



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Herbal Medication of Recurrent Aphthous Stomatitis: A Narrative Review

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ARTICLE INFO

Keywords:

Recurrent aphthous stomatitis
Infection
Herbs
Clinical trial
In vitro test

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

<https://doi.org/10.37275/bsm.v6i1.438>

ABSTRACT

A mouth ulcer or recurrent aphthous stomatitis (RAS) is a mouth mucous tissue inflammation. This disease mainly occurs in patients 10-40 years of age, preferably in women and high socioeconomic backgrounds. The cause of mouth ulcers or RAS could be trauma, infection, digestive problems, or blood disorders. Herbal practitioners widely use herbs, folks, and society to treat various diseases. This research aimed to describe the herbal treatment for RAS. The review results show there are nine plants with the ability to cure RAS, they are *Persea americana* Mill., *Averrhoa bilimbi* L., *Abrus precatorius* Linn., *Camellia sinensis* (L.) Kuntze., *Psidium guajava* L., *Kaempferia galanga* Linn., *Aloe vera*, *Curcuma longa* and *Citrus hystrix* DC. The most parameters used in the studies are clinical trials and in vitro tests.

1. Introduction

The most common diseases that occur globally, especially Indonesia, are dental and oral diseases.¹ Mouth ulcer or recurrent aphthous stomatitis (RAS) is an inflammatory disease in mucous tissue. This could be found in 10-25% of Indonesian society with mild severity with minor gripes. RAS initiated with the appearance of necrotic ulcer (lesion). The lesion sites in the mouth are mucous yet rarely located on the gums.^{2,3} Mouth ulcers often happen in patients aged 10-40 years, especially women and high socioeconomic people.^{2,4,5}

The cause of canker sores or RAS is still unknown; suspected reasons include trauma, infection, digestive disorders, blood disorders, HIV infection (human

immunodeficiency virus), emotional disorders, immunologic disorders, nutritional deficiencies, and hormonal disorders. According to clinical presentation, RAS is classified as minor ulcer, major ulcer and herpetiform ulcer.⁶ Minor ulcer marked by the appearance with less than 1 cm lesion, rarely accompanied by pain in the glands or prodromal symptoms and can be single or multiple. Major ulcers are round, more than 1 cm in diameter, painful in some patients with prodromal symptoms, such as burning 2-48 hours before the lesion appears. A herpetiform ulcer is a small ulcer and grouped (multiple) and started with a small ulcer surrounded by erythema and merged afterward. The lesions look similar to herpetic lesions

and cause pain. The healing process is usually faster, but new ulcers are immediately formed. This condition is persistent and can be bothering because it is difficult to get rid.⁶

Nature has been blessed with various medicinal plants widely used by herbal practitioners, folks, and society to treat various diseases, especially in rural and tribal areas separated from modern facilities and residents. They have traditionally used several plant species in the area to meet their health care needs.⁷ Indonesia is a country with various medicinal plants in the world. There are 40.000 species of plants in the world, 30.000 of the species can be found in Indonesia, and 940 plants are known to have medicinal properties and have been used traditionally as medicinal plants

hereditarily by so many ethnics in Indonesia.⁷

Herbal treatment for mouth ulcer

The plant is a rich resource that has been used for centuries to treat various diseases. There are many herbs with medicinal properties. Parts of a plant can be used to treat many types of diseases.⁸ A study by Panche et al.,⁹ mentions that plants with flavonoid compounds have antioxidant, antibacterial, antiviral, anti-inflammation, antiallergic and anticancer activities. Therefore, several plants can treat mouth ulcers. The table below lists plants that can help treat mouth ulcers.

Table 1. Herbal plants for mouth ulcers

Plant	Part	Compound	Activity	Method	Mechanism
<i>Persea americana</i> Mill ¹⁰	Leaf	Flavonoids	Antifungal	Invitro	Flavonoids work by denaturing proteins.
<i>Averrhoa bilimbi</i> L. ¹¹	Fruit	Flavonoids, tannins	Antibacterial	Invitro	1. Form complex compounds with extracellular proteins 2. Shrink the cell walls of bacteria.
<i>Abrus precatorius</i> Linn. ¹²	Leaf	Saponins Flavonoids	Antibacterial	Invitro	1. Increase cell membrane permeability resulting in hemolysis of cells. 2. Inhibit cell membrane function and bacterial energy metabolism.
<i>Camellia sinensis</i> (L.) Kuntze ^{13,14}	Leaf	1. Flavonoids 2. Tannin	Antibacterial	Clinical Trial	1. Form extracellular and soluble protein complexes with microbial walls. 2. Forming complexes with proteins through hydrogen bonds with hydrophobic bonds causing proteins denaturation
<i>Psidium guajava</i> Linn. ^{15,16}	Fruit	Flavonoids	Anti-inflammation	Clinical Trial	1. Inhibits the action of xanthine oxidase and protein kinase C enzymes that produce superoxide anion radicals (O ₂ ⁻). 2. Inhibits the cyclooxygenase (COX) I enzyme
<i>Kaempferia galanga</i> Linn. ¹⁷	Rhizoma	p-methoxycinnamic acid	Anti-inflammation	Clinical Trial	- Inhibits the release of chemical mediators serotonin and histamine to the site of inflammation. - Inhibits the synthesis of prostaglandins.
<i>Aloe vera</i> ¹⁸	Leaf	Salicylic Acid, indometacin	Anti Inflammation	Clinical Trial	Reducing edema, inhibiting the cyclooxygenase enzyme and inhibiting the motility of polymorphonuclear leukocytes (PMN).
<i>Curcuma longa</i> ¹⁹	Rhizoma	Saponins	Antibacterial	Clinical Trial	Damage the cell wall of bacteria, so that cell division in the bacteria itself is inhibited.
<i>Citrus hystrix</i> DC. ²⁰	Fruit peel	1. Saponin, 2. Tannins, 3. Flavonoids 4. Coumarins	Antifungal	Invitro	1. Disrupt the cell membrane of fungi. 2. Affect changes in cell membrane permeability which can cause a decrease in the volume of fungal cells. 3. Denaturing fungal cell proteins 4. Damage cells by forming cell wall pores.

