Texila International Journal of Public Health
ISSN: 2520-3134
DOI: 10.21522/TIJPH.2013.12.04.Art058

A Review of Biomedical Applications of *Ormocarpum cochinchinense*

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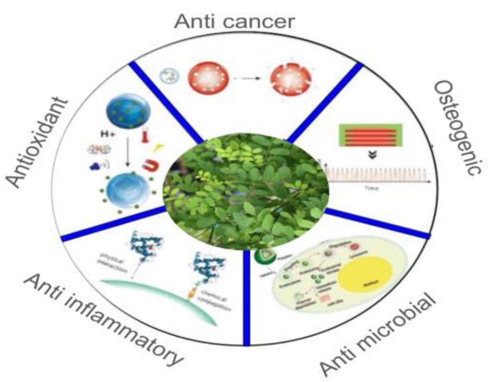
Abstract

Traditional bone-setting (TBS) techniques were widely used in India before the advent of modern orthopaedics. Among the plants used in these practices, *Ormocarpum cochinchinense*, a medicinal plant native to Southeast Asia, has shown promising therapeutic properties in treating bone-related ailments. This review explores the biomedical applications of *Ormocarpum cochinchinense*, particularly focusing on its role in orthopaedics and dentistry. Phytochemical studies have revealed that this plant is rich in bioactive compounds such as flavonoids, tannins, and alkaloids, which contribute to its antioxidant, anti-inflammatory, and antimicrobial properties. In orthopaedics, *Ormocarpum cochinchinense* has demonstrated significant potential in enhancing bone fracture healing, facilitating bone regeneration, and promoting osseous repair in preclinical studies. The plant has been shown to enhance calcium, phosphorus, and alkaline phosphatase levels, which are critical for bone repair. These properties position *Ormocarpum cochinchinense* as a promising candidate for developing novel treatments for bone fractures and other orthopaedic conditions. In the field of dentistry, *Ormocarpum cochinchinense* exhibits anti-inflammatory effects that may be beneficial in treating periodontal diseases such as periodontitis. Its antioxidant properties help reduce oxidative stress, a key factor in chronic inflammation and tissue degradation in periodontal conditions. Additionally, the plant shows potential as a bioscaffold for dental implants, promoting osseous regeneration and improving the healing process after dental surgeries. This review aims to provide a comprehensive analysis of the phytochemical profile of *Ormocarpum cochinchinense* and its potential applications in both orthopaedic and dental fields, offering insights into future therapeutic uses.

Graphical Abstract



Keywords*: Bone, Dentistry, Fracture Healing, Ormocarpum cochinchinense, Tribal Healing Practice, Orthopedics.*

Received: 29.08.2024 ***Accepted: 14.10.2024*** ***Published on: 27.12.2024***
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Introduction

Bone lesions pose a significant public health concern, resulting in substantial socioeconomic burdens. The repair of bone tissue involves a complex inflammatory process orchestrated by osteoprogenitor cells located in the periosteum and endosteum, which are responsible for generating new bone matrix. Bone injuries can arise from various traumas and diseases, initiating a multi-stage healing process. While the body can often naturally address most bone injuries, severe cases with critical size defects may necessitate intervention. Although autografts are conventionally regarded as the preferred method for promoting fracture healing, their limitations underscore the need for alternative solutions [1].

Orthobiologics, a field exploring novel approaches such as scaffolds, bioactive molecules, and stem cells, has emerged for treating bone defects. Phyto-bio actives, derived from plants and widely utilized in alternative medicine and traditional practices, are believed to offer therapeutic benefits through the synergistic action of their bioactive components, which target various signal transduction pathways to aid in bone healing. Traditional bone setting (TBS) methods, ancient practices predating modern orthopaedics, have long been established in India. TBS, categorized as one of the 32 external therapies in the Siddha system as "Kattu" (Bandaging), remains prevalent, particularly in southern India, where an estimated 5,000 to 7,000 traditional bone setters operate. There is a growing interest in exploring the therapeutic efficacy of these traditional methods. Many wild and cultivated plants play integral roles in tribal healing practices, reflecting a deep-rooted interrelationship developed over generations of experience and tradition [2].

Ormocarpum cochinchinense, a plant classified within the Moraceae family, is indigenous to Southeast Asia and is found abundantly across nations like Vietnam, Cambodia, and Laos. It has a long history of traditional use as a medicinal plant to treat various ailments, including those related to bone health. With the increasing prevalence of osteoporosis and other bone-related disorders, exploring the potential of natural remedies such as *Ormocarpum cochinchinense* becomes crucial [3]. We aimed to explore the biomedical applications of *Ormocarpum cochinchinense* in literature.

