Review Article

Herbal Medicated Chewing Gum Used To Treat Mouth Ulcer

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Abstract

Mouth ulcers are a prevalent oral mucosal condition that significantly affects daily activities such as eating, drinking, and speaking. While various pharmaceutical treatments exist, they often have side effects or provide only temporary relief. Herbal formulations present a safer, more effective alternative with minimal adverse effects. This review focuses on the formulation and evaluation of herbal medicated chewing gum (HMCG) incorporating liquorice (Glycyrrhiza glabra) and guava leaves (Psidium guajava) for treating mouth ulcers. The medicinal properties of these herbs, their mechanism of action, different formulation techniques, and essential evaluation parameters are explored in detail to provide insight into their potential as a novel therapeutic option.

Keywords: Herbal chewing gum, mouth ulcer, liquorice, guava leaves, formulation, evaluation

Introduction

As human beings, we are constantly engaged in a battle against diseases, and nature has provided us with a variety of powerful tools to aid in this fight. In ancient times, we relied heavily on natural remedies to combat ailments. However, as time progressed, we developed the ability to synthesize drugs, creating our own arsenal against illnesses. While synthetic drugs have gained popularity over the years, there are still certain areas where natural drugs are favored over their synthetic counterparts. One notable area is the development of antiulcer drugs.

Mouth Ulcer: An ulcer that forms on the mucous membrane of the oral cavity is referred to as a mouth ulcer, also known as an oral ulcer or a mucosal ulcer. These painful, round or oval sores typically appear on the inside of the cheeks vitamin C), poor dental hygiene, infections, stress, indigestion, mechanical injuries, food allergies, hormonal imbalances, and skin conditions. Mouth ulcers, also known as aphthous ulcers, can be painful, especially when eating, drinking, orbrushing teeth. They result from the erosion or loss of the upper mucosal layer and are among the most frequently encountered pathological conditions of the oral cavity. These sores are typically painful and are most commonly found on the inner sides of the lips and cheeks. The exact cause of stomatitis remains unclear, but various factors are believed to contribute to their development. These include different viruses, fungi, Treponema bacteria, autoimmune diseases, malnutrition, hormonal fluctuations, psychological stress, and other potential factors.

Mouth ulcers can be classified into three main types based on their size and quantity: minor, major, and herpetiform ulcers. These are usually small, measuring between 2 to 8 mm in diameter. They are the most common type and typically heal within 10 days to 2 weeks without leaving any scars Major ulcers are larger and deeper, often with a raised or uneven border. Healing can take several weeks, and there is a possibility that they may leave a scar in the mouth. These consist of a cluster of numerous tiny lesions, approximately the size of pinheads. They can be quite painful and may also take longer to heal compared to minor ulcers. Each type of mouth ulcer has its own characteristics and healing times, and understanding these differences can help in managing symptoms and seeking appropriate treatment Ulcerative conditions in the mouth, such as mouth ulcers, are quite common and can often be attributed to trauma. This trauma may come from factors like ill-fitting dentures, broken teeth, or dental fillings. While most mouth ulcers heal on their own, it is crucial to monitor their duration and characteristics.

If a mouth ulcer persists for more than three weeks, it is recommended that the patient undergo a biopsy or other diagnostic tests. This is important to rule out more serious conditions, including cancer or other severe disorders, such as chronic infections. Early detection and diagnosis are key to ensuring proper treatment and management of any underlying issues[1]

- **Viral infections:** Certain viruses can lead to the formation of mouth ulcers.
- **Toothpastes and mouthwashes containing sodium lauryl sulfate:** This ingredient can irritate the mucous membranes in the mouth, leading to ulcers.
- **Mechanical trauma:** Injuries from dental work, biting the cheek, or other physical damage can cause ulcers.
- **Emotional stress / Psychic stress:** Stress can weaken the immune system and trigger ulcer formation.
- **Nutritional deficiencies:** Lack of essential nutrients, particularly vitamins B12, folate, and iron, can lead to ulcers.
- **Allergies and sensitivities:** Reactions to certain foods or substances can result in mouth ulcers.
- **Hormonal changes:** Fluctuations in hormones, such as during menstruation, can be associated with ulcer outbreaks.

