Int. J. Pharm. Investigation, 2024; 14(2):327-337.
https://www.jpionline.org

Review Article

A Review on Pharmacological Potential of Various Synthetic and Phytoconstituents in Managing Recurrent Aphthous Stomatitis

Vaibhav Rastogi*, Mayur Porwal, Anurag Verma, Umair Khan, Prabal Chauhan, Prashant Kumar

Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, INDIA.

ABSTRACT

Recurrent Aphthous Stomatitis (RAS) is a condition characterized by the development of ulcers and lesions, in the mouth. It affects a wide portion of the population ranging from 5% to 25%. RAS more commonly affects labial mucosa, buccal mucosa, and tongue. Managing RAS involves treatment approaches that can be applied directly to the affected area as well as can be administered internally. Topical therapies involve using anesthetics, corticosteroids, and anti-inflammatory agents to alleviate symptoms. Systemic options include medications like colchicine, dapsone, clofazimine, levamisole, thalidomide and zinc supplements. However, for managing RAS no standardized and curative treatments are available. Thus, the objective of any treatment should be to lessen pain, reduce the duration of ulcers, and inhibit recurrence. Also, this work enlists various cells, receptors and pathways which need to be considered while developing an efficient therapy for RAS. Furthermore, herbal remedies can be beneficial in managing RAS without many side effects as in the case of some synthetic drugs. Some herbal treatments that have shown promise include *Punica granatum* var. *pleniflora, Curcuma longa* (turmeric), *Hangeshinto* and many more are reviewed in this work which will be a promising herbal drug to develop polyherbal dosage form for the same.

Keywords: Recurrent Aphthous Stomatitis, RAS, RAS Etiology, Mouth Ulcer, Herbal Drugs.

Correspondence:
Dr. Vaibhav Rastogi
Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad-244001, Uttar Pradesh, INDIA.
Email: vaib.asa@gmail.com

Received: 25-10-2023;
Revised: 14-12-2023;
Accepted: 28-02-2024.

INTRODUCTION

Recurrent Aphthous Stomatitis (RAS), which causes stinging ulcerations on the movable or nonkeratinized oral mucosa (Figure 1), is one of the most prevalent illnesses affecting the oral mucosa.[1] RAS affects 5-25% of the population.[2] Studies have reported the prevalence of RAS in the United States and United Kingdom to be about 20% of the population. A study conducted in Mangalore, India, reported a prevalence of 47.2% among college students within six months preceding the study.[3] Another study conducted in North India reported an overall prevalence of 18.93% among patients who visited a dental college for routine checkups.[4] In the United States, the lifetime prevalence of aphthous stomatitis in the pediatric population is 40.18%.[5] Activation of the cell-mediated immune system is most likely one of the reasons for aphthous stomatitis, while there are many other potential causes as well. Aphthous ulcers are not communicable since they are not brought on by acute infections. Menstruation, localized injury, increased emotional or physical stress, allergies or sensitivities to some foods like cinnamon, cheese, citrus fruits, figs, or pineapple, as well as contact with sodium lauryl sulphate found in toothpaste and oral hygiene products, are just a few of the variables that cause the RAS to become active. Additionally, toxin exposure, such as nitrates present in drinking water, and variations in the oral microbiome can also contribute to the development of RAS.[6] This work delves in the understanding of RAS, its aetiology, immunopathogenesis and disease management by using synthetic and herbal drugs. However, various synthetic and herbal drugs are present to get relief in RAS, but due to some side effects associated with synthetic treatments more research is now focusing towards herbal remedies. Phytoconstituents which poses different pharmacological action in managing RAS can be combined together in a polyherbal dosage form or other type of dosage forms like mucoadhesive dosage forms.

Aetiology of RAS

RAS is a member of the group of long-term inflammatory conditions affecting the oral mucosa. Although it is thought to be a complex condition and some triggers have been documented, its aetiology and pathogenesis are still unexplored. It is believed that certain circumstances in patients who are genetically prone cause a proinflammatory cytokine cascade to start that targets

DOI: 10.5530/ijpi.14.2.40

particular regions of the oral mucosa.[7] Figure 2 enlist the various factors that are responsible for RAS.

Genetic factors

About, 30% to 40% of patients with aphthous ulcers have a familial history of the ailment, indicating that the condition has a genetic component. Numerous genetic variants have been linked to RAS (recurrent aphthous stomatitis). For instance, it was discovered that the frequency of an E-selectin polymorphism was around ten times greater in RAS patients than in controls. This specific genetic variant may increase leukocyte buildup and epithelial barrier penetration, which may increase vulnerability. A large rise in Toll-like receptor 4 polymorphism was also discovered in people with RAS. The innate immune system and cellular immunological response both depend on toll-like receptor 4. These genetic discoveries point to a possible connection between genetic differences and the development of RAS.[8]

Stress

Stressful life experiences may cause the formation of new lesions in patients. One research found that stressful life events had a stronger correlation with the start of episodes than with the length of them and that mental stressors had a stronger correlation with RAS than physical stressors.[9] Also, some diseases like Behçet disease, deteriorate after a period of high emotional stress and eventually progress to aphthous ulcers.[10]

Nutritional deficiency

RAS may be brought on by hematinic deficiencies, notably those in iron, folic acid, and Vitamin B12. About, 20% of patients with hematinic deficiencies (microcytic and macrocytic anemia) have been associated with Recurrent Aphthous Ulceration (RAU).[11] Through a poorly understood mechanism, RAS and hematinic deficiencies are connected. However one of the theories might be that vitamin B12 and folic acid are vital for DNA synthesis and subsequent cell division. The epithelial barrier and mucosal integrity may be harmed by oral epithelial cells atrophying in the presence of deficiencies. Patients with RAS who have anemia or high blood homocysteine levels may experience oral epithelial barrier degradation, which will subsequently increase the risk of developing RAS. Furthermore, multiple investigations found that RAS patients and healthy controls had significantly different blood vitamin B12 levels. Other investigations revealed that compared to the control group, RAS patients had significantly reduced iron and ferritin concentrations. Therefore, it is advised that individuals with RAS undergo hematologic tests, particularly if they have severe or mild RAS. Some of these dietary deficiencies could be connected to other illnesses too.[12]

Drugs

The occurrence of oral ulcerations has been linked to several drugs, including antihypertensives, immune-suppressants, anti-cholinergic bronchodilators, platelet aggregation inhibitors, protease inhibitors, vasodilators, β-blockers, antibiotics, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and anti-retrovirals. Particularly well-known for their propensity to result in mouth ulcers, NSAIDs are often prescribed drugs. Furthermore, drugs used to treat chronic conditions such as diabetes, angina pectoris, rheumatoid arthritis, and osteoporosis have been linked to mouth ulcers too.[13]

Food allergy

Food sensitivity (to foods like cheese, chocolate, tomatoes, citrus, shellfish, and citrus) shows the occurrence of RAS. In patients with a family history of RAS, there has been evidence of a high association between atopy and allergy or food intolerance. Some individuals may have specific food allergies or sensitivities, and when they consume these trigger foods, it can lead to an immune response in the body. The immune system may recognize these substances as foreign invaders and mount an inflammatory reaction in response. Foods and beverages with high acidity levels, such as citrus fruits, tomatoes, and carbonated drinks, can create an acidic environment in the mouth. This acidity can irritate and weaken the oral tissues, making them more susceptible to injury and ulceration. In some cases, allergic reactions to food additives, preservatives, or other substances can trigger an immune response that leads to inflammation and the development of aphthous ulcers. Inadequate intake of certain essential nutrients, such as vitamin B12, iron, folic acid, and zinc, can impair the body's ability to maintain healthy oral tissues. Nutritional deficiencies can make the oral mucosa more susceptible to damage and ulceration.[14]

Local Factor

Individuals who are sensitive to RAS are thought to be affected by local trauma.[15] Trauma causes edema, early cellular inflammation, and a rise in the viscosity of the ECM (extracellular matrix) in the oral submucosa, all of which raise the risk of RAS.[16] However, not

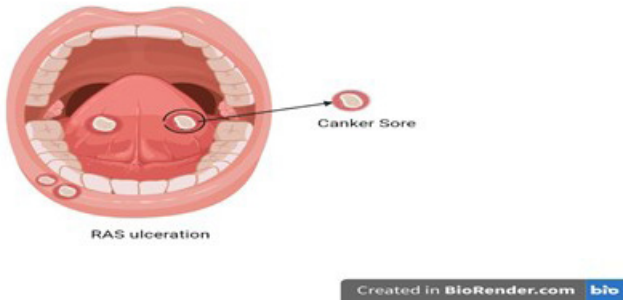

Figure 1: RAS ulceration.