Methodology

We conducted a systematic search to identify studies examining the impact of *Ormocarpum cochinchinense*, on bone fracture healing. Utilizing predetermined search terms, we searched electronic databases such as PubMed, Scopus, and Google Scholar. Our inclusion criteria encompassed studies investigating the effects of *Ormocarpum cochinchinense*, on bone fracture healing across vitro, animal, and human models. Selected studies underwent critical appraisal for quality assessment and data extraction.

Botanical and Phytochemical Analysis

Ormocarpum cochinchinense is a small, deciduous tree with distinctive fruit (Fig. 1). The plant contains a rich array of phytochemicals, including flavonoids, phenolics, triterpenoids, and alkaloids (Table 1). These active compounds are recognized for their antioxidative, anti-inflammatory, and anti-osteoporotic characteristics, indicating their possible influence on bone well-being [4, 5].

Figure 1. *Ormocarpum cochinchinense* Plant

Table 1: Phytochemical Compounds of *Ormocarpum cochinchinense*

S. No	Phytochemical Compounds Methanol Extract	Phytochemical Compounds Aqueous Extract	Reference
1	Alkaloids	Alkaloids	[55]
2	Betacyanin	Betacyanin	[4]
3	Cardiac glycosides	Cardiac glycosides	[4]
4	Coumarins	Coumarins	[4]
5	Flavonoids	Flavonoids	[47]
6	Phenol	Phenol	[56]
7	Saponins	Saponins	[56]
8		Steroids	[4]
9	Tannins	Tannins	[9]
10	Terpenoids	Terpenoids	[57]

Secondary plant metabolites play a crucial role in contemporary drug discovery endeavours. Ormocarpum species have demonstrated efficacy in managing diverse disease conditions within both human and animal traditional medicine practices. Notable species within the Ormocarpum genus include *Ormocarpum kirkii S. Moore*, *Ormocarpum sennoides* (Willd.) DC., *O. trichocarpum*, *O. cochinchinense*, and *O. keniense* [4-7]. Investigations have identified secondary metabolites from various chemical groups in different solvent extracts of *O. cochinchinense* leaves. For instance, alkaloids were detected in extracts obtained using ethyl acetate, ethanol, methanol, and aqueous solvents, which play a vital role in anti-inflammatory activity [8]. Cardiac glycosides were observed in methanol and petroleum ether extracts, which may be involved in managing various cardiac ailments and heart issues. Tannins were also observed in *O. cochinchinense*, contributing to its anti-inflammatory and antioxidant activity [9]. Studies have shown that ethyl acetate extracts, rich in alkaloids, exhibit significant antifungal activity, while ethanol extracts, containing high amounts of flavonoids, tannins, and saponins, demonstrate antioxidant activity [10].

Anti-Microbial Activity

The antimicrobial potential of *Ormocarpum cochinchinense* has been extensively studied (Fig 2). Research indicates that the plant's fractions contain several biologically active substances, including alkanes, polyphenols, hydrogen-bonded phenols, aromatics, aliphatic amines, and flavonoids, which were validated by FT-IR vibrational bands [11, 12]. Among these, the methanol extract of O. cochinchinense showed the most potent antibacterial effects against a range of human pathogens, suggesting its potential therapeutic use for treating bacterial infections [13].

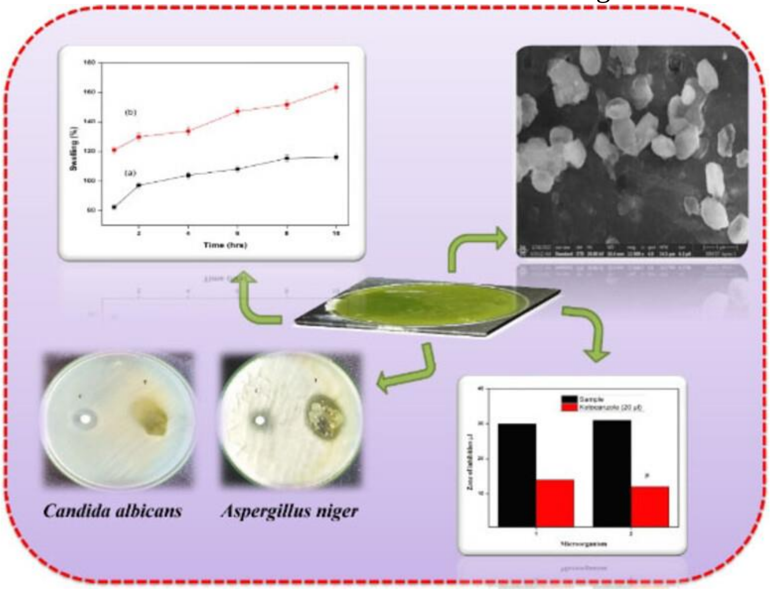

Figure 2. Antimicrobial activity of *Ormocarpum cochinchinense* (copyright: Narayanan et al. 2023)

