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## **A systematic review on herbal phytoconstituents and their antimicrobial potential in the treatment of recurrent aphthous stomatitis**

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### **Abstract**

Today dental diseases have become a big hurdle in day-to-day life. The Major causes of the various dental diseases are Environmental factors, Microbial infection, and Eating habits. Recurrent Aphthous stomatitis (RAS) is a type of mouth ulcer caused by tissue inflammation. The main cause of Recurrent Aphthous stomatitis is unknown but few chances are due to Trauma, Infection, and Digestive problem. There are many natural herbs that act on RAS. The general herbs are Tulsi, Clove, Garlic, Cinnamon, Chamomile, Aloe vera, and Turmeric. These herbs have been applied for dentistry since pre-historic times in different kinds of societies for both therapeutic and preventive oral health care. The Phytochemical/Phytoconstituent present in medicinal herbs has a complementary approach to dental health maintenance, Therapy & support. Herbal medicine has been used in the treatment of RAS for reducing pain and promoting ulcer healing. Most of the herbal products are in the form of mouthwashes. Herbal medicine is also used as an alternative therapy for RAS. This reviewed article has the main aim to pay attention to the various herbal product which are used in the RAS and investigate their efficiency in the treatment of RAS.

**Keywords:** Recurrent aphthous stomatitis, phytoconstituent, herbal products

### **Introduction**

From the ancient era, human has searched the various kind of medicine to treat human ailments. Today people are suffering from various kinds of dental diseases in which Recurrent Aphthous stomatitis is very common. There are various types of herbal products, that are available to treat this problem. The general herbs we used, to treat the disease are Turmeric, Aloe vera, and Tulsi. These herbs have an impactful effect on Recurrent Aphthous Stomatitis. It is a deep concern to study how herbal drug can show their activity and cure such kind of dental disease. Since RAS is not only defined to a specific age group but also affects both genders equally. There are various etiopathogenic factors associated with this disease. This disease not only causes physical injury but also affects psychologically to the patient. Patients are unable to perform their routine work including that of mastication, swallowing, and speaking. Previous researches suggest that RAS incidence is linked to changes in the oral microbiome. According to previous studies, a decreased population of Streptococcus salivarius and an increased population of Acinetobacter are observed in RAS incidences. RAS was also observed in patients infected with Helicobacter pylori. Heat shock proteins of streptococci may also be involved in disease pathogenesis by inducing immunopathological reactions which result in RAS lesions This review article helps us to understand the work and mechanism of herbal drugs to cure the disease.

### **Recurrent Aphthous Stomatitis**

RAS is the most common oral mucosal pathos. It is also called canker sores. On average, the prevalence rate is 50-86%. There are various etiopathogenic factors responsible for the occurrence of this disease. Analysis of the peripheral blood in patients with aphthae shows a decreased ratio of CD4+ to CD8+ T lymphocytes, increased T cell-receptor gamma cells, and increased tumor necrosis factor-  $\alpha$ . Histological proofs of epithelial destruction are actually the results of these lymphocytes. Various associated systemic disorders include Celiac Disease, Bechet's Syndrome, Cyclic neutropenia, IgA deficiency, Sweet's syndrome, etc.

## Causes

**Various causes are associated with RAS. These include**

- 1) Genetic predisposition
- 2) Allergies
- 3) Hematological abnormalities
- 4) Immunological and Hormonal factors.
- 5) Stress
- 6) Smoking
- 7) Trauma
- 8) Nutritional deficiencies. Etc.

RAS demonstrates a definite tendency to occur along blood relations. When both parents are infected, their children develop lesions as well. Stress, associated with immune response, directly correlates with the presence of aphthous stomatitis in some groups. In patients, with AIDS, an increased surge of RAS is seen, since an elevated CD8+/CD4+ ratio is the result of the reduction of CD4+ T Lymphocytes. Keratinization plays a vital role in the prevention of aphthous stomatitis. A person involved in smoking may witness RAS, in case of smoking cessation since the level of oral temperature and keratinization decreases. The increased mucosal barrier has been correlated with decreased chances of ulcers. Certain allergic substances that play a role in occurrence include sodium lauryl sulfate, toothpaste, various allopathic drugs, nuts, flavoring agents, dyes, tomatoes, etc. Accidental trauma including cheek bites, may also result in ulceration, which may represent clinical pictures with that of RAS. In a study, it has been found that people with abnormal sleep cycles possess a greater threat to RAS than that with proper sleep and rest.

