An Overview of the Osteogenic potential of Indian herb Cissus quadrangularis (Veldt Grape)

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ABSTRACT
Cissus quadrangularis (CQ) is a widely known herb in India and southern part of India in particular. The bone healing ability of CQ is outlined in Ayurvedic medicine and other ancient medical texts. Bone loss in elderly especially osteoporosis is a public health problem across the globe. Bioactive molecules present in medicinal plants like CQ helps not only in bone healing but also in improving overall health. CQ is suggested as a plant herb in treatment of bone fractures and bone loss as it is safe or usage and side effects are not identified so far.

However, research on the effect of CQ in humans are few and far. This review attempts to give a clear picture on the available literature that describes the osteogenic role of CQ in improving bone health and healing fractures in general and maxillofacial fractures in particular. Also, the role of CQ in green synthesis of bone scaffolds and its osteogenic potential in regeneration of bone using scaffolds are also discussed.

1. Introduction

Cissus quadrangularis (CQ) also known as Veldt grape is a climbing tendril belonging to the Vitaceae family. The plant is widely distributed throughout tropical and subtropical regions of the world such as India, Sri Lanka, South Africa, Thailand, Java and Philippines. It grows well in hotter climate. The plant is widely used in Asia and Africa for its medicinal property[1].

The plant is known as Harishankar or Hadjod in Hindi means 'that which joins the bones', Due to its bone ligation properties, the plant is referred to as 'Asthisamharaka' in Sanskrit [2]. CQ is known as 'pirandai' in Tamil.

CQ is widely studied for its phytochemical constitution, pharmacological activities and toxicological evaluation. It has been proved safe and effective according to Grades of Recommendations Assessment Development and Evaluation (GRADE) in the treatment of bone fractures, haemorrhoids and body weight reduction[3].

The entire parts of the plant viz root, stem, and leaves have been cited in both Ayurvedic and Unani systems for its medicinal values. More specifically the stem extracts of CQ are traditionally used for treatment of bone fracture, piles, chronic ulcers, asthma, scurvy, irregular menstruation, constipation and blindness. There are also many available literatures that discusses the medicinal role of CQ in bone formation and fracture healing [4-7]. This review focuses the osteogenic potential of CQ in healing of fractured bone, bone mineralisation with respect to systemic, mandibular and alveolar bone. In addition, this review discusses the role of CQ in biomaterials used in bone tissue repair and regeneration.

2. Bioactive Components of CQ.

The major constituents found CQ are ascorbic acid, carotene A, ketosteroid, triterpenoids, unsymmetric tetracyclic triterpenoids along with β-sitosterol, β-amyrin, and β-amyrone. In addition, it also contains flavonoids, phytosterols, resveratrol, piceatannol, pallidol, parthenocissine, quadragularins [8]and water-soluble glycosides. The unique chemical constituents of CQ are -novel flavonoids and indanes, as well as phytosterols and keto-steroids that have shown promise as powerful and efficient antioxidants[9] .These substances improve healing by releasing Transforming Growth Factor(TGF)[1].

In addition to the bioactive phyto components *CQ* also contains high amount of vitamin C, vitamin A, anabolic steroidal substances, and calcium. The steroidal substances from CQ showed marked influence on early

regeneration of all connective tissue of mesenchymal origin, and thereby, improve bone formation and healing [10].

CQ is also a source of minerals including potassium calcium, zinc, sodium, iron, lead, cadmium, copper and magnesium[11,12]. The stem extracts contain rich amounts of calcium and phosphorus[13.]

3. Osteogenic Potential of Cissus quadrangularis

CQ is widely known for its osteogenic potential and ability to heal bone fractures by promoting bone formation. Osteogenic modulators play a key role in osteogenesis, that is bone formation. Osteogenic modulators such as Quercetin, resveratrol. [14]Kaemferol, Fatty acid methyl esters, steroids, phytols, triterpenes and osteogenic polyphenols are rich in CQ. These components synergistically promote bone formation[15]

Active constituents of Cissus quadrangularis may stimulate the proliferation and differentiation of mesenchymal cells and promote new bone formation through the WntLRP5-B-Creatnin signalling pathway of pre-osteoblast formation.CQ extracts stimulate the cells of mesenchymal origin, namely the fibroblasts, chondroblasts and osteoblasts that have a greater impact on osteoblastic proliferation[16].

In addition to osteoblastic proliferation CQ enhances bone mineralisation [17] as it increases the deposition of mucopolysaccharides which preludes bone formation[18]. CQ builds up the skeletal architecture of the fractured bone, namely its mucopolysaccharides, collagen, phosphorus, calcium, and others. CQ not only causes the greater accumulation of mucopolysaccharides but also an early disappearance of mucopolysaccharides from the fractured area, associated with the earlier calcification and firm callus formation.[19]

Furthermore, the role of CQ in preventing loss of bone and enabling thickening of trabecular and corticular bone in ovariectomised rats is reported by Jameela et al [20] Specifically, CQ plays a significant role in mineralization of corticular bone. CQ is used to treat various bone disorders and can also be used as a preventive measure for disorders that lead to decreased bone mineral density [21]

In ovariectomized rats, it was found that CQ increases apoptosis of osteoclasts thereby preventing boneloss. The same study has also reported the ability of CQ in converting procollagen to collagen[22]. A study done by Potu *et al* supplementing 500mg/kg of CQ powder on ovariectomized female has reported increase in the thickness of corticular bone[23].

Another study involving ethanolic extract of CQ has shown increased osteoblastic activity enabled through MAPkinase pathway[24].