Further research combined *Ormocarpum cochinchinense* leaf extract with hydrogel and synthetic polymers, such as PVP and PVA, focusing on its biodegradability and biocompatibility for use as wound dressings. Characterization of the synthesized biocomposite film, which included O. cochinchinense, PVA, and PVP, was conducted using X-ray diffraction, FTIR spectroscopy, SEM, and EDS analysis. The study also examined swelling and antibacterial activity, confirming the potential of these materials for wound dressing applications [13-15].

The antibacterial activity of biosynthesized CuO nanoparticles demonstrated a wide range of cytotoxic effects and antibacterial properties. Fabrics treated with CuO nanoparticles at a non-toxic dose of 100 μg/mL showed promising antibacterial effectiveness against pathogenic bacteria [16]. Qualitative antimicrobial susceptibility tests using agar were conducted against Methicillin-resistant S. *aureus, B. cereus, E. coli, P. aeruginosa, and C. albicans*. Analysis of variance and broth microdilution methods were used to determine minimum inhibitory concentrations, revealing that the organic crude extracts contained flavonoids, sterols, alkaloids, tannins, quinones, terpenoids, and saponins. These compounds exhibited significant antimicrobial activity, with the highest zone of inhibition against methicillin-resistant *S. aureus*, underscoring their potential for combating important human pathogens [17, 18].

Antiplasmodial Activity of *Ormocarpum cochinchinense*

Mosquito vectors are significant carriers of infections and parasites that pose public health risks, including Zika virus, dengue fever, chikungunya, Japanese encephalitis, and malaria [19]. To address this, *Ormocarpum cochinchinense* leaf extract was utilized to rapidly and safely synthesize silver nanoparticles (Ag NPs). Characterization of the bio-reduced Ag NPs was performed using energy-dispersive spectroscopy (EDX), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier-transform infrared spectroscopy (FTIR), and X-ray diffraction (XRD) [19]. The acute toxicity of both the leaf extract and synthesized Ag NPs was tested on larvae of *Aedes aegypti*, *Culex quinquefasciatus*, and *Anopheles stephensi*, which are vectors for malaria, dengue, and filariasis [20].

Antioxidant Activity of *Ormocarpum cochinchinense*

Extraction of *Ormocarpum cochinchinense* leaves was conducted using various solvents, including DMSO, ethyl acetate (EtoAc), ethanol (EtOH), methanol (MeOH), and chloroform ($CHCl_3$). Phytochemical screening and antioxidant capacity were assessed. The antioxidant capacity was evaluated using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging assay. All extracts demonstrated significant ($p < 0.001$) dose-dependent antioxidant potential. The phytochemical analysis identified the presence of alkaloids, steroids, terpenoids, saponins, gums, flavonoids, tannins, resins, coumarins, glycosides, and carbohydrates. This study highlights the bioactivity of various solvent extracts of *O. cochinchinense* leaf material [21].

Additionally, the phytochemical content was analyzed qualitatively and quantitatively in ethyl acetate extracts of endophytic fungi isolated from *Enicostemma axillare* and *O. cochinchinense*. The antioxidant activity was assessed using the DPPH free radical scavenging test. The primary phytochemicals identified in the endophytic extracts of E. axillare and *O. cochinchinense* included saponins, phenols, flavonoids, and cardiac glycosides. The antioxidant activity and phenolic content of the extracts were correlated. The findings suggest that *E. axillare* and *O. cochinchinense* potentially produce metabolites that could be sources of new antioxidant compounds [25-27].

Anti-cancer Activity of *Ormocarpum cochinchinense*

After examining morphological characteristics and microscopic structures, the anti-cancer potential of endophytic fungi extracted from two medicinal plants, Enicostemma axillare and *Ormocarpum cochinchinense*, was investigated and identified [28, 29]. The MTT assay, used to assess the cytotoxicity of the extracts against MCF-7 cell lines, indicated the highest level of cytotoxicity [28].

