

**Utilization of Nanogels Binahong Leaf Extract on Palatal Wound Healing****Chandra Lestari^{1*}, Syafruddin Ilyas², Olivia Avriyanti Hanafiah³**¹Master Program Student, Faculty of Dentistry, Universitas Sumatera Utara, Medan, Indonesia²Department of Biology, Faculty of Mathematics and Natural Science, Universitas Sumatera Utara, Medan, Indonesia³Department of Oral Surgery and Maxillofacial, Faculty of Dentistry, Universitas Sumatera Utara, Medan, Indonesia**ARTICLE INFO**

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***Corresponding author:** Chandra Lestari**E-mail address:** chandralestari98@gmail.com

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<https://doi.org/10.37275/amcr.v5i2.503>**ABSTRACT**

The palatal wound is challenging to cure due to eating and chewing activities; hence, a medication delivery system is required to expedite the healing process. The leaf of the binahong plant contains saponins, tannins, alkaloids, flavonoids, and vitamin C. Binahong leaves contain important antibacterial, antiviral, anti-inflammatory, analgesic, and antioxidant properties. However, further discussion is necessary regarding the use of nanogels and binahong leaf extract in biomedical and pharmaceutical applications. Analyzing the effectiveness of nanogels binahong leaves in healing palatal mucosa wounds has been examined in previous research. Multiple studies have revealed that using nanogels and binahong leaf extract can accelerate wound healing on the skin and within the oral cavity by boosting fibroblasts, collagen, and other factors. In conclusion, the use of nanogel binahong leaf extracts has the ability to accelerate the healing of palatal mucosa wounds.

1. Introduction

Palatal wounds are difficult to repair and often fail in the healing process, usually occurring in an inadequate oral environment.¹ As is known, in the oral cavity, there is saliva, which contains many microorganisms; repeated trauma and prolonged inflammation due to chewing and speaking activities can be a challenge to wound healing. This situation can cause failure in the healing process of palatal wounds.^{2,3} Wound treatment using herbal plants is starting to be developed in the world. WHO states that 60% of the population of developed countries and 80% of the population of developing countries use herbal medicines. One of the developing countries that is rich in plants with the potential to be used as herbal medicine to treat various diseases is Indonesia. More than 80% of medicinal plants in the world grow in

Indonesia. Wound treatment using drugs or modern medicine is known to have obstacles such as resistance and high costs. Treatment with herbal plants is starting to be developed in the world because it is relatively cheap and easy to use.^{4,5}

Binahong (*Anredera cordifolia* (Ten) Steenis) is a wild plant that grows widely in Indonesia, and its leaves are known to be used for wound healing.⁴ The content of chemical compounds such as tannins, saponins, alkaloids, flavonoids, phenolic acids, anthraquinones, terpenoids, steroids, and glycosides in binahong leaves provides pharmacological effects.^{5,6} This is the reason for using binahong leaves to speed up the wound healing process. A good drug delivery system affects the delivery of the drug to the target location precisely.⁷ Nanogels are biocompatible nanocarriers in biomedical science and biotechnology,



namely polymer network particles with dimensions less than 100 nm whose bioactive molecules can absorb a lot of water. Nanogels provide a new means of drug release by improving solubility, stability, and absorption at the cellular level. These reasons make nanogels an appropriate drug delivery system.^{8,9} The biomedical and pharmaceutical applications of nanogels in tissue regeneration and wound healing which are being developed have made the authors interested in discussing the use of binahong leaf extract nanogels for palatal mucosal wound healing.

Palatal mucosa wound healing process

The prevalence of oral mucosal injuries in patients visiting dental clinics ranges from 26.4% -26.7%. The causes of mucosal injuries can be classified as physical, chemical, and thermal. This condition will ultimately affect the patient's quality of life.^{10,11} Wound healing goes through 3 main phases, namely: inflammatory phase, proliferation phase, and maturation or remodeling phase. Wound healing is a gradual process involving the activity of leukocytes and platelets, where the response normally begins when tissue is injured.^{12,13} When injured, a mechanism occurs to restore damaged tissue components by forming new and functional structures in the body.¹⁴ The palatal mucosa is mucoperiosteum, namely the mucosa and periosteum, which are fused and attached to the palatal bone. Healing of palatal wounds can be seen with healthy underlying bone and no scar tissue forming. The general description of the healing process of palatal wounds is similar to that of skin.^{15,16}