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● **Genetics:** A family history of mouth ulcers may increase the likelihood of developing them.

● **Infectious agents:** Both bacterial and viral infections can lead to the formation of ulcers.

● **Medical conditions:** Certain underlying medical conditions, such as autoimmune diseases, can also contribute to the occurrence of mouth ulcers or lips. [2]

Mouth ulcers are quite common and can arise from various conditions and factors, although they often occur without any significant underlying cause. Common triggers include nutritional deficiencies (like iron, vitamin B12, and vitamin C), poor dental hygiene, infections, stress, indigestion, mechanical injuries, food allergies, hormonal imbalances, and skin conditions. Mouth ulcers, also known as aphthous ulcers, can be painful, especially when eating, drinking, or brushing teeth. They result from the erosion or loss of the upper mucosal layer and are among the most frequently encountered pathological conditions of the oral cavity. These sores are typically painful and are most commonly found on the inner sides of the lips and cheeks. The exact cause of stomatitis remains unclear, but various factors are believed to contribute to their development. These include different viruses, fungi, Treponema bacteria, autoimmune diseases, malnutrition, hormonal fluctuations, psychological stress, and other potential factor.

Mouth Ulcer types

Mouth ulcers can be classified into three main types based on their size and quantity: minor, major, and herpetiform ulcers.

● **Minor ulcers:** These are usually small, measuring between 2 to 8 mm in diameter. They are the most common type and typically heal within 10 days to 2 weeks without leaving any scars.

● **Major ulcers:** Major ulcers are larger and deeper, often with a raised or uneven border. Healing can take several weeks, and there is a possibility that they may leave a scar in the mouth.

● **Herpetiform ulcers:** These consist of a cluster of numerous tiny lesions, approximately the size of pinheads. They can be quite painful and may also take longer to heal compared to minor ulcers.

Each type of mouth ulcer has its own characteristics and healing times, and understanding these differences can help in managing symptoms and seeking appropriate treatment.

● Cause of Ulcers: - Ulcerative conditions in the mouth, such as mouth ulcers, are quite common and can often be attributed to trauma. This trauma may come from factors like ill-fitting dentures, broken teeth, or dental fillings. While most mouth ulcers heal on their own, it is crucial to monitor their duration and characteristics. If a mouth ulcer persists for more than three weeks, it is recommended that the patient undergo a biopsy or other diagnostic tests. This is important to rule out more serious conditions, including cancer or other severe disorders, such as chronic infections. Early detection and diagnosis are key to ensuring proper treatment and management of any underlying issues.[2]

Factors contribute to the development of mouth ulcers

● Viral infections: Certain viruses can lead to the formation of mouth ulcers.

● Toothpastes and mouthwashes containing sodium lauryl sulfate: This ingredient can irritate the mucous membranes in the mouth, leading to ulcers.

● Mechanical trauma: Injuries from dental work, biting the cheek, or other physical damage can cause ulcers.

● Emotional stress / Psychic stress: Stress can weaken the immune system and trigger ulcer formation.

● Nutritional deficiencies: Lack of essential nutrients, particularly vitamins B12, folate, and iron, can lead to ulcers.

● Allergies and sensitivities: Reactions to certain foods or substances can result in mouth ulcers.

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● Genetics: A family history of mouth ulcers may increase the likelihood of developing them.

● Infectious agents: Both bacterial and viral infections can lead to the formation of ulcers.

