Archives of The Medicine and Case Reports
Journal Homepage: https://hmpublisher.com/index.php/AMCR
eISSN: 2747-2051

The Potential of Binahong Leaves Extract Nanogel for Alveolar Bone Healing

Bernard Bernard[1*], Syafruddin Ilyas[2], Olivia Avriyanti Hanafiah[3]

[1]Master Program Student, Faculty of Dentistry, Universitas Sumatera Utara, Medan, Indonesia

[2]Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara, Medan, Indonesia

[3]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Universitas Sumatera Utara, Medan, Indonesia

ARTICLE INFO

Keywords:
Alveolar bone
Binahong leaves
Biological mechanisms
Nanogel
Wound healing

***Corresponding author:**
Bernard Bernard

E-mail address:
doktergigibernard@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/amcr.v5i1.480

A B S T R A C T

Alveolar bone defects pose a significant challenge in dental and oral health, requiring the exploration of novel therapeutic approaches for effective bone healing. The binahong (*Anredera cordifolia*) leaves are known for their rich bioactive compounds with diverse therapeutic properties, while nanogels, a drug delivery system, offer advantages such as controlled release and enhanced bioavailability. This review explores the potential of binahong leaf extract nanogel as a promising candidate for alveolar bone healing by discussing its preparation, characterization, and properties. Furthermore, it delves into the cellular and molecular mechanisms underlying alveolar bone healing. Based on our review, the effects of binahong leaves extract on bone cells and animal models indicate its therapeutic potential in alveolar bone healing by increasing the expression of growth factors and cells that are essential in bone healing. This review suggests that binahong leaves extract nanogel holds promise as a novel therapeutic intervention for alveolar bone healing. Further research and clinical studies are warranted to fully explore its potential.

1. Introduction

Bone defects in the craniomaxillofacial structure range from minor periodontal defects to extensive bone loss due to injuries, surgeries, congenital deformities, or extensive resorption following tooth loss.[1] This phenomenon is observed in both clinical and preclinical investigations.[2] Insufficient alveolar bone volume can complicate subsequent tooth replacement strategies, emphasizing the significance of bone healing in dentistry, especially prostheses, implants, and surgery.[2,3]

Numerous approaches address post-tooth extraction bone loss, such as simple application of hyaluronic acid gel and non-steroid anti-inflammatory drugs; other alternatives include bone grafts and recombinant proteins, which are invasive, complex, and costly.[4–6] As medicine advances, herbal medicines have emerged as alternatives to synthetic drugs. These plant-derived treatments offer fewer side effects, lower toxicity, good therapeutic potential, and are more affordable.[7,8]

Anredera cordifolia, commonly known as binahong in Indonesia, belongs to the *Basellaceae* family. This plant is recognized for its high adaptability to diverse climates and has a longstanding history of traditional medicinal use in Indonesia, China, and Taiwan.[7,9] Flavonoids, terpenoids, tannins, saponins, ascorbic acid and oleanic acid are secondary metabolites derived from binahong leaves. These compounds have been investigated for their anti-inflammatory, antimicrobial, and wound-healing properties.[6,7,9] Several studies were performed to delve into the wound-healing effect of binahong leaf extract and showed its potential to promote soft to hard tissue healing.[6,7,9–12] Additionally, several studies have indicated that the use of binahong leaves extract gel expedites tooth socket wound recovery and enhances alveolar bone healing, as evidenced by an increase in fibroblast, osteoblast, and osteocyte counts.[6,9] Furthermore, binahong leaves extract gel has been confirmed to accelerate wound healing by upregulating the expression of HIF-1, FGF-2, and BMP-2 in post-tooth extraction wounds in Wistar rats.[10–12]

Utilizing larger materials for drug delivery presents considerable hurdles, including instability within the body, limited bioavailability and solubility, reduced absorption, challenges in precise targeting, suboptimal efficacy, and potential adverse reactions.[8] Nanotechnology significantly advances in medicine and drug formulations, enabling precise targeting and controlled delivery. It bridges the gap between biological and physical sciences through nanostructures, notably in fields like nanomedicine and drug delivery systems.[8] Nanogels consist of hydrogel particles on a nanoscale, exhibiting characteristics of both hydrogels and nanoparticles.[13] Nanogels can host a diverse array of agents, making them widely employed as carriers for pharmaceutical substances.[14] Medications based on nanogels have found applications in cancer treatment, autoimmune disease management, inflammation reduction, ophthalmic treatment, and addressing neurodegenerative conditions.[15]

Considering the facts presented, this review seeks to present a preliminary exploration of binahong leaves extract nanogel as an approach for alveolar bone healing. By analyzing relevant studies on the therapeutic properties of binahong leaf extract and the context of nanogel-based delivery, this review aims to shed light on this promising yet uncharted approach to promoting alveolar bone healing.