all oral injuries result in RAS, however, persons who wear dentures are three times more likely to acquire oral mucosal ulcers.[17] RAS has been linked to several alterations in salivary composition, such as pH shifts that impact the spatial characteristics of saliva and stress-induced increases in salivary cortisol.[18]

Hormonal factors

Aphthous ulcer occurrence has been linked to the menstrual cycle, according to reports. In contrast to pregnancy and women using hormonal contraception, ulcers are less common during menopause or the luteal phase.[11] The decreased level of progesterone and estrogen causes a decrease in blood in blood flow which causes thinning of oral epithelium and slows the process of keratinization which causes inflammation and the occurrence of RAS.[19]

Viral and Bacterial factors

Streptococcus bacteria, particularly *Streptococcus sanguinis* 2A, and other microbes have been the subject of numerous investigations that have sought to link RAS to them *Epstein-Barr virus, Helicobacter pylori*, and *Lactobacillus* are some examples. However, no distinct causal association has been demonstrated by the studies so far.[20-22] *Streptococcus oralis* has been detected in aphthous ulcers, and one idea suggests that it may cause a response with mitochondrial heat shock proteins, causing damage to the oral mucosa. Although the existence of *Helicobacter pylori* infection in recurrent aphthous stomatitis (RAS) lesions is debatable, a meta-analysis suggests a link between RAS and *Helicobacter pylori* infection.[23]

Immunopathogenesis

RAS, a prevalent mucosal condition, still lacks a clear pathophysiology. First proposed in the 1960s was an autoimmunity-related function for RAS.[24] In a healthy immune system, immune cells (such as T cells and B cells) work together to recognize and eliminate harmful micro-organisms, such as bacteria and viruses. They do this by distinguishing between the body's own cells and foreign invaders. In the case of aphthous ulcers, it's thought that an abnormal immune response occurs. Instead of correctly identifying and attacking pathogens, the immune system may mistakenly target the body's own healthy cells. In the oral mucosa, which lines the mouth, immune cells may target the epithelial cells, leading to inflammation and tissue damage. The immune system's attack on healthy oral mucosal cells results in localized inflammation. Inflammation is part of the body's defense mechanism, but in this case, it leads to the characteristic redness and swelling seen around the ulcer. The inflammation and damage caused by the immune system's attack can result in the formation of an ulcer. The tissue at the site of the inflammation breaks down, creating a sore that is often round or oval in shape.[25]

Heat shock protein (Hsp) is an agent that may cause cross-reactions.[26] Studies have shown that the peptide sequence of mycobacterial Hsp65 antigen is recognized by T cells from individuals with RAS. Additionally, the human 60-kDa Hsp peptide 116-130 elicited a potent immunological response. These results show that the microbial Hsp peptide may have a role in RAS by stimulating autoreactive T-cell clones that have been made sensitive to the homologous peptide by mucosal Langerhans cells. Further investigation has revealed that the peptide epitope inside the 65-kDa mycobacterial Hsp that causes a reaction in people with RAS is 91-105.[27] Thus several observations provide credence to the idea that Hsp peptides have a role in the pathophysiology of RAS. First off, Behcet's syndrome patients react to a particular peptide, supporting the idea of Hsp peptides that have a role in the development of the condition. Furthermore, it has been shown in animal experiments that this peptide vaccination causes a Behcet's-like illness, which may be avoided by creating oral tolerance in Behcet's models or real patients. Finally, these results add to the mounting evidence that Hsp peptides may have a role in causing RAS.[28] Alternative theories have been put forth suggesting that the pathophysiology of RAS could involve the activation of Toll-like receptor-2 (TLR2), prominent to the stimulation of peripheral blood mononuclear cells.[29]

TLRs, which are membrane receptors, can distinguish between compounds produced by fungi, viruses, and bacteria. These receptors are crucial for controlling immune system activity and

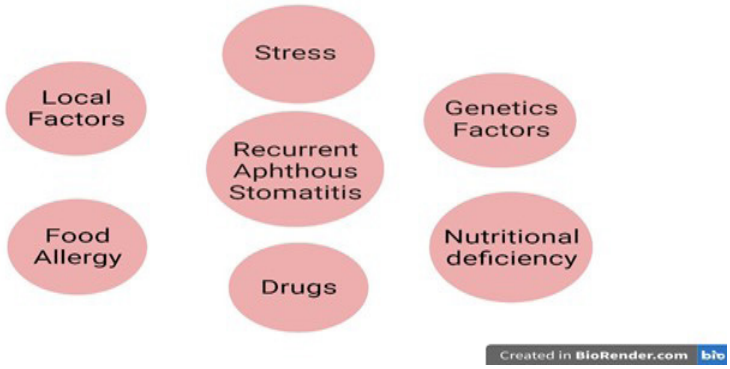

Figure 2: Factors responsible for RAS.

Table 1: Cells and receptors associated in RAS that need to be managed.

Cells/ Receptors involved in RAS		Role in RAS that need to be managed
Epithelial Cells	Keratinocytes	These cells that make up the mucous membranes and the skin's outer layer. They contribute to the development and maintenance of the epithelial lining.
Immune Cells	T Cells	They are a particular class of white blood cell that are essential to the immunological response. Recurrent aphthous ulcers have been linked to abnormalities in T cell function as a potential cause.
	Macrophages	These immune cells are responsible for the recognition and eradication of foreign objects and cell debris. They contribute to the inflammatory reaction.
	Neutrophils	Neutrophils, a different class of white blood cell, play a key role in the early phases of inflammation and the immune response.
Cytokines	Interleukins (IL)	These are signaling proteins that control inflammatory processes and immunological reactions. Aphthous ulcer recurrence has been linked to abnormal cytokine production. These pro-inflammatory cytokines, Interleukin-1 (IL-1) and IL-6, are implicated in the beginning and spreading of inflammation. IL-1 and IL-6 levels have been found to be higher in conjunction with RAU.
Receptors	Toll-Like Receptors (TLRs)	These receptors have a role in the immune system's activation and pathogen identification. They participate in the inflammatory reactions linked to RAU. TLRs that are abnormally activated may be a factor in the inflammatory response found in RAU.
	Integrins	These are cell adhesion molecules that aid in the migration of cells to areas of inflammation and the attachment of immune cells to the epithelium. Pathogenesis of RAU may be influenced by dysregulation in these molecules' expression or function.
Cell Signalling pathways	NF-κB (Nuclear Factor-Kappa B) Pathway.	A transcription factor called NF-B is essential for controlling inflammatory and immunological reactions. Activation of it can cause the production of several genes that promote inflammation. The possibility of abnormal NF-B activation in the setting of RAU has been raised.
	MAPK (Mitogen-Activated Protein Kinase) Pathway	A family of kinases known as MAPKs is involved in the control of cellular reactions to numerous stimuli as well as signal transduction. Inflammatory mediators can be produced as a result of MAPK activation.

protecting the epithelial barrier's integrity. The aetiology of RAS is hypothesized to include compromised TLR2 pathways. Due to this damage, the epithelial barrier of the oral mucosa becomes dysfunctional and the Th1/Th2 immune response becomes unbalanced. Thus, oral antigens high in Th1 cytokines come into contact with immune-competent cells from the lamina propria, ultimately impacting the formation of RAS ulcers.[29,30]

Histopathologically, RAS may be identified by a substantial inflammatory infiltration that first mostly consists of lymphocytes and then gradually combines neutrophils as the illness advances[31] and surrounding keratinocytes display positivity for the MHC class II cell surface receptor HLA-DR and Intercellular Adhesion Molecule-1 (ICAM-1).[32,33] The target of the cytotoxic injury could be activated endothelial cells that display adhesion molecules including ICAM-1, VCAM-1, and E-selectin. The early production of ICAM-1 by keratinocytes may be required for the recruitment of lymphocytes. The association among keratinocytes and $CD8^+$ cytotoxic T lymphocytes interacting with keratinocyte ICAM-1 might be responsible for epithelial breakdown and ulcer formation.[33] It has been shown that $CD8^+$ cytotoxic T lymphocytes predominate in the ulcerative stage.[32,33]

Management

Management of RAS depends on the severity, size, and number of the ulcers. Patients with minor RAS are treated with topical therapies which contain agents such as local anesthetics, topical corticosteroids, and anti-inflammatory and analgesic agents which are used topically in managing aphthous ulcers. Topical therapy cannot prevent the formation of new ulcers so patients with major RAS ulcers are treated with systemic therapy such as colchicine used for managing RAS.[34]

Various cells and receptors are implicated in the development and healing of recurrent aphthous ulcers (Table 1). To create successful treatments for recurring aphthous ulcers, it is imperative to comprehend the intricate interplay between these distinct components. It's critical to remember that this field of study is still being explored, and knowledge of the precise cellular and molecular mechanisms at play may change over time.

