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A Review on unexplored Plants for Recurrent Aphthous Stomatitis

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Abstract : Recurrent Aphthous Stomatitis (RAS) is one of the most common pathological conditions with ulcers in the oral mucosa. Various conventional medicines are available in the market for RAS but due to a range of factors people are getting affected by RAS gradually. More over conventional medicines are all having the side effects so the alternative system for the treatment of RAS came in to the market. Although herbal medicines are widely used in India and other countries and multiple studies are conducted in this regard, but still many of the herbal plants are not utilized though they are having traditional claim. Aim of this is review is suggesting the herbal plants which are claimed for the treatment of mouth ulcer but scientifically validated for gastric ulcer by using animal models should also be validated for mouth ulcer by clinical trials and also which are used traditionally but not yet concentrated can be evaluated and used for the treatment of RAS..

Keywords : Recurrent Aphthous Ulcer (RAS), conventional medicines, Herbal and gastric ulcer.

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Introduction

An ulcer is found to be a well-circumscribed sometimes depressed lesion with an epithelial defect that is covered by a fibrin clot, leading to yellow-white appearance. Recurrent aphthous stomatitis (RAS) may be a sort of recurrent ulcer where it heals and reappears after a period of time. The term “aphthae” was first employed by Hippocrates¹. Recurrent aphthous ulcers (RAUs) are found to be one of the most common oral mucosal lesions, with about 5–25% of prevalence in the general population²⁻³. Though mostly they are self-limiting, they can affect the quality of life of the patients. RAU are often categorized into three different morphological types such as minor, major, and herpetiform aphthae. Minor aphthous is the most common subtype of the aphthous ulcers, which includes about 80%–85% of all RAUs⁴. The underlying aetiology of these ulcers remained unclear so far; however, the aetiological perspectives suggest that RAU is influenced by various factors such as genetics, nutritional deficiencies, and inflammatory conditions⁵. Other predisposing factors which can contribute to the formation of ulcers mechanical injuries, anxiety, some viral and bacterial infections, and certain allergic foods⁶. The choice of therapy for RAS depends upon the severity and frequency of ulceration, but the objectives of treatment are to alleviate discomfort, reduce secondary infection, promote healing of existing ulceration and prevent new ulcers occurring. Numerous treatment options are available which can be used based upon the severity of the disease (the amount of pain), the frequency of ulceration, and the potential adverse effects of the medications⁷. However, these therapies for aphthous ulcers are found to be producing unsatisfactory results and no optimal approach, due to the large effects produced. In today’s scenario many people prefer medicinal plants rather than conventional medicines for treating RAU.

Conventional treatment options are mentioned in table 1 and the various medicinal plants which have undergone clinical trials for this purpose are as listed in table 2

The various herbal medicaments available in market in India are

- Sorolin
- Smulcer
- HerbOpearl
- Safesmile
- Prince
- Hi Ora-SG
- Bioline

Table 1. Treatment options:

Category	Drug	Dosage form
Topical antiseptic	Chlorhexidine gluconate	Mouthwash
Topical analgesics	Benzydamine hydrochloride, Lignocaine	Mouthwash
Topical corticosteroids	Hydrocortisone hemisuccinate	pellets
	Triamcinolone acetonide	adhesive paste
	Betamethasone valerate,	mouthwash
	Beclometasone dipropionate (spray),	spray
	Budesonide	spray
	Triamcinolone	mouthwash
Topical antibiotic	Chlortetracycline	mouthwash
Systemic immunomodulators	Prednisolone, Azathioprine, Colchicine, Ciclosporin, Thalidomide	
Other therapies	Cimetidine, Low-energy laser, Carbenoxolone Levamisole, 5-Aminosalicylic acid Nicotine, Dapsone Interferon-a, Pentoxphylline, Sucralfate	

Table 2: Market available and scientifically validated herbals list:

Herb	Part used	Dosage form
<i>Chamomilla tincture</i>	Leaves	Mouthwash
<i>Ageratina pichinchensis</i>	Aerial parts	Paste
<i>Myrtus communis</i>	Leaves	Paste
<i>Yunnan baiyao</i>	Roots	Toothpaste
<i>Aloe vera</i>	Leaves	Oral mucoadhesive gel
<i>Myrrh</i>	Leaves	Oral mucoadhesive gel
<i>Rosa amascene</i>	Flowers	Mouthwash
<i>Purslane</i>	Leaves	Capsule
<i>Ginger</i>	Dried rhizome	Oral mucoadhesive gel
<i>LongoVital</i>	Leaves, flowers, seeds	Vitamin tablets
<i>Camel thorn</i>	Upper portion, roots, flowers	Mouthwash
<i>Turmeric</i>	Dried rhizome	Paste
<i>Rhizophora mangle</i> aqueous bark extract (RMABE)	Bark	Paste
<i>Satureja khuzistanica</i>	Flowers	Mouthwash
Essential oil of <i>Saturejakhuzistanica</i>	Leaves	Mouthwash
<i>Zataria multiflora</i>	Leaves	Mouthwash
<i>Anthemis nobilis</i>	Leaves	Mouthwash
<i>Myrtus communis</i>	Leaves	Mouthwash
<i>Olive</i>	Leaves	Mouthwash
<i>Zataria multiflora</i> + <i>Anthemisnobilis</i>	Leaves	Mouthwash
<i>Punica granatum</i>	Skin peel	Gel

