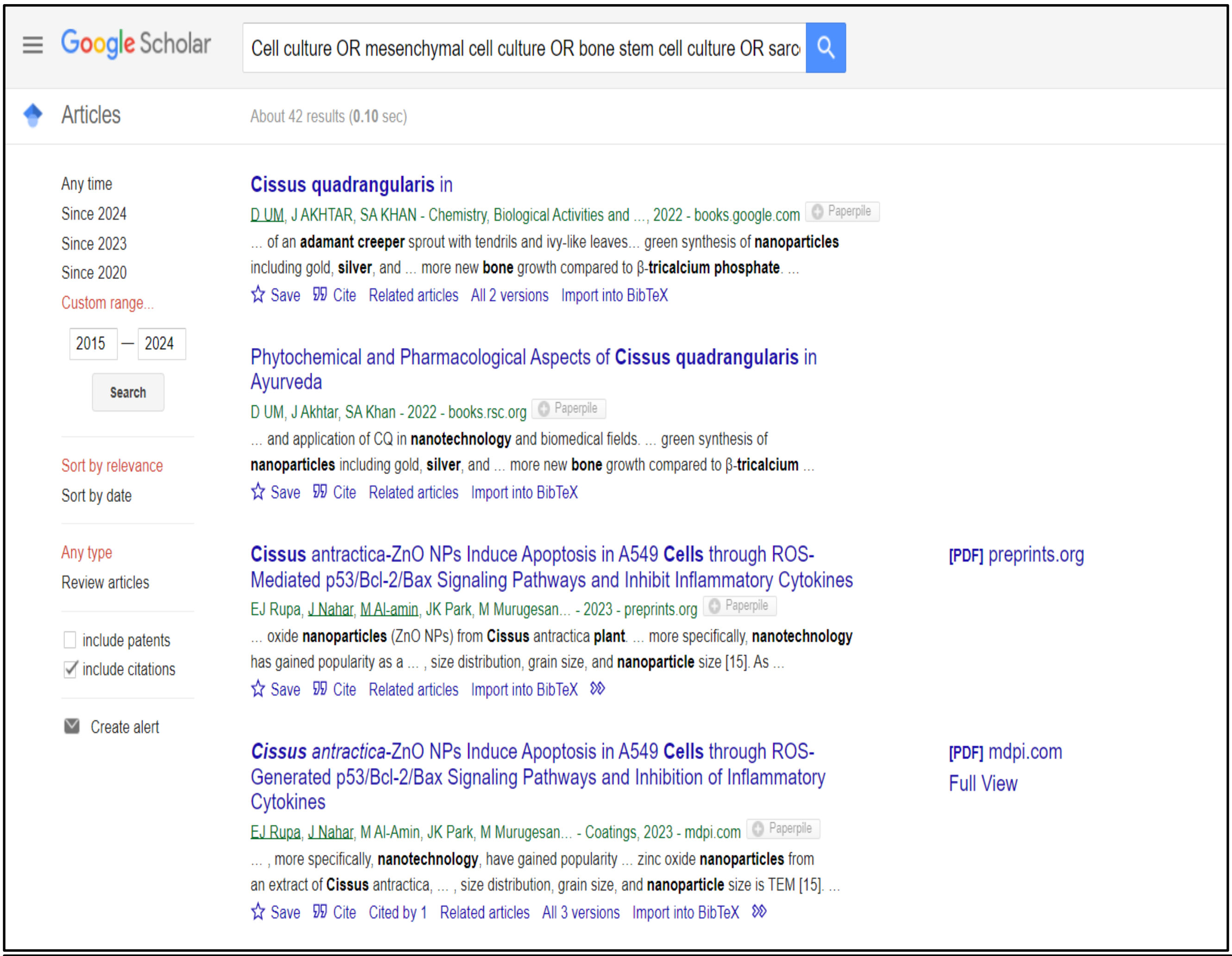
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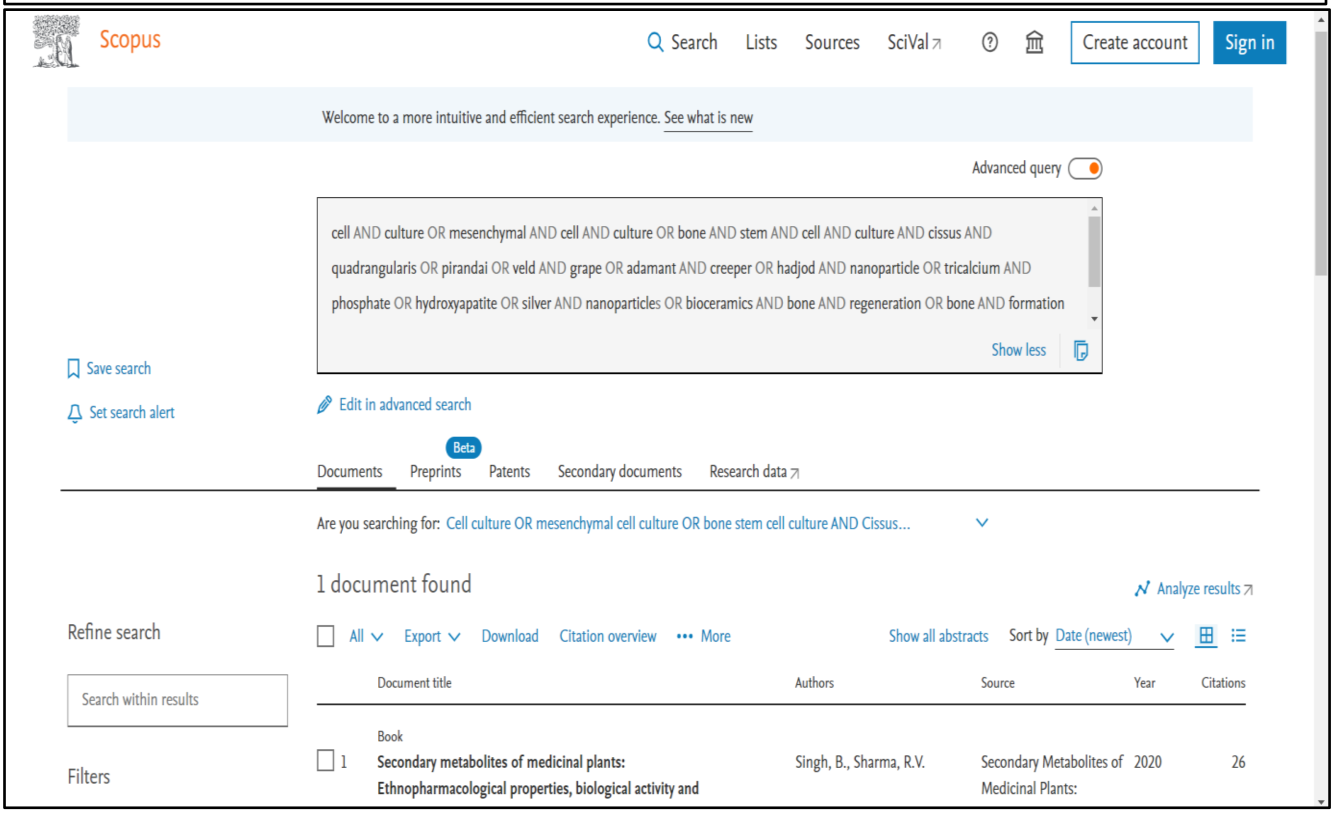
