

Polyherbal Gel for Treatment of Mouth Ulcer

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Abstract: The most frequent ailment we deal with is Aphthous stomatitis, sometimes known as mouth ulcers. Clinically, the lesions are deep-sealed, superficial, or numerous, and they are linked to microbial invasions. One of the most common conditions affecting the oral mucosa is oral ulcers. Numerous triggering variables and causes has been identified however the exact aetiology of oral mucosal ulcers remains to be determined. The illness usually takes 10 to 14 days to go away, though it can occasionally return quickly if there is no underlying systemic cause. Eating, drinking, and swallowing are all impacted during the active stage of the disease, which lowers quality of life. The only forms of treatment are topical steroid application, antibiotics, and analgesics, which are usually used for symptoms. These over-the-counter medications can occasionally have serious side effects when used. Herbal medications offer a more secure and effective substitute for synthetic pharmaceuticals. This article reviews popular herbal remedies and looks into how well they work to heal mouth ulcers. The purpose of this study was to assess the efficacy of herbal remedies for the treatment of aphathous stomatitis. Using ethanolic extracts of Aloe barbedensis, Ocimum tenuiflorum, Psidium guajava, curcumin, and liquorice, oral ulcer gels were created as part of the study. The prepared formulations were evaluated for various parameters like physical appearance, pH, Spreadability, Homogeneity and antimicrobial activity against fungi and bacteria.

Key Words: Aphthous stomatitis or mouth ulcers, herbal drugs, Psidium guajava, Liquorice, Ocimum tenuiflorum, Aloe, Curcumin.

INTRODUCTION

Gels are primarily composed of a liquid phase that has been thickened with additional ingredients, making them semi-solid formulations. Topical gel preparations are used to apply medication topically, penetrate the skin, or have a localised effect on specific mucosal surfaces.^[1] Small sores or abrasions that appear in the mouth or at the base of the gums

are called mouth ulcers. Aphthous ulcers and canker sores are other names for mouth ulcers. A mouth ulcer can also be defined as a break or breach in the mucous membrane lining the oral cavity. Usually, it starts off as a whitish or yellowish depression in the mouth. Many factors, including biting the inner layer of the cheek, food allergies, vigorous tooth brushing, hormonal fluctuations, vitamin shortages, bacterial infections, and illnesses, can result in mouth ulcers.^[2]



Nonetheless, a number of elements are thought to be significant contributors to the genesis of mouth ulcers, including heredity, psychological stress, topical trauma, microbiological infections, dietary disorders, immunological, hormonal fluctuations, allergies, and prescription drugs.^[3] Mouthwashes that are calming or antiseptic, including chlorhexidine or povidone iodine, as well as the usage of gel formulations containing antibiotics or anaesthetics, can aid in the treatment of mouth ulcers.^[4] Gel with a liquid phase that is later thickened by additional ingredients is referred to as a semi-solid formulation. In order to achieve local action or percutaneous penetration of medication formulations, topical gels are designed to be applied to the skin or specific mucosal surfaces.^[5] Mouth ulcers can be treated with a variety of synthetic and semi-synthetic medications, including steroidal and non-steroidal anti-inflammatory medicines, antibiotics, antiseptics, and local anaesthetics and analgesics. The most

commonly used therapies are topical steroids, such as triamcetonolone and prednisolone, although they have several major side effects when taken continuously, including immunosuppression, osteoporosis, hyperglycemia, gastrointestinal disturbances, and adrenal insufficiency. Furthermore, due to their high alcohol concentration and organic compound content, commercially available formulations with synthetic and semi-synthetic active ingredients have been reported to cause burning sensations, tooth discoloration, and local irritation.^[6] Because of these negative consequences and the need for improved patient compliance, plant-based medicine is becoming more and more commonplace worldwide. Several studies have shown the use of extracts or parts of herbal plants as mouthwash, paste, or mucoadhesive gels to heal oral ulcers.^[6-11] Due to their diverse classes of phytochemicals, several Indian medicinal plants are associated with a range of pharmacological effects. These herbal compounds offer a suitable alternative to traditional synthetic medications, which have a lot of adverse effects.^[12] A significant portion of health care programmes in underdeveloped nations involve herbal medications. Approximately 80% of people on the planet still get their primary medical care from medicinal plants. Given that India is known for its herbal plant

diversity, any particular information on these plants may be significant from a therapeutic standpoint.^[13]

