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REVIEW ARTICLE

Medicinal Plant and Their Bioactive Phytochemicals in the Treatment of Recurrent Aphthous Ulcers: A Review of Clinical Trials

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ABSTRACT

Considering the unclear etiology of recurrent aphthous ulcers (RAUs), the clinical management of RAU is based on no optimal therapeutic approach. The current study aimed to review the clinical trials on the effectiveness of medicinal plants and their active phytochemicals in the treatment of RAU. Five databases including PubMed, Science Direct, Web of Science, Scopus, and Cochrane Library were searched for retrieving all the relevant clinical trials. The results indicate that a wide range of scientific evidence has approved the therapeutic benefits of natural medicaments in the management of RAU, including *Satureja khuzistanica, Aloe vera, Myrrh, Glycyrrhiza glabra, Alchemilla vulgaris, Myrtus communis, Melissa officinalis, Rhizophora mangle, Chamomile, Rosa damascena, Nicotiana tabacum, Punica granatum, Ageratina pichinchensis, Norwegian LongoVital, Lavender* oil, and *Perilla* oil that are known anti-aphthous medical plants. Berberine and acemannan are bioactive substances with diverse pharmacological and therapeutic benefits in patients with aphthous, which made them as the promising alternatives for new pharmacological drugs. This review provides evidence that medicinal plants can be considered as future pharmaceutical drugs or adjuvant treatment with conventional therapeutic approaches to improve their efficacy and alleviate the side effects in the management of RAU. Further clinical studies are also necessary to confirm the efficacy and safety of plant-derived natural products with potential effects in treating RAU.

Key words: Herbs, mouth ulcers, phytochemical compounds, recurrent aphthous ulcer

INTRODUCTION

Recurrent aphthous ulcers (RAUs) are considered as one of the most common oral mucosal lesions, with about 5%–25% of prevalence in the general population.[1-3] Although the ulcers are often self-limiting, they can affect the patients' quality of life.[2,4] Based on the magnitude, number, and duration, RAU can be classified into three different morphological types including minor, major, and herpetiform aphthae. Minor aphthous is the most common subtype of the aphthous ulcers, which includes about 80%–85% of all RAUs.[2,5] The underlying etiology of these ulcers remained unclear so far; however, the etiological perspectives suggest that RAU is influenced by various factors such as genetics, nutritional deficiencies, and inflammatory conditions.[3,5-7] Other predisposing factors include mechanical injuries, anxiety, some viral and bacterial infections, and certain allergic foods.[8,9] Due to unclear and multifactorial pathophysiology of RAU, an absolute cure does not exist and the current treatment of RAU depends on the severity and frequency of disease symptoms.[10] Currently available treatments mostly focus on decreasing the severity of symptoms such as pain, frequency of recurrences, and dysfunctions. Some current treatments for RAU include topical analgesic and anesthetic agents, antibiotics, multivitamins, systemic corticosteroids, and varieties of combined therapies.[10-13] Nevertheless, these therapies of aphthous ulcers are unsatisfactory and no optimal approach, due to the observed side effect and palliative effect.[5,13,14] Nowadays, medicinal plants have been preferred to take treatments of aphthae rather than chemical medicines, and in this respect, wide range of plant extracts has been used for the treatment of pathos ulcers.[4,13] Medicinal plants are known to have antibacterial, antifungal, anti-inflammatory, and antioxidant activities.[13,15] Consequently, recent reports suggest that medicinal plants may be offered as alternatives in the treatment of this lesions, and several clinical trials have reported the efficacy of these medical plants.[6] We performed the present systematic review to assess studies on medicinal plants used for the treatment of RAU.

