Binahong leaf extract (*anredera cordifolia*) mucoadhesive patch as an alternative therapy for recurrent aphthous stomatitis

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ABSTRACT

Background: *Recurrent Aphthous Stomatitis (RAS) is one of the most common oral diseases of all ages. There has been no study that defines the leading cause of RAS. The utilization of binahong leaves (Anredera cordifolia) can be beneficial for the treatment of RAS as it acts as an anti-inflammatory and accelerates the proliferation of fibroblasts. The combination between binahong leaves and the mucoadhesive patch will increase the effectiveness of RAS treatment.*
Method: *Literature study through PubMed and Google Scholar databases was conducted using PRISMA flow chart looking for the efficacy of binahong leaves (Anredera cordifolia) for mucosa wound healing and mucoadhesive patches for the treatment of RAS.*
Result: *The search results found 31 articles that met the criteria for analysis. Flavonoids and saponins in binahong leaves extract act as an anti-inflammatory and increase the proliferation of wound healing. Mucoadhesive patch formulation can increase the effectiveness of RAS treatment on the mucosa.*
Conclusion: *Binahong leaves extract in the form of mucoadhesive patches can be used as an alternative treatment for Recurrent Aphthous Stomatitis.*

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INTRODUCTION

Recurrent Aphthous Stomatitis (RAS) or canker sore is the most common disease found within the oral mucosa in the form of relapsing ulcerative inflammation. The main etiology of this disease is still unknown to this day. Generally, RAS is associated with local trauma, hormonal changes, food allergies, stress, lack of nutrition or vitamins, local infection, chemical exposure, predisposing genes, or systemic disorders.[1]

Generally, RAS treatments focus on pain alleviation with the use of anti-inflammatory drugs.[2] Long-term use of corticosteroids raise side effect potentials in the form of oral candidiasis with burning sensation and hypogeusia. Currently, drug development is being carried out using natural ingredients because it has been proven that corticosteroid and non-steroidal anti-inflammatory drugs have long-term side effects.

Indonesia is rich in biodiversity and provides various herbal plants that can cure diseases, one of them is binahong (*Anredera cordifolia*) which is very abundant in Indonesia. Binahong plants can live and cultivate in both high and low altitudes within temperatures of 20-30℃, favorable to the Indonesian climate. The leaves of binahong contain chemical compounds such as flavonoids, saponins, tannins, alkaloids, triterpenoids, and polyphenols. Anti-inflammatory, analgesic, and antioxidant properties are found in flavonoids,[3,4] while saponin has the potential to stimulate fibroblast proliferation to accelerate the healing process.[5]

Up to this day, RAS treatments mainly use topical antiseptics, antibiotics, anti-inflammatory drugs, corticosteroids, and systemic drugs in the form of gels, creams, or ointments. These medications can adhere to the oral mucosa so that their anti-inflammatory effect has a strong potential.[6] Topical drugs that have been circulating inside the oral cavity have some drawbacks mainly the limited duration of attachment to oral mucosa and the side effects of oral candidiasis, and it can cause mucosal atrophy.[7] Therefore, an innovation needs to be developed in the form of a mucoadhesive patch.

Mucoadhesive patches are catching the eye as a treatment for oral diseases due to their superior advantages over conventional therapies.[8] Previous studies regarding the effectiveness of mucoadhesive patches as an alternative treatment for RAS have yielded varied results. Some studies reported mucoadhesive patches can reduce the diameter of the lesion, have a faster healing duration, and have high patient satisfaction.[9,10] Delivery of drug substances using this patch preparation is more controlled because of its ability to stick to the mucosa for a longer time compared to gel preparations, the ability to provide a protective barrier on the ulcer wound with the oral environment, and food, and it has lower side effects. Based on the potentials of binahong leaves and mucoadhesive patches, researchers are interested in conducting a deeper literature review and combining them to find more effective alternative treatments in cases of canker sores or RAS. The purpose of this study was to determine the effectiveness of binahong leaf extract (*Anredera cordifolia*) in the mucoadhesive patch formula for the RAS healing process.

RESEARCH METHOD

The articles were collected based on keywords, which are *Anredera cordifolia* AND recurrent aphthous stomatitis OR *sariawan, Anredera cordifolia* AND inflammation, *Anredera cordifolia* flavonoid, *ekstrak binahong (Anredera cordifolia) sebagai pengobatan sariawan, ekstrak binahong* AND stomatitis, mucoadhesive patch AND stomatitis*, ekstrak* AND mucoadhesive patch AND stomatitis. A literature search was done using

PubMed and Google Scholar databases to obtain articles published between 2011 and 2021, in Indonesian or English, original articles or reviews about the effectiveness of binahong leaves on wound healing in the mucosa and mucoadhesive patches for the treatment of RAS in both in vivo and in vivo studies, in vitro, and clinical trials.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) design was applied in selecting the appropriate articles. Based on the search results, there were 31 articles (figure 1).