It is evident that the cause of RAS may not be caused by a single factor but a combination of two or more, resulting in the final picture of the disease. Various clinical pictures are associated which provide sufficient information on the actual cause of the same.

## Clinical Features

The majority of affected individuals present their first case at an age, less than that of 32 years. The following are major clinical variations observed, in the case of RAS: -

1. Minor aphthous ulceration
2. Major aphthous ulceration
3. Herpetiform aphthous ulcerations.

## Minor Aphthous Ulceration

It represents a picture of the smallest lesion of all three. Patients with minor aphthous ulceration experience the least recurrence rate. The ulceration demonstrates a yellowish-white, removable fibrin-purulent membrane that is encircled by an erythematous halo. The average size of ulceration remains between 2.5-8.5 mm and heals completely without scar in 12-14 days. The most common site of infection includes labial and buccal mucosa which are non-keratinized in nature. Involvement of other parts including that of the palate, gingival, dorsal surface of the tongue, etc.

is seen occasionally. The recurrence rate is highly variable, from one ulcer in many years to 2-3 ulcers per month.



**Fig 1:** Major Aphthous Ulceration

These ulcers represent the longest duration of occurrence. They are larger in size than minor aphthous ulcers. The average size is generally between 1.25 cm to 2.75 cm. In contrast to minor aphthous ulcers which are more than one at a specific site, these lesions usually restrict to one. These ulcers are deeper as compared to minor ulcers and usually take a longer time for healing. The average time of healing is anywhere between 4-6 weeks. Labial mucosa, soft palate, and tonsillar fauces are involved most commonly. The onset of the lesion usually takes after puberty, and recurrent episodes may continue to develop for up to 20 years. Sometimes, mouth opening also gets affected due to the increased size of lesions.



**Fig 2:** Herpetiform Aphthous Ulceration

It represents the greatest number of lesions and the most frequent recurrences. The individual lesions are small with an average size of 0.75 mm to 2.25 mm. Because of their small size and large number, the lesions bear a superficial resemblance to a primary HSV infection, leading to a confusing designation, herpetiform. It is common that single lesions are combined together and form large lesions. Recurrence is high, in the first three years of the infected stage. This disease is highly female predominance and

typically onset in adulthood. The most common sites of occurrence are non-keratinized movable mucosa.



**Fig 3:** Histopathological Features

The early ulcerative lesions demonstrate a central zone of ulceration which is covered by a fibrinopurulent membrane. Deep to it, lies connective tissue with increased vascularity and a mixed inflammatory cellular infiltrate that consists of lymphocytes, histiocytes, and polymorphonuclear leukocytes. The epithelium at the margin of the lesion demonstrates spongiosis and numerous mononuclear cells in basilar one-third. A band of lymphocytes intermixed with histiocytes is present in superficial connective tissue and surrounding deep blood vessels.

#### **Herbal medicine used for the treatment of Recurrent Aphthous Stomatitis**

Medicinal plants are a rich source that has been used for centuries to treat various diseases. There are numerous herbal plants with a high-efficiency of medicinal properties. The parts of a plant can be used to treat many types of diseases. In this article, we have focused on the medicinal activity of three Plants only. Turmeric, Aloe vera, and Tulsi.

#### **Turmeric**

The botanical name of turmeric is *Curcuma Longa* Linn. Its chief active constituent is curcumin and which possessed anti-inflammatory, analgesic, and anti-bacterial. Curcumin has antioxidant and anti-inflammatory properties, which can reduce inflammation in ulcers and counteract free radicals' negative action, thereby accelerating ulcer healing. The saponin is present in compounds with antibacterial properties because it can damage the bacterial cell wall and inhibit the cell division of the bacteria. Through this

mechanism, mucous cells are more protected, increasing cell viability and reducing erythema during inflammation.

