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Review Article

A Review of novel combination therapy for mouth ulcer therapy

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Abstract

Mouth ulcers are a common and debilitating condition affecting millions worldwide. Conventional treatments often provide symptomatic relief but may have limitations and side effects. This review explores the potential of a combination therapy using Jasminum grandiflorum (jasmine) and *Ocimum tenuiflorum* (Tulsi) for mouth ulcer recovery. Both plants have been used in traditional medicine for their anti-inflammatory, antimicrobial, and wound-healing properties. The review discusses the therapeutic properties of each plant, their potential synergistic effects, and the various formulation options available for topical application. Future research directions, including clinical trials and chemical profiling, are also outlined. This natural combination therapy offers a promising alternative to conventional treatments, with potential benefits including enhanced wound healing, reduced inflammation, and improved patient satisfaction.

Keywords: Mouth ulcer, *Jasminum grandiflorum, Ocimum tenuiflorum,* Anti-inflammatory, Antimicrobial.

Introduction:

Mouth ulcers are also known as canker ulcers (Aphthous Ulcer) that occur in the mucosal of the mouth cavity. There are many types of ulcers like mouth ulcer, esophageal ulcer, genital ulcer. They can occur inside the cheeks, gums and lips or tongue. Ulcers appear as round or oval shaped surrounded by inflamed mucosa. [1,2] The etiology of mouth ulcer is not clearly known but there are several factors that are responsible for development of Aphthous ulcer including nutritional deficiencies (vitamin B12,folate),stress, trauma, coeliac disease, genetic, drugs and microbial factor .They cause severe pain during eating , brushing teeth and may cause irritation.[3,4]The treatment for aphthous ulcer is primarily focused on sympatomatic relief with three main objectives 1.pain management 2.enhance ulcer healing 3. Reduce the frequency of recurrences. Topical corticosteroids are the most frequently used anti-inflammatory medications for treating oral cavity inflammations, and their topical application is considered the primary treatment for mouth ulcers. This approach provides effective relief while minimizing systemic side effect. [5,6]

For treatment of mouth ulcers mucosal drug delivery systems are preferred due to the oral mucosa location of ulcers. Various formulation for the treatment of mouth ulcers are topical gels, mouth washes, oral liquids, cream, ointments, patches, lozenges and tablets.[7] Globally around 80% of individuals use herbal formulation for their healthcare needs. Medicinal plant plays important role in the treatment of various diseases as they show less or no side effects, as a result incorporation of herbal drugs into the formulation is vital for improving patient acceptance.[8,1]

Jasminum grandiflorum is a medicinal plant belonging to family Oleaceae. The leaves of this plant have therapeutic application in ayurveda for managing wounds. This plant is well known for its aromatic flowers, but its leaves and stems are equally valued for their therapeutic potential. One jasmine species is indigenous to various Asian regions, including China, Afghanistan, Persia, India, the Philippines, Myanmar, and Sri Lanka. [9,10]

In some rural communities they apply paste made from the leaves and flowers of variety of plants including jasmine.[11] Extracts from *Jasminum grandiflorum* are rich in bioactive compounds such as flavonoids, alkaloids, tannins, and saponins, carbohydrates which contribute to its anti-inflammatory, antimicrobial, Antiulcer, Antioxidant and analgesic properties.[9]

Ocimum tenuiflorum also known as tulsi is a medicinal plant with neumerous health benefits belonging to family Lamiaceae. There are two cultivated variants of O.

tenuiflorum: the green-leaved "Sri" or "Lakshmi Tulsi" and the purple-leaved "Krishna Tulsi".[12] In ayurveda, Tulsi is esteemed as “queens of herbs” due to its extraordinary medicinal properties. They are packed with phytochemicals including flavonoid’s, phenols, esters, sesquiterpenes, Triterpenoids, steroids and other secondary metabolites which exhibits potent antimicrobial, antidiabetic, antifertility, anti-inflammatory, and anticancer activity.[13]

This review aims to explore the potential of a novel combination therapy using *Jasminum grandiflorum* and *Ocimum tenuiflorum* for mouth ulcer recovery. The therapeutic potential of Jasmine and Tulsi suggests that a combination of these two plants could provide an effective solution for managing mouth ulcers. The anti-inflammatory and antimicrobial properties of jasmine, coupled with the wound-healing and antibacterial effects of guava, offer a synergistic approach that addresses both the symptoms and underlying causes of mouth ulcers.