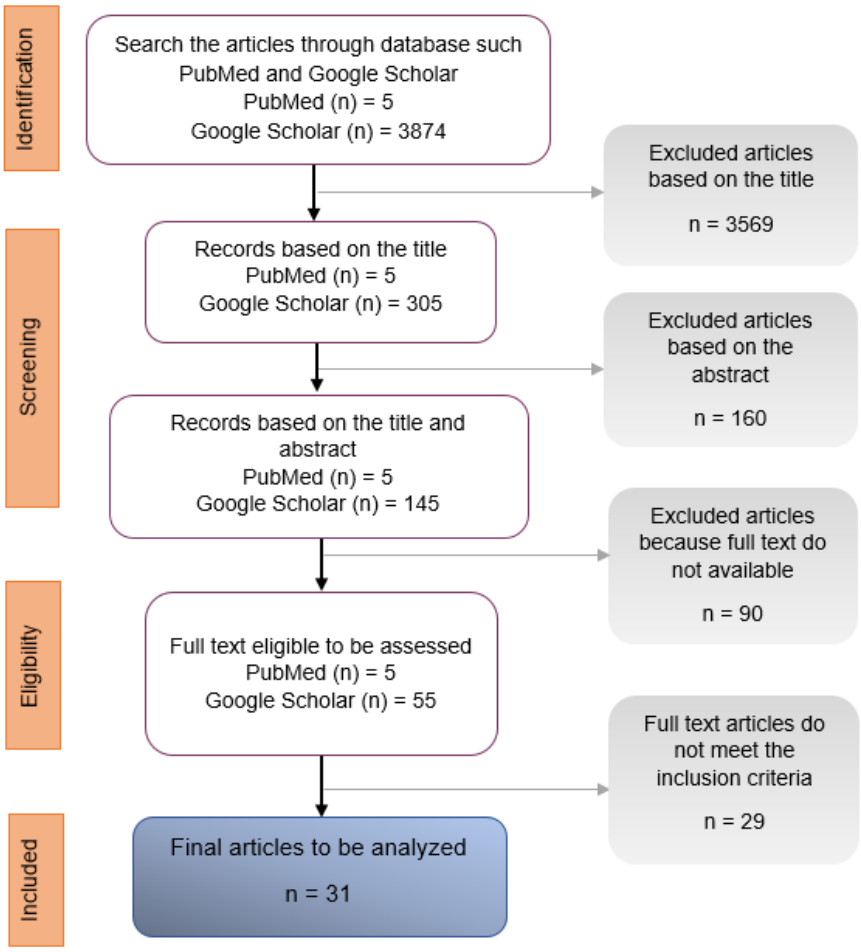

Figure 1. Data collection flowchart with PRISMA design

RESULTS

The aforementioned keywords yield a total of 3,879 articles. After undergoing a screening process based on the title, abstract, and full-text availability, the final articles used comprised 31 articles.

Table 1 shows the results related to information, content, advantages of binahong leaves, and the effect of binahong leaves on wound

healing in the mucosa. Table 2 shows the results of research on the effectiveness of mucoadhesive patch preparation.

Table 1. Study results on the effectiveness of binahong leaves on wound healing in the mucosa

Author	Aims	Subject	Method	Result
Sari *et al*, 2020	To compare the effectivity of extracts binahong leaves (*Anredera cordifolia (Ten.) Steenis*) concentrations of 25%, and 50% with Triamcinolone Acetonide in the healing process of minor Recurrent Aphthous Stomatitis (RAS).	Human	Experimental research with a pretest-posttest control group design approach. A total of 30 samples with minor RAS were divided into 3 groups. The first group used Triamcinolone Acetonide as a control group, the second group used 25% binahong leaf extract for the treatment, while the third group used 50% concentration of binahong leaf extract.	25% and 50% of Binahong leaf extract (*Anredera cordifolia (Ten.) Steenis*) effective against minor RAS. However, Triamcinolone acetonide was more effective in treating Minor Recurrent Aphthous Stomatitis (RAS) than 25% and 50% of binahong leaf extract (*Anredera cordifolia (Ten.) Steenis*).
Rawung *et al*, 2021	Produce a healthy snack cookie-based formula from fermented binahong and mango to find out the best formula with the highest level of vitamin C and antioxidant activity.	-	Samples were embedded with Lactobacillus paracasei 5% b/v for 14 days under an anaerobic environment. Vitamin C (mg/100g) quantities were analyzed from 3 samples of cookies using the Titration Iodometric Method, while the antioxidant activity was tested using 2.2-diphenyl-1- picrylhydrazyl (DPPH).	The cookie formulation which carried out the highest vitamin C and antioxidant activity was sample 3 with 3:2:2 of mango, binahong, and CO2-free water formulation.
Alba *et al*, 2020	Pharmacological tests for the determination of chemical content of *Anredera cordifolia*, its ecological and botanical classification.	-	Literature in the databases Web of Science, Scielo, Medline and BioOne, Scopus, books, and other sources.	Pharmacological test of *Anredera cordifolia* to determine its antimicrobial activity. The results of the phytochemical test have proven the presence of metabolites in the extract of binahong such as saponins, flavonoids, steroids, alkaloids, and terpenoids.
Leliqia *et al*, 2017	Collecting phytochemical content, pharmacological activity, and toxicity tests of *Anredera cordifolia* because the efficacy of this plant is still limited.	-	Study of literature in local scientific or international journals on Scopus and Google Scholar.	Contents such as terpenoids, steroids, glycosides, flavonoids, saponins, and alkaloids are found in *Anredera cordifolia* and are evident to have benefits in improving kidney function, as antifungal, antibacterial, antiviral, antioxidant, analgesic, anti-inflammatory, wound healing and cytotoxic. Toxicity tests showed that the ethanolic extract of *Anredera cordifolia* was safe for consumption.
Hanafiah *et al*, 2021	To analyze the effect of 3% binahong leaf extract gel on post-extraction wound healing.	Human	Clinical experimental using a post-test study design with a control group.	Binahong leaf extract gel 3% can decrease the duration of time on the socket wound healing process.