Turmeric includes volatile oil (6%) composed of a number of monoterpenes and sesquiterpenes, including zingiberene, curcumin,  $\alpha$ - and  $\beta$ -turmerone among others. The colouring principles (5%) are curcuminoids, 50-60% of which are a mixture of curcumin. The effect of turmeric on dental disease is Anti-carcinogenic, antibacterial, halitosis, pit and fissure sealant, and dental plaque detection system. Massaging the aching teeth with roasted, ground turmeric eliminates pain and swelling.

#### **Antimicrobial Potential of Curcumin**

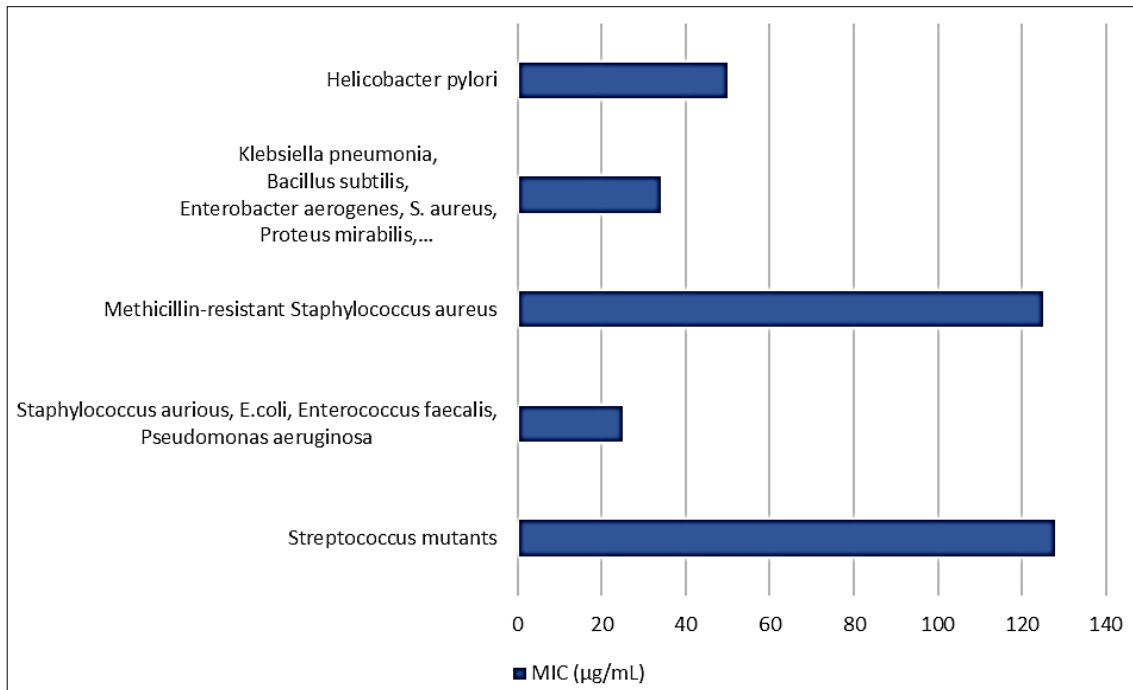
Curcumin is a bioactive substance that is present in turmeric and has strong antibacterial, antifungal, antiviral, anti-inflammatory, and antioxidant properties. Previous studies show that curcumin is effective against over 100 strains of pathogens belonging to 19 species.

Curcumin shows a positive result as an alternative against minor RAS. The strong antimicrobial activity of curcumin helps to eradicate the microbes which may play an important role in the etiopathology of RAS and thus contribute to improving healing and reducing ulcer size. Curcumin shows a bacteriostatic effect against both gram-positive and gram-negative bacteria. According to the current finding of the *In-vitro* research study curcumin inhibited the growth of all *Helicobacter Pylori* species in patients suffering from gastrointestinal disorders *in-vitro*.

Curcumin has a broad range of mechanistic pathways which may include DNA replication inhibition, modifications in plasmid gene expression, cell membrane deterioration, and motility reduction.