Causes of mouth ulcer:

Mouth ulcers are caused by a variety of factors that vary from person to person. Still, there are some common causes:

- Other foods high in acidity or spice, citrus fruits.
- Burns from hot drinks or food.
- Irritation from chemicals that are present in toothpaste or oral rinses.
- Chewing the insides of the cheeks or biting the tongue.
- Braces, poor-fitting dentures, and other instruments that may rub against the mouth and gum.
- Medications including beta-blockers and pain killers.
- Anxiety or stress.
- Some are the genetic factors.^[14]

Types of Mouth Ulcer:^[15-17]

Minor ulcers: These are usually small, ranging from 2 to 8 mm in diameter and may take up to 10 to 14 days to clear up.

Major ulcers: These are bigger, deeper with raised and irregular borders, often 1 cm or more. Healing time ranges from several weeks to months.

Herpetiform ulcers: These are a cluster of smaller ulcers, as small as the size of a pinhead.

MATERIALS AND METHOD

Plant material:

Materials and Methods:

Sr no	Common name	Scientific name	Family	Chemical constituents	Additional uses	References
1	Guava leaves, Amrood	Psidium guajava	Myrtaceae	Flavonoids (quercetin and its glycosides), tannins	Antimalarial, anthelmintic, antiulcer, antispasmodic, analgesic properties	[18]
2	Betel leaves Paan	Piper betle L.	Piperaceae	Alkaloids, carbohydrate, amino acids, tannins and steroids	Anti-ulcer, Anti-bacterial, Antifungal, Antioxidant, Antiinflammatory activities,	[19,20]
3	Turmeric Haldi	Curcuma longa	Zingiberaceae	Diarylheptanoids, curcumin, dimethoxy curcumin, and bisdemethoxycurcumin	Anti-inflammatory, antiulcer and antiarthritis	[21-23]
4	Liquorice, Mulethi	Glycyrrhiza glabra L.,	Leguminosae	Saponin, flavonoid, liquiritin, isoliquirtin liquiritigenin and rhamno-liquiriln	Anti-inflammatory and expectorant, controls coughing and has hormonal effects, Anti-ulcer	[24,25]
5	Aloe vera	Aloe barbadens	Liliaceae	Amino acids, anthraquinones, enzymes,	Properties that are anti-inflammatory, anti-	[26,27]