Chemical compounds and the properties of herbal medicine

***Persea americana* Mill (avocado)**

The avocado plant has flavonoids, saponins, tannins, and quercetins with antimicrobial activity. The leaf of this plant has properties as thrush and antihypertensive, and the seed of this plant is used to treat diabetes.¹⁰ Based on a study, avocado leaves extract can inhibit the growth of *Candida albicans*. This is because of the flavonoids and quercetin in the leaves, which work as antifungals.

Flavonoids are the largest group of polyphenolic compounds. They work by denaturing proteins, thereby increasing the permeability of cell membranes. Protein denaturation causes disturbances in cell formation so that it changes the composition of protein components. In addition, phenolic compounds through hydroxy groups will bind to the sulfhydryl groups of fungal proteins, causing the change of target cell membrane proteins conformation, resulting in fungal cell growth disruption and death.²¹

***Averrhoa bilimbi* L. (belimbing wuluh)**

Belimbing wuluh contains active substances, including flavonoids, tannins, and saponins which have antibacterial properties.¹¹ Based on previous research, the antibacterial activity of *belimbing wuluh* is related to the presence of flavonoid-derived bioactive substances such as luteolin and apigenin. *Belimbing wuluh* extract (*Averrhoa bilimbi* L.) shows that the flavonoid group contained is a type of flavonol. Flavonoids have antibacterial properties because they are phenolic group compounds. Steroid/triterpenoid compounds inhibit bacterial growth with protein synthesis inhibition and get accumulated, causing the change of components which consist of the bacteria. Terpenoid compounds are soluble in lipids; this property is why they penetrate easily through the cell walls of gram-positive bacteria and gram-negative bacteria cells.²² Tannins are complex compounds in the form of polyphenols that can react with cell walls and inhibit the synthesis of chitin cells, which are important components in fungi.

***Abrus precatorius* Linn. (saga)**

According to research by Garaniya et al.,¹² the content of saga leaves in the form of glycosides (abrusoside A-D and abrusgenin), saponins and flavonoids have antibacterial properties. Secondary metabolites for antimicrobial purposes are triterpenoids, steroids, and saponins. Saponins are a part of terpenoids with carbon frames based on isoprene. Saponins inhibit fungi by lowering the surface tension of the sterol membrane of the fungal wall. The permeability will increase and causes the death of fungi cells. Flavonoids are the largest group of phenols derived from plants with antimicrobial properties against fungi. The working mechanism of flavonoids as an antifungal is damaging fungal cell permeability and cell walls.²³

***Camellia sinensis* (L.) Kuntze (green tea)**

Green tea shows antifungal activity against *Candida* species due to its polyphenolic ingredients.¹⁴ As important metabolites of tea with high molecular mass, polyphenolic tannins can bond with other large molecules, such as proteins, alkaloids, cellulose, starch, and heavy metals. As one of the ingredients in green tea, tannins also have antibacterial activity through their molecular action, forming complexes with proteins through hydrogen bonds with hydrophobic bonds. Tannins also can inactivate microbial cell adhesion (molecules attached to host cells) on the cell surface, enzymes bound to cell membranes, and cell wall polypeptides. Tannins targeting polypeptides will destroy cell walls because tannin is a polyphenol compound.²⁴ Not only antimicrobial activity, but green tea also has anti-inflammatory, anti-oxidant, anti-mutation and anti-diabetic properties, which can play an essential role in treating erythema and mucosal inflammation.¹⁴

***Psidium guajava* L (guava)**

Guava is a plant that has high antioxidant activity. The content of polyphenols with higher antioxidant activity in white and red-fleshed fruits compared to other plants. The high polyphenols content with antioxidant activity in both white-fleshed and red-fleshed fruits is higher than other plants.¹⁵⁻¹⁶ The

bioactive compounds in the plant work as anti-inflammatory, antimicrobial, antioxidant, and hepatoprotective.¹⁵ Flavonoids can induce cellular antioxidants, inhibit xanthine oxidase and protein kinase C enzymes, which produce superoxide anion radicals (O_2^-) and inhibit the cyclooxygenase enzyme. lipoxygenase plays a role in the inflammatory process. Flavonoids inhibit prostaglandins' biosynthesis, which acts as inflammatory mediators that may cause vasodilation of blood vessels and edema (swelling). Guava effectively reduces pain with anti-inflammatory and analgesic effects, which inhibit the cyclooxygenase (COX) I enzyme, affecting prostaglandin biosynthesis, a mediator of pain formation.¹⁶