However, none have explored the potential of some plants which have the benefits of treating aphthous ulcer. Hence, this review is aimed at highlighting those medicinal plants *Averrhoa bilimbi*, *Solanum nigrum*, *Cocos nucifera*, *Sesbania grandiflora*, *Papaver somniferum*, *Trigonella foenum - graecum* which can be used as a significant sources for treating aphthous ulcer in future.

1) *Solanum nigrum*:

Patel A et al investigated protective effect of *solanum nigrum* leaves against chemotherapy and chemoradiotherapy induced oral mucositis in rats. The two rat models employed for this study are busulfan and infrared radiation (chemoradiotherapy) induced oral mucositis and methotrexate (chemotherapy) induced oral mucositis. Numerous parameters including body weight change, food intake, and mortality were recorded. The extract showed promising results in higher doses. A reduction in oral mucositis score ($P < 0.05$) was observed in the treatment groups. Significant ($P < 0.05$) improvement in food intake was also observed in AESN treated groups. Thus, aqueous extract of *Solanum nigrum* leaves was found to be having protective effect on chemotherapy and chemoradiotherapy induced oral mucositis in rats⁸.

Leaves of *Solanum nigrum* have been used as traditional folk medicine by the residents of southern India to treat mouth ulcers⁸.

Muthukumar, A et al investigated the effect of aqueous extract of *Solanum nigrum* Linn leaves on irritable bowel syndrome and gastric ulcers. Ulcer protective and anti spasmotic effect was explored in cold

restraint stress, aspirin induced and pyloric ligated ulcer models on experimental rats. The extract of *Solanum nigrum* (SNALE) was administered orally in two doses of 200mg/kg, and 400mg/kg. The dose of 400mg/kg promisingly inhibited the gastric ulcer induced by all three models when compared with the serum parameters' like Pylorus ligated (PL), Aspirin induced ulcerogenesis (APL) and cold resistant stress induced ulcer (CRSU) with the standard drug omeprazole. Anti spasmodic effect of *Solanum nigrum* was measured by rat ileum contractility. The anti-spasmodic activity may be produced because of presence of quercetin. The aqueous leaf extract of *Solanum nigrum* promisingly ($p < 0.001$) inhibited ulcer index, total and free acidity and significantly ($p < 0.01$) indicates gastroprotective in pylorus ligation and aspirin induced gastric ulcer models. This extract also significantly ($p < 0.01$) indicates spasmolytic effect in ileum contraction model. These results recommend that aqueous extract of *Solanum nigrum* leaves shows gastro protective, spasmolytic effect and anti-secretory effect⁹.

Fresh leaves are cooked in the form of curries and consumed once a day for 10 to 15 days to get relieved from wheezing and mouth ulcer¹⁰⁻¹².

Figure 1: *Solanum nigrum*



2) *Sesbania grandiflora*:

J. A. A. Sertié *et al* evaluated the ethanolic extract of the bark of *S. grandiflora* prevented acute gastric injury in rats. Stress and non-steroidal anti-inflammatory drugs-induced lesions were considerably prevented by the extract. At a dose is of 36.75 mg/kg (ED50, p. o.) the extract did not altered the volume, pH and hydrochloric acid contents of gastric secretion. At the doses used for the animals had not produced any depressive, excitatory or sleepness symptoms, which explains that probably centrally acting components involved in antiulcer action are not present in the extract. The results suggest that *S. grandiflora* has antiulcer potential¹³.

The powdered bark is recommended for ulcers of the mouth and alimentary canal¹⁴⁻¹⁶.

Figure 2: *Sesbania grandiflora*



3) *Papaver somniferum*:

Though there is only a limited research carried out, anecdotal evidence recommends that poppy seeds can help cure mouth ulcers. Poppy seeds are found to produce cooling effect in the body, which act as a beneficial role in treating mouth ulcer. Usually they are mixed with grinded dry coconut, added with sugar, and powdered poppy seeds. Shape it into a pellet and suck on this for instant relief from mouth ulcers¹⁷.

