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Review Article

Appraising the Clinical Efficacy of Herbal Topical Medications in the Treatment of Recurrent Aphthous Stomatitis - A Review

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ABSTRACT
Oral ulcers are common complaints to the dental clinic. Among these, Recurrent Aphthous Stomatitis/Ulcer (RAS) is frequently reported lesions of which recurrent minor aphthous ulcers are most prevalent. Though these mucosal lesions are self-limiting, painful ulcerative and inflamed mucosa could affect the patient's daily routine such as food intake, speaking and swallowing. Since precise etiology is unknown, various treatment options are tailor made to each individual patient's condition. Topical steroids are the widely prescribed medication as local therapy. In spite of a dearth in evidence based data on the effectiveness of plant based topical therapies for oral aphthous ulcers, these are used as primary medications which aids in natural cure of such lesions. These alternative medications are also useful to patients who refuse to take allopathic medicines, having history of drug allergies, history of multiple drug therapy, when allopathic medication is not recommended and in refractory cases. Hence the aim of this paper is to review the clinical efficacy of potential herbal medications for the topical management of recurrent aphthous ulcers. An electronic data search was performed using different search engines and the relevant articles were reviewed. All the placebo controlled studies have shown clinically significant results in the treated group in various outcome measures without noticeable side effects. Generally, topical herbal treatment were effective on RAS as palliative therapy, however more scientific evidence is needed for clinical recommendation in repeated cases.

Key words: Aphthous stomatitis /ulcer, Alternative medications, Topical herbs, Topical treatment, Recurrent oral ulcer,Herbal medications.

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INTRODUCTION

In recent times, consciousness towards the utilization of bio friendly and eco-friendly plant based products for the prevention and remedy of various human illnesses has paid considerable attention. The faith towards the herbal medicines has been growing worldwide. The phytochemical found in plants have protective and disease preventive properties which are non-nutritive in nature.[1]

Recurrent Aphthous Stomatitis (RAS) is considered as a mucosal disease which occurs locally and not a result of systemic disease. Since there is any definitive recommended treatment protocol for aphthous ulcer, patients are advised to attempt various medications, particularly in recurrent cases of aphthous ulcer. Many herbs which have potential for symptomatic treatment of aphthous are lacking scientific evidence for clinical use. Though many potential herbs were identified through ethno biological survey, the therapeutic isolation and clinical application of the herbal components are still lacking. Few herbs were tried on animal models and lab studies on human cells.

The recurrent ulcers appear periodically and heal completely between attacks. These ulcers have comparatively few common reasons. The common recurrent oral ulcers include recurrent aphthous ulcer (RAU), erythema multiforme, occasional traumatic ulcers and ulcers associated with gastro intestinal diseases.[2] RAU otherwise referred to as the common canker sore is a painful ulcerative lesion of an uncertain etiology. These recurring ulcers are T cell mediated solitary or multiple lesions, frequently seen in childhood and adolescent females.

Nutritional deficiencies, inflammatory bowel diseases, celiac disease, Behcet's syndrome, HIV are few conditions associated with aphthous stomatitis. The clinical forms include recurrent aphthous minor, recurrent aphthous major and recurrent herpetiform ulcerations. The minor ulcers commonly involve non keratinized mucosa with ulcers ranging from 3-10 mm diameter and resolve within 1-2 weeks. The major ulcers usually appear on the detached buccal and labial mucosa with more than 1 centimeter in diameter and heal in six weeks' time. However, it has been suggested that these ulcers respond poorly to any kind of therapies. In many patients, resolution of the systemic disorder gives rise to a reduced incidence and severity of the mucosal ulcerations.[2,3]

The mucosal destruction in RAS patients appears to represent a T cell-mediated immunologic reaction with production of tumor necrosis factor-alpha. However, the initiating causes are variable. It has been theorized that aphthous ulcerations develop from an immunologic response to an oral antigen. This reaction may arise due to the presence of a highly antigenic reagent, a decrease in the mucosal barrier that previously masked the antigen, or immune dysregulation resulting in an abnormal response to a normally present antigen. The genetic factors, oral microbial flora and immunological factors plays major role in the etiology of RAS. Though there is multifactorial etiology, trauma, stress, allergy and smoking are considered as major predisposing factors.[4-6]

The major objective of the treatment is to reduce pain, amount and size of lesion, decrease the super infection, fastening the healing time and to

increase disease-free periods. The various treatment options comprise of topical therapies, intralesional injections, laser therapy, systemic therapy and botulinum toxins. The agents used for topical treatment should have easy application, tolerable, acceptable taste; best muco-adhesive properties with less side effects.[6,7] These are mostly aimed for treating the current ulcers. Topical steroids are commonly prescribed medication for local therapy. Herbal topical agents have the advantages such as cheaper in cost, less side effects, easy availability with better patient acceptance. Some of these drugs also have the advantage of systemic administration along with local applications in needed circumstances. Table 1 describes the topical herbal medicines used in clinical trial for the treatment of Recurrent Aphthous Stomatitis.[8-29]

The significance of this review is to identify the potential herbal medicines utilized for topical management of RAS, to appraise the clinical effectiveness of topical herbal medicine in treating RAS and to identify the properties and mechanism of action of herbal topical medicine in treating RAS.