With respect to osteogenic potential of CQ in humans much literature is not available.An invitro study by Kanwar et al on human chondrocytes has reported osteoprotective effects of CQ, via the inhibition of P38 MAPK pathway by upregulating survivin [25].

Human studies with respect bone mineralisation and healing of fractures by CQ are far and few. Human trials have also shown anti osteoporotic effect with the same.[30] In an invitro study with human osteoblast cell lines ethanolic extract of CQ was found to increase RunX2 expression and ALP levels in mouse osteoblasts.[31]

A study carried out by Mishra et al,2010 has shown a 53% reduction in fracture healing on external application of CQ paste [32]. A study by Singh et al using a formulation called osteoseal, that contains CQ, Asparagus and Moringa in the ratio 4:1:2, is shown to hasten the rate of mandibular fracture healing [33].

The 3 ketosteroid present in CQ is osteogenic in nature and acts on estrogen receptor o the bone cell [34]. Also, the ketosreroid has antagonistic property of glucocorticoid receptor and helps in maintaining bone health [35].

Furthermore, Phyto steroids found in CQ are found to be precursor of vitamin D3. Along with this the saponins present in CQ have been reported to affect the permeability of the small intestinal mucosal cells due to its strong surface-active properties and thus have an effect on active nutrient transport [36], which includes easy absorption of dietary calcium through the enterocytes.

4. Anti osteoporotic potential of Cissus quadrangularis

A study by Guerra *et al* in ovariectomized rats have shown improvement in microarchitecture of long bone following the administration of CQ extracts, suggesting CQs potential role in treating post-menopausal osteoporosis[26]. One of the phyto constituents, 6-O trans cinnamoyl in CQ is found to have anti osteoporotic activity[27].

Besides, phytoestrogen component of CQ upon oral administration was shown to increase bone density in ovariectomized rats radiographically as well as histologically [28]. Petroleum ether derived CQ extracts also decreased osteoclast activity in ovariectomised rats[21,29] The anti-osteoporotic effects were further confirmed by using ethanolic extracts showing an increase in bone strength in ovariectomized rats [28]

In dentistry, experiments are done to test the ability of CQ to heal Maxillofacial fractures.The maxillofacial fractures take at least 12–16 weeks to heal. A study by Nayak et al have shown an increase in the expression of biochemical markers of bone formation and increased callus formation when CQ was used as an adjunct to treat mandibular fractures [16]

Cissus quadrangularis is rich in vitamin C and beta-carotene. a study in 9 people observed that taking 500 mg of Cissus quadrangularis 3 times per day for 6 weeks helped speed the healing of fractured jaw bones. It also appeared to reduce pain and swelling. CQ was reportedly shown to increase bone density in distracted area on mandibular alveolar bone facilitating implant installation.[37]CQ (500mg) capsules was found to improve healing of bone, pain and inflammation in maxillofacial fractures [38]

With the available evidence CQ is considered as a potent component to treat mandibular fractures. The role of CQ in PDL regeneration of intra bony periodontal defects has been evaluated in association with hydroxyapatite bone filler [36]. The same author has also mentioned the use of CQ as a biomaterial in dentistry.

Still deeper research is the needed to elucidate the use of CQ in dentistry and to understand the potential role of CQ in oral health.

5. Osteogenic potential of Cissus quadrangularis in bone regenerative scaffold

Although the bioactive components of CQ have a wider osteogenic potential its applicability is found to be limited due its poor solubility in aqueous solution. Therefore, modern bioengineering methods are exploring the uses of nano delivery of bioactive components of CQ.

Bone replacement generally involves autogenic and allogenic bone grafts. Bone replacement scaffolds especially, 3D printed calcium and phosphorus-based bone scaffolds are used in recent times. To improve the efficiency, scaffolds are impregnated with bioactive molecules to enable better healing of the bone tissue. CQ extracts are also used in this regard to enhance osteogenesis.

A study using carageen based injectable hydrogel with CQ has shown it to be a good biocompatible scaffold with anti-microbial activity at 20% concentrations of CQ extract [39].

Another study by Jain et al has shown that combination of CQ with bovine graft was efficient in periodontal bone regeneration it was not statistically significant [40]

The osteogenic potential of CQ in bone composites are also explored. CQ filled composite containing gelatin,Pectin and β tricalcium phosphate has shown increased osteogenesis by activating RUNX2 and osteocalcin genes in vitro in human Bone Marrow stem cell lines.[41]CQ used in the green synthesis of Novel Europium-Doped-Monetite Calcium Phosphate has shown increased osteogenic potential in vitro in human osteoblast-like cells.[42]

6. Conclusion

Bone formation is a complex process that requires the proper microenvironment and supply of nutrients such as vitamin C, minerals, mucopolysaccharides in addition to calcium, phosphorus, anabolic steroids and Vitamin D3. Maintaining a good bone health and healing of bone lesions is a public health problem involving a huge cost. With the increase in geriatric population across the world there is a growing interest in phytochemical prospecting to treat and cure bone disorders. CQ is complete in this aspect and its bone healing property due to the abundance of phytosterols and flavonoids, further enhanced by the presence of minerals and other nutraceutical substances in its bioactive components. CQ extracts and its osteogenic potential is principally studied in mouse model and invitro in human cell lines. The available literature gives promising insights in to the larger potential of CQ in disorders associated with the bone. Further research in human subjects would enable much larger and significant application of CQ as a natural product, biomaterial or its derivative in bone healing in general and alveolar bone in particular.

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Authorship contribution statement

Mathangi. R: Conceptualization, Methodology, Investigation, Writing – original

draft, Dr. Damel Lakshmi and Nalini Devarajan: writing review and editing.

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