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STUDY DESIGN

Electronic databases, including PubMed, Science Direct, Web of Science, Scopus, and Cochrane Library were investigated for the clinical trial studies that examined the efficacy of any herbal material on aphthous disease. Data were gathered from 1966 to 2017 (March). Language restriction was performed and just English language articles were incorporated in this review. The key words were "plant," "phytochemical," or "herb" and "aphthous," "Sutton disease" "canker sore," "aphthous stomatitis," "aphthae," "aphthous ulcer," "recurrent aphthous stomatitis," "recurring scaring aphthous," or "aphthosis." Results from early search were reviewed by two independent investigators. All the references of final retrieved papers were reviewed for related studies. Included studies were reviewed considering the plant scientific names, part/extract of the plants, disease, treatment duration and outcome, level of evidence, Jadad score, side effects, study design, and number of patients. Results were summarized in Table 1, and the rising and falling trends of each variable are also indicated.

FINDING AND RESULTS

From 2232 potentially relevant studies, 1099 articles were excluded because of duplication (same articles from different databases). Twenty-three articles were excluded since they were reviews. One thousand and seventy-eight articles were excluded according to their title and abstract, including the articles evaluated other types of disease rather than aphthous (such as cancer and peptic ulcer), or nonclinical trial studies. From the 32 retrieved articles, two articles were excluded because they were not in English, eight papers since these studies were not about plants, three articles because there were about plant + other components, and two because they were human studies other than randomized clinical trials (case reports or case series). Finally, 17 clinical trials were included in this review [Figure 1].

Satureja khuzistanica

Satureja khuzistanica Jamzad (family *Lamiaceae*), also named *Marzehe Khuzistani* in Persian, is an endemic plant of western and southern part of Iran.[16] It has been consumed as an analgesic and antiseptic in the traditional Persian medicine.[17,18] Carvacrol is the main component of its essential oil, which has antimicrobial and antioxidant activities.[19] Evidence has supported pharmacological activity of *S. khuzistanica* extract as anti-inflammatory, antinociceptive, antimicrobial, anti-allergic, neuroprotective, and anti-apoptotic.[16,20,21] In a randomized, double-blind, placebo-controlled clinical trial, the curative efficacy of *S. khuzistanica* Jamzad essential oil and hydroalcoholic extract (25%) preparations (four times a day, typically up to complete healing) was evaluated in patients with RAU-type minor. Statistical analysis showed significant differences (P = 0.0001) between *S. khuzistanica* extract-treated group (5.90 ± 1.24 days) and *S. khuzistanica* essential oil-treated group (6.85 ± 1.3 days) with control group (10.40 ± 1.66 days) in healing of the lesion. No significant difference was detected between groups, i.e. extract and essential oil (P = 0.10), with respect to healing period of the lesions. The average time of pain relief presented significant differences (P = 0.0001) between groups extract (3.40 ± 0.50 days) and essential oil (3.20 ± 0.41 days) with group control (5.70 ± 1.12 days). No significant difference was observed (P = 0.085) between groups extract and essential oil with respect to average time of pain relief. Slight burning sensation has been reported in two patients in essential oil group after application of medication for the first time.[15]