MATERIALS AND METHODS

Electronic databases such as MEDLINE-PubMed, GOOGLE SCHOLAR AND SCIENCE DIRECT were explored for the literature search on topical applications of herbal medicine in treating Recurrent Aphthous Stomatitis. MeSH terms such as aphthous ulcer, herbal treatment, randomized clinical trials, topical applications, alternative medications were used. Publication types i.e. reviews and original research articles with Randomized clinical Trial were sourced. Age, sex, geographical distribution restrictions were not set. Case reports and articles published in other languages were omitted from the pool. Supplementary data was collected from reference list of articles and other relevant articles. By using filters, articles were sourced from years 2008 -2018.

Two reviewers were assigned to choose and draft the articles with a set of suitability principles and for the valuation of articles that fit the criteria.

Table 1: Topical herbal medicines used in clinical trial for the treatment of Recurrent Aphthous Stomatitis.[8-29]

Ageratina pichinchensis
Allicin
Aloe vera
Berberine gelatin
Camel thorn
Centella asiatica (Brahmi)
Chamomilla recutita
Citrus oil
Curcuma longa (Turmeric)
Ginger officinale
Iralvex
Kasmitad
Lavandula angustifolia (Lavender)
Licorice (Glycyrrhiza glabra)
Myrrh
Myrtus communis (Myrtle)
Nicotina tobacum
Ocimum sanctum (Tulsi)
Proaftal
Psidium guajava (Guava)
Pumpkin seed
Punica granatum (Pomegranate)
Rosa damascene

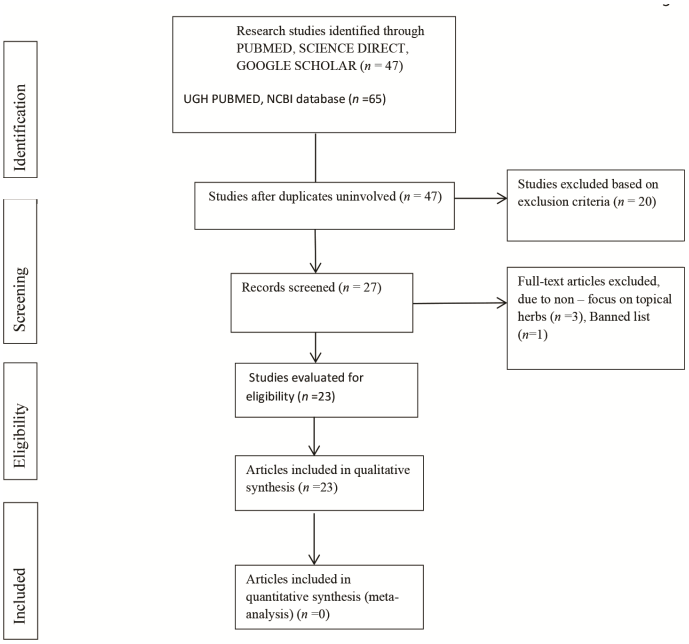

Figure 1: The flow diagram depicts the method of selection of articles for the review.

The reviewers were un-blinded and some difference among them was organized through acceptance between all five authors. After removing the duplication of articles, the review was done with the abstracts and full text of accessible ones. As abstracts only articles and different study designs of Randomized Clinical Trial (RCT) were included in this study while appraising the positive outcomes, some amount of recording bias could be anticipated. Figure 1 Flowchart.

RESULTS

The following data were collected from each included study

(1) Name of the herb and preparation method (2) Author (3) study cohort

(4) Number, amount and duration of the topical application

(5) Outcome measures such as effects on pain, healing time, and size of the ulcers, number of ulcers, erythema, exudation, recurrence rate and side effects.

(6) Relevant statistical analysis of study results.

The reviewers depicted their suggestions against each study based on the above mentioned data. Only 23articles that fulfilled the inclusion criteria from a total of 47 were included. In descending order all the data are presented consecutively from the articles beginning from year 2018 until 2008 with summaries in Table 2.[2-26]

Most of the studies were from Asian region in which majority of the studies are from Iran (9) and others include North America, Africa and Europe region. Among the 23 studies, four studies were active controlled, 14 were placebo controlled; another five studies were self-controlled studies. Regarding the form of application, mouthwash/mouth rinse was the commonly used topical preparation followed by gel preparation. Mucoadhesive patch/membrane is the recently explored form of topical herbs. Majority of the studies utilized preparations with single herb (69.6%) and remaining studies (30.4%) used combined preparations. None of the studies showed any noticeable side effect. Maximum of the studies focused on effect of herbal preparations over aphthous stomatitis minor. All the placebo controlled studies have shown clinically significant

Table 2: Review of randomized clinical trials of herbal topical medicine for Recurrent Aphthous Stomatitis.