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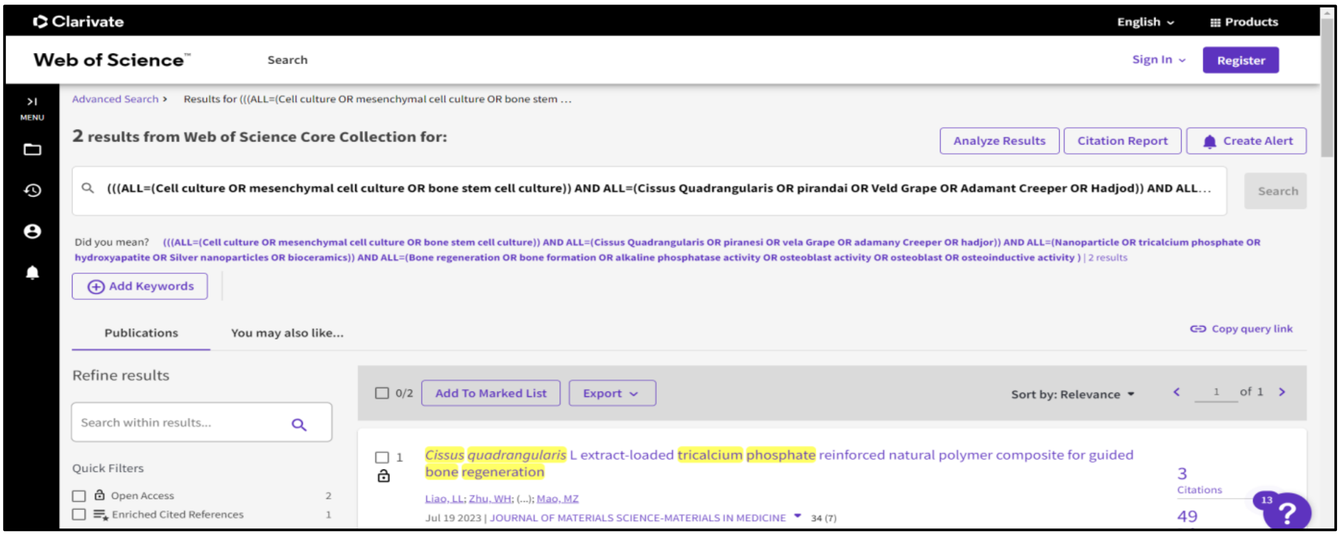