Moreover, curcumin also helps in decreasing the antimicrobial resistance in pathogens by restoring the effectiveness of ineffective antimicrobials by reducing their minimum inhibitory concentrations (MIC). In combination with other antibiotic curcumin slightly decreases the viable cell count and decrease the microbial colonies *in-vitro*.

A Summary of experimental studies on the antibacterial effect of Curcumin on different microorganisms is illustrated in Figure 4. This demonstrates the effect of different MIC on different pathogens including *Helicobacter pylori*, *Klebsiella pneumonia*, *Bacillus subtilis*, *Enterobacter aerogenes*, *S. aureus*, *Proteus mirabilis*, *P. aeruginosa*, *Escherichia coli*, Methicillin-resistant *Staphylococcus aureus*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Streptococcus mutans*.



**Fig 4:** An overview of the experimental studies on the antibacterial effect of curcumin

**Tulsi**

*Ocimum sanctum* Linn (Tulsi), an odoriferous herb, belongs to the family Labiatae. "Tulsi" in Sanskrit means "the incomparable one" hence called as the queen of herbs. The herb helps in the treatment of various oral disorders.

Fresh leaves and stem of *Ocimum sanctum* extract yielded some phenolic compounds (antioxidants) such as curvilineal, circimaritin, is thymosin, apigenin and rosameric acid, and appreciable quantities of eugenol. The leaves of *Ocimum sanctum* contain 0.7% volatile oil comprising about 71% eugenol and 20% methyl eugenol. The oil also consists of carvacrol and sesquiterpene hydrocarbon caryophyllene. Two flavonoids orientin and vicenin from the aqueous leaf extract of *Ocimum sanctum* have been isolated.

**Antimicrobial Potential of *Ocimum sanctum***

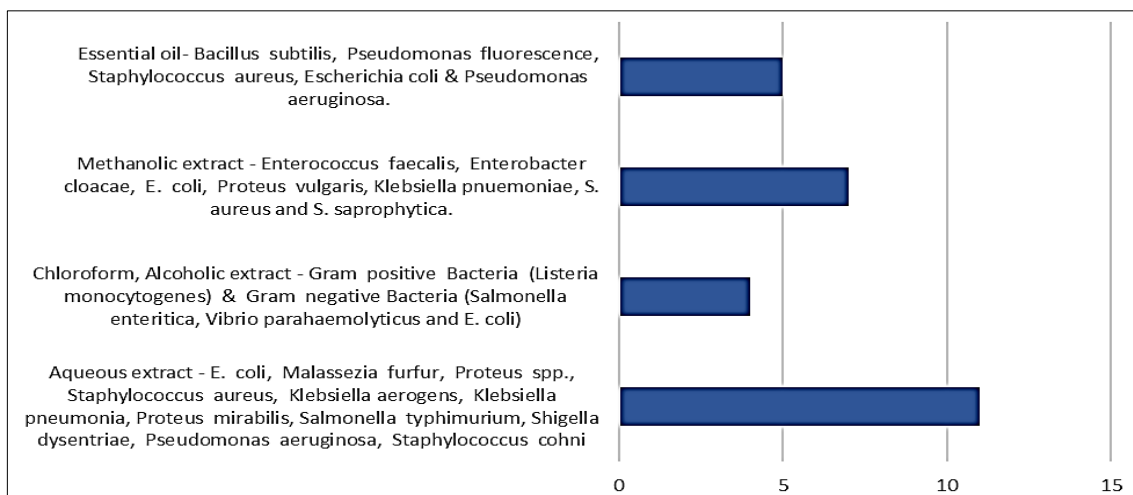
*Ocimum* and its constituents have anti-inflammatory, antioxidant, immunomodulatory, and antimicrobial properties. *Ocimum* shows growth-inhibiting properties

against *E. coli*, *Staphylococcus aureus*, *Klebsiella*, *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis* and *Prevotella intermedia*, *Streptococcus mutans*, and *Lactobacillus acidophilus*.

Researchers have reported that extracts of *Ocimum sanctum* are active against streptococcus mutants and *Lactobacillus acidophilus* which causes dental caries. The research was conducted in which the MIC of *Ocimum* is determined using the serial dilution method. The MIC was 2.5% (25 mg/ml) against streptococcus mutants and 10% (100 mg/ml) against *Lactobacillus acidophilus*.