Hanafiah *et al*, 2019	Discover the proliferation and migration activity of 3T3 fibroblast cell lines induced by ethanol extract of *Anredera cordifolia (Ten.) Steenis*.	In vitro (Mouse fibroblast)	Proliferation activity was observed using the MTT assay. While cell migration activity was confirmed using the scratch assay. Then the data were interpreted statistically with data analysis.	The extract of *Anredera cordifolia (Ten.) Steenis* leaf has chemical compounds, such as flavonoid, saponin, triterpenoid, alkaloids, phenolics, tannins, glycosides, and steroids. The extract stimulates the proliferation of fibroblast cells and is potentially effective as a wound healing agent.
MBunga, D., dan Fernandez, S, 2018	To know the effective dose of binahong extract within its analgesic activity.	In vivo (Swiss Webster mice)	Binahong leaves were extracted by the reflux method. Peripheral analgesic activity of binahong leaf extract was conducted using the Siegmund method in different doses, namely 50 mg/kg bw (body weight), 100 mg/kg bw and 200 mg/kg bw and induced with 0.6% acetic acid.	The best analgesic activity was shown by the aqueous extract of binahong leaves at doses of 100 mg/kg bw and 200 mg/kg bw which was statistically identical to the activity of aspirin.
Ulfah *et al*, 2019	To assess the effect of increasing sorbitol and sodium carboxymethyl-cellulose (CMC) on the anti-ulcer activity of *Anredera cordifolia* leaf extract in male wistar rats.	In vivo (Wistar rats)	Making binahong leaf extract preparations; extract-sorbitol combination; combination extract-sorbitol and sodium CMC. Then the test animals have induced with peptic ulcers and observed directly and histopathological tests.	The formulation results showing the highest anti-peptic ulcer properties were in sorbitol preparations, the second highest was the combination of sorbitol and sodium CMC preparations, while the least was in the leaf extract preparations without any combination.
Mulia *et al*, 2017	To determine the effectiveness of the Natural Deep Eutectic Solvent (NADES) made of betaine and 1,4 butanediol as solvents during the extraction process of the binahong leaf vitexin compound.	-	Combining betaine-based NADES with 1,4 butanediol in a ratio of 1:3 as a solvent for the extraction process of binahong leaves. Vitexin was analyzed qualitatively and quantitatively using HPLC.	NADES containing betaine and 1,4 butanediol are an environmentally friendly solvent for extracting vitexin from binahong leaves. The extraction process can also be carried out above the ambient temperature, as long as it does not surpass the degradation temperature of the extracted bioactive compounds.
Rahmawati *et al*, 2016	To check the standard requirements of effervescent granules from binahong leaves extract and determine the best formulation from it.	-	Binahong leaves extract were obtained from a maceration method using 70% ethanol solvent. Effervescent granules are prepared by using wet granulation methods. Then several physical tests were conducted such as moisture content test, the volume of shrinkage test, pH test, dispersion test, pour volume test, flow capacity test, and organoleptic test.	The effervescent granules of binahong leaves were proven to meet the standard requirements as good granules because they passed all the tests. The best formulation for effervescent granules was using 22,2% of binahong leaves extract.