Figure 1 (a-d) . The search in different databases

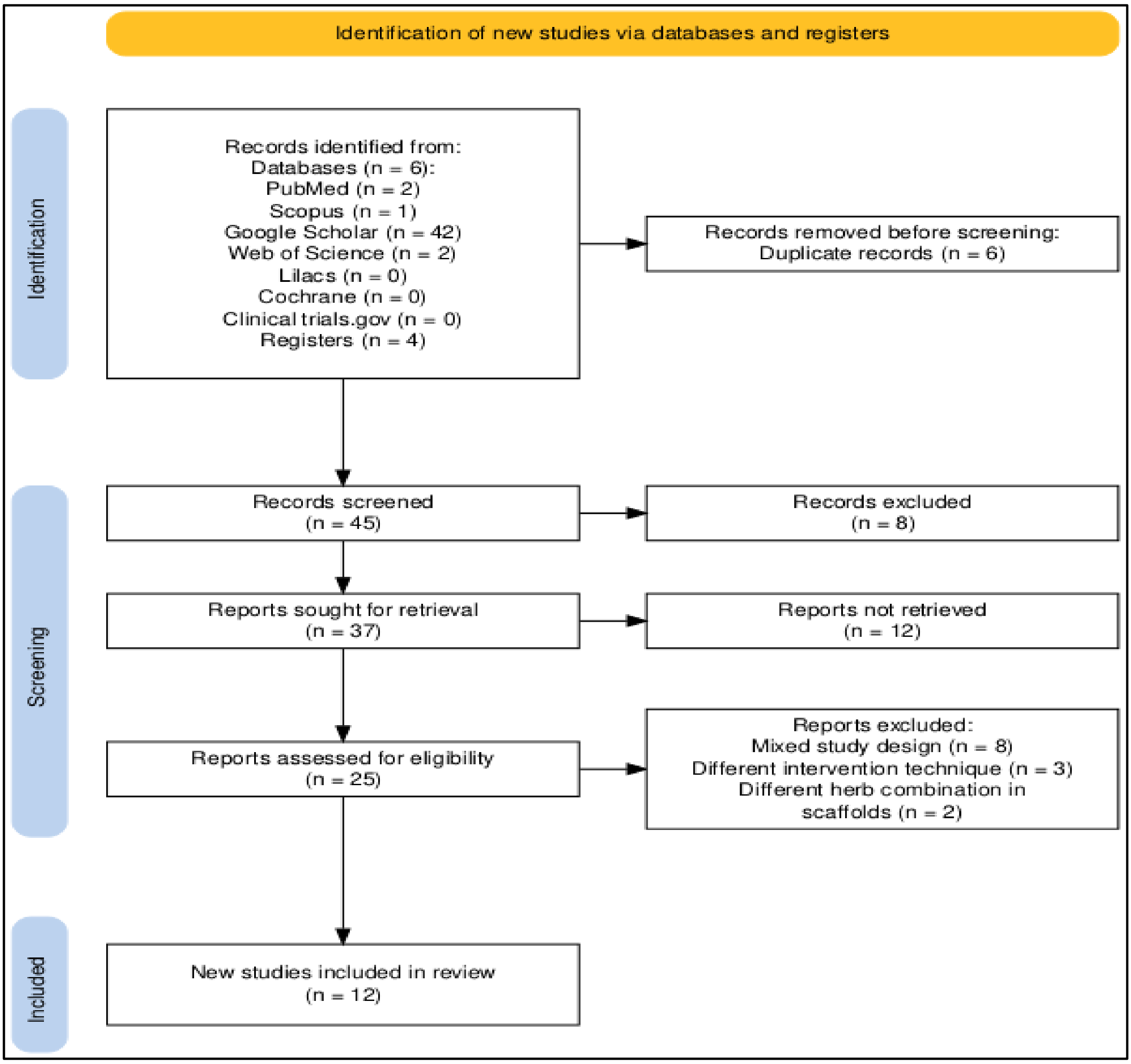

Figure 2. Prisma Flowchart for included studies

Using the databases Open Grey and GreyNet International, a search for grey literature was conducted in order to locate additional research that might be included in the review. References to the studies that were part of the review were also looked through in order to locate any research that might be included in the process of review.

The search was conducted independently by the two writers. First, a screening procedure was used to determine whether the article titles that the inquiry had turned up were eligible. Before beginning the qualitative investigation, we looked for and evaluated pertinent full-text studies. To discover if there was any more study that the initial search had missed, we browsed the references of the listed papers. A third reviewer was consulted multiple times during the search and review process in order to settle disputes that came up amongst the principal reviewers..

Data extraction

Two reviewers were needed for the data retrieval process. The following data was extracted and input into an already-prepared Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) from the studies that met the inclusion and eligibility requirements: This research includes the following: the number of samples, the degree of evidence, the intervention and control group, the first author, the nation, the year the study was published, the study design, the inclusion and exclusion criteria, and the key study outcomes. A third reviewer was used to verify the selection process. The final decision of inclusion into the article was decided by all the reviewers with voting process. Determined by the PRISMA flow diagram, Figure 2 illustrates the steps that go into selecting an article [17]. After the data extraction, each reviewer was assigned to specific number of articles to collect the data from the article manually.