● Medical conditions: Certain underlying medical conditions, such as autoimmune diseases, can also contribute to the occurrence of mouth ulcers.[3]

Herbal Remedies

Herbal remedies have been traditionally used by herbalists and indigenous healers for the prevention and treatment of mouth ulcers. Here's an overview of some commonly used medicinal herbs and their active ingredients that exhibit anti-ulcer properties:

● Flavonoids: These compounds have been recognized for their anti-inflammatory and antioxidant effects. Some examples include:

● Quercetin

● Naringin

● Silymarin

● Anthocyanosides

● Soforadin derivatives

● Saponins: Found in plants like Panax japonicus and Kochia scoparia, these compounds can help reduce inflammation and promote healing.

● Tannins: Present in Linderae umbellatae, tannins have astringent properties that can help in healing ulcers.

● Gums and Mucus: Substances like guar gum and myrrh are known for their soothing properties and can provide relief from ulcers.

● Some specific medicinal herbs that are commonly used include:

● Licorice: Known for its anti-inflammatory and soothing properties, licorice can help alleviate ulcer pain and promote healing.

● Aloe gel: This natural remedy is well-known for its soothing and healing properties, making it effective for treating mouth ulcers.

● Capsicum (chili): While it may seem counterintuitive due to its spiciness, certain compounds in capsicum can help with pain relief and have anti-inflammatory effects.Various ethnomedical systems utilize different plant extracts for treating ulcers, showcasing the

diversity and effectiveness of herbal medicine in managing this condition. [3-4]

Benefits of herbal medicines

Medicinal herbs offer numerous benefits, making them a valuable resource in healthcare. some key advantages are:

● **Long History of Use:** Herbal medicines have been utilized for centuries, which contributes to their established safety and efficacy. This history fosters better patient tolerance and public acceptance compared to some synthetic medications.

● **Renewable Resource:** Medicinal plants are a sustainable source of healing compounds. This renewability allows for cheaper production of medicines, which is essential for meeting the needs of the growing world population.

● **Biodiversity:** Developing countries, like India, possess rich agroclimatic, cultural, and ethnic biodiversity. This diversity ensures a wide availability of various medicinal plants, enhancing the potential for discovering new therapeutic agents.

● **Organic Cultivation and Processing:** The cultivation and processing of medicinal herbs can often be done organically, minimizing the use of synthetic fertilizers and pesticides. This organic approach not only benefits the environment but also enhances the quality of the medicinal products[6]

Disadvantages of herbal medicines

Herbal medicines indeed have several disadvantages that should be considered:

● **Delayed Effects:** While herbal medicines can be beneficial, they often take longer to show effects compared to conventional drugs. This means that individuals who choose herbal remedies must be patient and may not experience immediate relief.

● **Self-Administration Risks:** Many herbal medicines are self-administered without professional guidance. As a result, there are often no standardized dosages or warnings provided. This can lead to misuse or overuse, especially if taken alongside prescription medications, potentially causing harmful interactions.

● **Risk of Toxicity:** Some plants used in herbal medicine can be toxic rather than healing. Certain parts of a plant may be safe to consume while others are poisonous. For example, rhubarb roots are used as a laxative, the stalks are edible, but the leaves are toxic. This presents a risk for those who may not be able to identify which parts of a plant are safe.

● **Identification Challenges:** Many individuals may lack the knowledge to accurately identify medicinal versus poisonous plants. This lack of awareness can lead to accidental poisoning, posing serious health risks.

● **Treatment:** Mouth ulcers are indeed capable of healing on their own within about two weeks, but medical treatments can offer significant relief. The primary functions of these treatments include numbing the pain, providing a protective barrier over the ulcer to prevent further irritation, and reducing the risk of bacterial infections. Additionally, certain medications can promote faster healing if applied early in the ulcer's development.

There are various forms of treatment available, such as paste treatments, gel treatments, mouthwashes, and liquid paint applications. These options help to neutralize the discomfort and create a more conducive environment for healing. By addressing both pain and protection, these treatments can greatly improve the overall experience for individuals suffering from mouth ulcers.[7]

Medicated Chewing Gum[8-10]

Medicated chewing gums are indeed an innovative pharmaceutical dosage form that combines active pharmaceutical ingredients (APIs) with a gum base. These gums are designed to be chewed in the mouth for a specific duration, allowing the active ingredients to be released into the saliva. When chewed, the drug can either be absorbed through the oral mucosa directly into the bloodstream or travel to the stomach for gastrointestinal absorption. This dual pathway means that medicated chewing gums provide both local effects (in the mouth) and systemic effects (through the bloodstream).