***Kaempferia galanga* Linn (galangal rhizome)**

Kaempferia galanga Linn, commonly called *kencur*, is a medicinal plant that belongs to the Zingiberaceae family. This plant benefits larvicidal, antioxidant, antiulcer, anti-inflammatory, and antihypertensive activity.¹⁷ Rhizome empirically is known to have anti-inflammation activity. The primary substance of the galangal rhizome is ethyl p-methoxycinnamate. This compound in the body undergoes hydrolysis into a biologically active compound, p-methoxycinnamate acid, and this compound works by inhibiting the cyclooxygenase enzyme to convert arachidonic acid into prostaglandins is inhibited.²⁵

Aloe vera

Aloe vera can be used to heal internal and external wounds, such as skin wounds, burns, itching, and stomatitis.¹⁸ Topical administration of *Aloe vera* can help reduce pain and accelerate the healing process of recurrent aphthous stomatitis (RAS) because *Aloe vera* contains various substances such as anthraquinones (aloin) and carbohydrate complexes which have anti-inflammatory, antibacterial, antifungal, and cell regeneration functions.

The healing mechanism of minor RAS using *Aloe vera* starts from the ulcerative stadium. The enzymes contained in *Aloe vera*, such as glucomannan and acemannan, work together with oxidase, amylase, catalase, lipase, and protease enzymes break down the painful mucosal tissue due to specific damage and help

break down bacteria so that it can stimulate the growth and repair of the skin mucosa and remove dead cells from the mucosa.

Aloe vera also contains natural salicylates and a few substances with the ability to inhibit the production of inflammatory mediators such as bradykinin and thromboxane. The chrysophanic acid, seristanol, and cinnamic acid esters in *Aloe vera* are antiseptic²⁶. After five days, the epithelium regeneration begins to cover the ulcer, reducing the pain.

***Curcuma longa* (turmeric)**

One of the compounds contained in turmeric, which works as an anti-inflammatory, analgesic, and antibacterial, is curcumin.¹⁹ Curcumin has antioxidant and anti-inflammatory properties, which can reduce inflammation in ulcers and counteract free radicals' negative action, thereby accelerating ulcer healing.²⁷ Saponin is one of the compounds with antibacterial properties because it can damage the bacterial cell wall and inhibit the cell division of the bacteria. Through this mechanism, mucous cells are more protected, increasing cell viability and reducing erythema during inflammation.

***Citrus hystrix* DC (kaffir lime)**

The content of kaffir lime peel is saponins, tannins, flavonoids, and coumarins²⁰. Kaffir lime peel compounds that show antifungal activity are saponins that react by disrupting fungal cell membranes, one of which is *Candida albicans*. In addition, the content of other antifungal compounds such as tannins affects changes in cell membrane permeability which can cause a decrease in cell volume²⁸.

Similar to saponins and tannins, flavonoids can also damage cell membranes, resulting in cell permeability changes. While coumarins damage cells by forming cell wall pores, causing cell death. Saponins are secondary metabolites found in various plants and exhibit antifungal activity. Saponins are soluble in water and insoluble in ether. The antifungal mechanism of saponins is from the ability of complex molecules with sterols in the fungal membrane, causing the formation of pores in the lipid bilayer, which can eliminate membrane integrity and increase cellular permeability.

Tannin is a water-soluble active compound in a plant with a 500-3000 gr/Mol molecular weight. Tannin influences cell membrane permeability which causes a decrease in cell volume; cells perforate and shrink and then lose their metabolic function and eventually crumble. Flavonoids are water-soluble active compounds in a plant. Flavonoid denatures cell protein, shrinks the cell wall, and causes fungal cell lysis. It bonds complexly with a cell membrane protein. The damage of cell membranes occurs because of the cell permeability alteration and the loss of cell contents or cell death.

Coumarins are water-soluble secondary metabolites with very few amounts.²⁹ Coumarin's work mechanism destroys cells by creating pores in the cell walls that might change the structure and functions of plasma membranes, increase transmembrane and lack of amino acid and other cytoplasm components, causing the shrinkage and breakdown of cells.

2. Conclusion

This study describes the latest research related to herbal medication for recurrent aphthous stomatitis. The review shows 9 plants with RAS medication activity: *Persea americana* Mill, *Averrhoa bilimbi* L., *Abrus precatorius* Linn, *Camellia sinensis* (L.) Kuntze, *Psidium guajava* L., *Kaempferia galanga* Linn, *Aloe vera*, *Curcuma longa*, *Citrus hystrix* DC. From several studies, it is known that the most widely used parameters as a method in testing are clinical trials and in vitro tests.

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