Name of the Herb	Preperation Method	Authors	Study design	Outcome	Inference
Pumpkin seed	Oil (100%)	Sharquie *et al.*,[8]	Single blind clinical trial on 25 patients two times daily for three months	Within four days, the mean oral clinical manifestation index score was started to decline to lower level which was statistically significant. The mean size of the ulcer was reduced significantly to a lower level within four days.	Effective therapeutic and prophylactic agent against RAS and the remission occurred three months after discontinuing the treatment with no adverse effects.
Ocimum sanctum(Tulsi)	Fresh yoghurt,[5] fresh *Tulsi* leaves, one table spoon of Aloe chewed and swallowed once daily in the morning for three weeks week	Khuje *et al.*,[9]	A clinical study on 40 night shift workers of 30-60 years of age	Recurrence of aphthous ulcers were significantly decreased in 29 patients after four weeks.	Reduction in the recurrence of aphthous ulcer
Nicotina tobacum	Mouthwash	Vaziri *et al.*,[10]	Randomized double-blinded placebo controlled clinical trial on 60 patients with 10 ml of mouthwash three times a day for 5 days.	Pain score and ulcer size were reduced than control group which was significantly greater than control group	The decoction prepared with *Nicotina tobacum* leaves were well-accepted and harmless adjunctive remedy for the management of aphthous ulcer.
Zingiber officinale(Ginger)	Mucoadhesive gel	Haghpanah *et al.*,[11]	Double blind placebo controlled trail of 15 patients for 20 min two times daily for 7 days	Significant reduction in the severity of pain while the diameter, zone of lesion and duration of treatment did not show significant effect.	*Ginger* containing mucoadhesive gel can reduce the severity of pain.
Ageratina pichinchensis	Plant extract o12f 5% in a gel form.	Romero-Cerecero *et al.*,[12]	Randomized double blind clinical trial controlled with 0.1% Triamcinolone on 56 patients, 3 times a day for two weeks.	No significant differences between groups.	100% therapeutic effectiveness was achieved at the end of the study.
Allicin	Mouth rinse	Nair *et al.*, [13]	42 patients with minor RAS were randomly allocated into two groups of allicin mouth rinse 5 ml four times a day and allicin capsule 250 mg once daily for two months for 7 days with 6 months follow up	There were no statistical difference between the groups in regarding to ulcer size,pain and erythema.	Both treatment means are equally effective with good safety record and recurrence was observed in both the groups.
Punica granatum(pomegranate)	Water, alcoholic extracts of flower among three different varieties of *Punica granatum* as mouthwash	Gavanji *et al.*,[14]	Double blinded 210 participants with comparison of three varieties of *punicagranatum.*	*p.granatum Var.pleniflora* extract showed significant decrease in pain and time of recovery.	The duration of the whole treatment was reduced with *P.granatum var.pleniflora* and meaningfully satisfactory for the patients.
Chamomilla recutita	*Chamomillamouth rinse (tincture)*	Seyyedi *et al* .,[15]	Triple blind randomized placebo control trail of 50 (25+25) patients, three times with 10 drops each time(day 2,4,6 and weekly)	There was a significant regression in number of lesions, pain, burning sensation, healing period and lesion size after each visit.	By controlling pain and burning sensation, *Chamomilla*mouth rinse was effective in the treatment of RAS without any side effects.
Iralvex	Gel	Khademi *et al.*,[16]	randomized double-blinded placebo controlled clinical trial on 40 patients, 1 cm of gel, three times a day for a week	Experimental group showed significant lower mean pain duration, time of complete healing and in pain intensity compared to control group.	Effective in pain relief and healing of oral ulcers with no side effects.

continued...

Table 2: Cont'd.

Name of the Herb	Preperation Method	Authors	Study design	Outcome	Inference
Kasmitad	Gel	He *et al.*,[17]	A self-controlled before and after trial on Seventy patients with recurrent minor aphthous ulceration was randomized into prodromal and ulceration group. Parameters were recorded before and after treatment with 0.2 cm gel four times a day for 10 days	Significant differences in reduction of ulcer size, ulcer duration with no significant difference in pain score.	Early application is effective in preventing ulcer development and providing symptomatic relief of ulcers that do occur.
Proaftal	Spray	Stojanovska *et al.*,[18]	Randomized double blind placebo controlled study on 20 patients with two sprays 3-4 times a day for 8 days	Significant faster reduction of diameter of ulcers and reduction in the pain magnitude in the experimental group.	The practice of proaftal stimulates the epithelization rate and reduction of pain.
Curcuma longa (Turmeric)	Gel	Deshmukh *et al.*,[19]	Randomized double blind clinical trial with 60 patients of group A, curcumin gel and group B Triamcinolone three times a day application for 7 days.	No significant differences in size, number and duration of ulcers in between groups.	In the treatment of minor aphthous stomatitis, curcumin gel could be used as safer and effective substitute to steroids.
Psidium guajava (Guava)	mouthwash	Guintu *et al.*,[20]	Randomized prospective open label clinical study on 32 aphthous patients and mouthwash given thrice a day for 7 days.	Significant marked improvement of pain symptoms and faster resolution of ulcer size in the treatment group than the control group.	Effective on reduction pain and earlier decrease of ulcer size compared to isotonic sodium chloride solution.
Berberine	Gelatin	Jiang *et al.*,[21]	Randomized double blind placebo controlled clinical trial on 87 subjects four times a day for 5 days.	Significant lower erythema and exudation, reduction in pain score and ulcer size	Berberine gelatin could be a safe and well tolerated for the management of minor aphthous stomatitis with no side effects.
Aloe (0.5%)	Mucoadhesive gel	Mansour *et al.*,[22]	Five days of application with 4 times a day compared with *myrrh* and placebo gel	Significant reduction in ulcer size and highest reduction in erythema and exudation at day 6.	*Aloe* was superior in decreasing the ulcer size, erythema and exudation without any side effects.
Myrrh	Mucoadhesive gel	Mansour *et al.*,[22]	Five days of application with 4 times a day compared with *Aloe-vera* and placebo gel	Significant pain reduction on minor aphthous ulcer.	*Myrrh* was superior in reducing the pain in minor aphthous ulcer patients with no side effects.
Lavandula angustifolia(Lavender)	Oil (2%)	Altaet *et al.*,[23]	Randomized placebo control both in animal experiment and 115 subjects for 4 days. 2 drops (36mg/drop) three times daily.	The inflammation level, ulcer size, healing time was significantly reduced and relief from pain presented after 5 min of application and completely invisible after 20 min.	Lavender oil had ulcer and pain relief properties with good tolerance
Rosa damascene	Mouthwash	Hoseinpour *et al.*,[24]	Randomized double blind placebo controlled investigation of 50 patients.	The efficacy over pain size and number of ulcers were compared with placebo group on 4,7,11 1nd 14 days. Statistically significant difference on days 4, 7.	More effective in the treatment of recurrent aphthous stomatitis.
Myrtus communis(Myrtle)	paste	Babee *et al.*,[25]	Randomized double blind, placebo controlled before and after clinical trial on 45 patients four times a day for 6 days	Statistically significant reduction of ulcer size, pain severity, erythema and exudation level with significantly improved oral health impact profile.	Well tolerated and effective treatment modality for RAS.