Alveolar bone healing

One of the most common causes of bone loss is post-tooth extraction procedures. Tooth extraction is frequently performed for various reasons, from health to aesthetics.[2,16] This procedure triggers a series of biological changes that affect the balance and structure of the surrounding periodontal tissues, which lead to gradual weakening and irreversible alveolar bone loss.[2,16,17] Bone loss is a major concern in dentistry, impacting tooth support, speech, aesthetics, chewing, implant success, and denture stability.[17] Therefore, effective oral rehabilitation is essential due to the intricate three-dimensional structural support of these defects, which can result in extensive damage to surrounding structures, deformations, and limited function.[1,17]

Alveolar bone healing is known to be complicated and systematic process that engage various types of cells and chemical mediators.[18] Fundamentally, the process of wound healing comprises same four separate yet interconnected stages, which are hemostasis, inflammatory, proliferative and remodeling or maturation. This general principle of wound healing also applies to the healing of alveolar bone, with variation observed in the healing time.[6,9,16,19,20] Initially, blood seals the socket and triggers inflammation within a week, eliminating debris and fostering fibroplasia.[6] Following blood clot formation, bone cell death occurs on both sides of the fracture, causing degradation of the bone matrix. This initiates a recovery phase where deceased cells, the clot, and the deteriorated bone matrix are cleared. Nearby tissue stimulates revascularization, angiogenesis, and robust cell growth. The type of tissue formed relates to fracture stability and tissue vascularization. In less stable fractures or with inadequate vascularization, a cartilaginous callus arises, which then transforms into endochondral bone, followed by woven bone and eventual conversion to secondary (lamellar) bone as stability improves. For highly mobile bone fragments, extensive gaps, or when the periosteum is damaged, a connective tissue-like callus forms, resembling a pseudarthrosis where opposing bone fragments stay mobile.[20,21]

Osteoblasts are one of the cells that play significant roles during alveolar bone healing. Osteoblasts are responsible for producing the osteoid matrix and have a significant role throughout the healing process, especially the proliferation phase to the remodeling phase. As osteoblasts generate bone, they may become enclosed within the bone matrix they produce and transform into osteocytes, which contribute to bone remodeling by preserving the strength and viability of the newly formed bone.[9] Bone morphogenetic protein-2 (BMP-2) and osteoblasts are key components with significant functions during the proliferation phase of wound healing. BMP-2 primarily functions in the generation of alveolar bone, a process facilitated by osteoblasts.[10] Alkaline phosphatase (ALP) is one of the various proteins involved in bone metabolism and associated with the initial phases of osteoblast differentiation and has a role in facilitating the early growth of hydroxyapatite crystals during bone formation.[22]

Enhancing alveolar bone healing with binahong leaves extract

Anredera cordifolia has a rich history of traditional use for treating various diseases worldwide. In its native region of South America, it has been employed to address injuries, serving as an antibacterial and antifungal agent. In Indonesia, it finds application in the treatment of injuries, thrush, digestive issues, peptic ulcers, hypertension, inflammations, urinary tract infections, kidney inflammations, and impairments. Phytochemical analysis of *Anredera cordifolia*'s stem, leaves, and tuber revealed the presence of terpenoids, steroids, glycosides, and alkaloids. The majority of research has predominantly focused on the leaves, given their abundant availability from the *Anredera cordifolia* plant.[23]

Binahong leaf extract contains several secondary metabolites with noteworthy effects on wound healing. Flavonoids, encompassing vitexin and apigenin, stand out for their anti-osteoclastogenic characteristics, effectively curbing osteoclast formation and bone resorption stimulated by receptor activator of nuclear factor-κB (RANKL) and lipopolysaccharides (LPS).[24] Rutin, another integral flavonoid, bolsters the expression of β-catenin, osteoblasts, and osteocytes.[25] Icariin, a significant flavonoid glycoside, amplifies BMP-2 expression, a critical factor in osteoblast development while quelling CTGF.[26] Additionally, rutin contributes positively to ALP activity.[27]