Furthermore, research indicates that *Ocimum* leaves have higher concentrations of linoleic acid in fixed oil of *Ocimum* extracts which shows an antibacterial effect against *P. aeruginosa*, *S. aureus*, *Bacillus*, and *S. aureus*.

Another finding indicates that the aqueous extracts of *Ocimum* leaves show strong antifungal and antibacterial activity against *Candida albicans*, *E. coli*, *Proteus*, *S. Aureus*, *Shigella*, *P. aeruginosa*, *Aeromonas hydrophila*, *Enterococcus faecalis*, and *Klebsiella*.



**Fig 5:** Antimicrobial activity of different *Ocimum sanctum* (Tulsi) Extracts

The broad effect of different ocimum extracts on different pathogens is illustrated in Figure 5.

**Aloe vera**

*Aloe barbadensis* Miller or Aleo is also known as Kumari, belonging to the family Asphodelaceae. Aloe leaves contain a clear gel and the green part of the leaf that surrounds the gel is used to produce juice or dried substance.

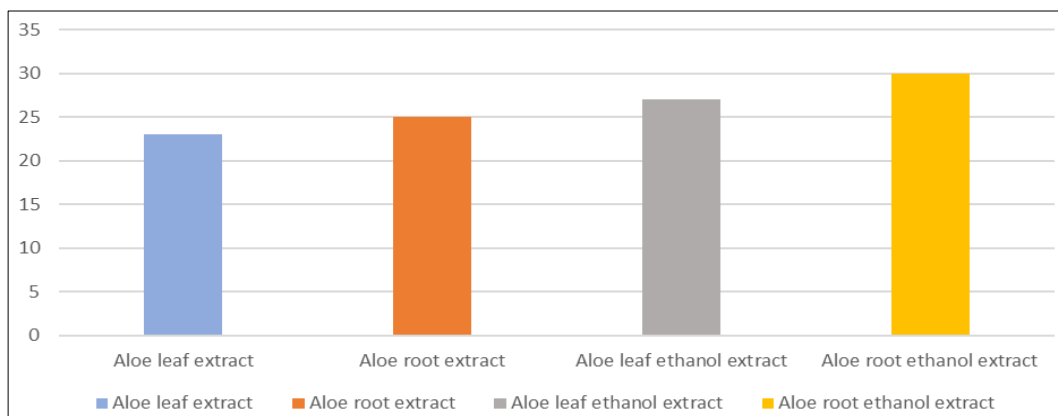
Chemical constituents: Aloins and barbadoins as the main chemical constituents. The chemical constituents in Aloe vera are Anthraquinones, Saccharides, Prostaglandins, and fatty acids. Others: Enzymes, amino acids, vitamins, minerals. Other compounds: Cholesterol, triglycerides, steroids, uric acid, lignins betasitosterol, gibberellin, salicylic a. Anthraquinone components of aloe vera are vitamins, enzymes, minerals, sugars, fatty acids, amino acids, and salicylic acid. Aloe vera (in the form of a gel) improves healing and so can be used for other skin lesions. Aloe juice can also be taken as a drink. This is used in conjunction with any topical treatment for skin lesions. The juice is also used as a strong detoxifying agent if it is used in conjunction. Aloe vera also brings relief to other oral disorders such as candidiasis, and desquamative gingivitis, and the applications in dentistry are producing a promising effect on the anti-inflammatory, antiviral, and immunological benefits on the dental disease.

In the case of Recurrent aphthous stomatitis, the daily dose of aloe vera juice is 1-3 tablespoons used as a mouthwash and then swallowed three times daily.

**Antimicrobial Potential of Aloe vera**

Aloe vera contains many pharmacological activities such as anti-microbial, antioxidant, wound healing, anti-inflammatory, and immunomodulating properties. Many findings indicate that microbial dysbiosis in the oral microbiome would cause RAS, so aloe vera gel is a good alternative for treating minor RAS. Many clinical trials support that aloe vera reduces ulcer size and promotes rapid healing. Aloe vera has bacteriostatic and bactericidal activity against *E. coli*, *Enterococcus faecalis*, and *Staphylococcus aureus*, which helps restore the oral microbiome. Aloe vera is said to promote healing by increasing collagen production and increasing the proliferation of epithelial and fibroblast.