Callus of *Ormocarpum cochinchinense* (Willd.) DC was studied using aqueous, methanol, and ethyl acetate as solvents [11]. The MS medium, enriched with 2.0 mg/L BAP and 3.0 mg/L IAA, exhibited the highest percentage of callus induction at 86.7%, accompanied by a maximum callus weight of 1.03 g [30]. Phytochemical examination demonstrated the presence of various phytochemical compounds in both the aqueous, methanol, and ethyl acetate extracts of the plant and callus samples [31]. The aqueous extract from both the plant and callus exhibited a maximum inhibition zone of 10 mm and 9 mm, respectively, against *Staphylococcus aureus* [32].

Anticancer investigations revealed that the in vivo plant exhibited an inhibitory percentage of 24.9%, while the callus showed a lower inhibitory percentage of only 9.3% against HeLa cells [33, 34].

Anti-inflammatory Activity of *Ormocarpum cochinchinense*

Natural herbs play a crucial role in tribal healing practices. *Ormocarpum sennoides* (Family: Fabaceae), also known as Elumbotti in Tamil, is particularly effective in healing bone fractures. It contains a range of chemical components, including alkaloids, steroids, flavonoids, tannins, and glycosides, and exhibits anti-inflammatory, antibacterial, antimicrobial, and antioxidant properties [35, 36]. *Ormocarpum cochinchinense* is noted for its antioxidant and anti-inflammatory phytocompounds. The leaves of *O. cochinchinense* were collected, and an ethanolic extract was prepared to investigate its anti-inflammatory effectiveness through protein denaturation inhibition and membrane stabilization approaches, as well as antioxidant properties using 2,2-DPPH and Ni. O tests [37]. Significant anti-inflammatory and antioxidant properties were observed in *O. cochinchinense*. The ethanolic extract demonstrated dose-dependent activity ($p < 0.05$) with 85% anti-inflammatory effectiveness and 95% antioxidant activity in the Human Red Blood Cell (HRBC) Membrane Stabilization test. This suggests that *O. cochinchinense* may be used in conjunction with conventional therapies to treat chronic inflammatory disorders [38, 39].

The anti-inflammatory characteristics of Ormocarpum extract were further examined through both in vivo and in vitro assays, including HRBC membrane stabilization and protein denaturation methods. The extract showed dose-dependent inhibition of hemolysis and protein denaturation, with effective concentrations ranging from 50 to 500 µg/mL. In an in vivo study with Wistar male albino rats, the extract significantly reduced paw licking and abdominal writhing at doses of 200 mg/kg and 300 mg/kg body weight, respectively, compared to standard diclofenac sodium ($p < 0.05$). These results suggest the potential therapeutic utility of Ormocarpum extract in managing painful inflammatory conditions and arthritis [40].

Osseous Regenerative property of *Ormocarpum cochinchinense*

For centuries, natural herbs have been integral to orthopaedic therapeutic practices in China, India, and other countries. The growing older population and increasing incidence of osteoporosis highlight the need for new treatments and dietary supplements to promote bone health [40, 41]. Common herbs used in Indian cuisine, such as onion, garlic, clover, walnuts, and beans, have been shown to possess osteoprotective qualities [42, 43].

Before the advent of modern orthopaedics, traditional bone setting (TBS) techniques were extensively used in India. TBS, part of the Siddha system's 32 external treatments, is often referred to as bandaging or "kattu." Approximately 5,000 to 7,000 traditional bone setters, particularly in southern India, practice these techniques [44].

In contemporary orthopaedics, the field of orthobiologics has advanced with innovative methods involving scaffolds, bioactive compounds, and stem cells. Phyto-bio actives, frequently used in folklore and alternative medicine, are believed to interact synergistically to provide therapeutic benefits for bone disorders. Plant extracts work on various signal transduction pathways to promote bone repair [45]. Examples of such plants include *Withania somnifera*, *Tinospora cordifolia*, and *Cissus quadrangularis*. These extracts are a safe and effective option for bone damage, with no significant side effects even at higher doses. Future research may explore the localized delivery of these extracts to the injury site and the potential integration of herbal extracts with ortho biologics for enhanced bone healing [46].

In Tamil Nadu, India, *Ormocarpum cochinchinense* has a long history of use for treating bone fractures. Experimental studies with albino Wistar rats demonstrated significant bone fracture repair. Radiological assessments showed that animals receiving only topical treatment had poorer healing outcomes compared to those treated both topically and orally. The combined treatment resulted in a favourable correlation with increased blood calcium (Ca), inorganic phosphorus, and alkaline phosphatase levels—key indicators involved in bone repair. On the seventh day, calcium levels initially decreased, but by the fourteenth and twenty-first days, they increased, reflecting the effectiveness of the treatment [47].