Fig 1: Chewing gum.

History of chewing gum

History Chewing gums have indeed been utilized for cleaning and freshening purposes for centuries. The Mayan Indians, around 1000 years ago, chewed sapodilla tree resin to clean their teeth and freshen their breath. The history of chewing gum development is less extensive compared to other dosage forms. The first commercially available chewing gum called "STATE OF MAINE PURE SPRUCE GUM" was launched in 1948 in the U.S.A. However, the first patent for chewing gum was filed in 1869 by Dr. William F. Semple, a dentist from Mount Vernon, Ohio. His patent (U.S. patent no. 98,304) involved a chewing gum made from Licorice and rubber dissolved in alcohol and naphtha, which he promoted as a dentifrice, viewing it as both a confectionery and a dental product.In 1924, the first medicated chewing gum, known as 'Aspergum', was introduced by Frank M. Dillard and William C. Nalle. They established the Dillard-Nalle company in December 1927 and sought trademark protection for Aspergum, which they began selling in 1928. This gum contained acetylsalicylic acid, an analgesic, as its active pharmaceutical ingredient .Chewing gum wasn't recognized as a drug delivery system until 1978, which came after the introduction of nicotine-containing chewing gum. Additionally, in 1892, William Wrigley Jr. marketed his chewing gum product as 'LOTTA AND VASSAR'.[11]

Merits of MCG

● No need for water to swallow, so it can be taken anywhere.

● Provides accurate dosing of medication.

● Counteracts dry mouth, prevents candidiasis and caries.

● Highly acceptable by children due to its taste and appearance.

● Less first-pass metabolism leads to improved bioavailability of the active ingredients.

● The gum does not reach the stomach, minimizing the gastrointestinal effects of excipients.

● Reduces the risk of intolerance of the gastric mucosa by avoiding direct contact with high concentrations of active ingredients.

● Continuous delivery of the product to the stomach through saliva increases the duration of action.

● Treatment can be easily terminated at any time.

● Medications like Aspirin, Dimenhydrinate, and Caffeine show faster absorption through medicated chewing gum than traditional tablets.

● Stimulates saliva flow in the mouth, aiding in digestion and oral health.

● Neutralizes plaque acids that form in the mouth after consuming fermentable carbohydrates.

● Helps whiten teeth by reducing and preventing stains.

Demerits of MCG

Disadvantages of medicated chewing gum include:

● Prolonged chewing can cause pain in facial muscles and earache, especially in children.

● There is a risk of overdose compared to chewable tablets or lozenges, as it may be easier to consume more than intended.

● Sorbitol, which is often present in medicated chewing gum, can cause flatulence and diarrhea.

● Chewing gum may adhere to various degrees to dental enamel, dentures, and fillings, potentially causing issues.

● Additives like flavoring agents and cinnamon can lead to ulcers in the oral cavity, while Licorice can cause hypertension.

● Chlorhexidine, used for oromucosal application, has an unpleasant taste and staining properties on teeth and tongue, limiting its use to short-term applications.[12-14]