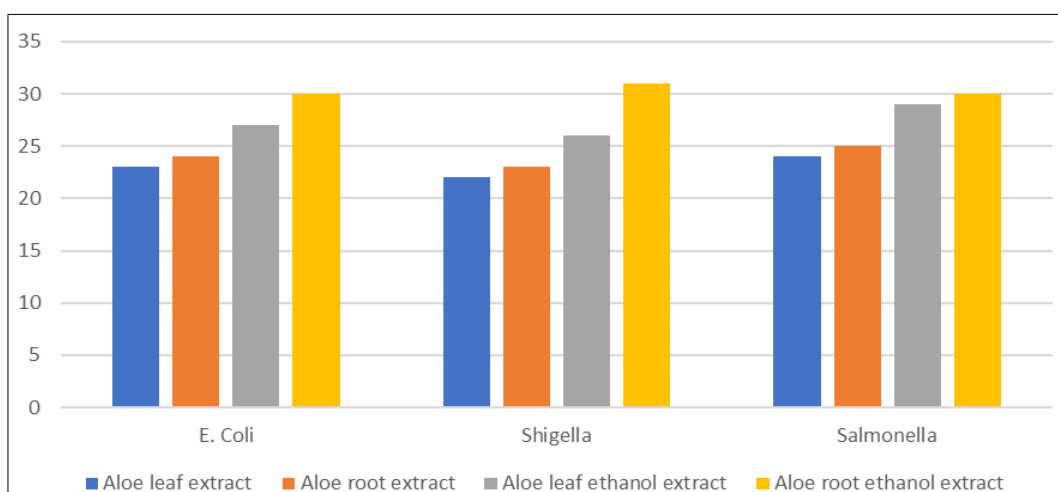
According to the findings, the different extracts of aloe vera have been evaluated against gram-positive and gram-negative bacteria by disc diffusion method and well diffusion method. The pure extracts of aloe vera leaf and root show quite zone of inhibition at 100 µl against gram-positive bacteria *S. aureus*. Whereas ethanol extracts of leaf and root show strong antibacterial activity as illustrated in Figure 6.



**Fig 6:** Effect of different aloe vera extracts on gram-positive bacteria *S. aureus*

The gram-negative species show quite sensitive reactions against pure extracts of aloe vera leaf and root. The ethanol extracts of aloe vera leaf and root show higher antibacterial

activity against gram-negative bacteria as illustrated in Figure 7.



**Fig 7:** Effect of different aloe vera extracts on gram-negative species *E. coli*, *Shigella* and *Salmonella*

### Summary and Conclusion

The following article states that there is a good impact of herbal drugs on dental diseases. Through this article, we have shown the effect of Turmeric, Aloe vera, and Tulsi on Recurrent Aphthous Stomatitis disease. The effect of microbe which causes the disease and the study of the anti-bacterial spectrum of the phytoconstituent of three different plants. Recurrent Aphthous Stomatitis is one of the major problems by which most of the population had been suffered or suffering now. Though the exact Etiology is not known, several factors combine together of cause and many factors play vital roles in treatment. Herbal treatment is the common, economical, and beneficial measure to treat such kind of disease. Nowadays wide research has been done to treat different kinds of health-related disorders. In this review article, we have shown the effectivity of the plant for the same dental disease and the microbial potential of three different herbal drugs which can be used as alternatives in treatment against allopathy in case of recurrent aphthous ulcers. All three drugs show antimicrobial activity against a broad range of pathogens that play a role in the progression of aphthous ulcers and some other diseases. The herbal drugs also increase the effectiveness of other antibiotics in combination against antimicrobial resistance which opens a large area for research.

By this review article, we have shown that there is a large scope of study of the phytoconstituent work on the treatment of Recurrent Aphthous Stomatitis and a large research study is needed in the future. The future scope of study involves the need for the isolation of the phytoconstituent responsible for the activities.

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