continued...

Table 2: Cont'd.

Name of the Herb	Preperation Method	Authors	Study design	Outcome	Inference
Camel thorn distillate	Oral solution	Pourahmad *et al.*,[26]	Randomized double blind placebo control study on 93 patients for 14 days ,40 ml of solution four times a day for one minute then swallow	After three days of treatment the intensity of pain and diameter of the lesion were significantly reduced with less complete resolution time compared to placebo.	Camel thorn distillate may be more efficacious for the treatment of RAS with no side effects.
Centella asiatica(Brahmi)	Standardized extract of *Centella asiatica* ECa 233with 0.05%,0.10,0.20% in paste form	Ruengprasertkit *et al.*,[27]	A randomized single blind placebo controlled trial on 24 subjects(day 0-10)	Significant reduction in mean ulcer size and in pain score compared to placebo.	Effective and safe in reducing pain, ulcer size and erythema in RAS with no unwanted events.
Citrus oil with magnesium salts	Mucoadhesive patch	Shemer *et al.*,[28]	48 patients of two groups treated with citrus oil mucoadhesive patch once daily and oral solution containing benzocaine and benzoin tincture three times a day.	Significantly reduced ulcer healing time and pain intensity compared to benzocaine oral solution.	Muco adhesive patch is more effective in terms of healing time, pain intensity with better tolerance.
Liquorice extract (Glycyrrhiza glabra)	Bio adhesive hydrogel patches (1%)	Moghadamnia *et al.*,[29]	15 patients four times a day for 20 min for five days compared with placebo group	When compared to placebo the treated group showed significant reduction in pain score, diameter of the inflammatory halo and necrotic center	Effective in the reduction of pain, inflammatory halo and necrotic center of aphthous ulcers

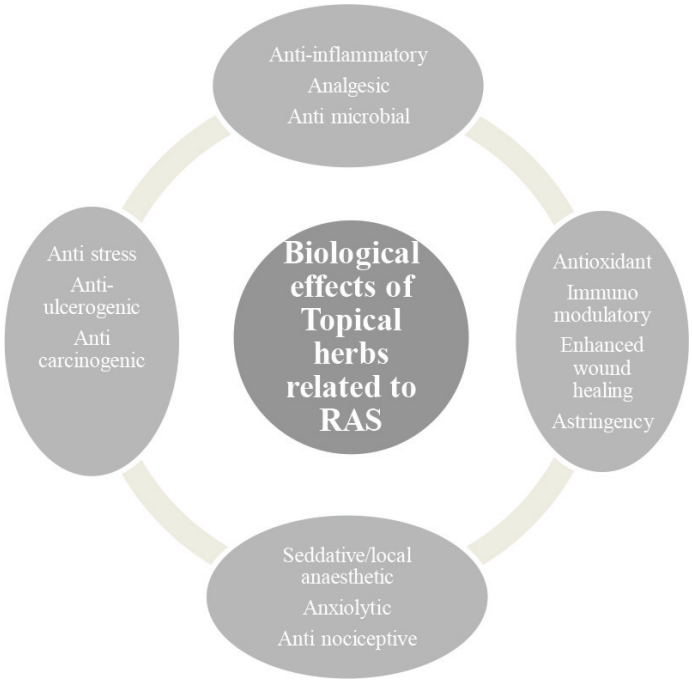

Figure 2: Biological effects of topical herbs related to RAS.

results in the treated group in various outcome measures. Two of the active controlled studies showed no significant results among the groups and another two studies have shown statistically significant results. The self-controlled trials also have presented clinically significant results on various tested parameters in aphthous ulcer patients within the study limits.

All the studies primarily focused on symptomatic treatment of RAS between test and control groups, and topical herbal treatment was effective on reducing the symptoms. Whereas, two studies also focused topical herbs (*pumpkin seed oil, Kasmitad gel)* as a prophylactic/ preventive therapy and proved to be effective in preventing the ulcer development during the study period. Two studies (*Allicin, Ocimum sanctum*) included both topical and systemic intake as study component and the recurrence of ulcer was also included as an outcome measure. A comparative study stated recurrence of aphthous ulcer occurred in both the forms of (mouth rinse and capsule) treatment. The study on *Ocimum sanctum* showed a statistically significant result in reduction in the recurrence of aphthous ulcer. This might be due to the combined herbal therapy as well as the systemic effect of the herbs.