Hemostatic phase

The inflammatory phase is divided into two, namely the initial inflammatory phase or hemostasis and the final inflammatory phase. A severed blood vessel in a wound causes bleeding, where the body's first reaction is to try to stop the bleeding by activating intrinsic and extrinsic coagulation factors, leading to platelet aggregation and clot formation. Hemostasis occurs immediately at the onset of injury to stop bleeding

through platelet aggregation and platelet-mediated vasoconstriction.^{13,17}

Inflammatory phase

The inflammatory response lasts for 4 days and is dominated by PMN leukocyte cells and macrophages. Once hemostasis is achieved, acute inflammatory cells and neutrophils will invade the inflammatory area and destroy all debris and bacteria. Neutrophils secrete pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6 also secrete proteases to degrade the remaining extracellular matrix. After carrying out the function of phagocytosis, neutrophils will be phagocytosed by macrophages or die. The presence of neutrophils will initiate an inflammatory response characterized by cardinal symptoms, namely tumor, calor, rubor, dolor, and functio laesa.¹³

Proliferation phase

The proliferation phase occurs after the inflammatory phase, which is characterized by the formation of new blood vessels and collagen synthesis. Taking place from days 3 to 14 post-trauma, it is characterized by the migration of fibroblast cells and the gradual deposition of extracellular matrix synthesis, replacing the provisional matrix, which is dominated by platelets and macrophages. Fibroblast proliferation and collagen synthesis continued for two weeks. This phase aims to establish a balance between scar tissue formation and tissue regeneration.¹³

Neovascularization occurs in the proliferation phase, namely the process of forming new blood vessels that occurs both in healthy and pathological (sick) conditions, which is very important in the wound healing process. During angiogenesis, endothelial cells produce and secrete cytokines. In addition, several growth factors are involved in angiogenesis, such as vascular endothelial growth factor (VEGF), angiopoietin, fibroblast growth factor (FGF), and TGF- β . Once the tissue is sufficiently formed, migration and proliferation of endothelial cells decreases, and excess cells die in the process of apoptosis.^{13,18}



Maturation phase (remodeling)

The remodeling phase takes place on days 8-21, and collagen deposition occurs. Remodeling functions to balance the synthesis of new collagen and the process of degradation or replacement of damaged tissue. The cellular granular tissue transforms into an acellular mass within a few months to 2 years.^{14,17} This phase begins immediately after the wound cavity is filled with granulation tissue and the reepithelialization process is complete. Wound contraction and collagen remodeling occur in this phase due to the activity of fibroblasts, which differentiate due to the influence of the cytokine TGF- β into myofibroblasts. Myofibroblasts will express α -SMA (α - smooth muscle action), causing the wound to contract. The intracellular matrix will experience maturation, and hyaluronic acid and fibronectin will be degraded.¹³

Nanogel

Nanogels have emerged as an intermediary for administering and releasing suitable drugs in patients in recent years. Nanotechnology opens up many opportunities for the production and delivery of drugs (nanomedicine) through approaches that include the characterization, synthesis, and design of molecules or materials, as well as devices, with effective functionality at the nanometer scale. The main aim of such techniques is to improve current therapeutic and diagnostic procedures.^{19,20} The advantages of nanogel include the following²¹: Nanogel has high biocompatibility and bio-degradable formulation; Nanogels can be controlled for sustained release of drug formulations by the addition of polymer networks. The polymer network also controls the particle size formulation; free-flowing pearlescent solutions of the nanogels are easily dispersed in aqueous media. Nanogels are readily administered by parenteral and mucosal administration. The greatest advantage of nanogels is that they reduce the premature leakage of the drug from the solution. Hydrophilic and hydrophobic drugs can be formulated in nanogel formulations. The disadvantage of nanogels

is that at the end of the process, an expensive technique is required to remove the solvent and surfactant completely, and the residual surfactant can sometimes cause toxicity.²⁰

Binahong

The binahong plant belonging to the Baselleaceae has great potential to be used as medicine to treat various diseases. Originating from the Chinese plains and spreading to Southeast Asia, it is a type of plant that can be used as medicine by exploiting its enormous potential.²² The characteristics of Binahong are rhizomes, namely a special stem structure with the main axis in the ground, branching, and from the ends can grow shoots that appear above the ground, functioning as a breeding tool and a place to store food reserves.²³ Single binahong leaves arranged alternately, green in color, heart or heart-shaped, smooth surface, grooved base, pointed tip, leaves range from 5-10 cm long and 3-7 cm wide. The flowers of the binahong plant are about 3-5 mm in diameter, have a distinctive smell, are greenish-white to brownish in color, and are short-lived. The crown is white and slightly oval with a length of 1-3 mm.²⁴