Types of mouth ulcers [14]

1.Minor Ulcers:

-Small, 2-8 mm in diameter

- Heal within 10-14 days

2. Major Ulcers:

- Larger, deeper with raised and irregular borders
- 1 cm or more in diameter
- Healing time: several weeks to months

3. Herpetiform Ulcers:

- Cluster of smaller ulcers
- Ulcers as small as a pinhead

Causes of Mouth Ulcer [15]

The main cause of the mouth ulcer is unknown but there are certain factors that causes mouth ulcer.

Predisposing Factors

Xerostomia (dry mouth) and epithelial atrophy (thinning of mucous membrane) make the mouth causes of mouth ulcers more susceptible to trauma and ulceration.

Trauma and Breach

Trauma from teeth, food, or other factors causes a breach in the mucous membrane, leading to ulceration.

Inflammation and Infection

The ulcer becomes inflamed, and bacteria in the mouth can cause secondary infection, leading to further complications

Tissue Damage

The ulcer can penetrate deeper into the tissue, causing damage to the underlying lamina propria and leading to the formation of a crater-like lesion.

Chronic Trauma and Scarring

Chronic trauma can lead to the formation of a keratotic margin (white, thickened mucosa) around the ulcer, and scarring can occur if the ulcer is deep or persistent.

Systemic Factors

Systemic factors such as immunodeficiency, autoimmunity, nutritional deficiencies, and certain diseases (e.g., Crohn's disease, HIV) can contribute to the development and persistence of mouth ulcers.

Therapeutic Properties of *Jasminum grandiflorum*

Anti-inflammatory activity

The anti-inflammatory property of J. grandiflorum is attributed to its high phenolic content, particularly secoiridoids like ligstroside and oleuropein. These compounds have been shown to reduce inflammation by inhibiting pro-inflammatory enzymes and cytokines. They also possess immunomodulatory effects, modulating the immune response to prevent excessive inflammation. The anti-inflammatory activity of J. grandiflorum makes it a potential natural remedy for inflammatory diseases, offering a safer alternative to conventional anti-inflammatory drugs. Further studies are warranted to explore its therapeutic potential.[16]

Anti-ulcer activity

The 70% ethanolic extract of *Jasminum grandiflorum* leaves demonstrated significant antiulcer activity in rat models. The extract reduced gastric ulcers induced by aspirin and pylous ligation, protected against alcohol-induced acute gastric ulcers, and accelerated healing of acetic acid-induced chronic ulcers. The antiulcer effect was attributed to the extract's antisecretory activity, reducing gastric acid secretion, and antioxidant potential, mitigating oxidative stress.[17]

Antimicrobial activity

Jasminum grandiflorum has demonstrated significant antimicrobial activity against a wide range of microorganisms, including bacteria, yeast, and fungi. The plant's extracts, essential oils, and leaves have shown inhibitory effects against various pathogens, including Gram-positive and Gram-negative bacteria, as well as yeast and fungi. The antimicrobial activity of Jasminum grandiflorum has been attributed to its bioactive compounds, which have been shown to inhibit the growth of microorganisms and prevent biofilm formation, suggesting its potential as a natural antimicrobial agent for the development of new drugs and therapies.[18]

Antioxidant activity

Jasminum grandiflorum has demonstrated significant antioxidant activity. The polar extracts of its leaves have shown potent free radical scavenging potential, with a 50% inhibitory concentration of 15 µg/ml comparable to ascorbic acid. The extract also exhibited reductive ability, nitric oxide radical scavenging, and inhibition of iron-induced lipid peroxidation. Additionally, the leaf methanol extracts trapped ABTS, superoxide, and

hydroxyl radicals, and affected nitric oxide release without impacting cell viability. The essential oil of Jasminum grandiflorum also showed DPPH radical scavenging ability, highlighting the plant's potential as a natural antioxidant.[9]