Topical Management

The greatest difficulty in treating aphthous ulcers with topical medications is ensuring efficient drug delivery since regular

chewing motions and saliva can readily rub or rinse the medicine from the target region. Because they are straightforward to use and patients can tolerate their flavor and consistency, gels are frequently used as a delivery technique. Different adhesive carriers, such as isobutyl-cyanoacrylate, also known as Iso-Dent from Ellman International or Orabase from Bristol-Myers Squibb, can be used to compound topical medicines. The efficiency of the medicine in treating aphthous ulcers is increased by these vehicles, which aid in boosting the adhesion and retention of the medication on the afflicted region. The local anesthetics, anti-inflammatory, anti-inflammatory, glucosteroids are combined with different vehicles to deliver these agents to the targeted site.

Local Anesthetics

Symptomatic treatments that work locally can reduce symptoms and shorten the length of an incident. Commonly, a satisfactory pain reduction can be accomplished through the placement of anesthetics locally such as topical lidocaine at 2% concentration in either solution, spray, and/or gel.[35] Several drug combinations can be used to treat aphthous ulcers. Examples include Mepivacaine at 1.5% and Polidocanol at 1% concentration in Meaverin gel, Tetracaine at 5% and Polidocanol at 1%, and Benzocaine and Benzalconium chloride. For effective treatment, these combinations frequently have two or more components. The use of the spray is an additional choice that may be simple to apply. Benzocaine, Cetylpyridinium chloride, Cetyl puridin with Amine fluoride, and Ezafluor are a few additional components included in pre-made mouthwashes. Two examples of local anesthetic solutions that can be delicately applied with an applicator directly on the lesions are Xylocaine viscous 2% lidocaine solution and Gingicaine D solution containing Tetracaine.[36]

Topical antiseptic and anti-inflammatory agent

These drugs help guard against bacterial and fungal superinfections and enhance dental health. The use of Zinc sulphate in ethanol with 0.15 percent triclosan is one such instance. This drug has been demonstrated to lessen the number, intensity, and length of ulcer episodes when taken orally three times daily, resulting in longer intervals between each recurrence.[37] Rinse with 5 mL of chlorhexidine (0.12%-0.2%) in oral solution for 1-2 min after brushing your teeth and before going to bed.[37] In terms of pain relief after 2-6 hr, diclofenac 3% in hyaluronic acid gel was more effective than lidocaine in the gel.[37-39] Triclosan is a kind of broad-spectrum antibiotic. When used as toothpaste or mouthwash, it has analgesic, antibacterial, and anti-inflammatory properties.[40] After brushing your teeth and before going to bed, it is advised to rinse your mouth for 1-2 min with 5 mL of chlorhexidine 0.12%-0.2% oral solution. This routine supports keeping a clean oral environment and boosting oral health.[41] Prostaglandin E2 gel (0.3 mg) used topically twice daily in a small-scale trial demonstrated good outcomes in lowering the incidence of new aphthous ulcers.[42] If five milliliters of topical sucralfate are used four times a day, RAU can be treated. Sucralfate solution's soothing properties induce mucous membrane tissues to form again, acting as a protective barrier.[36,43]

Topical Corticosteroids

Strong or super-strong topical corticosteroids are still effective even after brief contact periods when paired with mucosal adherents. Topical corticosteroids are administered to RAU patients to lessen the inflammatory response that results in the formation of aphthae. T lymphocytes may be directly impacted by corticosteroids, which may also alter how effector cells respond to substances that cause immunopathogenesis. (for instance, a food allergy, trauma, or microbes).[44] In comparison to stronger glucocorticoids like Fluocinonide (0.05%) or Clobetasol propionate (0.05%), Triamcinolone acetonide with Orabase is less effective.[36]

Systemic Treatment

Consider adding a systemic medicine to routine medical treatment if a patient has severe and/or recurring RAS and is not responding to topical treatments (see above). The patient's preferences, coexisting illnesses, the severity of their symptoms, as well as their tolerance and preferences for different therapies, all play a role in the selection of systemic treatment.[7]

Colchicine

When tested on small groups of RAS patients, colchicine is clinically advantageous.[45,46] According to research, Colchicine (1.5 mg/day for two months) expressively decreased the number of self-reported ulcers and pain levels in 20 patients involved in this study. Not all patients respond well to colchicine medication, and at least 20% of people can experience uncomfortable gastrointestinal problems including diarrhea.[47] Moreover, young males who utilize it for the long-term may develop infertility.[48]

Lynde *et al.* Investigated the effectiveness of Colchicine and Dapsone for treating RAS. A therapeutic ladder was used to treat 55 patients with complex aphthosis, it started with colchicine and included dapsone for patients who did not significantly improve (>75% improvement) after receiving colchicine or who stopped taking it due to side effects. The majority of patients (44 or 80%) experienced a significant response to medication and reported no serious side effects, according to the results.[47-49] However, diarrhea was the most common adverse effect in patients taking colchicine.

Dapsone

Dapsone is well known for its ability to exert antibacterial and anti-inflammatory actions, hence reducing the increased neutrophil chemotactic activity. It has shown effective in treating oral and vaginal ulcers when taken daily in amounts between 100 and 150 mg. It should be noted, nevertheless, that stopping

treatment frequently causes ulcers to return. A progressive treatment plan was used in a trial including 14 patients with complicated aphthosis, reaching a daily dose of 125-150 mg of dapsone and 1.8 mg of colchicine at the end. The results showed that the combination treatment was well-tolerated by 71% (n=10) of these patients. The authors propose that even if patients with hard instances of aphthosis initially do not show a good response when treated just with dapsone, they may eventually react to colchicine.[47-49,51] Methemoglobinemia and hemolysis are the adverse effects of dapsone that are most frequently seen. Agranulocytosis and distal motor neuropathy are possible risks as well. It is advised to do a baseline laboratory examination, which should include a Complete Blood Count (CBC) with a differential count, as well as renal and hepatic function tests, to assure patient safety. It's also suggested to measure the amount of glucose-6-phosphate dehydrogenase and do other pertinent procedures. Regular monitoring is essential throughout the first 12 weeks of therapy, including a CBC with reticulocyte and differential count every second week. Additionally, as part of the monitoring procedure, it is advised to carry out complete urinalysis, routine tests of liver and kidney function, and detailed urinalysis.[51]

Clofazimine

An oral lipophilic phenazine dye called Clofazimine was created as a treatment for Mycobacterium tuberculosis.[52] However, clofazimine as a repurposed drug in managing RAS was evaluated. In a controlled partially blind study, Clofazimine was given to 23 individuals at a dose of 100 mg per day for 30 days, followed by 100 mg every other day. A placebo pill was given twice to 20 subjects. All subjects took medicine for six months. The findings show that in the clofazimine group, more people (17%-44% versus 6% in the other groups) experienced no more aphthous events. People in the clofazimine group who nevertheless experienced aphthous stomatitis displayed improved outcomes for the assessed variables.[53] Serious responses are uncommon; skin, gastrointestinal, and eye problems are the most common adverse effects.