Assessment of Risk of Bias

Specific risk of bias namely QUIN guidelines for in vitro studies were used to measure the risk of bias [18]. The requirements were broken down into 12 primary categories that namely

1. Clearly Stated Aims/Objectives
2. Detailed Explanation of Sample Size Calculation
3. Detailed Explanation of Sampling Technique
4. Details of Comparison Group
5. Detailed of Methodology
6. Operator Details
7. Randomization
8. Method of Measurement of Outcome
9. Outcome Assessor Details
10. Blinding
11. Statistical Analysis
12. Presentation of Results

Each study criterion was rated as 2 points for adequately specified; 1 point for inadequately specified, 0 points for not specified and NA for not applicable. The sum of all scores is assessed for risk of bias by a formula Sum of scores* 100/ 2* Number of applicable criteria.

The result of this above formula is categorised into low risk if its more than 70, moderate if its 50 - 70 and high risk if its less than 50. One reviewer assessed the possibility of bias, and the other cross-checked the results.

RESULTS

The search identified a total of 51 studies from various databases and registers. Six articles were removed due to duplication. Out of the remaining 45 studies screened, eight were excluded based on their abstracts as ineligible. From the 37 studies sought for full-text retrieval, 12 articles were excluded because their full texts could not be accessed. Consequently, 25 articles were reviewed in full text. Among these, eight were excluded due to containing both in vitro and in vivo experiments, three were removed because the intervention groups differed, and two were excluded due to the use of different herb combinations. After thorough screening, 12 studies were included in the review.