Chemical constituents of *Jasminum grandiflorum*

Jasminum grandiflorum is composed of various chemical compounds, including (Z)-β-Ocimene (1.1%), m-Methylphenol (0.3%), (E)-Hexenyl propionate (0.2%), Linalool (9.6%), Benzyl acetate (37.0%), 2-Undecanone (0.5%), Eugenol (2.1%), (Z)-Jasmone (5.0%), (E,E)-α-Farnesene (0.9%), Caryophyllenyl alcohol (1.9%), (Z)-Methyl jasmonate (0.3%), Benzyl benzoate (34.7%), (Z,Z)-Farnesyl acetone (0.6%), Methyl hexadecanoate (0.8%), and Isophytol (3.3%). Additionally, Jasminum grandiflorum absolute sample from India contains Benzyl acetate (23.7%), Benzyl benzoate (20.7%), Linalool (8.2%), Phytol (10.9%), and Isophytol (5.5%), as well as Eugenol (2.5%), cis-Jasmone (1.9%), Indole (1.8%), Methyl anthranilate (1.0%), and Geraniol (1.0%). Other compounds present in smaller percentages include cis-3-Hexenol (0.01%), 6-Methyl heptan-2-one (0.01%), and α-(E, E)-Farnesene (1.1%).[19,20]

Therapeutic Properties of *Ocimum tenuiflorum*

Ociumum tenuiflorum also known as tulsi which is also known as elixier of life providing various pharmacological activities such as antimicrobial, anticancer, antioxidant, antidiabetic and insecticidal activity.

Antimicrobial activity

Tulsi exhibits significant antimicrobial activity against various pathogenic bacteria, making it a natural substitute for synthetic drugs. Its leaf extracts and oil contain compounds like eugenol, terpenoids, and urosolic acid, which demonstrate potent antibacterial properties. Studies show that Tulsi extracts effectively inhibit the growth of E. coli, Staphylococcus aureus, and other bacteria. Consuming Tulsi in tea, leaf extract, or powder form may boost immunity, support gut health, and offer protection against harmful microorganisms, promoting a healthy lifestyle.[21]

Anti-cancer activity

Ocimum tenuiflorum L, commonly known as Holy Basil or Tulsi, is a medicinally significant plant in traditional Southeast Asian medicine, validated for its anti-inflammatory, analgesic, antipyretic, antidiabetic, hepatoprotective, hypolipidemic, antistress, and immunomodulatory properties. Preclinical research has demonstrated Tulsi's chemo preventive effects against various cancers, including skin, liver, oral, and lung cancers, by enhancing antioxidant activity, modulating gene expression, inducing apoptosis, and inhibiting angiogenesis and metastasis. Additionally, the essential oil of Tulsi (OTEO) has shown potent anticancer activity against gastric cancer cells (AGS), exerting cytotoxicity, suppressing cancer cell migration and invasion, and inducing apoptosis through both intrinsic and extrinsic pathways, with caryophyllene and α-pinene identified as its major chemical constituents, suggesting Tulsi and its essential oil as potential natural remedies for cancer treatment.[22]

Antioxidant activity

Ocimum tenuiflorum leaf extract exhibits moderate to significant antioxidant and free radical scavenging activities, surpassing that of the stem extract. Although the extracts' activities are lower compared to standard antioxidants like BHT and ascorbic acid, the findings suggest that Ocimum tenuiflorum can be a valuable source of natural antioxidants for pharmacological applications, warranting further investigation and development.[23,24]

Antidiabetic activity

The extracts of Ocimum species, including green tulsi, jungli tulsi, and black tulsi, demonstrated significant antidiabetic activity by inhibiting α-amylase activity. The acetone extracts showed the highest inhibition (61-69%), followed by methanol (59-60%) and ethanol (51-59%) extracts. The water extracts showed the lowest inhibition (20-27%). These results suggest that tulsi extracts have hypoglycemic potential, which may be attributed to the presence of flavonoids and phenolics. This finding is consistent with previous reports on the inhibition of α-amylase activity by medicinal plant extracts, highlighting the potential of Ocimum species as a natural remedy for managing diabetes.[25]

Chemical Constituents of *Ocimum tenuiflorum*

Ocimum tenuiflorum, also known as Holy Basil, contains a diverse range of chemical constituents. The volatile compounds present in Ocimum tenuiflorum include Eugenol (43.6%), β-Caryophyllene (10.8%), and β-Elemene (8.1%). Additionally, the species contains phenolic compounds such as Rosmarinic acid (22.3%). Terpenoids like Oleanolic acid (33.60%) and Ursolic acid (8.50%) are also present. Furthermore, flavonoids including Luteolin, Apigenin, Quercetin, and Epicatechin are found in Ocimum species. Methyl eugenol is present in a significant amount (12%) in some Ocimum species, while other compounds like δ-3-Carene, α-Terpinene, p-Cymene, β-(E)-Ocimene, and β-(Z)-Ocimene are also identified. The main constituents of Ocimum tenuiflorum are Methyl eugenol (82.9%), β-Caryophyllene (4.1%), Borneol (2.4%), Germacrene D (2.3%), and α-Copaene (1.9%). Phenyl derivatives (83.8%) are the prominent group of compounds, followed by sesquiterpene hydrocarbons (11.1%), oxygenated monoterpenes (3.1%), monoterpene hydrocarbons (0.6%), and oxygenated sesquiterpenes (0.3%).[26,27,28]