		is Miller		minerals, vitamins, lignins, monosaccharides, polysaccharides, salicylic acid, saponins, and sterols are among the many substances found in plants.	oxidant, anticancer, healing, anti-ulcer, and anti-diabetic	
6	Tulsi	Ocimum sanctum.	Lamiaceae	Linoleic acid, Linolenic acid, oleic acid, Palmitic acid. eugenol, cubenol, Linalial, carinene Minerals: Vitamin C, Vitamin A, calcium, Zink, iron.	Anti-cancer, antiulcer, antiarthritic, antibacterial, antifungal, antioxidant, antiinflammatory.	[28,29]
7	Cotton tree	Bombax ceiba	Bombaceae	Bombicbone, Scopoletin, Lupeol, Quercetin, Rutin	Antioxidant, Anti-ulcer, analgesic effects, anti-inflammatory,	[30,31]
8	Dragon fruit	Selenicereus undatus	Cactaceae	29.77% triterpenoids, 16.44% steroids, β -amyirin, α -amyirin, γ -sitosterol, 1-tetracosanol, campesterol,	Anti-inflammatory, Anti-ulcer, Anti-diabetic, Reduces risk of cancer, Immune booster.	[32]
9	Neem	Azadirachta indica	Meliaceae	nimbin, nimbidin, nimbolide, and limonoids, quercetin and sitosterols.	antibacterial, antifungal and anti-inflammatory activity, Anti-ulcer	[33,34]
10	Catechu	Acacia catechu	Fabaceae	Tannin flavonoids	Antiulcer, Anti-bacterial, astringent	[35]
11	Pomegranate	Punica granatum	Punicaceae	flavonoids (anthocyanins and catechins) and hydrolyzable tannins (punicalin, punicalagins, gallic acid and ellagic acid)	antiulcer	[36]
12	Peppermint	Mentha piperita	-	Essential oil like menthol, menthyl acetate	Anti-ulcer, Anti-inflammatory, anesthetic, fungicidal	[37,38]
13	Fennel	Foeniculum vulgare	Apiaceae	9.5% protein, 10% fat, 13.4% minerals, 18.5% fibre and 42.3% carbohydrates	Ani-ulcer, anti-inflammatory	[39]
14	Honey	Honey	-	80-85% carbohydrate, 15-17% water, 0.3% proteins, 0.2% ashes, phenols, amino acid, ascorbic acid	Anti ulcer, Wound healing property, Anti-inflammatory	[40]
15	Noni fruit	Morinda citrifolia linn	Rubiaceae	anthraquinones, flavonoids and phenolics	acne/ boils, gastric ulcers, Anti-ulcer	[41,42]
16	Capsicum	Capsicum annum	Solanaceae	capsaicin, paprika oleoresin, and Dihydrocapsaicin.	Anti-ulcer	[43]
17	Papaya	Carica papaya Linn	bgygy	papain and chymopapain, strong proteolytic enzymes	Anti-ulcer.	[44,45]
18	Myrtle	Myrtus communis	Myrtaceae	monoterpene hydrocarbons, phenols, carvacrol and eugenol.	Anti-inflammatory, Anti-ulcer, Antioxidant, Anti-bacterial	[46]
19	Marshmellow root	Althea Officinalis	Malvaceae	25% mucilage, tannins, pectin, asparagine, essential oil	Anti-ulcer, Anti-inflammatory, Wound healing	[47,48]
20	Coconut	Cocos Nucifera	Arecaceae	Cellulose, Lignine, Pentosans	Anti-ulcer, Anti-fungal, anti-microbial	[49]
21	Green tea	Camelia sinesis	Theaceae	Catechin, flavonols, Caffein, Theanine, Aspartic acid,	Mouth ulcer, Boost brain health.	[50]

				Glutamic acid		
22	Sesame	Sesamum Indicum	Pedaliaceae	High in protein, vitamin B1, Dietary fiber	Anti-ulcer, Antioxidant, Skin wounds	[51]
23	Rosehip	Rosa canina L.	Rosaceae	Linolenic acid, monounsaturated oleic acid	Mouth ulcer	[52]
24	Garlic	Allium sativum	Amaryllidaceae	Allicin, alliin, diallyl sulfide	Anti-ulcer, antiseptic	[53,54]
25	Red clover	Trifolium pratense	Fabaceae	Calcium, vit.c, niacin, thiamine	Mouth ulcer	[55]
26	Black walnut	Juglans nigra	Juglandaceae	Vit.A, iron, minerals, fiber	Anti-ulcer, antibacterial	[56]
27	Ginger	Zingiber officinale Roscoe	Zingiberaceae	Phenolic and terpene compounds	Anti-ulcer	[57]
28	Thyme	Thymus vulgaris	Lamiaceae	Thymol, p-cymene	Mouth ulcer	[58]
29	Tasmanian blue gum	Eucalyptus globulus	Myrtaceae	Flavonoids, volatile aromatic oil known as eucalyptus oil	Anti-ulcer	[59]
30	White willow bark	Salix alba	Salicaceae	salicin	Anti-ulcer, anti-inflammatory	[60]
31	Elderberry	Sambucus	Adoxaceae	Vit.c, phenolic acid, flavonoids	Mouth ulcer, laxative	[61,62]
32	Meadowsweet	Filipendula ulmaria	Rosaceae	Tannins, flavonoids	Mouth ulcer, Analgesic	[63]
33	Catnip	Nepeta cataria	Lamiaceae	Citral, carvacrol, pulegone	Anti-ulcer	[64]
34	Marshmallow	Althaea officinalis	mallow	Sugar, corn syrup, gelatin	Anti-ulcer, antibacterial	[65]
35	Arnica	Arnica montana	Asteraceae	Lactones, volatile oils	Mouth ulcer	[66]
36	Hops	Humulus lupulus	Cannabaceae	Lupulone, humulone	Anti-ulcer	[67]
37	Yarrow	Achillea millefolium	Asteraceae	Fatty acids, phenolic acids	Anti-ulcer, wound healing, antimicrobial	[68]
38	calendula	Calendula officinalis	Asteraceae	Carotenoids, auroxanthin	Mouth ulcer, anti-inflammatory	[69]
40	Lavender oil	Lavandula angustifolia	Lamiaceae	Linalool, linalyl acetate, camphor	Antiolytic, antioxidant, Anti-ulcer	[71]
41	Nettle	Urtica	Urticaceae	Protein, fat, dietary fiber	Mouth ulcer, used as diuretics	[72]
42	Spearmint	Mentha spicata	Lamiaceae	Limonene, carvone and carveol	Anti-ulcer	[73,74]
43	Frankincense	Boswellia sacra	Burseraceae	Pentacyclic triterpenoids, essential oils	Mouth ulcer, Anti-inflammatory, Anti-ulcer	[75]
44	Rose	Rosa Damascene	Rosaceae	phenyl ethylalcohol, citrenellol, nerol, geranial	Anti-bacterial, Anti-ulcer, analgesic, anti-inflammatory, reduces duration of aphthous.	[76]
45	Myrrh	Commiphora myrrha	Burseraceae	2-8% volatile oil, 23-40% resin (myrrhin), 40-60% gum	Analgesic, Anti-ulcer, anti-fungal, anti-inflammatory, Antiseptic	[77]