Levamisole

This often-prescribed medication by gastroenterologists has been used successfully as monotherapy and an adjuvant to treatment in many disorders. It has a broad range of immunomodulatory activities. It has been effective in treating bacterial, viral, and parasitic illnesses, as well as inflammatory skin conditions.[54]

In three trials, 124 individuals with RAS (RAS) lasting 2 to 53 years participated in research conducted by Meyer *et al.*[55] to evaluate the efficacy of levamisole and to create an appropriate regimen. Levamisole 150 mg per day (or placebo) was administered on three successive days every two weeks in the first of two double-blind studies and the first part of phase 2. Only the latter two months of studies 2 and 3, as well as the open trial (study 3), which took place across RAS episodes, were three-day sessions. The results show that levamisole medication markedly improves RAS symptoms in individuals. However, a report by Liu *et al.* shows the induction of leukoencephalopathy after the levamisole treatment.[50] Other frequent adverse effects include a rash, nausea, stomach cramps, changes in taste, alopecia, arthralgia, and a flu-like illness.[51]

Thalidomide

The data supporting the effectiveness of thalidomide as a systemic drug for the management of RAS and the treatment of chronic mouth ulcers is well reported. However, it is still unknown how exactly Thalidomide heals oral ulcers. However, it is postulated that Interleukin-6 (IL-6), IL-10, and Tumor Necrosis Factor (TNF) are a few of the cytokines that it is hypothesized to interact with and modulate the inflammatory cascade to decrease inflammation. Moreover, the use of thalidomide is restricted despite the drug's strong efficacy because of the seriousness of its potential side effects, which include teratogenicity and embryo-fetal damage, thromboembolic illness, and peripheral neuropathy.[56] In a study performed by Hello *et al.*,[57] Ninety-two people were involved in a multicenter retrospective cohort research that lasted for five years and five months from January 2003 to May 2008; 16 of them had Behçet disease and 76 had oral or bipolar aphthosis. Following the findings, thalidomide started to take effect within a median of 14 days, and 85% (78/92) of patients achieved Complete Remission (CR). The initial thalidomide dose did not affect response time (r=0.04). 84% (77/92) of patients reported experiencing adverse events. Most patients (78%) had minor symptoms, but 21% occasionally had severe ones. Nevertheless, 60% of patients were still needing continuous or intermittent maintenance medication with good efficacy/tolerance ratios after 40 months of follow-up. Thalidomide is therapeutically effective in open and double-blind trials of patients with non-HIV-related RAS, HIV-related oral ulcers, and various case reports. Up to 75% of people on thalidomide may experience mild side effects, such as intolerance and libido loss, while around 5% may develop polyneuropathy. The danger of teratogenicity prevents thalidomide from being used effectively to treat RAS.[58] According to, Mimura *et al.* when thalidomide, colchicine, pentoxifylline, and dapsone were compared for the treatment of RAS, thalidomide was found to be the most effective and well-tolerated drug. It was given to a total of eight patients, seven of whom (87.5%) experienced complete remission. Nine patients were prescribed dapsone; five of them had complete remission, and eight (89%) of them experienced symptom improvement. Colchicine was given to 10 patients in all; nine of them observed benefits (or 90%), and four of them obtained complete remission. Three of the five patients who took pentoxifylline had favorable benefits (60%) and one patient experienced full remission.[59]

Zinc supplement

It was suggested that Zinc sulphate could be utilized to treat or prevent mouth ulcers by aiding in wound healing and preserving epithelial integrity. An essential trace element called zinc serves as a cofactor for more than 300 enzymes. It is essential for the differentiation, development, regeneration, and healing of cells. Also, zinc inhibits the activity of T-helper-17 cells, reduces neutrophil chemotaxis, prevents the release of inflammatory cytokines, and suppresses the expression of TRL-2 in keratinocytes, all of which are crucial immune system regulators.[60]

To examine the efficacy of dapsone and oral zinc sulphate in treating RAS, Sharquie *et al.*[61] undertook a double-blind, placebo-controlled research. 45 RAS patients were subjected to the trial and were split into three equal groups: Group A received 150 mg b.d of zinc sulphate, Group B received 50 mg b.d of dapsone, and Group C received 250 mg of glucose as a control. The mean Oral Clinical Manifestation Index (OCMI) and ulcer diameter in Group A both significantly decreased after a twelve-week therapy period. Although, Group B showed a slower and less significant improvement however it was nonetheless statistically significant. Group C, the control group, displayed only minimal improvement (p=0.034 for ulcer diameter and p=0.028 for OCMI). Notably, zinc sulfate demonstrated superior performance compared to dapsone in reducing the OCMI of the ulcers during the sixth week of therapy (p=0.007).

Recent Herbal Drugs Used in RAS Management

Natural herbal remedies have been utilized extensively as an alternative therapy for RAS for a decade. Clinical trials on its use have shown positive effects for patients by shortening the duration and suffering of ulcers.[62] Synthetic drugs which are used for RAS management like Colchicine, Dapsone, Clofazimine, and Thalidomide show adverse effects like male infertility, gastrointestinal problems, hemolysis, methemoglobinemia, eye problems, skin discomfort, and peripheral neuropathy.[48,51,56] So, to avoid these adverse effects herbal drugs can be used as an alternative therapy for managing RAS.

Punica granatum var. pleniflora

In addition to lowering oral inflammation, microorganism (fungus and bacterial) counts in periodontal disease, and Candida-associated denture stomatitis, *P. granatum* (pomegranate) formulations administered topically are particularly effective.[63] *P. granatum* var. *pleniflora* contains flavonoids that possess anti-microbial, antioxidant, anti-inflammatory, and immune system activating properties and thus can be used in managing aphthous ulcers.[64] Tannins like gallic acid, ellagic acid and punicalagen have astringent properties which are used in wound treatment.[65] A study on 210 patients with minor aphthous ulcers reveals that the *P. granatum var. pleniflora* alcoholic and water extract shows a good therapeutic effect on minor aphthous ulcers due to its antioxidant activity.[66]

Gahalayani *et al.*[64] performed a randomized, double-blind, and placebo-control study on 40 patients. The 10 % Pomegranate gel (PG) is used in three occurrences of the ulcer. The findings show a significant difference in the PG group (3.4±1.09 days) as compared to Placebo (5.9±0.6 days). The difference in the average time it took for full recovery between the PG group (5.3±0.81 days) and the placebo group (8.6±0.99 days) was statistically significant (p=0.001).

Curcuma longa (curcumin)

Curcumin is a powerful anti-bacterial as well as anti-inflammatory substance that is used in managing a variety of oral disorders.[67] Curcumin reduces proinflammatory cytokines by inhibiting phospholipase, lipidase, and cyclo-oxygenase-2. These pathways may contribute to curcumin's high analgesic qualities in people with recurrent aphthous stomatitis (RAS).[68] The efficiency of 0.1% Triamcinolone acetonide and 5% curcumin in treating recurrent aphthous ulcers were compared in the research. 29 patients in total were split into two groups, Group A receiving 5% curcumin treatment while Group B receiving 0.1% Triamcinolone acetonide treatment. Before starting therapy, as well as on days 1, 4, 7, and 10, data on lesion size, pain intensity (as determined by the Visual Analogue Scale), and effectiveness index were gathered. The outcomes show that 5% curcumin and 0.1% Triamcinolone acetonide are equally effective at treating recurrent aphthous ulcers.[69]

Hangeshashinto

Hangeshashinto is a Japanese (kampoo) medicine traditionally used medicine for managing oral ulcers.[70] It exhibits anti-bacterial, anti-oxidant, and anti-inflammatory effects. Hangenshashinto inhibits the production/metabolic activity of prostaglandin E_2 induced by lipopolysaccharides and interleukin 1 shows anti-inflammatory properties and can help manage oral ulcers.[71] A study conducted on oral ulcer-induced pain in a rat model shows that the topical application of hangenshashinto reduces the pain after topical application for 60 min. without any side effects.[70]

Myrtus communis L.