Dwitiyanti *et al*, 2019	To know the characteristics of binahong leaves simplicia.	-	Extraction of binahong leaves with an ethanol solvent by maceration method. Macroscopic and microscopic observations were then made to determine the values for the standard parameters. The active compounds were identified semi-quantitatively with the LCMS parameters.	The results of the phytochemical test for binahong leaf extract showed the presence of flavonoid, tannin, alkaloid, steroid, phenolic, and saponin compounds. The LCMS profile showed that 40%, 70%, and 96% ethanol extracts all contained vitexin.
Rusli *et al*, 2020	To know the most effective binahong leaf extraction formulation for producing flavonoids and antioxidant activity.	-	Binahong leaf extraction process using Microwave assisted extraction (MAE) method. Extract quality parameters were carried out based on the Response Surface Method (RSM) with several variables.	The levels of antioxidant activity and flavonoids are known to reach the optimal point after extraction for 13.84 minutes using 81.49% ethanol.
Mulangsri *et al*, 2020	To determine the antibacterial activity profile of ethanolic extract and purified extract of binahong leaves against S. epidermidis bacteria.	-	Maceration method extraction using 96% ethanol as solvent. The ethanol extract of binahong leaves was then purified with n-hexane as solvent. Ethanol extract and purified extract of binahong leaves were tested for antibacterial activity on S. epidermidis bacteria by agar diffusion method.	The purified extract of binahong leaves has better antibacterial activity than the ethanol extract. The concentration of purified extract required is smaller than the ethanol extract of binahong leaves in providing antibacterial activity.
Surbakti *et al*, 2018	Determine the secondary metabolite compounds and the potential toxicity of the binahong leaves.	-	The cytotoxicity of binahong leaves ethanol extract was tested by using Brine Shrimp Lethality Test (BSLT) method.	Ethanol extract of binahong leaves contains saponins, steroids, and flavonoids. The extract also carries the potential of toxicity through the BSLT test.
Laksmitawati *et al*, 2017	Observe the anti-inflammatory potential of *A. cordifolia* and *P. crocatum* extracts on murine LPS-induced macrophage cells.	-	Extraction of *A. cordifolia* and *P. crocatum* using the maceration method. Cell culture was performed and cell viability was evaluated using the MTS test.	The anti-inflammatory activity of *A. cordifolia* and *P. crocatum* was achieved through the inhibition of inflammatory mediators like IL-6, NO, and TNF-alpha.
Sjahid *et al*, 2020	To provide a solution to the limitations of obtaining phenol and flavonoid levels from binahong leaves (*Anredera cordifolia*) so that the efficiency of the extraction process can be achieved if needed on a large scale.	-	Binahong leaf extraction using ultrasonic cleaning bath with 70% ethanol solvent. Then the phenol content was determined using the Folin-Ciocalteu technique, while the determination of the flavonoid content was using the aluminum colorimetric technique.	The ethanol extract of binahong leaves contains phenolic content of 10.16% Gallic Acid Equivalent (GAE) and 10.58% Quercetin Equivalent (QE) where the results are higher than conventional extraction methods.

Table 2. Study results on the effectiveness of mucoadhesive patches

Author	Aims	Subject	Method	Result
Daněk *et al*, 2017	To compare the outcomes of treating aphthous lesions using a conventional local oral gel enhanced by the use of a buccal flexible film applied as dressing covering the lesion.	Human	A clinical study with 36 volunteers with aphthous lesions. Group 1 was treated with oral gel, while group 2 was treated with gel plus the application of a mucoadhesive film.	Compared to the usual method, buccal film as a protector for aphthous lesions improved the healing process significantly. It can also reduce the duration of discomfort the patient feels.
Hashemi *et al*, 2017	To develop oral patches with Myrtle (*Myrtus communis L*.) as an active compound and used box-behnken design to assess the effect of polymers.	In vitro	Assess the patches' properties such as mucoadhesive strength, tensile strength, thickness, swelling index, folding endurance, and the pattern of myrtle release. Then, the model was modified according to the equation with box behnken design.	The ideal formula was achieved with 20 mg of Myrtle (*Myrtus communis L*.) extract, 7.22 mg of Pectin, 35.04 mg of Gelatin, 50.52 mg of methylcellulose, and 7.20 mg of polyvinylpyrrolidone. The patch has a swelling ratio of about 300%, a degradation time of more than 24 hours, and a release rate of 27.5 minutes.
Yildir *et al*, 2018	Observe the cellulose-based formulations to obtain proper hardness, adhesion to the mucosa, and release of active substances on the mucous membrane over an extended period.	In vitro	Manufacture of cellulose composite polymers consisting of cellulose disks and other polymer components, such as polyethylene glycol and ethyl cellulose.	The non-dispersive buccal disk has good hardness, with a good drug content and in-vitro release as well. The precise mucoadhesive formulation requires further study.
Colley *et al*, 2018	Examine the physicochemical and mucoadhesive properties under development, with an electrospun patch design, and evaluate the buccal, gingiva, and tongue clinically.	Human	The manufacture of structural patches using the electrospinning method creates high porosity and bioavailability of surface area for drugs and increases the interaction of the patch with the oral mucosal epithelium.	Clobetasol-17-propionate from the buccal mucosa demonstrated steroid release from the electrospun patch into the epithelium.
Gürleyen *et al*, 2016	To assess patient satisfaction with a mucoadhesive biopatch with citrus essential oil and the change in pain severity, also the oral health-related quality of life in patients with recurrent aphthous stomatitis.	Human	In 37 patients with recurrent aphthous stomatitis, a mucoadhesive patch was applied over the ulcer. The study was conducted on the fifth post-therapy day based on baseline personal data, ulcer assessment, visual analog scale, and documented oral health impact.	Mucoadhesive biopatch with citrus essential oil succeeded in significantly reducing pain and restoring oral function on quality of life-related to oral health.
Wahid, Rahmat A Hi, 2020	Find out the effect of the use of PVP as a mucoadhesive polymer on the physical characteristics of patch preparations containing pomegranate peel extract (PPE).	-	Form the patch with a solvent casting method then evaluate the patch's properties such as uniformity of thickness, pH, swelling index, tensile and mucoadhesive strength.	PVP as a mucoadhesive polymer can o affect the physical properties of the resulting patch. Increasing the amount of PVP takes effect on more weight, dimension, swelling index, time, and mucoadhesive strength.
Wahid, Rahmat AHi., dan D Vella Laili, 2021	To determine the effectiveness of the pomegranate peel extract formulation in healing wounds.	In vivo (mouse)	The formulation patch was obtained by the maceration method using PVC, HPMC, and chitosan, as well as a physical evaluation test.	Pomegranate peel extract formulation has an effectiveness of 10% in reducing ulcer diameter in the positive control group.