Synergistic Potential of *Jasminum grandiflorum* and *Ocimum tenuiflorum*

The combination of Tulsi and Chameli may exhibit synergistic potential in treating mouth ulcers. Tulsi has demonstrated antibacterial and anti-inflammatory properties, making it a potential treatment for mastitis. The plant's essential oil and extracts have shown inhibitory effects against various pathogens, including S. aureus, E. coli, and Klebsiella pneumoniae. Additionally, Tulsi's anti-inflammatory properties have been

attributed to its ability to reduce the expression of nuclear factor-B (NF-dB).[29]

On the other hand, Jasminum species exhibit various pharmacological properties, including antioxidant, antiaging, antiulcer, antimicrobial, anti-inflammatory, and wound healing activities, making them a potential natural remedy for the recovery of mouth ulcers. With their ability to accelerate wound healing, reduce inflammation, and combat bacterial infections, Jasminum extracts may provide relief from the discomfort and pain associated with mouth ulcers. Specifically, Jasminum grandiflorum L. has shown promise due to its antisecretory and antioxidant properties, which may help soothe and protect the mucous membranes, promoting faster healing and recovery. Furthermore, their antimicrobial properties may help prevent infection and promote a healthy oral environment. The synergistic potential of Tulsi and Chameli warrants further investigation, and their combination may offer a promising natural remedy for mouth ulcer treatment.[30,31]

Potential formulation

While developing the formulation for treatment of mouth ulcer from Jasminum grandiflorum and *ociumum tenuiflorum* several formulation options can be considered to enhance e the therapeutic effect and improve patient compliance.

Topical gels

Topical gels are an attractive drug delivery system, but traditional synthetic and semi-synthetic polymers used in their preparation can be expensive and less biocompatible. Plant-based products offer a promising alternative, being locally accessible, environmentally friendly, affordable, and non-toxic. Olibanum gum, derived from Boswellia serrata, is a natural polymer that can be used in gel preparation, offering anti-inflammatory properties and sustained release capabilities, making it an attractive option for topical gel formulations. gel exhibits optimal characteristics, including suitable viscosity, ensuring ease of application and retention at the site of action. Moreover, its potent antimicrobial activity effectively combats microbial infections, thereby facilitating the healing process. As a natural, cost-effective, and side-effect-free remedy, this herbal gel formulation caters to the growing demand for alternative therapeutic options, offering a reliable and efficient solution for mouth ulcer management.[32,33]

Lozenges

Lozenges are solid, sweet, and sugary oral preparations that dissolve in the mouth or throat, providing a localized or systemic effect. Designed to release medication slowly, often lasting up to 30 minutes, they effectively treat conditions like oral thrush, sore throat, cough, gingivitis, and pharyngitis. Containing various medications, including analgesics, antihistamines, antimicrobials, and decongestants, lozenges cater to diverse therapeutic needs, offering a convenient treatment option for patients who have difficulty swallowing solid oral forms. Available over-the-counter (OTC) or by prescription, lozenges also facilitate systemic drug absorption, making them valuable for conditions like smoking cessation and pain relief, and an essential part of pharmaceutical care.[34,35]

Medicated chewing gums

Medicated chewing gum (MCG) is a recognized drug delivery system that releases medication into the saliva, which is then absorbed through the oral mucosa or ingested for gastrointestinal absorption. MCGs have been utilized to administer various medications, including anti-allergic, nicotine, anti-emetics, aspirin, caffeine, and nystatin, to treat conditions such as oral fungal infections, motion sickness, and to aid in cigarette cessation. Additionally, chewing gum has been shown to increase alertness, attention, and relaxation, making it a popular choice for nicotine replacement therapy and other medicinal uses, with Aspergum being the first medicated gum, paving the way for the development of various MCGs.[36,37]