Popular Iranian herb *Myrtus communis* L. has been used for centuries to heal aphthous ulcers. Essential oil (Myrtenyl acetate, α-pinene, 1,8-cineole, linalool, and limonene) obtained from the herb reduces the average amount of pain time that patients with mild RAS had and also decreases the ulcer size without having any adverse side effects. *M. communis* L. inhibits the (Tumour Necrosis Factor) TNF-α and other inflammatory cytokines and thus prevents the formation of new ulcers.[72]

Ageratina pichinchensis

Ageratina pichinchensis is a plant that is native to Mexico. 7-O-(β-D-glucopyranosyl) galactin found in this plant promotes wound healing and can be used to manage lesions caused by RAS.[72] The efficacy of *Ageratina pichinchensis* in treating RAS was assessed in pilot research by Romero-Cerecero *et al*. The control treatment included 0.1% triamcinolone, whereas the treatment used phytoconstitutents of unpigmented *A. pichinchensis* hexane-ethyl acetate extract at a 5% concentration. According to the findings, individuals given *A. pichinchensis* experienced no discomfort for 0.1 days, which was equal to the impact of 0.1% triamcinolone therapy.[73]

Aloe barbadensis Miller

Due to its therapeutic benefits, *Aloe barbadensis* miller is a plant that is extensively distributed throughout Asia and Africa. According to recent studies, *Aloe vera* plants can reduce inflammation and heal wounds, making them a promising treatment option for mouth ulcers.[74] Aloe vera's wound-healing effects are linked to its capacity to promote epithelial cell migration. The inclusion of glucomannan (a polysaccharide high in mannose) and gibberellin (a growth hormone) in *Aloe vera* extract aids in collagen formation. Furthermore, gibberellin stimulates fibroblast activity and proliferation via interacting with growth factor receptors. *Aloe vera* also increases the production of hyaluronic acid and dermatan sulphate in wound granulation tissue, which aids in wound healing. Furthermore, *Aloe vera* includes numerous components, such as acemannan, that have wound-healing potential by encouraging the repair process and epithelial cell proliferation via the activation of wound-healing factors such as fibroblasts and collagen. Aloe vera's antioxidant qualities boost its anti-inflammatory benefits by decreasing the synthesis of reactive oxygen metabolites, hence avoiding oxidative stress. Furthermore, *Aloe vera* gel promotes the healing process and the normal microbiota of recurring aphthous ulcers by lowering the number of dangerous oral bacteria such as Actinomyces, Granulicatella, and Peptostreptococcus. As a consequence, *Aloe vera* can improve the quality of life for people suffering from recurring aphthous ulcers.[75]

Mansour *et al.* assessed the therapeutic potential of an oral gel comprising *Aloe vera* and myrrh in 90 patients with moderate aphthous ulcers in controlled research. Three types of gels were used: a normal mucoadhesive gel as a control, and two gels containing *Aloe vera* and myrrh at 0.5% w/w, respectively. The gels had to be applied to ulcers that were less than 48 hr old four times each day for five days, according to the instructions given to participants. On days 4 and 6 following the commencement of the experiment, changes in the size of the ulcer, the intensity of pain, erythema (redness), and oozing (exudation) were evaluated to determine clinical effectiveness. A significant number of patients using the *Aloe vera* gel (86.7% for erythema and 80% for exudation) experienced a noticeable reduction in redness and oozing, particularly observed during the sixth-day evaluation, according to the study's findings, which also included participants being asked about any possible negative effects. In addition, by day 6, the vast majority of patients (76.7%) receiving the myrrh gel experienced almost total pain alleviation. Importantly, none of the subjects who used any of the three gels suffered any ill effects.[76]

Cinnamomum verum (Cinnamon)

Anti-fungal, antioxidant, and cytotoxic properties of cinnamaldehyde found in *Cinnamomum verum* (cinnamon) bark oil make it suitable for the management of RAS. Cinnamaldehyde, found in cinnamon oil, has been shown to decrease IL-1β and TNF-α production in macrophages while decreasing the amounts of active oxygen species. It also suppresses the phosphorylation of protein kinase, which is caused by lipopolysaccharides. In a clinical trial, the potential of a cinnamaldehyde mucoadhesive patch was evaluated and the findings show that the cinnamaldehyde mucoadhesive patch reduced the ulcer dimensions and intensity of the pain.[77,75]

Glycyrrhiza glabra (Licorice)

One of the earliest known medicinal plants, licorice (*Glycyrrhiza glabra*) can be used to treat a variety of medical conditions, including stomach ulcers, wounds, urinary tract infections, and asthma. Glabridin and glycyrrhizic acid are licorice's two primary ingredients. Licorice and its active components block the lipoxygenase and 5-cyclooxygenase enzymatic pathways. It suppresses Reactive Oxygen Species (ROS) and consequently prevents arachidonic acid metabolism and vascular permeability ultimately reducing inflammatory reactions.[78]

Myristica fragrans

The nutmeg tree, or *Myristica fragrans* Houtt., is a popularly growing commercial plant in various countries including India, Thailand, Indonesia, China, Japan, and South Africa. It is an evergreen tropical tree with a nice fragrance and flavor. This plant is a member of the order Magnoliales Myristicaceae family, which includes more than 3000 species and roughly 150 genera. About 72 tropical species of the genus, in addition to being grown in many tropical countries in both hemispheres, including South Africa, myristica is a plant that may be found in the Moluccas, India, Sri Lanka, and Indonesia.[79] *Myristica fragrans* inhibits the gram-positive and gram-negative bacteria and also decreases the level of Nitric Oxide (NO), TNF-α thus decreasing the inflammation.[80]

Mace aril of the nutmeg seed possesses anti-microbial antioxidant, and anti-inflammatory, properties.[81] The constituent myristicin found in the methanol extract of mace is responsible for its anti-inflammatory properties.[82]

Acacia catechu

Acacia catechu is also referred to by the names Babul (Hindi), Khadir (Hindustani and Punjabi), Khair (Hindi), Kattha (Urdu), Kaath (Marathi), Kachu (Malay), and Khoyer (Bengali and Assamese). It is native to East Africa, several Asian nations, and India. A. catechu has historically been used to cure obesity and diabetes, repair wounds, coagulate blood, prevent diarrhea, and maintain oral hygiene. It also contains anti-bacterial, anti-inflammatory, and antifungal properties.[83] *Acacia catechu* inhibits both the Cyclooxygenase (COX) and Lipoxygenase (LOX) enzymes, resulting in a decrease in inflammation.[84]

Piper cubeba

Tropical locations, such as South Borneo and Indonesia, are home to a member of the Piperaceae family.

Cubeb resin, cubebic acid, volatile oil, and lignans are the primary components of cubebs. Cubebin and hinokinin, two of its lignans possess antioxidant, numbing, anti-bacterial, anti-microbial, and anti-inflammatory activities.[85] Flavonoids including quercetin, kaempferol, and luteolin have been shown to decrease the production of pro-inflammatory cytokines. *Piper cubeba* L. has anti-inflammatory action in THP-1 cells by reducing IL-6 stimulation generated by Lipopolysaccharide (LPS). This inhibits the Cyclooxygenases (COX-1 and COX-2) as well as the 5-lipoxygenase (5-LOX).

CONCLUSION

Recurrent Aphthous Stomatitis (RAS) is a common condition that affects a significant portion of the global population. Managing RAS involves employing various therapeutic approaches, including both topical and systemic treatments. Topical therapies, such as local anesthetics, corticosteroids, and anti-inflammatory agents, provide symptomatic relief and promote ulcers' healing. For more severe or refractory cases of RAS, systemic treatments can be considered. Medications like Colchicine, Dapsone, Clofazimine, levamisole, thalidomide, and Zinc supplements are potential options in this regard. Additionally, herbal treatments like *Punica granatum* var. *pleniflora, Curcuma longa, Hangeshinto*, etc. show promise as alternative treatment choices for RAS with minimal adverse effects.

In cases where severe conditions require systemic treatment, concerns arise regarding the adverse effects associated with such medications. To mitigate these adverse effects, an alternative approach could involve exploring the use of herbal drugs as a substitute for systemic medications. Researchers should prioritize the development of a specialized dosage form that adheres to the oral mucosa through the utilization of mucoadhesive polymers. This novel dosage form can be combined with one or two herbal medications known for their analgesic, anti-inflammatory, anti-microbial, and wound healing properties. Such an innovative approach holds promise in providing effective relief while minimizing the potential drawbacks of traditional systemic treatments.

ACKNOWLEDGEMENT

The authors express their sincere thanks to the Honorable Chancellor and Vice-Chancellor of Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India, for their constant encouragement to carry out this work and also for providing necessary facilities for the same.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

ABBREVIATIONS

RAS: Recurrent aphthous stomatitis; **RAU:** Recurrent aphthous ulceration; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **ECM:** Extracellular matrix; **Hsp:** Heat shock protein; **TLR2:** Toll-like receptor-2; **ICAM-1:** intercellular adhesion molecule-1; **IL:** Interleukins; **NF-κB:** Nuclear factor-kappa B; **MAPK:** Mitogen-activated protein kinase; **TNF:** Tumor Necrosis Factor.