Binahong's saponins, as observed in studies involving Radix Dispaci total saponins (RTS) via BMP-2 through the RUNX-2 pathway, promote osteoblastic differentiation, potentially revolutionizing bone formation dynamics.[28] Handayani et al. found that containing saponins leaves extract increases RUNX-2 and ALP expression during bone remodeling in orthodontic tooth movement studies.[29] Furthermore, tannins and alkaloids within binahong leaves extract emerge as potent attributes like antioxidant, anti-inflammatory, antiseptic, and antimicrobial properties. These characteristics collectively safeguard against free radicals and impede the growth of harmful bacteria.[16,30,31] Lastly, triterpenoids and steroids, vital components within the extract, exhibit profound antimicrobial attributes. Beyond their antimicrobial role, triterpenoids stimulate osteoblasts, the key to accelerated bone generation.[7,32]

The potential of nanogel as binahong leaves extract carrier

Nanomedicine constitutes a medical field applying nanotechnology to prevent and treat a range of diseases through the use of materials on the nanoscale.[8] Nanogels are hydrogel dispersions formed through cross-linking polymers at the nanoscale, offering versatility for applications such as medications for cancer, autoimmune diseases, hemostasis, inflammation, ophthalmic issues, and neurodegenerative disorders.[13–15] They efficiently transport drugs, enabling controlled and targeted release, and excel at low quantities, distinguishing them from other alternatives.[13,15]

In the context of topical oral application, nanogels exhibit several advantages. Their high biocompatibility and controlled drug release make them suitable for localized treatment. Nanogels can efficiently carry both hydrophilic and hydrophobic drugs, a crucial attribute for addressing diverse oral health conditions. Their rapid swelling and de-swelling behavior in aqueous environments facilitate drug loading and release, enhancing therapeutic effectiveness. Nanogels' small size allows them to permeate oral tissues effectively. Additionally, their colloidal stability ensures prolonged drug retention and efficient application.[13,15] However, the presence of residual surfactants or monomers from preparation may raise concerns about potential toxicity upon oral application. Addressing these traces might be essential to ensure the safety of oral nanogel administration.[15]

Nanogels ranging from 20 nm to 200 nm possess properties ideally suited for oral topical application. This size range balances effective penetration while avoiding excessive uptake by the body. Nanogels' ability to solubilize hydrophobic drugs complements their utilization in delivering diverse oral therapies. Colloidal stability and minimal immunological response further support their viability for oral topical use. The customization of nanogel properties, influenced by factors like temperature, cross-linking density, and surfactant concentration, offers opportunities for tailoring formulations to specific oral health needs.[13,15]

Passive diffusion stands as a prevalent mechanism for drug release from hydrogels. Concerning nanogels, drug release mechanisms can be categorized into three types: diffusion-controlled, swelling-controlled, and chemically controlled.[13,14] The mechanism of drug release is influenced not only by the physicochemical attributes of the drug compound but also by the method of drug incorporation into nanogels. Commonly, drug loading into nanogels is achieved through physical entrapment, as well as covalent and noncovalent interactions.[13] Bone loss significantly impacts dentistry, affecting tooth support, aesthetics, speech, and implants. Therefore, effective oral rehabilitation is crucial due to the intricate three-dimensional structural impact of these defects.[1,5] Alveolar bone healing is a complex and overlapping four stages of healing that involve cells and molecules.[6,9,19] Osteoblasts are vital cells in alveolar bone healing, orchestrating the production of osteoid matrix from the proliferation to remodeling phases.[9,10] BMP-2 and osteoblasts collaborate in generating alveolar bone during the proliferation phase, while ALP initiates osteoblast differentiation and assists in the early growth of hydroxyapatite crystals during bone formation.[10,12,22]

Evidently, binahong leaf extract's secondary metabolites wield a diverse array of benefits for wound healing, with a pronounced focus on their interaction with pivotal elements like BMP-2 and ALP, which substantially contribute to effective bone regeneration and remodeling.[24–27,29–31,33] In essence, the adaptable nature of nanogels, combined with their advantageous properties for topical oral application, positions them as a promising carrier for binahong leaf extracts.[13–15] The convergence of advanced drug delivery technology and the natural healing potential of binahong leaves signifies a potent avenue for addressing diverse oral health concerns.