Sizílio *et al*, 2018	Developed Chitosan/pvp-based mucoadhesive membranes containing betamethasone-17-valerate as a drug delivery system for RAS. Also evaluate the effect of PVP on drug release profile thermal properties, mucoadhesive ability, and swelling capacity.	-	Manufacture of the mucoadhesive membrane as a drug delivery system for betamethasone-17-valerate (BMV) by a solvent evaporation method. The first membrane uses chitosan polymer, while the second membrane uses chitosan and polyvinylpyrrolidone (PVP) polymers.	Mixing PVP with chitosan on the membrane can increase thermal stability. Then PVP increases the rate of swelling ratio resulting in faster drug release (80% in less than an hour) and increases the strength of mucoadhesion.
Abo-shady *et al*, 2020	To develop a drug delivery system with a controlled release mucoadhesive buccal film containing HA to solve the issues with the fast wash-off of mouth rinses and gels used to treat aphthous ulcers.	In vitro	Hyaluronic acid (HA) films were made using crosslinked coagulation technique and then evaluated for physicochemical properties, mucoadhesive properties, tensile strength, and in vitro drug release ability.	Hyaluronic acid (HA) formulation produces a stronger effect and resistance to saliva and food so that it is safe, effective, and stable when used as a treatment for aphthous ulcers.
Wei *et al*, 2019	Investigated the drug release behaviors, antioxidant properties, anti-inflammatory attributes, and cytotoxicity of the mucoadhesive patches combined with curcumin-loaded polylactic acid (PLLA) nanofibrous meshes as RAS therapy.	In vitro	Generated the electrospinning to produce curcumin-encapsulated PLLA nanofibrous meshes. Then prepare the mucoadhesive patches and combine them with the curcumin PLLA nanofibrous meshes.	The mucoadhesive patches can bring a great treatment effect for RAS because the pain was reduced, and act as an anti-inflammatory, antioxidant and antibacterial. The high curcumin dose showed a good antioxidant and anti-inflammatory activity than the low dose. Also, the patch can adhere greatly to the pig buccal mucosa.
Haghpanah *et al*, 2015	To assess the effectiveness of bioadhesive-containing ginger for RAS treatment.	Human	A randomized clinical study in 15 patients. Supplied 2 mucoadhesives; placebo (non-medicated mucoadhesive) and mucoadhesive containing the ginger extract. Then evaluated for pain, zone of inflammation, and ulcer diameter for 10 days.	Inflammation was significantly reduced on day one. However, this muco-bioadhesive containing ginger has not been able to relieve pain in RAS patients.
Zhang *et al*, 2019	To know the characteristics of mucoadhesive buccal films containing Ornidazole (OD) and Dexamethasone sodium phosphate (DEX).	In vivo and In vitro	Develop the OD and DEX films using the casting method or solvent printing according to the desired mucoadhesive characteristics and properties.	The combination of OD and DEX in the mucoadhesive buccal film can increase the effectiveness of the treatment of oral ulcers by distributing the drug evenly and an impermeable layer that can control the direction of drug release.
Carvalho et al, 2020	To determine the effect of bacterial nanocellulose (BNC) based patch containing hyaluronic acid (HA) and diclofenac (DCF) on the stimulation of ulcer healing in RAS.	In vitro	Patches were prepared via diffusion of aqueous solutions of HA and DCF, with different concentrations of DCF, into the wet BNC three-dimensional porous network. Patch thickness was measured with a Mitutoyo coolant-proof digimatic micrometer MDC-25PX.	Patches with multiple polysaccharides (HA and DFC) demonstrate a drug release mechanism to target RAS.