REFERENCES

1. Chiang CP, Yu-Fong Chang J, Wang YP, Wu YH, Wu YC, Sun A. Recurrent aphthous stomatitis - etiology, serum autoantibodies, anemia, hematinic deficiencies, and management. J Formos Med Assoc. 2019;118(9):1279-89. doi: 10.1016/J.JFMA.2018.10.023, PMID 30446298.
2. Belenguer-Guallar I, Jiménez-Soriano Y, Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis. A literature review. J Clin Exp Dent. 2014;6(2):e168-74. doi: 10.4317/jced.51401, PMID 24790718.
3. Manoj MA, Jain A, Madtha SA, Cherian TM. Prevalence and risk factors of recurrent aphthous stomatitis among college students at Mangalore, India. PeerJ. 2023;11:e14998. doi: 10.7717/peerj.14998, PMID 37214085.
4. Kaur R, Behl AB, Punia RS, Nirav K, Singh KB, Kaur S. Assessment of prevalence of recurrent aphthous stomatitis in the north Indian population: A cross-sectional study. J Pharm Bioallied Sci. 2021; 13(5);Suppl 1:S363-6. doi: 10.4103/jpbs.JPBS_581_20, PMID 34447110.
5. Mirowski GW, Mirowski GW, Rosengard HC, Messadi DV. Aphthous stomatitis [cited Dec 14, 2023]. Available from: https://emedicine.medscape.com/article/1075570-overview?form=fpf#a6.
6. Plewa MC, Chatterjee K. Aphthous stomatitis. Eur Handb dermatological treat. 3rd ed Published online 2022:67-71. doi: 10.1007/978-3-662-45139-7_6.
7. Sánchez J, Conejero C, Conejero R. Recurrent aphthous stomatitis. Actas Dermo-Sifiliogr (Engl). 2020;111(6):471-80. doi: 10.1016/J.ADENGL.2019.09.006.
8. Saikaly SK, Saikaly TS, Saikaly LE. Recurrent aphthous ulceration: a review of potential causes and novel treatments. https://doi.org/101080/0954663420171422079. J Dermatolog Treat. 2018;29(6):542-52. doi: 10.1080/09546634.2017.1422079, PMID 29278022.
9. Huling LB, Baccaglini L, Choquette L, Feinn RS, Lalla RV. Effect of stressful life events on the onset and duration of recurrent aphthous stomatitis. J Oral Pathol Med. 2012;41(2):149-52. doi: 10.1111/J.1600-0714.2011.01102.X, PMID 22077475.
10. Miura T, Ohtsuka M, Yamamoto T. Sweet's syndrome-like eruption in association with the exacerbation of Behçet's disease after the Great East Japan Earthquake. Actas Dermo Sifiliogr. 2017;108(1):70-2. doi: 10.1016/J.AD.2016.07.006, PMID 27543190.
11. Natah SS, Konttinen YT, Enattah NS, Ashammakhi N, Sharkey KA, Häyrinen-Immonen R. Recurrent aphthous ulcers today: a review of the growing knowledge. Int J Oral Maxillofac Surg. 2004;33(3):221-34. doi: 10.1006/IJOM.2002.0446, PMID 15287304.
12. Milia E, Sotgiu MA, Spano G, Filigheddu E, Gallusi G, Campanella V. Recurrent aphthous stomatitis (RAS): guideline for differential diagnosis and management. Eur J Paediatr Dent. 2022;23(1):73-8. doi: 10.23804/EJPD.2022.23.01.14, PMID 35274547.
13. Jinbu Y, Demitsu T. Oral ulcerations due to drug medications. Jpn Dent Sci Rev. 2014;50(2):40-6. doi: 10.1016/J.JDSR.2013.12.001.
14. Riera Matute G, Riera Alonso E. Recurrent aphthous stomatitis in rheumatology. Reumatol Clin. 2011;7(5):323-8. doi: 10.1016/j.reuma.2011.05.003, PMID 21925448.
15. Wray D, Graykowski EA, Notkins AL. Role of mucosal injury in initiating recurrent aphthous stomatitis. Br Med J (Clin Res Ed). 1981;283(6306):1569-70. doi: 10.1136/BMJ.283.6306.1569, PMID 6796169.