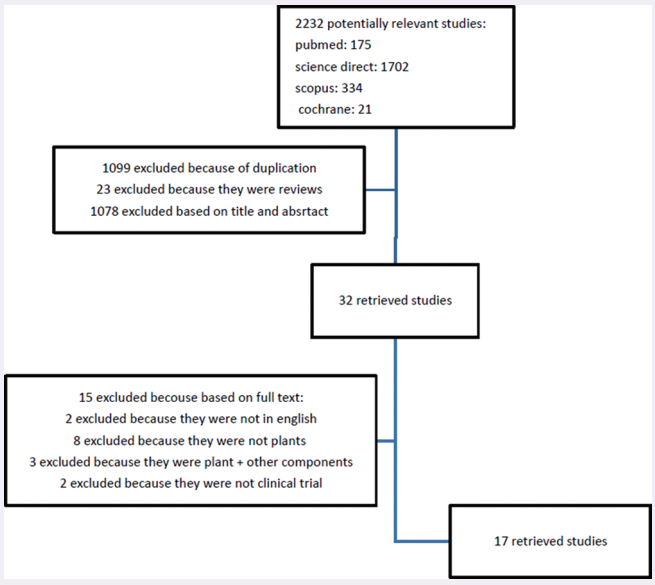

Figure 1: Search diagram

Aloe vera

The *Aloe vera* (Aloe barbadensis Miller) plant has been used for eras because of its health-promoting effects, medicinal properties, skin care characteristics, and treatment of different kinds of skin problems such as wounds and burns and diminishing of sunburn pain.[22,23] Previous articles have offered that aloe gel has a positive effect on healing of oral lichen planus[23,24] and gingivitis.[25] It has been established that *A. vera* can stimulate dermal wound healing by growing collagen and glycosaminoglycan synthesis.[26] Antifungal, anti-inflammatory, anticancer, and immunomodulatory activities are among the biological effects reported for *A. vera*.[23] Acemannan is a main bioactive polysaccharide present in *A. vera* leaf gel[27] which hastens healing of sores.[28] It fosters expression of cyclin D1 protein which leads to cell and fibroblast proliferation.[29] It also has been proved that acemannan can accelerate oral wound healing and immunomodulatory activity of *A. vera* gel.[30,31] In a randomized double-blind controlled clinical trial by Bhalang *et al.*, 180 subjects with recurrent aphthous ulceration participated to assess the effectiveness of acemannan in the management of oral aphthous ulceration. Before trial, safety of acemannan was evaluated in 50 healthy participants by application on the lower labial mucosa (three times day, for 7 days) that demonstrated acemannan causes no side effect or allergic reactions in the subjects, and blood parameters such as serum glutamic pyruvic transaminase, alkaline phosphatase, T-protein, T-bilirubin, creatinine, blood urea nitrogen, serum glutamic oxaloacetic transaminase, and albumin had no significant difference before and after 7 days of acemannan application ($P > 0.05$). In that study, treatment group received 0.5% acemannan in Carbopol® 934P NF, three times a day for 7 days, which resulted in reducing pain in comparison to placebo, but the difference was not significant. However, it was seen that 0.1% triamcinolone acetonide noticeably diminished the pain level as compared to acemannan and control. Furthermore, analysis of wound size reduction revealed that acemannan and 0.1% triamcinolone acetonide decreased the ulcer size compared to control and baseline, but 0.1% triamcinolone acetonide was superior to that of acemannan as well as there was a significant difference in ulcer reduction by acemannan from that of control ($P \leq 0.05$).[32]

Myrrh

Myrrh, dehydrated resin of shrubs and trees of *Commiphora* species, which made of volatile essential oil, sesquiterpenes, commiphoric

Table 1: Clinical trials evaluating the efficacy and safety of medicinal plants and their bioactive phytochemicals for treatment of recurrent aphthous ulcer

Scientific name	Part/extract	Preparation		Study design	Disease	Number of patients	Treatment duration	Outcome	Level of evidence	Jadad score	Side effects and tolerance	References
		Treatment group	Control group									
S. khuzistanica Jamzad	Aerial parts/ hydroalcoholic extract and essential oil	Groups A: *S. khuzistanica* extract Groups B: *S. khuzistanica* essential oil	Group C: Hydroalcoholic solution	Randomized, double-blind placebo-controlled clinical trial	Minor recurrent aphthous stomatitis	60 patients	Up to complete healing	↓ Average time of pain elimination ↓ Duration of complete lesion healing	2	3	Mild burning sensation after first application	[15]
A. vera (L.) Burm.f.; *Commiphora* spp.	Gel and dried resin	Group I: Mucoadhesive gel with *A. vera* as active ingredient Group II: Mucoadhesive gel with myrrh extract as active ingredient	Group III: Plain mucoadhesive gel (placebo)	Randomized, double-blind, placebo-controlled study	Minor recurrent aphthous stomatitis	90 subjects	5 days	↓ Ulcer size ↓ Pain intensity ↓ Erythema levels ↓ Exudation levels	1	5	No adverse effects; tolerable	[12]
M. chamomilla	Flower/ chamomile extract	Group T: Triamcinolone in Orabase Group C: Chamomile extract in Orabase	Group O: Orabase only as placebo	Randomized, double-blind, placebo-controlled clinical trial	Minor recurrent aphthous stomatitis	45 patients	6 days	↓ Pain intensity ↑ Patient's satisfaction ↓ Ulcer size: Group T > Groups O and C	2	4	Not mentioned	[70]
R. mangle L.	Bark/aqueous bark extract	RMABE group: Aqueous extract of the bark of *R. mangle*	Placebo group: Solution of water and the excipients present in RMABE	Randomized, single-blinded, placebo control trial	Minor oral aphthous ulcers	32 patients	5 days	↓ Time to heal↓ Time necessary for removal erythema, ardor and pain	2	3	No adverse effects	[62]
M. communis	Leaves/ aqueous extract	Myrtle oral paste	Placebo paste	Randomized, double-blind, controlled before-after clinical trial	Recurrent aphthous stomatitis	45 subjects (17 males and 23 females)	6 days	↓ Ulcer size ↓ Pain severity ↓ Erythema level ↓ Exudation level ↑ Oral health impact profile ↑ Satisfaction of treatment	2	4	No adverse side effects	[54]