Out of the 12 studies included, 11 of them were published after 2016, only one was from 2009. Out of the 12 studies included, 10 were done on human cell culture and 2 were done on animal derived cell line which was specifically murine cell line. In the 10 human cell culture studies, 6 were done on mesenchymal cell culture, three were done on osteoblast cell line and one was done on human osteosarcoma cell line. Hydroxy apatite scaffolds were used in one study by Balaji et al, 3D printed β-Tri calcium Phosphate scaffolds were used in a study by Samuel F. Robertson.

There were different combinations of Cissus Quandrangularis were experimented in the studies. There were 5 one group intervention studies without comparison. In the other 7 studies Hydroxy apatite was used in the study Balaji et al, Hexane extract (HE), chloroform extract (CE), ethyl acetate extract (EE), methanol extract (ME) and aqueous extract was used in the study by Praseetha Nair et al. Europium-Monetite calcium phosphate complex was used in the experiment in the study by Niditha Suresh et al. poly ε-caprolactone scaffold and graphene oxide were used in a study by Shivaji Kashte et al. In the other 3 studies, different concentration of Cissus Quandrangularis extracts were compared.

The main test used in the included studies for bone regeneration was alkaline phosphatase activity. This was used in 9 out of 12 included studies.The enzyme alkaline phosphatase, which is involved in dephosphorylation processes, can be measured using a biochemical assay called alkaline phosphatase activity (ALP activity). It is frequently employed as a marker for mineralization and cell differentiation. In the other studies Alizarin Red Staining or sirius red staining was used to assess bone regeneration. It is important to note that Alizarin red staining is used in detecting calcium deposits in tissues whereas Sirius red staining was used assess collagen fibres. One study by Lele Liao et al, osteogenic marker genes Runt-related transcription factor, Vascular Endothelial Growth Factor and Osteocalcin were done to assess osteogenic activity.

Cissus Quandrangularis has been showed to increase periodontal tissue regeneration when its added in HA and tendon scaffolds. When it was added along with natural polymer in 3D printed β-Tri calcium Phosphate scaffolds, it increased the proliferation and alkaline phosphatase expression. When CQ was incorporated into nanovesicles, it was used as plant-derived extracellular vesicles (PDEVs) for bone regeneration and local drug delivery system in a study by Ritu Gupta. When CQ based Europium-Monetite composite was assessed for alkaline phosphatase activity on MG-63 cell line, it showed 10% higher ALP activity than that of the control (Monetite) in a study by Niditha Suresh et al. When CQ was mixed with a poly ε-caprolactone and graphene oxide scaffold it showed that its synergistic effect tenhanced osteoblastic differentiation, osteoconduction and osteoinduction potential of scaffolds in a study by Shivaji Kashte et al. When CQ based natural fibre was assessed on murine bone marrow Mesenchymal Cells, it increased the ALP activity in a study by Praseetha Nair et al.

The hexane extract and aqueous extract form of CQ proved to have strong osteogenic potential in a study by Praseetha Nair et al. When different concentrations, 300 µg/mL had the strong osteogenic potential compared to 100 and 200 µg/mL in the bone marrow mesenchymal cells. Also in a study by Parvathi K et al, ALP activity was measured in a herbal fiber sheet containing high weight percentages of CQ in 20, 40, and 60 wt% in poly (L-lactic acid) (PLLA). Although it has been demonstrated that the 40% CQ has substantial ALP activity, the 60% sheet has much lower cell survival after 14 days and should not be employed. When CQ was used in different concentration on the murine pre-osteoblast cell line, 200 mg/ml CQ had strong osteoblast differentiation in a study by Raazia Tasadduq et al. (Table 1)

QUIN guidelines showed that 11 of the included studies had low risk of bias and one study had unclear/ moderate risk of bias. (Table 2)