16. Stone OJ. Aphthous stomatitis (canker sores): a consequence of high oral submucosal viscosity (the role of extracellular matrix and the possible role of lectins). Med Hypotheses. 1991;36(4):341-4. doi: 10.1016/0306-9877(91)90007-L, PMID 1809853.
17. Espinoza I, Rojas R, Aranda W, Gamonal J. Prevalence of oral mucosal lesions in elderly people in Santiago, Chile. J Oral Pathol Med. 2003;32(10):571-5. doi: 10.1034/J.1600-0714.2003.00031.X, PMID 14632931.
18. McCartan BE, Lamey PJ, Wallace AM. Salivary cortisol and anxiety in recurrent aphthous stomatitis. J Oral Pathol Med. 1996;25(7):357-9. doi: 10.1111/J.1600-0714.1996.TB00278.X, PMID 8890048.
19. Kusiak A, Ossowska A, Grzybowska ME, Tchounwou PB, Ciesielska A, Kusiak A, *et al.* Changes in the oral cavity in menopausal women—A narrative review. Int J Environ Res Public Heal 253 2021; 19(1):253. 2022;19. doi: 10.3390/IJERPH19010253.
20. DONATSKY O, BENDIXEN G. *In vitro* demonstration of cellular hypersensitivity to strep 2A in recurrent phthous stomatitis by means of the leucocyte migration test. Acta Allergol. 1972;27(2):137-44. doi: 10.1111/J.1398-9995.1972.TB01410.X, PMID 5068538.
21. Shimoyama T, Horie N, Kato T, Kaneko T, Komiyama K. Helicobacter pylori in oral ulcerations. J Oral Sci. 2000;42(4):225-9. doi: 10.2334/JOSNUSD.42.225, PMID 11269381.
22. Sun A, Chang JG, Chu CT, Liu BY, Yuan JH, Chiang CP. Preliminary evidence for an association of Epstein-Barr virus with pre-ulcerative oral lesions in patients with recurrent aphthous ulcers or Behiçet's disease. J Oral Pathol Med. 1998;27(4):168-75. doi: 10.1111/J.1600-0714.1998.TB01935.X, PMID 9563572.
23. Giannetti L, Murri Dello Diago A, Lo Muzio L. Recurrent aphtous stomatitis. Minerva Stomatol. 2018;67(3):125-8. doi: 10.23736/S0026-4970.18.04137-7, PMID 29332375.
24. Challacombe SJ, Alsahaf S, Tappuni A. Recurrent aphthous stomatitis: towards evidence-based treatment? Curr Oral Heal Rep. 2015;2(3):158-67. doi: 10.1007/S40496-015-0054-Y/TABLES/3.
25. Thomas DW, Bagg J, Walker DM. Characterisation of the effector cells responsible for the *In vitro* cytotoxicity of blood leucocytes from aphthous ulcer patients for oral epithelial cells. Gut. 1990;31(3):294-9. doi: 10.1136/GUT.31.3.294, PMID 2323592.
26. Phipps PA, Stanford MR, Sun JB, Xiao BG, Holmgren J, Shinnick T, *et al.* Prevention of mucosally induced uveitis with a HSP60-derived peptide linked to cholera toxin B subunit. Eur J Immunol. 2003;33(1):224-32. doi: 10.1002/IMMU.200390025, PMID 12594851.
27. Hasan A, Shinnick T, Mizushima Y, Van Der Zee R, Lehner T. Defining a T-cell epitope within HSP 65 in recurrent aphthous stomatitis. Clin Exp Immunol. 2002;128(2):318-25. doi: 10.1046/J.1365-2249.2002.01757.X, PMID 11985522.
28. Hasan A, Childerstone A, Pervin K, Shinnick T, Mizushima Y, Van Der Zee R, *et al.* Recognition of a unique peptide epitope of the mycobacterial and human heat shock protein 65-60 antigen by T cells of patients with recurrent oral ulcers. Clin Exp Immunol. 1995;99(3):392-7. doi: 10.1111/J.1365-2249.1995.TB05563.X, PMID 7533679.
29. Gallo C, Barros F, Sugaya N, Nunes F, Borra R. Differential expression of toll-like receptor mRNAs in recurrent aphthous ulceration. J Oral Pathol Med. 2012;41(1):80-5. doi: 10.1111/J.1600-0714.2011.01047.X, PMID 21554403.
30. Seoudi N, Bergmeier LA, Hagi-Pavli E, Bibby D, Curtis MA, Fortune F. The role of TLR2 and 4 in Behçet's disease pathogenesis. Innate Immun. 2014;20(4):412-22. doi: 10.1177/1753425913498042, PMID 23940075.
31. Poulter LW, Lehner T. Immunohistology of oral lesions from patients with recurrent oral ulcers and Behçet's syndrome. Clin Exp Immunol. 1989;78(2):189-95. PMID 12412747.
32. Savage NW, Seymour GJ, Kruger BJ. T-lymphocyte subset changes in recurrent aphthous stomatitis. Oral Surg Oral Med Oral Pathol. 1985;60(2):175-81. doi: 10.1016/0030-4220(85)90287-7, PMID 3162131.
33. Healy CM, Thornhill MH. Induction of adhesion molecule expression on blood vessels and keratinocytes in recurrent oral ulceration. J Oral Pathol Med. 1999;28(1):5-11. doi: 10.1111/J.1600-0714.1999.TB01986.X, PMID 9890450.
34. Akintoye SO, Greenberg MS. Recurrent aphthous stomatitis. Dent Clin North Am. 2014;58(2):281-97. doi: 10.1016/J.CDEN.2013.12.002, PMID 24655523.
35. Montgomery-Cranny JA, Wallace A, Rogers HJ, Hughes SC, Hegarty AM, Zaitoun H. Management of recurrent aphthous stomatitis in children. Dent Update. 2015;42(6):564-72. doi: 10.12968/DENU.2015.42.6.564, PMID 26506812.
36. Altenburg A, Abdel-naser MB, Seeber H, Abdallah M, Zouboulis CC. Practical aspects of management of recurrent aphthous stomatitis. J Eur Acad Dermatol Venereol. 2007;21(8):1019-26. doi: 10.1111/J.1468-3083.2007.02393.X, PMID 17714120.
37. RATTAN J, SCHNEIDER M, ARBER N, GORSKY M, DAYAN D. Sucralfate suspension as a treatment of recurrent aphthous stomatitis. J Intern Med. 1994;236(3):341-3. doi: 10.1111/J.1365-2796.1994.TB00805.X, PMID 8077892.
38. Lalla RV, Choquette LE, Feinn RS, Zawistowski H, Latortue MC, Kelly ET, *et al.* Multivitamin therapy for recurrent aphthous stomatitis: A randomized, double-masked, placebo-controlled trial. J Am Dent Assoc. 2012;143(4):370-6. doi: 10.14219/JADA.ARCHIVE.2012.0179, PMID 22467697.
39. ***39***. Scopus preview - Scopus - Document details - the efficacy of sucralfate and chlorhexidine as an oral rinse in patients with recurrent aphthous stomatitis.
40. Skaare AB, Herlofson BB, Barkvoll P. Mouthrinses containing triclosan reduce the incidence of recurrent aphthous ulcers (RAU). J Clin Periodontol. 1996;23(8):778-81. doi: 10.1111/J.1600-051X.1996.TB00609.X, PMID 8877665.
41. Barrons RW. Treatment strategies for recurrent oral aphthous ulcers. Am J Health Syst Pharm. 2001;58(1):41-50; quiz 51. doi: 10.1093/AJHP/58.1.41, PMID 11194135.
42. Taylor LJ, Walker DM, Bagg J. A clinical trial of prostaglandin E2 in recurrent aphthous ulceration. Br Dent J. 1993;175(4):125-9. doi: 10.1038/sj.bdj.4808250, PMID 8357678.
43. Altenburg A, Zouboulis C. Current concepts in the treatment of recurrent aphthous stomatitis. Skin Therapy Lett Published online 2008.
44. Field EA, Allan RB. Review article: oral ulceration--aetiopathogenesis, clinical diagnosis and management in the gastrointestinal clinic. Aliment Pharmacol Ther. 2003;18(10):949-62. doi: 10.1046/J.1365-2036.2003.01782.X, PMID 14616160.
45. Ruah CB, Stram JR, Chasin WD. Treatment of severe recurrent aphthous stomatitis with colchicine. Arch Otolaryngol Head Neck Surg. 1988;114(6):671-5. doi: 10.1001/ARCHOTOL.1988.01860180085037, PMID 3284550.
46. Gatot A, Tovi F. Colchicine therapy in recurrent oral ulcers. Arch Dermatol. 1984;120(8):994-. doi: 10.1001/ARCHDERM.1984.01650440024010, PMID 6465923.
47. Katz J, Langevitz P, Shemer J, Barak S, Livneh A. Prevention of recurrent aphthous stomatitis with colchicine: an open trial. J Am Acad Dermatol. 1994; 31(3 Pt 1):459-61. doi: 10.1016/S0190-9622(94)70211-X, PMID 8077473.
48. Grinspan D, Blanco GF, Agüero S. Treatment of aphthae with thalidomide. J Am Acad Dermatol. 1989;20(6):1060-3. doi: 10.1016/S0190-9622(89)70132-8, PMID 2754056.
49. Lynde CB, Bruce AJ, Rogers RS. Successful treatment of complex aphthosis with colchicine and dapsone. Arch Dermatol. 2009;145(3):273-6. doi: 10.1001/ARCHDERMATOL.2008.591, PMID 19289756.
50. H M Liu, W J Hsieh, C C Yang, V C Wu, K D Wu, Leukoencephalopathy induced by levamisole alone for the treatment of recurrent aphthous ulcers, Neurology. 2006;67(6):1065-7. doi: 10.1212/01.wnl.0000237344.06122.79.
51. Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. J Am Acad Dermatol. 2001;45(3):420-34. doi: 10.1067/MJD.2001.114733, PMID 11511841.
52. Kumar B, Kaur S, Kaur I, Gangowar DN. More about clofazimine--3 years experience and review of literature. Indian J Lepr Published online. 1987;59(1):63-74. PMID 3611862.
53. de Abreu MAMM, Hirata CHW, Pimentel DRN, Weckx LLM. Treatment of recurrent aphthous stomatitis with clofazimine. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;108(5):714-21. doi: 10.1016/J.TRIPLEO.2009.05.009, PMID 19699111.
54. Sharma S, Ali FM, Saraf K, Mudhol A. Anti-helminthic drugs in recurrent apthous stomatitis: A short review. J Pharm Bioallied Sci. 2014;6(2):65-8. doi: 10.4103/0975-7406.129169, PMID 24741272.
55. Meyer JD, Degraeve M, Clarysse J, De Loose F, Peremans W. Levamisole in aphthous stomatitis: evaluation of three regimens. Br Med J. 1977;1(6062):671-4. doi: 10.1136/BMJ.1.6062.671, PMID 321087.
56. Deng Y, Wei W, Wang Y, Pan L, Du G, Yao H, *et al.* A Randomized controlled clinical trial on dose optimization of thalidomide in maintenance treatment for recurrent aphthous stomatitis. J Oral Pathol Med. 2022;51(1):106-12. doi: 10.1111/JOP.13259, PMID 34773292.
57. Hello M, Barbarot S, Bastuji-Garin S, Revuz J, Chosidow O. Use of thalidomide for severe recurrent aphthous stomatitis: A multicenter cohort analysis. Med (Baltim). 2010;89(3):176-82. doi: 10.1097/MD.0b013e3181dfca14, PMID 20453604.
58. Porter SR, Hegarty A, Kaliakatsou F, Hodgson TA, Scully C. Recurrent aphthous stomatitis. Clin Dermatol. 2000;18(5):569-78. doi: 10.1016/S0738-081X(00)00147-4, PMID 11134852.
59. Mimura MAM, Hirota SK, Sugaya NN, Sanches JA, Migliari DA. Systemic treatment in severe cases of recurrent aphthous stomatitis: an open trial. Clinics (Sao Paulo). 2009;64(3):193-8. doi: 10.1590/S1807-59322009000300008, PMID 19330244.
60. Halboub E, Al-Maweri SA, Parveen S, Al-Wesabi M, Al-Sharani HM, Al-Sharani A, *et al.* Zinc supplementation for prevention and management of recurrent aphthous stomatitis: a systematic review. J Trace Elem Med Biol. 2021;68:126811. doi: 10.1016/J.JTEMB.2021.126811, PMID 34146924.
61. Sharquie KE, Najim RA, Al-Hayani RK, Al-Nuaimy AA, Maroof DM. The therapeutic and prophylactic role of oral zinc sulfate in management of recurrent aphthous stomatitis (ras) in comparison with dapsone. Saudi Med J. 2008;29(5):734-8. PMID 18454224.
62. Li CL, Huang HL, Wang WC, Hua H. Efficacy and safety of topical herbal medicine treatment on recurrent aphthous stomatitis: A systemic review. Drug Des Dev Ther. 2016;10:107-15. doi: 10.2147/DDDT.S96589, PMID 26770058.
63. Gavanji S, Larki B, Bakhtari A. Comparative analysis of extract of *Punica granatum var. pleniflora* (Golnar-e-Farsi) to some antibiotics on pathogens. 2015;18(1):168-78. doi: 10.1080/0972060X.2014.960272. doi: 10.1080/0972060X2014960272.
64. Ghalayani P, Zolfaghary B, Farhad AR, Tavangar A, Soleymani B. The efficacy of *Punica granatum* extract in the management of recurrent aphthous stomatitis. J Res Pharm Pract. 2013;2(2):88-92. doi: 10.4103/2279-042X.117389, PMID 24991610.
65. Aslani A, Zolfaghari B, Davoodvandi F. Design, formulation and evaluation of an oral gel from *Punica granatum* Flower extract for the treatment of recurrent aphthous stomatitis. Adv Pharm Bull. 2016;6(3):391-8. doi: 10.15171/APB.2016.051, PMID 27766223.
66. Gavanji S, Larki B, Bakhtari A. The effect of extract of *Punica granatum var. pleniflora* for treatment of minor recurrent aphthous stomatitis. Integr Med Res. 2014;3(2):83-90. doi: 10.1016/J.IMR.2014.03.001, PMID 28664082.
67. Gharibpour F, Fakheran O, Parvaneh A, Shirban F, Bagherniya M, Sathyapalan T, *et al.* The clinical use of *curcumin* for the treatment of recurrent aphthous stomatitis: A