Arafa *et al*, 2018	Developed oromuco-adhesive films containing propolis extract as a new therapy for treating aphthous ulcers.	In vitro	The propolis extract was prepared in the form of niosomes, then the mucoadhesive film was prepared using the solvent casting method. The patches were evaluated for their physical properties and tested on 24 RAS patients.	Mucoadhesive films containing propolis niosomal can persist in the oral cavity in the long term, it also can reduce the size of the ulcer, and eliminate pain, hence resulting in faster healing time.
Wathoni *et al*, 2019	Develop and characterize chitosan-alginate based on α-M hydrogel film (ChAlg/α-M HF) as a new therapy for RAS.	In silico and In vitro (mouse buccal mucosa)	In silico studies to confirm hydrogen bonding between chitosan, alginate, and α-M occurred. Then made and tested the character of α-Mangostin Hydrogel Film. As well as in vitro studies using the Fickian diffusion model.	ChAlg/α-M HF has a lower crystalline, significantly increasing the swell ratio and tensile strength. α-Mangostin hydrogel based on chitosan and alginate has good mucoadhesive properties. The resulting alginate and chitosan-based hydrogel films have potential as α-M carriers for RAS therapy.

DISCUSSION

Therapeutic Management of Recurrent Aphthous Stomatitis (RAS)

Recurrent Aphthous Stomatitis (RAS) is an oral mucosa inflammation without the presence of symptoms of another disease. There are three types of RAS, which are major RAS, minor RAS, and herpetiform RAS.[11] Clinically, the general form of RAS is a single or multiple ulcers, rounded or oval, with clear borders, the base of the lesion is yellow or grayish and surrounded by erythematous haloes.[12]

Therapeutic management for treating RAS focused on suppressing the local immune, reducing pain and discomfort like burning sensation, and preventing secondary infection and relapse. The medications in RAS aim to accelerate the regeneration of tissue cells. Scientifically, the application of topical antiseptics, local anesthetics, or corticosteroids has been shown to have a positive effect on the treatment of RAS.[13] In addition, the use of anti-inflammatory, analgesic, or antimicrobial in gel or spray formulations and mouthwash containing hyaluronic acid (AH) can also help reduce inflammation and pain in ulcers. Hyaluronic acid is a linear polymer of the disaccharide N-acetylglucosamine and glucuronic acid which has the potential as a healing agent to regenerate tissue and as a wound protector. However, the analgesic effect of hyaluronic acid is known to be less effective in reducing pain. Therefore, the combination of hyaluronic acid with NSAIDs can accelerate ulcer healing and pain from RAS. However, gel, cream, or paste formulations have a disadvantage since they can be smudged from the wound or target area so they need to be applied several times a day to form a protective layer over the RAS, and it also causes side effects in long-term use.[14]

Binahong Leaf Extract (*Anredera cordifolia*) for RAS

Binahong leaf (*Anredera cordifolia*) is a type of plant that comes from the *Basellaceae* family and is often used by people to help the healing process of various diseases. Various primary data studies conducted phytochemical tests to determine the content of compounds contained in binahong leaf extract (Table 4).

Table 4. Phytochemical Test Results of Binahong Leaves Extract in Various Study

Author	Flavonoid	Saponin	Tanin	Alkaloid	Steroid
Dwitiyanti *et al*, 2019	(+)	(+)	(+)	(+)	(+)
Hanafiah *et al*, 2019	(+)	(+)	(+)	(+)	(+)
Mbunga *et al*, 2018	(+)	(+)	(+)	(+)	(+)
Rusli *et al*, 2020	(+)	(+)	(+)	(+)	(-)
Sjahid *et al*, 2020	(+)	(+)	(+)	(+)	(+)
Surbakti *et al*, 2018	(+)	(+)	(-)	(-)	(+)
Ulfah *et al*, 2019	(+)	(+)	(+)	(+)	(+)

Based on the table above, all binahong leaf extracts that have been studied contain flavonoids and saponins. Flavonoids act as an anti-bacterial, strong antioxidant, and as a strong vasodilator. Flavonoids as antimicrobials work by inhibiting the synthesis of proteins, lipids, and bacterial DNA. Not only that, saponins which are anticarcinogenic and antiseptic can inhibit the growth of microorganisms present in the wound, so it does not aggravate wound infection.[15,16] Other content in saponins also plays a role in increasing the proliferation of fibroblast cells. Other compounds, such as alkaloids and tannins that act as antioxidants and antimicrobials are also able to accelerate wound healing by protecting the wound area from free radicals and bacterial growth.