Active Pharmaceutical ingredient:-

Liquorice

Liquorice Known as *Glycyrrhiza glabra*, belongs to the Leguminosae family and is recognized for its expectorant and demulcent properties. It is particularly beneficial in alleviating pain and inflammation associated with stomatitis and mouth ulcers. When applied to these ulcers, licorice root extract can help reduce the size of the ulcers and promote faster healing.The licorice plant is a robust herb or undershrub that can grow up to 2 meters tall, featuring long, thick, multi-branched roots. The parts of the plant used for medicinal purposes are its roots and rhizomes. Notably, licorice contains a watersoluble, physiologically active complex that constitutes about 40-50 percent of its total dry weight. This complex includes various components such as triterpene saponins, flavonoids, polysaccharides, pectin, simple sugars, amino acids, mineral salts, and other substances.The sweet flavor of licorice root is mainly due to glycyrrhizin, a triterpenoid compound. Glycyrrhizic acid, which is a natural saponin, has a structure that includes a hydrophilic component, two molecules of glucuronic acid, and a hydrophobic fragment known as glycyrrhizic acid. The yellow color of licorice is attributed to its flavonoids, which include liquiritin, isoliquiritin (a chalcone), and other compounds. Additionally, glabridin and hispaglabridins A and B are isoflavones found in licorice that exhibit strong antioxidant properties, with both glabridin and glabrene showing estrogen-like activity. Clinically, Glycyrrhiza has demonstrated several pharmacological activities, including anti-ulcer, anti-asthmatic, anti-diuretic, and anti-hepatotoxic effects. This makes licorice a valuable herbal remedy for various health condtions.[15-17]

Guava

Guava known as *(Psidium guajava)* as a chewing gum for swollen gums and ulceration of the mouth and also for bleeding gums.Guava leaves have anti-inflammatory 3action and antibacterial ability that fights infections and kills germs and people consuming guava leaves at home will help curb toothaches. The juice from the guava leaves is also said to provide relief from oral ulcers

Guava leaves contain vitamins A, C and antioxidants that can protect skin layers [18]. And flavonoids in guava leaves can be used as antibacterial and antimicrobial. The activity of flavonoids can reduce the number of bacteria and reduce infection so that it can reduce the production of exudate. Help Reduce Menstruation Pain Guava leaves may relieve menstrual pain and discomfort, especially for women. Their soothing properties can ease cramps and make periods more manageable. Good for hair and skin: Guava leaves have antibacterial and antioxidant properties that can help to treat skin conditions like acne.[19]

COMPOSITION OF INGREDIENTS

- Liquorice Extract (Glycyrrhiza glabra): Provides glycyrrhizin, which has anti-inflammatory, antimicrobial, and wound-healing properties, making it suitable for treating mouth ulcers.
- Guava Leaf Extract (Psidium guajava): Contains quercetin, a flavonoid that offers antioxidant, anti-inflammatory, and antimicrobial benefits, aiding in the healing process of mouth ulcers.
- Gum Base: The main structural component of the gum, typically composed of a mixture of gum arabic or polyethylene glycol, providing the chewable texture.
- Glycerin and Sorbitol: Both serve as plasticizers and humectants, ensuring the gum remains flexible and does not dry out during storage. They also improve the mouthfeel of the gum.
- Sweeteners: Xylitol, sorbitol, or stevia are used to sweeten the gum, counteracting the bitterness of the herbal extracts, while also contributing to oral health (especially xylitol, which has dental benefits).
- Mint/Clove Oil: These flavoring agents not only make the gum more palatable but also provide additional oral health benefits such as antimicrobial properties.
- Natural Binder: Binders like cellulose derivatives or natural resins are used to ensure the herbal and structural components of the gum stay uniformly mixed.
- Preservatives:- Preservatives like Sodium benzoate and ,HPMC, Titanium dioxide protect the formulation from microbial growth.

Formulation of herbal medicated chewing gum

Ingredients	Function
Active Ingredients	
Guava Leaf Extract	Antimicrobial, wound healing
Liquorice Extract	Anti-inflammatory, soothing
Gum Base	Provides chewability
Sweeteners	
Xylitol	Sweetener, anti-caries
Sorbitol	Sweetener, bulking agent
Mannitol	Sweetener, cooling effect
Plasticizers	
Glycerin	Improves texture
Propylene Glycol	Improves flexibility
Flavors & Cooling Agents	
Menthol	Cooling sensation
Peppermint Oil	Flavoring
Preservatives & Excipients	
Sodium Benzoate	Preservative
Acacia Gum / HPMC	Coating Agent
Titanium Dioxide	Coloring Agent

Method of Preparation

Preparation of Herbal Extracts:

- Liquorice and guava leaf extracts are obtained using solvent extraction methods, followed by filtration and concentration.