systematic review of clinical trials. Adv Exp Med Biol. 2021;1291:229-38. doi: 10.1007/978-3-030-56153-6_13, PMID 34331693.

68. Al-Maweri SA, Alaizari N, Alharbi AA, Alotaibi SA, AlQuhal A, Almutairi BF, *et al.* Efficacy of curcumin for recurrent aphthous stomatitis: a systematic review. J Dermatolog Treat. 2022;33(3):1225-30. doi: 10.1080/09546634.2020.1819529, PMID 32893718.
69. Kia SJ, Mansourian A, Basirat M, Akhavan M, Mohtasham-Amiri Z, Moosavi MS. New concentration of curcumin orabase in recurrent aphthous stomatitis: A randomized, controlled clinical trial. J Herb Med. 2020;22:100336. doi: 10.1016/J.HERMED.2020.100336.
70. Hitomi S, Ujihara I, Ono K. Pain mechanism of oral ulcerative mucositis and the therapeutic traditional herbal medicine *Hangeshashinto*. J Oral Biosci. 2019;61(1):12-5. doi: 10.1016/J.JOB.2019.01.004, PMID 30929796.
71. Hitomi S, Ono K, Yamaguchi K, Terawaki K, Imai R, Kubota K, *et al.* The traditional Japanese medicine *Hangeshashinto* alleviates oral ulcer-induced pain in a rat model. Arch Oral Biol. 2016;66:30-7. doi: 10.1016/J.ARCHORALBIO.2016.02.002, PMID 26878477.
72. Mahboubi M. *Myrtus communis* L. and its application in treatment of Recurrent Aphthous Stomatitis. J Ethnopharmacol. 2016;193:481-9. doi: 10.1016/J.JEP.2016.09.054, PMID 27693775.
73. Romero-Cerecero O, Zamilpa A, Tortoriello J. Pilot study that evaluated the clinical effectiveness and safety of a phytopharmaceutical elaborated with an extract of *Ageratina pichinchensis* in patients with minor recurrent aphthous stomatitis. J Ethnopharmacol. 2015;173:225-30. doi: 10.1016/J.JEP.2015.06.021, PMID 26102552.
74. Babaee N, Zabihi E, Mohseni S, Moghadamnia AA. Evaluation of the therapeutic effects of *Aloe vera* gel on minor recurrent aphthous stomatitis. Dent Res J (Isfahan). 2012;9(4):381-5. PMID 23162576.
75. Yousef NJ, Aljoujou AA, Mashlah AM, Hajeer MY. Assessment of the effectiveness of *Aloe vera* Versus amlexanox in the treatment of recurrent aphthous ulcers: A three-arm placebo-controlled randomized clinical trial. Cureus. 2022;14(10):e30693. doi: 10.7759/CUREUS.30693, PMID 36320801.
76. Mansour G, Ouda S, Shaker A, Abdallah HM. Clinical efficacy of new aloe vera- and myrrh-based oral mucoadhesive gels in the management of minor recurrent aphthous stomatitis: a randomized, double-blind, vehicle-controlled study. J Oral Pathol Med. 2014;43(6):405-9. doi: 10.1111/JOP.12130, PMID 24164309.
77. Molania T, Malekzadeh Shafaroudi A, Saeedi M, Moosazadeh M, Valipour F, Rostamkalaei SS, *et al.* Evaluation of cinnamaldehyde mucoadhesive patches on minor recurrent aphthous stomatitis: a randomized, double-blind, placebo-controlled clinical trial. BMC Oral Health. 2022;22(1):235. doi: 10.1186/s12903-022-02248-5, PMID 35701773.
78. Akbari N, Asadimehr N, Kiani Z. The effects of licorice containing diphenhydramine solution on recurrent aphthous stomatitis: A double-blind, randomized clinical trial. Complement Ther Med. 2020;50:102401. doi: 10.1016/J.CTIM.2020.102401, PMID 32444056.
79. Ha MT, Vu NK, Tran TH, Kim JA, Woo MH, Min BS. Phytochemical and pharmacological properties of *Myristica Fragrans* Houtt.: an updated review. Arch Pharm Res. 2020;43(11):1067-92. doi: 10.1007/S12272-020-01285-4, PMID 33206347.
80. Dechayont B, Phuaklee P, Chunthorng-Orn J, Poomirat S, Juckmeta T, Phumlek K, *et al.* Antimicrobial, anti-inflammatory, and antioxidant activities of the wood of *Myristica Fragrans*. 2019;26(1):49-60. doi: 10.1080/10496475.2019.1676861. doi: 10.1080/1049647520191676861.
81. Suthisamphat N, Dechayont B, Phuaklee P, Prajuabjinda O, Vilaichone RK, Itharat A, *et al.* Anti-Helicobacter pylori, anti-inflammatory, cytotoxic, and Antioxidant Activities of Mace Extracts from *Myristica Fragrans*. Evid Based Complement Alternat Med. 2020; 2020:7576818. doi: 10.1155/2020/7576818, PMID 32308716.
82. Ozaki Y, Soedigdo S, Wattimena YR, Suganda AG. Antiinflammatory effect of Mace, aril of *Myristica Fragrans* HOUTT., and its active principles. Jpn J Pharmacol. 1989;49(2):155-63. doi: 10.1254/jjp.49.155, PMID 2487032.
83. Stohs SJ, Bagchi D. Antioxidant, anti-inflammatory, and chemoprotective Properties of Acacia catechu Heartwood Extracts. Phytother Res. 2015;29(6):818-24. doi: 10.1002/PTR.5335, PMID 25802170.
84. Yimam M, Brownell L, Hodges M, Jia Q. Analgesic Effects of a Standardized Bioflavonoid Composition from Scutellaria baicalensis and Acacia catechu. http://dx.doi.org/103109/1939021120127087l3. J Diet Suppl. 2012;9(3):155-65. doi: 10.3109/19390211.2012.708713, PMID 22877413.
85. Qomaladewi NP, Aziz N, Kim MY, Cho JY. *Piper cubeba* L. Methanol Extract Has Anti-Inflammatory Activity Targeting Src/Syk via NF-κB Inhibition. Evid Based Complement Alternat Med. 2019; 2019:1548125. doi: 10.1155/2019/1548125, PMID 30713566.

Cite this article: Rastogi V, Porwal M, Verma A, Khan U, Chauhan P, Kumar P. A Review on Pharmacological Potential of Various Synthetic and Phytoconstituents in Managing Recurrent Aphthous Stomatitis. Int. J. Pharm. Investigation. 2024;14(2):327-37.