Hydroxyapatite, a widely used biomaterial known for its strong biocompatibility, is common in orthopaedic and dental applications. Osteosarcoma, a primary malignant bone tumour often affecting children and adolescents, has recently been shown to be inhibited by hydroxyapatite. In a study, aqueous extracts of shadow-dried Mimosa pudica and *Ormocarpum cochinchinense* leaves were used to synthesize silver nanoparticles. Characterization using TEM, EDX, and XRD confirmed the stability and properties of these nanoparticles. The silver nanoparticles were combined with hydroxyapatite powder to enhance drug delivery. The cytotoxic and antibacterial properties of the bio-conjugate were evaluated, with potential applications for treating osteosarcoma as well as bone inflammations and injuries [48].

Biomaterial or Scaffold

One crucial aspect of nanoparticle biosynthesis is the utilization of plant extracts for their pharmacological response [16]. Metallic nanoparticles exhibit unique optical, electrical, magnetic, and chemical properties, and they are compatible with biological systems [49]. These nanoparticles find applications across various sectors, including pharmaceuticals, where they serve as biosensors, anticancer agents, antibacterial and antifungal agents, as well as antioxidants. Commonly used metal nanoparticles in the pharmaceutical industry include platinum, copper oxide, palladium, iron oxide, zinc oxide, gold, and silver [50].

Compared to other metals like gold, silver, or palladium, copper nanoparticles (CuNPs) offer several advantages, including a high surface-to-volume ratio, low production costs, potent antibacterial properties, enhanced reactant mobility, and attractive optical features [51]. The diverse applications of copper oxide nanoparticles (CuO NPs), synthesized using various plant extracts, include environmental remediation, sensing, catalytic reduction, photocatalysis, biological functions, and energy storage [52].

One of the most significant advancements in biomedical engineering is the development of bioscaffolds [53]. These scaffolds are crucial for the bone-healing process. *Ormocarpum cochinchinense* [54], a plant traditionally used for bone repair, was employed to create silver-infused, green-synthesized nanoparticles to accelerate the healing process and reduce the recovery time for bone fractures. It was found that alcohol played a key role in the reduction process, with the synthesized nanoparticles measuring approximately 88 nm in size [50]. The bioscaffold solution was developed as a freeze-dried scaffold with varying concentrations of nanoparticles, demonstrating an accelerated rate of bone regeneration [53].

Applications in Dentistry

Multiple inflammatory mechanisms are involved in the pathogenesis of periodontitis, a chronic inflammatory disease with a microbiological etiology, driven by oxidative stress. Maintaining periodontal health requires a balance between reactive oxygen species and antioxidants. *Ormocarpum cochinchinense* contains phytocompounds with both antioxidant and anti-inflammatory properties. The leaves of *O. cochinchinense* were air-dried in the shade, ground into a powder using an electric blender, and then used to prepare an ethanolic extract. In vitro studies assessed its antioxidant and anti-inflammatory effects through methods evaluating protein denaturation and membrane stabilization. Significant anti-inflammatory and antioxidant properties were found in *O. cochinchinense* [38].

The HRBC Membrane Stabilization assay revealed dose-dependent action in the ethanolic extract, which demonstrated 95% antioxidant and 80% anti-inflammatory activity. In the treatment of chronic inflammatory illnesses like periodontitis, *O. cochinchinense* may be utilized as an adjuvant complement to standard therapy. As it encourages osseous renewal and osteoinduction, it can be employed as a bioscaffold with green nanoparticles for bone regeneration as well as a surface coating for implants.

Conclusion

Assessing the effectiveness and safety of plant-derived products in bone regeneration poses challenges, primarily due to the lack or inadequate characterization of animal models and treatment protocols., phytochemical, and toxicological investigations. Future research in the area of bone healing may take an exciting turn towards the integration of herbal extracts and orthobiologics. The review revealed a very promising potential for *Ormocarpum cochinchinense* in orthopaedic and dental applications. In conclusion, while the potential of plant-derived products like *Ormocarpum cochinchinense* in bone regeneration is promising, overcoming the challenges related to animal model characterization, phytochemical analysis, and toxicological investigations is crucial. Future research should focus on addressing these challenges and exploring the integration of herbal extracts with ortho-biologics to develop effective and safe treatments for bone regeneration and repair.

Conflict of Interest

The authors declare no conflicts of interest

Acknowledgement

The authors acknowledge Saveetha Institute of Medical and Technical Sciences, Chennai for all their support.

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