The potential of binahong leaf extract

The results of the phytochemical test of binahong leaf extract show that it contains the chemical compounds saponins, tannins, triterpenoids, alkaloids, flavonoids, phenolics, steroids, and glycosides. Apart from that, binahong leaf extract also contains vitamin C and ursol. Antibacterial, antiviral, anti-inflammatory, analgesic, and antioxidant properties come from these ingredients.²⁵ The flavonoids in binahong leaves can function as wound medicine, having anti-inflammatory, analgesic, anti-inflammatory, and antioxidant effects. The antimicrobial effect of flavonoids is by inhibiting the synthesis of bacterial DNA, protein, and lipids.²⁶ Saponins can damage bacterial cell membranes, removing various important components from bacterial cells. Saponins also stimulate fibroblast proliferation and collagen formation.^{26,27}



Tannins and alkaloids are antimicrobial and antioxidant, which can prevent and protect the wound area from being damaged by free radicals and inhibit the growth of pathogenic bacteria in the wound. Binahong leaf alkaloids are antibacterial by interfering with the peptidoglycan component of bacterial cells so that the cell wall layer is not completely formed and cell death occurs.^{26,27} Ascorbic acid (vitamin C) functions to increase resistance to infection, maintain mucous membranes, and accelerate wound healing.²⁸

The use of nanogels in mucosal wound healing applications has been widely carried out, such as research conducted by Ameena et al. (2023) to determine the effect of cytocompatibility and wound healing activity of chitosan thiocolchicoside lauric acid (CTL) nanogel using human gingival fibroblast cells shows that CTL nanogel has a significant effect on cell proliferation at various concentrations, its use as a safe and effective drug delivery system.²⁹ Zheng et al. (2023) researched the use of GOx-CAT nanogel (GCN) multifunctional in oral mucosal ulcers in diabetics. The results show that multifunctional GCN can be used as a new therapeutic strategy for the treatment of oral mucosal ulcers in diabetics with good biocompatibility.³⁰ Pratiwi et al. (2022) investigated the effect of cherry leaf extract nanogel on stomatitis concluding that nanogel-based cherry leaf extract could reduce the number of macrophages and stimulate collagen in the minor RAS.³¹

The use of nanogel is not only on the oral mucosa. Dermatology and cosmetology applications have used nanogels as a delivery system for topical nonsteroidal anti-inflammatory drugs (NSAIDs) as well as for the treatment of allergic contact dermatitis and psoriasis plaques. Nanogels are ideal because they can overcome the limitations of topical delivery systems, namely the relatively short contact time between the active drug and the application site, by retaining water in the gel matrix and forming a uniform nanogel dispersion. Nanogel can effectively penetrate the deep layers of the skin, so it is very good for treating inflammatory disorders.³²

The use of binahong leaves in wound healing has also been widely studied. Previous research has proven that binahong leaves can speed up wound healing, as did Maula (2021) by observing open itchy wounds, stating that binahong leaves are very beneficial for healing itchy open wounds. The use of binahong leaves shows healing of itchy wounds, which are characterized by a decrease in wound diameter and drying of the wound with a characteristic reddish rash.³³ Hanafiah et al. (2019) comparing 3%, 5%, and 7% binahong leaf extract gel on palatal mucosal wounds showed that 3% binahong leaf extract gel could improve wound healing on the palatal mucosa compared to 5% and 7% binahong leaf extract gel. Another study by Hanafiah et al. (2021) regarding 3% binahong leaf extract gel in post-extraction tooth sockets showed that 3% binahong leaf extract gel could accelerate the healing process of socket wounds. Wound closure was seen to be faster using 3% binahong leaf extract gel in a study by Hanafiah et al. (2022), which was characterized by a greater decrease in RSV values compared to other treatment groups and accelerated alveolar bone healing by increasing the proliferation of fibroblasts, osteoblasts, and osteocytes.^{6,25,26}

2. Conclusion

Nanogel, as a new system for drug delivery, has shown good results. Its use in various medicinal applications, such as in wound healing and anti-inflammation, gives a better effect than other dosage forms. Binahong leaf extract, which has the effect of accelerating wound healing on the mucosa due to the chemical compounds contained in it, is predicted to have a better effect if given in nanogel dosage form. Thus, it is necessary to carry out further research to prove whether the binahong leaf extract nanogel can accelerate the healing of palatal mucosal wounds.

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