Figure 2 represents the general biological effects of herbal drugs related to topical treatment of RAS.

DISCUSSION

Pumpkin seed oil (Cucurbitapepo L)

Vitamins, minerals and anti-oxidants are present in huge amounts in pumpkin seed oils. The other active ingredients comprise fatty acids in particular high content of polyunsaturated fatty acids, tocopherol, carotenoids, phytosterols and few amino acids. It has antioxidant, anti-inflammatory, antimicrobial and anticarcinogenic effect. A recent animal study in rats revealed better cutaneous wound healing in pumpkin oil extract treated group compared to untreated groups. The pumpkin oil treated group in healed biopsies showed a complete re-epithelialization with re-emergence of skin appendages and also well-organized collagen fibers with the absence of inflammatory cells.[30]

Tulsi (*Ocimum sanctum*)

The chief active ingredients in *Tulsi* comprises eugenol and ursolic acid, β-caryophyllene, flavonoids with little bioactive components include methyl chevicol, linalool and 1,8-cineole. The nutritional content of its seeds include carbohydrates, fibre, fats, important vitamins and minerals. Many scientific studies have proved that *Ocimum sanctum* has anti-bacterial, antifungal and antiviral properties. It also has got immunomodulatory activity and induces cytokine secretion. In addition, anti-toxic, antitussive, hepatoprotective, hypoglycemic, hypolipidemic, chemo preventive, anti-estrogenic properties have also been proved with wide margin of safety. The rapid elimination, low bio availability and perceived toxicity make this herb a potential therapeutic agent.[31]

It has been proved that *Ocimum sanctum* reduces the gastric ulcer is dose-dependent manner. The anti-ulcer effect is mainly due to enhancement of antioxidant potential of gastric mucosa. Fixed oil and linolenic acid existing in tulsi are known to block cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism.[9] *Ocimum sanctum* at a dose of 100mg/kg was found to be effective antiulcer agent. This is due to its cytoprotective effect. The wound healing nature of *Ocimum sanctum* is mainly due to its anti-inflammatory, antimicrobial, anti-oxidant and immunomodulatory properties.

Tulsi is also known for its anti-stress activity by being able to control the balance of various metabolic processes of the body and prevent stress. The immuno-stimulant capacity of the herb helps in the adaptogenic activity. The aqueous, alcoholic, chloroform and essential oil extracts of leaves were equally effective against pathogenic gram positive and gram negative bacteria which also includes staphylococcal aureus.[32] Several animal studies concluded that the oral doses of *tulsi* aqueous extract enhances the RBC, WBC, hemoglobin and antibodies without affecting the bio-chemical parameters.[33]

Nicotina tobacum

The leaves of the *Nicotina tobacum* have got emetic, narcotic, sedative, antispasmodic activities and have been utilized for the skin disorders and rheumatic swelling. Isoflavones, phenolic acids, sesquiterpenes, diterpenoids and alkaloids are the important biological compounds found in *Nicotina tobacum*.[34] Literature report supports that smoking has protective activity in the occurrence of ulcer. The increased keratinization of oral mucosa is the consequence of the combustible products of smoking that could resist the formation of aphthous ulcers, decrease the microbial infiltration and trauma in smokers when compared to nonsmokers. Nicotine and its metabolites lead to reduction in inflammatory condition by exhibiting immunosuppressive therapy through various mechanisms. In addition, the inhibitory effect of the leaf extracts on diverse bacterial species effects in improvement of disease process.[10]

Ginger (*Zingiber officinale*)

Ginger has been used as a common herb in traditional medicine. *Ginger* a rhizome of zingiber officinale, is well known for its anti-inflammatory and anti-emetic effect. The sedative and pain regulator activity results from substance P release. Gingerols, shogaols, zingerone, paradol, gingerenone, galanal, gingerdiols and gingerdiones are the various bioactive ingredients reported from rhizomes. The gingerols and shogaols are known to be mutagenic.[35] A clinical study suggested that the dried ginger rhizome membrane is effective in pain relief, reducing the healing time of aphthous ulcers. It also reduces the salivary EGF levels and preventive influence on TNF-α release.[36]

Ageratina pichinchensis

Ageratina pichinchensis extract proves anti-inflammatory, anti-nociceptive and wound healing properties in various experimental and clinical studies. It contains phytochemicals like encecalin, 7-0-(β-D-glucopyranosyl)-gossypetin and 7-0-(β-D-glucopyranosyl)-galactin. Among this encecalin comprises a majority compound while galactin is identified as a wound healing promoting compound. This component was capable of constantly encourage cellular proliferation of normal human skin cells (HFS-30).[12]

Allicin mouth rinse

The chief constituent of *garlic* extracts is allicin. It shows anti-inflammatory, anti-oxidation, anti-microbial, and immunomodulation characteristics. In animal models, topical allicin promoted healing process of oral ulcer by promoting re-epithelialization. The bioactive components of allicin reach the cell via phospholipid membrane and the ulceration provides easy diffusion of allicin into the wound. It is known to increase the blood supply to the area by promoting the elastic property of blood vessel and capillary perfusion. The antimicrobial property is responsible for the decreased bacterial colonization that prevents wound infection. In vascular endothelial cells, glutathione production is up-regulated and pro-inflammatory cytokines level is down regulated by allicin thereby decreasing excessive inflammatory process associated with RAS and speeds the healing.[37]

Pomegranate (*Punica granatum*)