Preparation of Gum Base:

- The gum base was melted by heating it to 60-70°C in a heat-resistant container.
- To the melted gum base, glycerin (5-10%) and sorbitol (5%) were added as plasticizers. The mixture was stirred until a homogeneous mass was obtained.

Incorporation of Herbal Extracts:

- The concentrated liquorice extract (glycyrrhizin) and guava leaf extract (quercetin) were gradually added to the melted gum base under constant stirring to ensure uniform distribution.
- The final concentration of liquorice extract in the chewing gum was 5-10%, and the guava leaf extract was 2-5% of the total formulation.

Addition of Sweeteners and Flavoring:

- Sweeteners such as xylitol, sorbitol, or stevia were added (10-15%) to balance the bitterness of the herbal extracts.
- Flavoring agents, such as mint oil or clove oil, were added to enhance taste and provide additional oral health benefits. A concentration of 1-2% was used.

Molding and Cooling:

- The mixture was allowed to cool to approximately 40°C-50°C before being poured into molds to form small chewing gum pellets.
- The molded chewing gums were allowed to cool and solidify completely.

Packaging and storage:-

- The cooled gum was packaged in an airtight container to preserve its freshness and prevent degradation.[20-31]

Evaluation Parameters for Herbal Medicated Chewing Gum

1. Appearance and Color:-To ensure the uniformity in color and appearance of the chewing gum, which is essential for product consistency.

2.Texture :-Objective: To evaluate the texture, chewiness, and overall consistency of the gum.

3. Moisture Content:- To assess the moisture content of the gum, as this affects its shelf life and stability.

4. Thickness and Uniformity of the Gum:- To ensure uniform thickness of the gum to achieve consistent drug release and ensure ease of use.

5. Elasticity-Chewing gum's elasticity is one of its most important parameter. Elasticity is important for better patient compliance as well as proper release of the active ingredient from the product. The elasticity of herbal chewing was checked manually by stretching between two fingers.

6. Stickiness-The formulated herbal chewing was placed on plane surface and a mass of 250 gm was hammered on it for 10 mins. After 10 mins, the sticking of mass to hammered surface was observed.

7. Softening point-Softening point of gum base was observed by heating the base in petri dish. The base's softening point is the temperature at which it begins to melt. The standard softening point of herbal chewing gum is 55-60^{0}C.[32-41]

8.pH of the Gum:- The gum's pH should be neutral to slightly acidic (pH 5-7) for oral safety.

9.Stability studies:- The stability studies were performed after 1 month and the formulation was evaluated for colour, softening point and texture.

10.% drug content test:- One gram of formulation was taken in mortar, to this about 20ml of 6.8 phosphate buffer was added and triturate. This was transferred to conical flask. About 30ml of 6.8 phosphate buffer was added to this and shaken well for about 3 hours using orbital shaking incubator at 100rpm. Then was filtered and the filtrate was made up to make with the same buffer solution. Suitable dilutions were made, and the drug concentration was determined by measuring the absorbance at 266nm and 276nm.[42-45]

11.In Vitro Drug Release Study :-The in vitro release study is performed to evaluate the release profile of the active herbal ingredients from the chewing gum. The release is studied in simulated saliva (pH 6.8 buffer) under controlled conditions. The

dissolution profile helps in determining the efficacy and duration of drug action in the oral cavity.[46,47]

Conclusion

Herbal medicated chewing gum formulated with liquorice and guava leaves represents a novel, effective, and convenient treatment for mouth ulcers. The unique properties of the herbal extracts provide antimicrobial, anti-inflammatory, and wound-healing effects, while the chewing gum delivery system ensures prolonged contact with the affected oral mucosa, enhancing therapeutic efficacy. The formulation also offers advantages such as ease of administration, sustained drug release, and improved patient compliance.

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