It is known that the compounds contained in binahong leaf extract have the potential to heal ulcers and wounds. Research by Sari (2020) on the effectiveness of binahong leaf extract against RAS resulted that 25% and 50% concentrations of binahong leaf extract have the same effectiveness in curing minor RAS. Binahong leaf extract is known to have almost equal effectiveness when compared to commercial drugs containing the active ingredient Triamcinolone acetonide 0.1%. In addition, the application of binahong leaf extract every 2 times a day, in the morning after eating and at night before going to bed for 5 days is known to reduce the diameter of the ulcer.[11] Ulcer healing activity is influenced by the compounds contained in the binahong leaf extract.

To obtain the desired activity, the compound needs to be isolated. Extraction is a process to separate compounds from simplicia or matrix using a suitable solvent. Several extraction methods can be used to extract binahong leaves, one of which is the maceration method which is a simple extraction method by soaking simplicia powder in a liquid solution. The collected ethanol macerate is evaporated with a water bath to obtain a thick extract.[18] This is different from the Microwave Assisted Extraction (MAE) method which is an extraction technique that utilizes microwave energy. The advantage of using the MAE method is that it helps increase the amount of yield of the crude extract in a short time and the amount of solvent is relatively small compared to the conventional extraction method.[17] In addition, there is an ultrasonic-assisted extraction method by providing ultrasonic vibrations >20kHz on the surface of the simplicia.[19] Various Binahong leaf extraction methods with ethanol solvent with different concentrations can produce different yields (Table 4).

Table 4. Total Yield of Binahong Leaves Extracted with Various Methods and Solvents

Extraction Method	Solvent	Yield (%)	Author
Maceration	Ethanol 40%	10.9	Dwitiyanti *et al*, 2019
Maceration	Ethanol 70%	11.4	Dwitiyanti *et al*, 2019; Hanafiah *et al*, 2019; Rahmawati *et al*, 2016
Maceration	Ethanol 96%	12.32	Dwitiyanti *et al*, 2019
Microwave Assisted Extraction (MAE)	Ethanol 80%	7.33	Rusli *et al,* 2020
Ultrasonic Assisted Extraction	Ethanol 70%	40.098	Sjahid *et al*, 2020

Primary data analysis shows that 70% ethanol solvent with ultrasonic-assisted extraction method produces the largest yield compared to other extraction methods. In this method, simplicia will undergo several conditions which are erosion and fragmentation. The cause of erosion is that secondary metabolites are forced to break away from bonds in the cell, hence solvent ability must be increased to dissolve secondary metabolites. Fragmentation occurs due to the presence of simplicia particles that break into smaller sizes so that the surface area of the extracted particles becomes larger. As a result of these processes, there will be an increase in mass transfer from the simplicia to the solvent and there will be an increase in the amount of yield and the rate of extraction.

The Anti-Inflammatory Potential of Flavonoids in Binahong Leaves

Chemical compounds in binahong leaves contain secondary metabolites, including polyphenols, alkaloids, flavonoids, steroids, terpenoids, and saponins.[20,21] These secondary metabolites can provide pharmacological effects on human free radicals, increase the epithelialization process, and show anti-inflammatory activity in human red blood cells through membrane stabilization tests.[5] Inflammation is the body's response to injury that can occur in various diseases. Several inflammatory marker responses appear in macrophages such as reactive nitrogen species (RNS), reactive oxygen species (ROS), cytokines (IL-1, IL-6, TNF-α), and nitric oxide (NO) which are mediators of inflammation including prostaglandins. This results in increased vascular permeability, stimulation of pain fibers, and vasodilation.

Research by Laksmitawati et al (2017) proved that flavonoids inhibit several inflammatory mediators.[23] Anti-inflammatory effects were tested against several markers present in macrophages during inflammation. The results showed that TNF-α in the cell line induced by Bacteria lipopolysaccharide (LPS), *A. cordifolia* extract at a concentration of 50 g/mL resulted in a significant decrease in TNF-α levels (250.3 pg/ml), and IL-1 as much as 909,2 pg/mL which is comparable to normal cells as much as 890,2 pg/mL. A significant decrease in IL-6 levels is also shown (217.8 pg/mL) at a concentration of 10 g/mL and the lowest levels of NO (22.8 pg/mL) at a concentration of 50.0 g/mL. Extracts from *A. cordifolia* have anti-inflammatory potential as indicated by the inhibition of inflammatory mediators including NO, TNF-, IL-6, and IL-1β on LPS-induced macrophage cells.