Pomegranate extracts are having enormous medicinal value. *Pomegranate* is rich in tannins and polyphenols such as ellagitannins, punicalagins, punicallin and gallotannin. These polyphenols has antibacterial, antioxidant, anti-inflammatory, antiproliferative and DNA repair activities. The punicalagin exerts anti-inflammatory action by inhibiting the nuclear factor kappa B. (NF-kB) and by prevention of ERK-1 or ERK-2(mitogen-activated protein kinase cascades) activation. Pomegranate extracts also inhibits nitric oxide (NO) production by RAW 264.7 macrophage cells. The poly phenols from pomegranate extract have an inhibitory effect on IL-6 and IL-8. The punicalagin shows antioxidant property by increasing Nrf2-mediated HO-1 expression and also induces the P13K/Akt –mediated HO-1 expression. Punicalagin enhances the SOD1 mRNA expression and thereby inhibits reactive oxygen species generation and NO over production by macrophages. The tannins and polyphenols also induce fibroblast migration and proliferation, collagen formation and angiogenesis in wound healing. During the healing process, the pomegranate-treated wounds displayed better epithelialization and contractions of incised wounds with improved hydroxyproline content, dry weight and breaking strength of granulated tissues.[38]

Chamomilla recutita

As an alternative herbal medicine the *Chamomilla* has anti-inflammatory, antispasm, antibacterial, antifungal and analgesic properties and have been used in many inflammatory lesions. The essences (azolene, camazoline) and flavonoids are the two main ingredients of chamomilla. Camazolene has dose dependent anti-inflammatory and antispasm effects by inhibiting synthesis of leukotriene B4 [LTB4] synthesis and arachidonic acid peroxidation in neutrophils. Azolene possesses anti-inflammatory and analgesic properties. Flavonoids are also recognized to have anti-inflammatory properties. Chamomile also comprises bisaboloids, terpenoids, matricine, chamazulene and cumarins. The anti-oxidant potential of chamomile is responsible for the ulcer healing. The anti-inflammatory effects of flavonoid is due to the inhibition of STAT-1 and NF-κB activations and also the preventive effect on iNOS expression and NO formation in activated macrophages.[39]

Iralvex

Iralvex gel consists of 170 mg dried rhubarb extract and 10 mg of salicylic acid. The rhubarb extract comprises of anthraquinones,

anthrone, dianthrones, heterodianthrones, tannins, starch and calcium oxalate. Antraquinoneglycosides, tannin and salicylic acid in the gel react with the proteins of the mucous membrane epithelial cells leading to a tougher adhesion of mucosa which results in a decline in the penetrability of the cells. Gingival mucosal outer layer is thus protected against microbes and toxins by the astringency process. These chemicals also have antimicrobial effects that lead to better pain relief and earlier wound healing.[16]

Kasmitad gel

Kasmitad gel is a compound preparation by STADA pharmaceutical company and approved in 1978 for production in Germany. It has been used for topical treatment of recurrent oral ulcers which consists of 200 mg *chamomile* flower tincture (1:5.5), 20 mg lidocaine, 1 mg thymol and 1 mg of benzalkonium chloride as a preservative. *Chamomile* tincture has anti-inflammatory, antimicrobial and antioxidant effect. When combined with lidocaine it shows analgesic effect. Studies have shown that the gel provides immediate pain relief.[17]

Proaftal

Proaftal is made up of propolis and essential oils which comprises anti-inflammatory ingredients of plant origin. This contains 25% dry matter propolis, etheric oils from sage mint, anise, menthol mixed in 100ml of diluted alcohol. Propolis is well recognized for its antimicrobial effects against certain bacteria, fungi and viruses *etc*. Flavonoids, aromatic acids, esters, aldehydes, ketones, fatty acids, steroids, terpenes, amino acids, polysaccharides, hydroxybenzene, alcohol etc. are included in the chemical composition of propolis.[40] The flavonoids are found to strengthen the capillary walls and reinforce the association of serum proteins with histamine. Flavonoids also have anti-oxidant effect. Being a local anesthetic, propolis also regenerates and heals tissue, increases the value of properdin in serum which accounts for its immunomodulatory effects and stimulates alternative pathways for the complement system.[18]

Turmeric (*curcuma longa*)

The main ingredient of *turmeric* is curcumin which is proved to be non-toxic in nature. It has showed diversified effect s in various oral diseases. It has got antioxidant, anti-inflammatory, anti-microbial, immunomodulatory, chemopreventive properties. The anti-inflammatory properties are due to the inhibiting activity of NF-(κ) B transcription factor, reducing the production of TNF-α and IL-1 cytokines. The properties like low bio availability, rapid elimination and the less perceived toxicity are the therapeutic benefits of curcumin. Regarding wound healing properties, it has been inferred that it increases the micro circulation, increases angiogenesis, improves the granulation tissue formation and accelerates re-epithelialization.[41] It has been suggested that curcumin gel is a well-tolerated and effective treatment modality for aphthous. Curcumin holds limitations like low solubility, rapid metabolism and hence low bio availability.[19]

Guava leaves (*Psidium guajava*)

P. guajava possesses antimicrobial, anti-inflammatory, antitumor, antiallergic, antihyperglycemic and antimutagenic characteristics. Wounds, cough and dental diseases has been treated by *P. guajava*. It contains huge phytochemicals and antioxidants comprising polysaccharides, essential oils, minerals, vitamins, enzymes, alkaloids, steroids, flavonoids, tannins, triterpenoid acid, glycosides, saponins and other chemical compounds. Flavonoids have anti-inflammatory and analgesic actions.[42] They inhibit the biosynthesis of prostaglandins and inhibit protein kinase enzyme thereby producing anti-inflammatory effect.[20]