Table 1. Main characteristics of the included studies

S.No.	Author	Year	Stem Cell culture/ Scaffolds	Intervention groups	Test used	Results
1	Balaji Ganesh et al, Cureus [19]	2024	HA scaffolds in Mesenchymal cell culture	Group I – HA Group II - HA + CQ, Group III - HA + TENDON, Group IV- HA + CQ + TENDON	Differentiation analysis, and tenogenesis – Sirius red staining	Adding CQ significantly boosts the tenogenic potential of Extra cellular matrix /HA scaffolds, making them promising for periodontal tissue regeneration.
2	Samuel F. Robertson and Susmita Bose. Journal of the Mechanical Behavior of Biomedical Material [20]	2020	3D printed β-Tri calcium Phosphate scaffolds in Osteoblast cell cultures	natural polymer/drug coating of polydopamine and Cissus Quadrangularis extract	Alkaline phosphatase activity	Polydopamine in osteoblast cultures increased proliferation and alkaline phosphatase expression under dynamic flow, with further enhancement from Cissus Quadrangularis extract.
3	Praseetha Nair et al. Journal of Biosciences [21]	2021	Human Osteosarcoma cells	CQ stem based Hexane extract (HE), chloroform extract (CE), ethyl acetate extract (EE), methanol extract (ME) and aqueous extract (WE)	Alizarin Red Staining and Alkaline Phosphatase activity	The early bone marker alkaline phosphatase (ALP) confirms the strong osteogenic potential of HE and WE extracts compared to others, highlighting their rich content of bone-regenerative phytochemicals
4	Bhagath Kumar Potu et al. CLINICAL SCIENCE		Bone marrow mesenchymal stem cells	100, 200, and 300 µg/mL petroleum ether extract of Cissus quadrangularis and a control group	Alkaline phosphatase activity	Treatment with 100, 200, or 300 µg/mL petroleum ether extract of Cissus quadrangularis promoted differentiation of marrow mesenchymal stem cells. The 300 µg/mL concentration also enhanced cell proliferation

5	Sedef Tamburaci et al. Journal of Bioactive and Compatible Polymers [23]	2018	Osteoblast cell culture	Cissus quadrangularis with chitosan/Na-carboxymethyl cellulose blend scaffold	In vitro mineralization with von Kossa and Alizarin red staining and Alkaline phosphatase activity	A Cissus quadrangularis–loaded scaffold made from chitosan, and Na-carboxymethyl cellulose shows promise as a biomaterial for bone tissue engineering.
6	Lele Liao et al. Journal of Materials Science: Materials in Medicine [24]	2023	Human bone marrow mesenchymal stem cells	CQ extract with gelatin (Gel) and pectin (Pec) polymers collective through β- tricalcium phosphate (β-TCP) bioceramic	Osteogenic marker genes Runt-related transcription factor (RUNx), Osteocalcin (OCN), and Vascular Endothelial Growth Factor (VEGF); the mRNA levels were observed by utilizing Real-Time Polymerase Chain Reaction (RT-PCR)	CQ-loaded β-TCP/Gel-Pec composites are promising biomaterials for bone tissue repair and regeneration.
7	Ritu Gupta et al. Journal of Functional Biomaterials [25]	2023	Human-derived mesenchymal stem cells	CQ derived exosome-like nanovesicles	Alkaline phosphatase activity	An in vitro tissue culture system enables rapid, sterile growth and a reliable supply of plant-derived extracellular vesicles (PDEVs) for drug delivery applications.
8	Niditha Suresh and Karthikeyan. Cureus [26]	2024	MG-63 cell line	CQ based Europium-Monetite composite and Control - Monetite	Alkaline phosphatase activity	The osteogenic potential of the CQ-based Europium-Monetite calcium phosphate complex, as measured by ALP activity, calcium mineralization, and collagen staining, was 10% greater than that of the Monetite control.
9	Shivaji Kashte et al. Journal of Bioactive and Compatible Polymers [27]	2020	Human umbilical cord Wharton's jelly-derived mesenchymal stem cells	The modified PCL-GO-CQ scaffold was compared with plain poly ε-caprolactone scaffold and poly ε-caprolactone coated only with graphene oxide	Alizarin Red S staining	GO and CQ callus extract endowed the scaffold with osteoinductive properties, enabling hUCMSCs to differentiate into osteoblasts without additional media, growth factors, or external stimuli.