46	Lemon	Citrus sp	Rutaceae	odium (Na) 755.50±0.058 0.22 C carbohydrate, fibre, lipids and proteins, vitamin C Carbohydrate, Fiber, Lipid, Protein, Vitamin	Anti-inflammatory, Immuno-modulatory, Analgesic, Decrease the release of histamine, Anti-ulcer	[78]
47	Blackberry	Rubus sp.	Rosaceae	Anthocyanins, flavonols and ellagitannins and minerals like Potassium, calcium, sodium, magnesium	Analgesic, Anti- inflammatory, wound healing, Anti-ulcer	[79,80]
48	Jambul	Syzygium cumini	Myrtaceae	anthocyanins, glucoside, ellagic acid, isoquercetin,	Anti-inflammatory, Anti-ulcer	[81,82]
49	Lentil	Lens culinaris	Fabaceae	protein-, complex carbohydrate.	Antioxidant, Anti- inflammatory, Anti- ulcer	[83]
50	Cardamom	Elletaria Cardamo mum	Zingiberaceae	1,8-cineole (20.66 %), camphene, α -terpinyl acetate.	Anti-inflammatory, Analgesic, immune- modulatory, Anti-ulcer	[84]

Preparation of extracts:

The herbs are macerated with ethanol 95% for 3 days and then separated by centrifugation at 300 rpm to obtain the ethanolic extract. And then stored at room temperature.

Phytochemical screening:

All the prepared extracts were subjected to preliminary phytochemical screening tests to identify the presence of various components, by using different tests and reagents. [85,86]

Preparation of polyherbal gel:

Using a mechanical stirrer, enough Carbopol 934 was soaked in distilled water for an entire night before being combined with the water and continuously stirred. [161] Along with the necessary amount of methyl and propyl paraben, another solution was added while being continuously stirred. This solution contained different concentrations of EEA, EEO, and EEZ. Additionally, propylene glycol was added to the mixture. The produced solution was fully combined with the Carbopol 934 solution while being constantly stirred. The volume was increased to 30 millilitres using water, and triethanolamine was added to regulate the pH, resulting in the gel's desired consistency. [87,88]

Evaluation of Gel:

Visual appearance: The prepared gels were tested for color, clarity, texture, transparency and presence of any gritty particles. [89]

Measurement of pH: The pH of gel formulation were determined by using digital pH meter. Take 1 gm of gel and dissolved in 10 ml of distilled water and keep apart for two hours. Then the measurement of pH of

formulation is done by dipping the glass electrode completely into the gel system three times and the average values can be reported. [90]

Homogeneity: All prepared gel formulation were tested for homogeneity by visual inspection after the gels have been set in to the container. They were tested for their presence and appearance of any aggregates. [91]