Gummies

currently, there's a growing demand for herbal formulations due to their cost-effectiveness and lack of adverse effects. Experimental data shows that a gel formulation with herbal constituents like aloe, neem, and tulsi exhibits good characteristics, density, and antimicrobial properties, making it suitable for treating mouth ulcers. In contrast, commercial confectionery products like gummy jelly, made from sugar, fruit or herb juice, and gel substances, pose health concerns due to their high sugar content, artificial flavoring, and coloring agents, which contribute to an increased risk of type 2 diabetes and other health issues, highlighting the need for moderation and mindful consumption, and underscoring the appeal of herbal alternatives like the gummy formulation.[38,39]

Preparation technique

The preparation of herbal formulations for mouth ulcers requires careful attention to the extraction and preservation of bioactive compounds to ensure the stability and effectiveness of the final product. The choice of extraction methods plays a crucial role in maintaining the therapeutic potential of *Jasminum grandiflorum* and *Ocimum tenuiflorum*

Optimal Extraction Methods:

The bioactive compounds in both jasmine and tulsi are typically extracted using solvents like ethanol, methanol, Acetone or distilled water. These compounds include flavonoids, tannins, alkaloids, and terpenes, which are responsible for the plants' anti-oxidant, antimicrobial, and wound healing activity. To ensure maximum potency, gentle extraction methods such as cold maceration, Soxhlet extraction or ultrasound-assisted extraction may be used to prevent the degradation of sensitive compounds. The choice of solvent and extraction temperature must be optimized to preserve the integrity of the bioactive compounds, ensuring that they remain effective in the final formulation. [40,41]

Preservation of Bioactive Compounds:

The preservation of herbal extracts is crucial to maintain their quality, safety, and efficacy. Proper storage conditions, such as cool, dry, and dark places, can help prevent degradation and contamination. The use of airtight containers, desiccants, and nitrogen flushing can also minimize exposure to oxygen, moisture, and light. Additionally, the addition of natural preservatives, such as vitamin E or rosemary extract, can help prevent oxidation and spoilage. Regular monitoring of the extract's physical, chemical, and microbiological properties is also essential to ensure its stability and potency throughout its shelf life.[42]

The development of effective formulations for mouth ulcer treatments using jasmine and tulsi involves selecting the appropriate delivery method—whether a topical gel, lozenges, medicated chewing gums or gummies—each offering distinct advantages in terms of application, comfort, and sustained release. Coupled with optimal extraction and preservation techniques, these formulations can ensure that the therapeutic benefits of jasmine and tulsi are maintained, providing fast-acting and long-lasting relief for mouth ulcer sufferers.

Clinical validation and optimization

Future research should prioritize clinical trials to validate the effectiveness and safety of the combination therapy using *Jasminum grandiflorum* (jasmine) and *Ocimum tenuiflorum* (Tulsi) in treating mouth ulcers. While initial studies and traditional usage suggest promising results, it is essential to conduct well-designed, randomized, double-blind, placebo-controlled trials in diverse populations. These studies should aim to establish optimal dosages, treatment duration, and evaluate the potential for adverse effects. Comparative studies with existing treatments like corticosteroids or antimicrobial mouthwashes would also provide valuable insights into whether the combination offers superior therapeutic outcomes, including faster healing, reduced recurrence rates, and improved patient satisfaction.

Chemical Profiling and Bioactive Compounds

Identifying and isolating the specific bioactive compounds responsible for the therapeutic effects of jasmine and guava is a crucial next step in future research. Advanced analytical techniques, such as High-performance liquid chromatography (HPLC) and mass spectrometry, can help in mapping the chemical profiles of both plants. By isolating and characterizing the active constituents, researchers can better understand how these compounds interact with each other and contribute to their synergistic effects. Additionally, research should focus on the pharmacokinetics of these compounds to ensure their bioavailability and optimal absorption when used in topical or oral formulations.

Conclusion:

In conclusion, the combination of *Jasminum grandiflorum* (jasmine) and *Ocimum tenuiflorum* (Tulsi) offers a promising natural solution for managing mouth ulcers. This dual therapy addresses multiple aspects of the condition such as pain relief, inflammation reduction and infection prevention, making it a comprehensive and effective treatment option. While preliminary studies and traditional usage suggest its potential, further research and clinical trials are necessary to validate its efficacy, establish optimal treatment protocols, and ensure safety. If proven successful, this combination therapy could provide a valuable alternative to conventional treatments, improving the quality of life for those affected by mouth ulcers.

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