Berberine gelatin

Hydrastis Canadensis, Coptidis rhizome and berberis vulgaris are the medicinal herbal source of berberine. It is an isoquinoline alkaloid isolated from these plants. It possesses anti-inflammatory, antimicrobial, antitumour and anti-pyretic properties. Studies showed that via activated protein kinase activation in macrophages, berberine could inhibit pro inflammatory responses. It also downregulates the expression of pro-inflammatory genes (TNF –α, interleukin-1β, IL-6 *etc.)* and upregulates IL-10 which has major negative regulatory feedback on Th-1 cytokine production. Berberine gelatin contains 50 mg berberine, hydroxypropyl methylcellulose, polyethylene glycol 400, glycerine and flavoring additives. Berberine is known for its antimicrobial activity against *Staphylococcus*, *Streptococcus*, *Candida* and *Salmonella*. In addition, berberine is an immunosuppressive agent with safe drug profile.[21]

Aloe vera

Aloe vera contains many essential amino acids which are needed by our body and these amino acids aids in smooth functioning of our complex enzyme system. It is well known for its constituents like vitamins A, B, C, E and folic acid and minerals like calcium, sodium, potassium, magnesium, iron, copper and zinc. Studies demonstrated the antiviral, antibacterial and antifungal properties of *Aloe vera* and the use of this plant is favorable.[43] This is effective against oral bacteria like *Streptococcus mutans*, *Streptococcus mitis*, *Lactobacillus acidophilus*, *Prevotella intermedia* and *Enterococcus faecalis*. In addition, the antiseptic ingredients like lupeol, urea nitrogen, salicylic acid, cinnamonic acid, phenol and sulphur has repressive action over fungi, bacteria and viruses. The extract of *Aloe vera* gel has inhibitory action on the arachidonic acid pathway via cyclooxygenase inhibiting inflammation, thus proving the anti-inflammatory action with analgesic properties. Studies have also shown the antioxidant effect of some of the constituents of *Aloe vera* gel. The isorabichromone, feruoyl aloesin, p-coumaroyl aloesin derivatives of aloesin from aloe revealed potent free radical and superoxide anion activity. *Aloe vera* gel has been tried in various case control studies for aphthous ulcer treatment and given excellent clinical results by its anti-inflammatory and immunomodulatory effects.[22]

Myrrh (stem of different Commiphora species)

Terpenoids, steroids, carbohydrates, flavonoids, lignans and long chain aliphatic derivatives are the significant phytochemicals found in various *Myrrh* species. The most important species of *myrrh* is *Commiphora molmol* which has been used as an effective antimicrobial agent. *Myrrh* has local stimulant, wound healing and antiseptic properties. The *Myrrh* extract is used for sore throats, canker sores and gingivitis, acne, boils and arthritis. It has been shown to possess anti-hyperglycemic effect in diabetic rat models. *Myrrh* reduces cholesterol and triglycerides and increased the SD activity in hypercholesterolemic rabbit models. It shows strong antithrombotic activity.[44] *Myrrh* extract is used as digestive aid drug and it is used in food and oral healthcare drug products approved by FDA. In peritoneal macrophages, pretreatment with myrrh prevented formation of proinflammatory cytokines including IL-1β, IL 6, and TNF-α as well as nitric oxide and PGE2. The analgesic effect of myrrh could be due to the furanoeudesma-1, 3-diene and terpene existing in *myrrh* troubles opioid receptors in the mouse's brain, manipulating pain perception. In dentistry, *Myrrh* has been utilized as anti-inflammatory, anti-infectious and wound-healing substance. *Myrrh* can reduce toothache when applied to teeth.[22]

Lavender oil

Mori et al, in their recent research on an animal model topically treated skin wounds with lavender oil, for alternate 14 days. *Lavandula angustifolia* is a well-known traditional medicine having antibacterial and antifungal properties and exhibited positive effects over burns and insect bites. It also has anxiolytic and anti-inflammatory properties. As matched to control, there is a rapid progress in the cutaneous wound closure with the topical application of lavender oil with increased expression of growth factors like PDGF-A and EGF playing essential role in tissue remodeling and re-epithelialization. The area of the wound was decreased significantly compared to control. In addition, it promoted the synthesis of collagen, differentiation of fibroblasts by upregulation of TGF-β. These are important for the early granulation tissue formation, tissue remodeling by collagen synthesis and late phase wound contraction.[45]

Rosa damascene

Rosa damascene has got analgesic, anti-inflammatory, antinociceptive and wound healing properties. The analgesic effect is due to the presence of non-water soluble ingredients such as Quercelin and Kaempferol. The phenolic compounds, Vitamin C and tannins possess anti-inflammatory effects. The wound healing effect is mainly due to the initiation of growth factor release. β-citronellol, geraniol, nerol, nonadecane, and Kaempferol compounds could be accountable for the wound healing properties.[46]

Myrtle (*Myrtus communis*)