Contd...

Table 1: Contd...

Scientific name	Part/extract	Preparation		Study design	Disease	Number of patients	Treatment duration	Outcome	Level of evidence	Jadad score	Side effects and tolerance	References
		Treatment group	Control group									
A. vera (L.) Burm.f.	Leaf/pulp gel	Group I: 0.5% acemannan in Carbopol® 934P NF Group II: 0.1% triamcinolone acetonide	Group III: Pure Carbapol 934P NF as placebo	Randomized double-blind controlled clinical trial	Recurrent aphthous ulceration	180 subjects	7 days	↓ Ulcer size ↑ Patient's satisfaction	2	3	No side effects	[32]
M. communis and *M. officinalis*	Aerial parts/ essential oil	Group A: Solution 5% of *M. communis* and *M. officinalis* essential oils/ ethanol 80 Group B: Solution 10% of *M. communis* and *M. officinalis* essential oils/ ethanol 80	Group C: Placebo containing ethanol 80	Randomized double-blind controlled clinical trial	Recurrent aphthous stomatitis	137 patients	Group A: 4.5 days Group B and C: 8.5 days	↓ Time for burning relief ↓ Period for complete healing of ulcers	2	3	No side effects	[58]
P. granatum var. pleniflora; *P. granatum* var. Sweet Alak; P. granatum var. Saveh Black	Flower/ alcoholic extracts and water extract	Groups a–c: Alcoholic extracts of *P. granatum* var. pleniflora, *P. granatum* var. Sweet Alak and *P. granatum* var. Saveh Black Groups d–f: Water extracts of *P. granatum* var. pleni-flora, *P. granatum* var. Sweet Alak and *P. granatum* var. Saveh Black	Group g: Nothing (negative control)	Double-blind clinical trial	Minor recurrent aphthous stomatitis	210 patients	10 days	↓ Lesion size (Groups a, d, b and e) ↓ Pain degree (Groups a, d and e) ↑ Patient's satisfaction (Groups a, d and e) ↓ Recovery time (Groups a, d and e) The best result in recovery time and pain relief reported of Group d	2	2	Irritation of alcoholic extracts	[88]

Contd...

Table 1: Contd...