2. Conclusion

It can be concluded that nanogels present a promising avenue for delivering binahong leaf extract, particularly in topical oral applications. Their biocompatibility, controlled release mechanisms and efficient drug loading align well with oral health needs. By harnessing nanogels' advantages alongside the therapeutic potential of binahong leaf extract, a synergistic approach emerges that could reshape oral health interventions. As we delve further, we'll explore the intricate details of this fusion and its exciting potential for effective topical oral application in alveolar bone healing. Further research and clinical studies are warranted to explore its potential fully as an alternative for alveolar bone healing treatment.

3. References

1. Adamička M, Adamičková A, Danišovič L, Gažová A, Kyselovič J. Pharmacological approaches and regeneration of bone defects with dental pulp stem cells. Stem Cells International. Published online 2021: 4593322.
2. Avila-Ortiz G, Gubler M, Romero-Bustillos M, Nicholas CL, Zimmerman MB, Barwacz CA. Efficacy of alveolar ridge preservation: a randomized controlled trial. Journal of Dental Research. 2020; 99(4): 402-9.
3. Haghighat A, Hekmatian E, Abdinian M, Sadeghkhani E. Radiographic evaluation of bone formation and density changes after mandibular third molar extraction: a 6 month follow up. Dental research journal. 2011; 8(1): 1-5.
4. Paulini M, Ruggieri INC, Ramallo M. Recombinant proteins-based strategies in bone tissue engineering. Biomolecules. 2022; 12(1): 1-17.
5. Alcântara CEP, Castro MAA, de Noronha MS. Hyaluronic acid accelerates bone repair in human dental sockets: a randomized triple-blind clinical trial. Brazilian Oral Research. 2018; 32: 1-10.
6. Hanafiah OA, Hanafiah DS, Syaflida R. The effect of 3% binahong leaf extract gel on the wound healing process of post tooth extraction. Dental Journal (Majalah Kedokteran Gigi). 2021; 54(2): 57-62.
7. Hanafiah OA, Abidin T, Ilyas S, Nainggolan M, Syamsudin E. Formulation and evaluation of binahong leaves extract gel on wound healing of the palatal mucosa. Journal of Biomimetics, Biomaterials and Biomedical Engineering. 2020; 48: 85-91.
8. Patra JK, Das G, Fraceto LF. Nano-based drug delivery systems: Recent developments and future prospects. Journal of Nanobiotechnology. 2018; 16: 71.
9. Hanafiah OA, Hanafiah DS, Dohude GA. Effects of 3% binahong (*Anredera cordifolia*) leaf extract gel on alveolar bone healing in post-extraction tooth socket wound in Wistar rats (*Rattus norvegicus*). F1000Research. 2022; 10:923.
10. Khoswanto C. Optimum concentration *Anredera cordifolia* (Ten.) Steenis gel in increasing the expression BMP-2 and the number of osteoblasts post tooth extraction in Wistar rats. Journal of International Dental and Medical Research. 2019; 12(3): 959-63.
11. Khoswanto C, Soehardjo I. The effect of Binahong Gel (*Anredera cordifolia* (Ten.) Steenis) in accelerating the escalation expression of HIF-1α and FGF-2. Journal of International Dental and Medical Research. 2018;11(1):303-307.
12. Khoswanto C. Microvascular Activity from the Wound Healing Process in Wistar Rats Due to Administration of *Anredera cordifolia* (Ten.) Steenis. Journal of International Dental and Medical Research. 2021; 14(4): 1351-6.
13. Suhail M, Rosenholm JM, Minhas MU. Nanogels as drug-delivery systems: a comprehensive overview. Therapeutic Delivery. 2019; 10(11): 697-717.
14. Li C, Obireddy SR, Lai WF. Preparation and use of nanogels as carriers of drugs. Drug Delivery. 2021; 28(1): 1594-602.