10	Parvathi K et al. International Journal of Biological Macromolecules [28]	2017	Mesenchymal stem cells	Group I – Poly fibres containing 20wt CQ Group II – Poly fibres containing 40wt CQ Group III - Poly fibres containing 60wt CQ	Alkaline phosphatase activity	Mesenchymal stem cells differentiated into osteoblasts without osteogenic supplements, demonstrating the scaffold's osteoinductive capability. The herbal sheet also promoted mineralization after 14 days in simulated body fluid.
11	Raazia Tasadduq et al. Journal of Cellular Physiology [29]	2016	Murine pre-osteoblast cell line, MC3T3-E1	Group I - CQ-E 200 mg/m, Group II – CQ-E 100 mg/m, Group III – CQ-E 50 mg/m, Group IV – CQ-E 25 mg/m, Group V – CQ-E 10 mg/m, Group VI – CQ-E 1 mg/m, Group VII – CQ-E 0.1 mg/m Group VIII - Dimethyl sulfoxide (DMSO) – control	Alkaline phosphatase activity	Cell proliferation significantly increased with lower concentrations of CQ-E. CQ-E also enhanced osteoblast differentiation, as shown by higher ALP activity and extracellular matrix mineralization compared to controls, indicating that lower CQ-E concentrations have anabolic and osteogenic effects
12	Praseetha R. Nair et al. Cellulose [30]	2021	Murine Bone marrow Mesenchymal Cells	Natural fiber derived from Cissus quadrangularis (CQ) stem	Alkaline phosphatase activity	The time-dependent ALP activity in BMC confirms osteoblast formation, making CQF a promising natural osteoinductive substrate for bone tissue engineering.

Table 2. Risk of Bias of the included studies by QUIN guidelines

S. No.	Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	ROB
1	Balaji Ganesh et al, 2024	2	2	1	2	2	1	2	1	1	0	1	2	Low
2	Samuel F. Robertson and Susmita Bose. 2020	2	1	1	2	2	0	2	1	2	1	1	2	Low
3	Praseetha Nair et al. 2021	2	2	2	2	2	0	2	2	2	1	1	2	Low
4	Bhagath Kumar Potu et al. 2009	2	2	2	2	2	1	1	2	2	1	2	1	Low
5	Sedef Tamburaci et al. 2018	2	1	1	2	1	1	1	2	2	1	1	2	Low
6	Lele Liao et al. 2023	2	1	0	0	2	2	2	1	2	2	2	2	Low
7	Ritu Gupta et al. 2023	2	2	2	2	2	2	0	1	0	2	1	1	Low
8	Niditha Suresh and Karthikeyan. 2024	2	2	0	0	2	2	1	1	1	1	2	2	Medium
9	Shivaji Kashte et al. 2020	2	2	0	2	1	2	1	2	2	1	1	2	Low
10	Parvathi K et al. 2017	2	2	1	1	2	1	1	2	1	1	2	2	Low
11	RAAZIA TASADDUQ et al. 2016	2	2	2	2	2	1	2	1	2	0	2	2	Low
12	Praseetha R. Nair et al. 2021	2	2	2	0	2	1	2	1	2	0	1	2	Low

DISCUSSION

Human bone is made up of a mineralized organic matrix and various bone cells. Osteoblasts, which are mature bone cells, play a crucial role in forming the organic matrix and managing the mineralization of bone [31]. When a bone defect is too large to heal on its own, advanced therapeutic techniques are necessary to stimulate new bone growth. Osteogenesis, or bone formation, is a complex process that begins with the proliferation of mesenchymal stem cells, which then differentiate into pre-osteoblasts [32,33].

Next, these pre-osteoblasts mature into osteoblasts that produce type I collagen, the primary protein in the organic bone matrix or osteoid, accounting for approximately 90% of it. The active osteoblasts secrete large amounts of alkaline phosphatase, an enzyme that facilitates the deposition of minerals[34]. Calcium hydroxyapatite, which constitutes about 70% of bone mass, crystallizes within the collagen network, making the bone hard and capable of withstanding external forces while supporting the body and protecting internal organs. The rate of bone formation is influenced by the proliferation and activity of osteoblasts, and efficient bone repair depends on accelerated osteoblast growth [35].