Several other types of flavonoids such as vitexin, isovitexin, morin, myricetin, and sapogenins such as ursolic acid can be isolated from the

extract.[20] The flavonoid glycoside compound in binahong leaves is known as vitexin (8-beta-D-Glucopyranosylapigenin).[24] Dwitiyanti *et al.* (2019) stated that the total vitexin content was obtained through spectrophotometric analysis of the 96% ethanol extract of binahong leaves showing 1.031%. Analysis using LCMS parameters showed that 40%, 70%, and 96% ethanol extract of binahong leaves contained vitexin at a retention time of 5.02 minutes and a mass spectrum fragmentation of vitexin ion 433.1111 m/z.[18]

Potential of Saponins in Binahong Leaves to Increase Proliferation

One of the accelerated healing processes of RAS is characterized by the increased proliferation of fibroblast cells. The saponin content of *Anredera cordifolia* can stimulate fibroblast proliferation and myofibroblast differentiation in ulcers, thereby accelerating ulcer closure. The mechanism of action of saponins in ulcer healing is by stimulating the production of type I collagen which has an important role in the wound closure process and increases the speed of tissue epithelialization.[5]

Saponins obtained after extracting binahong leaves act as angiogenetic agents that can increase cell activity in the formation of blood vessels during the proliferative phase of wound healing.[15] In vitro research conducted by Hanafiah *et al.* (2019) observed the proliferative activity of fibroblast cells 3T3.[5] Binahong leaves extract was shown to increase the proliferation rate of 3T3 fibroblast cells from 0 hours to 72 hours with the highest proliferation rate recorded at a concentration of 62.5 g/mL (127.89 ± 16.12). The proliferation rate of the binahong leaf extract was the fastest and there was a significant difference when compared to the control group and the commercial drug administration group.

Other than increasing proliferation, saponins also have antibacterial properties because they can interfere with the permeability activity of the bacterial cell membrane until damage occurs which causes various important components to come out of the bacterial cell such as nucleic acids, proteins, and nucleotides. Cell hemolysis eventually occurs and causes the killing of bacteria in the ulcer and will not inhibit the ulcer healing process.[11] Meanwhile, the potential for saponins as antioxidants is shown through their ability to reduce superoxide through the formation of hydroperoxide intermediates to prevent biomolecular damage caused by free radicals.[17]

Effectiveness of Mucoadhesive Patch in RAS healing process

The mucoadhesive patch is a drug delivery system that is used by attaching a patch to the gingiva mucosa or the inner cheek membrane. The mucoadhesive drug delivery system is more suitable for the treatment of RAS because it targets effects such as analgesic, anti-inflammatory, and antimicrobial with a longer duration of stay so that the effectiveness of the drug delivery process is high. because it has a barrier effect, where the drug agent can be in contact with the lesion on the mucosa for a longer time which results in speeding up the healing process and reducing the perception of pain.

In recent years, various studies have combined mucoadhesive patches with ready-made drugs to be used as RAS therapy. Carvalho *et al.* (2020) used Diclofenac and hyaluronic acid on cellulose-based patches, suggesting that the mucosal patch has the potential to treat aphthous stomatitis. Cellulose as the main ingredient of the patch was developed by Yildir *et al.* (2017) with a fairly good drug release, content, and hardness.28 Meanwhile, research conducted by Sizilio *et al.*

(2018) on the delivery of the drug betamethasone-17-valerate (BMV) in RAS using an adhesive membrane of polymer polyvinylpyrrolidone (PVP) and chitosan (CHI) has been shown to increase the rate release of BMV as much as 80% for 1 hour.[29]

Many studies using herbal plant extracts as the main ingredient of mucoadhesive patches for RAS have shown varying results. The mucoadhesive patch containing ginger extract can relieve RAS pain but cannot reduce lesion diameter and treatment time, while the mucoadhesive patch containing 10% pomegranate peel extract can reduce lesion diameter.[30,31] Both studies did not produce a very significant effect on RAS, because it is still considered almost the same as conventional RAS treatment and placebo. On the other hand, some studies use propolis with natural flavonoid content in mucoadhesive patches to produce satisfactory therapeutic effects with a reduction in lesion size and healing duration, pain relief, and high patient satisfaction.

The flavonoids contained in binahong leaves have the potential to be anti-inflammatory. Delivery of flavonoids using patch preparations can accelerate the healing process of RAS compared to oral gel preparations.[27,14] Mucoadhesive patch formulations can increase the effectiveness of RAS treatment on the mucosa in terms of drug distribution that is directly on the target, longer contact ability with lesions, stronger resistance to saliva

CONCLUSION

Binahong leaf extract (*Anredera cordifolia*) in the preparation of mucoadhesive patches can be used as an alternative treatment for Recurrent Aphthous Stomatitis. Based on the results of the article analysis, the chemical compounds of binahong leaf extract such as flavonoids and saponins act as an anti-inflammatory and increase the proliferation of wound healing. The preparation of mucoadhesive patches can increase the effectiveness of the treatment of RAS on the mucosa because the distribution of the drug directly contacts the target for a longer duration.

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