15. Gupta S, Sharma S. Potential of nanogel for dental disorder: a comprehensive review. Journal of Natural Product and Plant Resources. 2021; 11(5): 1-10.
16. Sari RW, Pranata N, Sugiaman VK. Viability test of ethanol extract of beluntas *(Pluchea indica*) leaves on in vitro fibroblast cells. Scientific Dental Journal. 2019; 3(3): 90-94.
17. Alcântara CEP, Castro MAA, de Noronha MS, et al. Hyaluronic acid accelerates bone repair in human dental sockets: a randomized triple-blind clinical trial. Brazilian Oral Research. 2018; 32: 1-10.
18. Vieira AE, Repeke CE, De Barros Ferreira S. Intramembranous bone healing process subsequent to tooth extraction in mice: Micro-computed tomography, histomorphometric and molecular characterization. PLoS ONE. 2015; 10(5): 1-22.
19. Cho YD, Kim KH, Lee YM, Ku Y, Seol YJ. Periodontal wound healing and tissue regeneration: a narrative review. Pharmaceuticals. 2021; 14(5): 456.
20. Gomes P de S, Daugela P, Poskevicius L, Mariano L, Fernandes MH. Molecular and cellular aspects of socket healing in the absence and presence of graft materials and autologous platelet concentrates: a focused review. Journal of Oral and Maxillofacial Research. 2019; 10(3): 1-18.
21. Politis C, Schoenaers J, Jacobs R, Agbaje JO. Wound healing problems in the mouth. Frontiers in Physiology. 2016; 7: 1-13.
22. Rodrigues WC, Fabris AL da S, Hassumi JS, Goncalves A, Sonoda CK, Okamoto R. Kinetics of gene expression of alkaline phosphatase during healing of alveolar bone in rats. British Journal of Oral & Maxillofacial Surgery. 2016; 54: 531-5.
23. Sukandar EY, Ayuningtyas DK. *Anredera cordifolia* (Ten.) v. Steenis: a new emerging cure with polypharmacological effects. In: Ghosh D, Mukeherjee PK, eds. Natural Medicines Clinical Efficacy, Safety and Quality. Taylor & Francis; 2020.
24. Jiang J, Jia Y, Lu X. Vitexin suppresses RANKL-induced osteoclastogenesis and prevents lipopolysaccharide (LPS)-induced osteolysis. Journal of cellular physiology. 2019; 234(10): 17549-60.
25. Abdel-Naim AB, Alghamdi AA, Algandaby MM. Rutin isolated from *Chrozophora tinctoria* enhances bone cell proliferation and ossification markers. Oxidative medicine and cellular longevity. 2018; 2018: 5106469.
26. Xu B, Wang X, Wu C, Zhu L, Chen O, Wang X. Flavonoid compound icariin enhances BMP-2 induced differentiation and signalling by targeting to connective tissue growth factor (CTGF) in SAMP6 osteoblasts. PLoS ONE. 2018; 13(7): 1-16.
27. Liu XW, Ma B, Zi Y, Xiang LB, Han TY. Effects of rutin on osteoblast MC3T3-E1 differentiation, alp activity and Runx2 protein expression. European Journal of Histochemistry. 2021; 65(1): 1-6.
28. Niu YB, Kong XH, Li YH, et al. Radix Dipsaci total saponins stimulate MC3T3-E1 cell differentiation via the bone morphogenetic protein-2/MAPK/Smad-dependent Runx2 pathway. Molecular Medicine Reports. 2015; 11(6): 4468-72.
29. Handayani B, Mieke Sylvia Margaretha AR, Ridwan RD, Aljunaid M. The effect of apis mellifera propolis on runx-2 and alp during remodeling of orthodontic tooth movement. Research Journal of Pharmacy and Technology. 2021; 14(5): 2363-6.
30. Agyare C, Dwobeng AS, Agyepong N. Antimicrobial, antioxidant, and wound healing properties of *Kigelia africana.* Advances in Pharmacological Sciences. 2013;

2013: 10.

31. Hanafiah OA, Abidin T, Ilyas S, Nainggolan M, Syamsudin E. Wound healing activity of binahong (*Anredera cordifolia* (Ten.) Steenis) leaves extract towards NIH-3T3 fibroblast cells. Journal of International Dental and Medical Research. 2019; 12(3) :854-8.
32. Ismardianita E, Nasrul E, Yanwirasti Y, Hemiawati M. The effect of ethanol extract of myrmecodia pendens to TGF-β1 expression and osteoblast cells after tooth extraction (the experimental research on *Cavia cobaya*). Journal of Dentomaxillofacial Science. 2017; 2(3):150-4.
33. Niu YB, Kong XH, Li YH. Radix Dipsaci total saponins stimulate MC3T3-E1 cell differentiation via the bone morphogenetic protein-2/MAPK/Smad-dependent Runx2 pathway. Molecular Medicine Reports. 2015; 11(6): 4468-72.