Mouth ulcers, fungal infection and cold have been treated with *Myrtus communis* leaves and fruits. The leaves are having anti-inflammatory, antioxidant, antibiotic or antiseptic effects. The main compounds of these plants are essential oils, phenolic compounds, tannins, flavonoids and proanthocyanidins. Various studies have explored the effectiveness of myrtle on aphthous ulcer as topical medicine in the forms of oral solution, paste and decoction. The clinical efficacy on aphthous ulcer is mainly due to its anti-inflammatory, analgesic, antiseptic, antiviral and antibacterial effects. The new ulcer formation can be prevented by the management of inflammatory cytokines, inhibiting the TNF-α. It also has anti-nociceptive, anesthetic and wound healing properties which could progress the ulcer healing and decrease pain duration. The antimicrobial effects prevent secondary infections thereby improving the symptoms.[47]

Camel thorn

Camel thorn otherwise known as *Alhagi Camelorum* is a folk medicine used in Iran to treat gastric disorders. *Camel thorn* contains some flavanones, such as alhagitin and alhagidin. Studies have proved that the nitric oxide (NO) level is significantly higher in aphthous ulcer patients than that the individuals without RAU. Studies have stated that in oral aphthous ulcer patients, lipid peroxidation and NO can inhibit the wound healing activity of epidermal growth factor (EGF). It is recognized that flavanones could prevent macrophage and consequently the formation of NO and TNF-α. This could result in improved and earlier healing of the aphthous ulcers. It has been implied that the plant has a potential to decrease the number of episodes of ulcers in patients with RAU.[26]

Centella asiatica

The biologically active component of *Centella asiatica* is triterpenes and saponis. The important compound of triterpenes includes Asiatic acid, medecassic acid, asiaticosside and madecassoside. It also contains flavonoids and volatile oils. It is popularly known for its antioxidative and neuroprotective effects. It was revealed that 0.50,1 and 2% *Centella asiatica* gel and triamcinolone acetonide shown indifferent decreasing rate of lesion size with significantly greater rates in comparison with placebo ($p<0.05$).[48] A study report stated that enhanced wound healing ability of *C. asiatica* is by preventing inflammation, enhancing collagen production, supporting angiogenesis, promoting vasodilation and decreasing oxidative stress in the wound. The fibroblast growth factor and vascular endothelial growth factors are responsible for the wound healing activity. In injured tissues, the *C. asiatica* extracts has been revealed to disturb cellular growth and proliferation.[27]

Citrus oil and magnesium salts

The citrus oil is known to have anti-bacterial and anti-inflammatory properties. Magnesium has mild anesthetic properties. β-pinene and limonenes are the two major monoterpenes found in citrus lemon essential oil. This oil is well known for its anti ulcerogenic and antibacterial effects. The limonene might also have immunomodulatory effects. The magnesium salts has anti-nociceptive effects and it provides significant reduction in pain. A study report stated that the mucoadhesive patch containing citrus oil and magnesium salts, seal and defends the oral ulcer from oral pathogens and trauma. The patch is also effective in reduction in mean duration of pain and considerable improvement in oral functions after the treatment.[49] The magnesium salt did not exhibit any antibacterial effects whereas citrus oil is known to have an antibacterial effect with the minimum inhibitory concentration (MIC) of 1mg/ml. The mixture effected in decreased levels of TNF-α and leukocyte migration while the levels of anti- inflammatory interleukin-10 is maintained.[28]

Liquorice

This is otherwise known as *yashtimadhu, sweet wood, Atimaduram or mulhatti* which belongs to the genus *Glycyrrhiza* which is known for its immense medicinal values. The bioactive ingredients of *liquorice* are glabridin, licoricidin, licorisoflavan A, licochalcone and glycyrrhizin. It is well identified for, anti-inflammatory, anti-ulcerative, antioxidant, antiviral; glucocorticoid, anti-carcinogenic and many more properties.[50] A recent *in vivo* study assessed the clinical effectiveness of licorice bio adhesive hydrogel patches in recurrent aphthous ulcer patients. According to the study results, liquorice bio adhesive can be efficient in decreasing the pain, the inflammatory halo and the necrotic center of aphthous ulcers. The authors stated that the effect is mainly due to the anti-inflammatory effect of the *liquorice*. Among the 30 species of liquorice, the anti-inflammatory action is mainly concentrated on *G. glabra and G. uralensis*. The anti-inflammatory effects are increased superoxide dismutase enzymatic defense system of the colonic mucosa. There was a dose dependent reduction in TNF α, NO and IL-6 levels. It also decreases the MMPs, PGE2 and other free radicals. These effects are primarily due to the effects of triterpenoids and flavonoid compounds of liquorice.[29]

CONCLUSION

The isolation, characterization of active components, defining exact safety margin of drug, concentration of the active components, standardization and scientific validation are the most crucial factors to be considered while designing the herbal medicine. Herbal medications are the most preferred and well accepted drugs by the patients in a few clinical scenarios. In general, the topical herbal medications were effective over minor aphthous ulcer in various clinical outcomes within the study limits. The recent clinical studies have focused on herbal mucoadhesive patches for topical interventions of aphthous ulcer. All the topical herbal preparations were clinically effective in reducing the ulcer symptoms with improved healing. Most herbs share few common biological actions like anti-inflammatory, analgesic and immunomodulatory effects. There

is scarcity of data to warrant the clinical efficacy of combined systemic administration and topical application of the same herbal drugs in repeated cases. Further evidence based research is needed for the effective use of the herbal therapy in repeated cases of RAS. Research over the ability of topical herbal application to manage other kinds of acute painful oral ulcers can be recommended.

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