Viscosity: The measurement of viscosity of the formulated gel were determined by Brookfield Viscometer with spindle no. 1 at 25°C. The gels were rotated at speed 0.3, 0.6 and 1.5 rotations per minute and at each speed, the corresponding dial reading was noted. Then viscosity of the prepared gels were obtained by multiplication of the dial reading with factor given in the Brookfield Viscometer catalogues. [92]

Spreadability: Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel that is placed in between the slides under the direction of certain load. If the time taken for separation of two slides is less then better the spreadability. [93]

Extrudability: The formulated gel were filled in standard capped collapsible aluminium tubes and sealed by crimping to the end. The weight of filled tubes were recorded and the tubes were sandwiched between two glass slides and were clamped. 500gm weight was placed over the slides and then the cap was removed to extrude. The amount of extruded gel was collected and weighed. Extrudability was determined by calculating the percentage of extruded gel. When it is greater than 90% then extrudability is

excellent. When it is greater than 80% then extrudability is good. When it is 70% then extrudability is fair.^[94]

Gel strength: Gel strength was determined by the time in seconds required by the weight to penetrate in the gel. A 3.5 gm weight was placed on the surface of 5 gm formulated gel. Gel strength was determined by reporting the time in seconds required by the weight to penetrate 0.5 cm in the gel.^[95]

Anti-fungal Activity: The Antifungal activity of all optimized formulation and blank formulation were carried out by Cup-plate method in comparison with marketed antifungal formulation (Daktarin oral gel). The antifungal formulation test were performed by using *Candida albicans*. Prepared nutrient brought and poured in to sterile petri plates and kept aside for drying and cooling. After that *Candida albicans* culture were spread by micron wire loop. A sterile cork borer 6 mm diameter was used to drill holes 4 mm deep. Then place 0.5 gm of gel from each formulation to this holes. Plates were then incubated at 27°C for 48 hr. Then the zone of inhibition (diameter in mm) should be measured.^[96,97]

Stability study: Stability studies were performed to observe the effect of environmental condition or storage condition on formulation. The optimized formulation was kept in accelerated stability condition at 25°C temperature 60 ± 5% relative humidity, 30°C temperature 65 ± 5% relative humidity and 40°C temperature 75 ± 5% for a period 3 months as per ICH guidelines. The placed sample was withdrawn at 1 to 3 months interval and evaluation was carried out for physical appearance, pH, viscosity, spreadability, extrudability and gelling strength.^[98]

Advantages:^[99]

Stay away from the first-pass metabolism.

Convenient, acceptable, and simple to implement.

Allowing for the use of medicines with a short biological half-life.

Improving the drug's physiological and pharmacological response.

Increase patient adherence.

It can be used for self-medication.

Avoid the risks and drawbacks of intravenous therapy, as well as the varying conditions of absorption, such as enzyme presence and pH variations.

It is easily able to terminate the medications, when needed.

Disadvantages:^[100]

The medication and/or excipients can cause skin irritation in people with contact dermatitis.

Some medications have a low permeability through the skin or mucous membrane, which might lead to allergic responses.

Only used for drugs that require a very low plasma concentration to function.

Drugs may be denatured by an enzyme in the epidermis.

Drugs with bigger particle sizes are more difficult to absorb via skin.

Uses:^[101]

As medication delivery methods for drugs that are taken orally.

To provide a topical medication to the skin, mucous membranes, or eyes.

Gels for dental care prophylactic like Sodium fluoride and Phosphoric acid gel.

Gels as lubricant for catheters.

CONCLUSION

The entire conversation demonstrated that antediluvian herbal medicine and its products had been utilised for centuries to treat a variety of illnesses. Because natural remedies are thought to be safer and less likely to cause side effects than synthetic pharmaceuticals, they are becoming more and more popular. On the international market, herbal formulations are gaining popularity. This study demonstrates the continued importance of medicinal herbs in the management of oral ulcers. Plant-based flavonoids are most likely the source of the anti-ulcer action. Flavonoids are found in guava leaves, aloe vera, turmeric, liquorice (mulethi), ocium santum leaves, and betal (paan) leaves. Herbal remedies are less harmful, more compatible with the human body, and more socially and culturally acceptable. The best medicine is herbal.

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