In osteoporosis, bone mass decreases due to an imbalance where bone resorption outpaces formation. Key risk factors include aging, estrogen deficiency in postmenopausal women, decreased testosterone in men, smoking, low body weight, poor nutrition, alcohol use, and exposure to heavy metals like cadmium [36,37]. Bone marrow mesenchymal stem cells are the source of osteoblasts, and high bone turnover that results in bone loss is characteristic of osteoporosis. It is projected that by 2050, more than half of osteoporotic fractures will occur in Asia. Plant-based treatments may offer an affordable alternative for managing this condition [38].

Natural bioactive compounds have been used in medicine for decades and have proven highly beneficial in treating and preventing diseases. Cissus quadrangularis L. has traditionally been used for treating fractures, scurvy, tumors, hemorrhoids, peptic ulcers, menstrual disorders, and leucorrhea. It is also commonly used as a dietary supplement [39,40]. The bioactive compounds in CQ, such as glycosides, polyphenols, Vitamin C, and β-sitosterol, are believed to have antiulcer effects and enhance healing by releasing polyamines [21,41].

Research in recent years has explored the use of CQ's bioactive compounds in biomaterials for biomedical applications. For example, Tamburaci et al. previously investigated a scaffold made from chitosan and Na-carboxymethyl cellulose loaded with CQ extract, which showed osteoinductive properties and potential for bone tissue regeneration. Similarly, the construction of osteoinductive scaffolds, such as electrospun polycaprolactone scaffolds combined with CQ extract and graphene oxide, has been explored for bone repair [23,42].

In the present systematic review, 10 human and 2 animals cells were studied for bone regeneration in which C.quandrangularis has showed positive results. This showed that whether it is human or animal cell culture, bone regeneration was evident. Similarly, a study by Suganya et al in which polymeric nanofibrous scaffolds with CQ extract are assessed for bone regeneration, it showed potential biocomposite material [43].

Alkaline Phosphatase (ALP) test was done in most of the included studies. This served as the main biological markers. It is involved in the mineralization process, which is essential for healthy bone growth and repair. These are produced by bone-forming cells called osteoblasts, ALP helps integrate calcium and phosphate into the bone matrix, which is vital for bone strength and proper mineralization [44]. High levels of ALP typically indicate that bone formation is actively taking place and can be a sign that bone repair processes are working effectively. Clinically, measuring ALP levels helps diagnose conditions like osteoporosis and Paget's disease [45,46]. This ALP marker was used in many studies for assessing invivo, invitro bone repair and healing [47–49].

One interesting included study by Ritu Gupta showed that CQ was incorporated into nanovesicles, it was used as plant-derived extracellular vesicles (PDEVs) for bone regeneration and local drug delivery system. Similar herbal PDEV were used in different studies [50–53].

This present review also had few limitations. The review only included qualitative analysis of the studies. Another is it only included invitro studies and invivo studies were excluded. Quantitative analysis or meta analysis could not be done because of lack of homogeneity in the included studies. Future review should include more different type of studies with meta analysis.

CONCLUSION

In summary, this systematic review consolidates findings from twelve studies that evaluated the bone regenerative potential of Cissus quadrangularis-infused scaffolds using both animal and human cell cultures. The techniques employed, such as alkaline phosphatase (ALP) activity assays and alizarin red staining, consistently indicated positive effects on bone regeneration across all studies.

These results suggest that Cissus quadrangularis holds significant promise as an active component in scaffolds for improving bone repair and regeneration. However, it is important to acknowledge that this review is limited by its focus exclusively on in vitro studies. While these studies offer useful preliminary data on the regenerative potential of Cissus quadrangularis-infused scaffolds, they do not fully capture the complexities of biological systems in living organisms. Future research should address this gap by conducting well-designed in vivo studies to assess the effectiveness and safety of these scaffolds in real-world settings. Additionally, exploring the long-term impacts and interactions of Cissus quadrangularis with various biological systems will be critical for its advancement in bone regenerative treatments.

DECLARATIONS

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Competing interests

The authors declare no competing interests.

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