Poppy juice is one of the traditional medicines used for ulcer treatment¹⁸.

Figure 3: *Papaver somniferum*



4) *Trigonella -foenum graecum*:

Azari O *et al* studied the protective effects of fenugreek seeds against experimental gastric ulcer in rats. For this study, 24 male rats were randomly separated into 4 groups. Control group are encountered with gastric ulcer (by ligating the pylorus). Treatment group was administered with fenugreek seeds extracting via oral gavage for 1 week before provoking gastric ulcer. Groups I and II were administered with normal saline and extracted orally, respectively, without provoking gastric ulcer. After the experiment, the glandular stomach was separated and the tissues were processed for macroscopic and histopathologic examination. The results of present study showed that the fenugreek seeds extract promisingly reduced erosion and ulcer in the treatment group in comparison to the control group. Prominent increase in the number of inflammatory cells was found in the control group while no noticeable lesions were seen in the gastric mucosa of treatment group. Normal gastric mucosa was noticed in the groups I and II. According to the results of this study, it can be concluded that fenugreek seed extract oral usage could safeguard the gastric mucosa from injury¹⁹.

Fenugreek is used to cure mouth ulcers, chapped lips and stomach irritation²⁰. Dried leaves of fenugreek used for flavour and for recurrent mouth ulcers the infusion of leaves are used as a gargle²¹. As a folk medicine Fenugreek seeds are used for mouth ulcer²²⁻²⁴.

Figure 4: *Trigonella -foenum graecum*



5) *Cocos nucifera*:

Jie Meng *et al* investigated the gastro-protective effects of virgin coconut oil (VCO). Omeprazole was used as standard. 3 groups of rats (6 rats per group for each ulcer model) were taken pre-treated with distilled water for the negative control group, 30 mg/kg of omeprazole for the positive control group and VCO (2 ml per rat) for the treatment group. Animals were pre-treated for 7 days and ulcers were provoked by using cold restraint stress, piroxicam, ethanol and pylorus ligation. On 8th day, animals were sacrificed and ulcer scores were measured using macroscopic evaluation. The gastric volume, pH, total acidity and mucus content were determined in the pylorus-ligated model. The levels of antioxidants were assessed from the gastric tissue homogenates. Virgin coconut oil promisingly ($p < 0.001$) inhibited the ulceration caused by various inducers. The percentage of inhibition for the VCO-treated group was found to be 78.3%, 84.7%, 72.7% and 73.1%, whereas for the omeprazole-treated group it was 60.8%, 61.5%, 59% and 53.8% in cold restraint stress, ethanol, piroxicam and pylorus-ligated ulcer models, respectively. Virgin coconut oil significantly ($p < 0.001$) inhibited gastric juice volume and total acidity for VCO and omeprazole treated groups as compared to the non-treated negative control group. Moreover, VCO and omeprazole caused a prominent ($p < 0.001$) increase of gastric mucus content and pH. Virgin coconut oil also proved to have promisingly increased glutathione (GSH) and nitrite levels, whereas the levels of SOD, GP, MDA and CAT were promisingly ($p < 0.001$) reduced by VCO relative to the control group. Virgin coconut oil also promisingly ($p < 0.001$) increased the level of prostaglandin in rat tissue homogenate, similar to that of standard. Virgin coconut oil showed a strong correlation with antioxidant properties to control the regulation of prostaglandin synthesis and safeguard against ROS damage²⁵.

Figure 5: *Cocos nucifera*



6) *Averrhoa bilimbi*

Averrhoa bilimbi (Bilimbi) is *medicinally* used as a folk remedy for aphthous ulcer and as a cooling drink²⁶⁻²⁷.

Figure 6: *Averrhoa bilimbi*



Conclusion

Plant-based natural products could be considered as future therapeutic agents or adjuvant treatment with conventional therapeutic approaches to enhance their efficacy and reduce the side effects in the management of oral disorders, including RAU. *Solanum nigrum*, *Sesbania grandiflora*, *Trigonella foenum graecum*, *Cocos nucifera* are scientifically validated for gastric ulcer activity in animal model and its significant too. It also having the ability to cure the mouth ulcer which has mentioned in the folk lore medicine but there is no work has been carried out and *Papaver somniferum*, *Averrhoa bilimbi* are also having the ability to treat the mouth ulcer which was claimed in traditional use but so far there is no work carried out in these plants.

Hence this review suggesting the researcher can do the research work on mouth ulcer activity for above mentioned plant. Further clinical studies are needed to be carried out to confirm the efficacy and safety of these natural products with potential effects in treating RAU. Further investigations in this area could lead to the origin of many new drugs.

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