Scientific name	Part/extract	Preparation		Study design	Disease	Number of patients	Treatment duration	Outcome	Level of evidence	Jadad score	Side effects and tolerance	References
		Treatment group	Control group									
P. frutescens (L.) Britt.	Seed/oil	Perilla oil	Soybean oil	Randomized, placebo-controlled, double-blind trial	Minor recurrent aphthous stomatitis	30 subjects	8 month	No significant differences between groups in occurrences of minor aphthous in experimental phase	2	3	No side effects	[111]
R. damascena	Flower and petal/aqueous extract	Mouthwash containing *R. damascena* extract	Placebo contained mouthwash ingredients except R. damascena extract	Randomized, double-blinded, placebo-controlled clinical trial	Recurrent aphthous stomatitis	50 patients	2-week	↓ Ulcer size (day 4 and 7) ↓ Aphthae number (day 4 and 7) ↓ Pain (day 4 and 7) ↑ Efficacy index (day 4 and 7) No significant difference in middle ulcer size, pain, efficacy index and number of aphthae at days 11 and 14	1	5	No side effects	[78]
H. canadensis; C. chinensis and B. vulgaris	Fruit, root, rhizome	Gelatin-containing berberine (5 mg/g)	Gelatin (vehicle) only	Randomized, double-blind, placebo-controlled, clinical trial	Minor recurrent aphthous stomatitis	87 patients	5 days	↓ Ulcer size ↓ Erythema and exudation levels ↓ Pain score	1	5	No adverse side effects	[4]
C. pepo L.; *R. officinalis* L.; *C. annuum; A. millefolium*	Seeds, leaves, flowers and fruits	Group I: LV tablets Group II: Herbal Component of LV alone	Group III: Placebo	Randomized, double-blind, placebo-controlled	Minor recurrent aphthous stomatitis	52 patients	4 months	No statistically significant differences in number of new ulcers and ulcer-free days between any of the three groups	1	4	Mild indigestion problems	[98]

Contd...

Table 1: Contd...

Scientific name	Part/extract	Preparation		Study design	Disease	Number of patients	Treatment duration	Outcome	Level of evidence	Jadad score	Side effects and tolerance	References
		Treatment group	Control group									
G. glabra	Root/ chloroform extract	Episode III: Patches containing Licorice 1%	Episode II: Base of patches (placebo group) Episode I: No-treatment	Placebo-controlled, observer-blind, consecutive-group clinical trial	Minor recurrent aphthous stomatitis	15 patients	15 days	↓ Pain intensity (compared with the no-treatment) ↓ Diameter of inflammatory halo (compared with the placebo) ↓ Diameter of necrotic zone of the ulcer (compared with the placebo)	2	2	Not mentioned	[40]
A. pichinchensis	Aerial parts/ unpigmented hexane–ethyl acetate extract	Extract of *A. pichinchensis*	Triamcinolone 0.1%	Minor recurrent aphthous stomatitis	Double-blind, randomized, and controlled pilot study	56 patients	Uptime of complete healing, maximum to 2 weeks	No statistically significant differences between experimental and the control group	1	5	No side effects	[93]
A. vulgaris	Arial parts/ extract	Standard 3% extract of *A. vulgaris* in glycerin	-	Minor recurrent aphthous ulceration	An open-label study	48 patients	Up to complete healing of ulcers	Accelerate the complete wound healing in the majority of cases (↓ Complete healing time)	2	1	Slight irritation (18.2%) Moderate irritation (13.6%); tolerable	[44]
N. tabacum (L.)	Leaves/ decoction	Tobacco mouthwash preparation	Blank mouthwash as placebo	Minor recurrent aphthous	Randomized double-blinded placebo-controlled clinical trial	60 patients	5 days	↓ Ulcer pain score ↓ Ulcer size	1	5	No side effect	[83]

Contd...

Table 1: Contd...

Scientific name	Part/extract	Preparation		Study design	Disease	Number of patients	Treatment duration	Outcome	Level of evidence	Jadad score	Side effects and tolerance	References
		Treatment group	Control group									
L.angustifolia	Leaves, flowers and buds/oil	Lavender oil: Standard lavender oil (2%) in glycerin	Glycerin without active ingredients	Recurrent aphthous ulceration	Randomized, double-blind placebo-controlled trial	115 patients	Up to complete healing of ulcers	↓ Level of inflammation ↓ Level of ulceration ↓ Pain score ↑Peak intensity of pain reduction ↓ Time of complete healing	2	3	No side effects	[107]

S. khuzistanica=Satureja khuzistanica, A. vera=Aloe vera, M. chamomilla=Matricaria chamomilla, R. mangle=Rhizophora mangle, RMABE=*Rhizophora mangle* aqueous bark extract, *M. communis=Myrtus communis, M. officinalis=Melissa officinalis, P. granatum=Punica granatum, P. frutescens=Perilla frutescens, R. damascene=Rosa damascene, H. canadensis=Hydrastis canadensis, C. chinensis=Coptis chinensis, B. vulgaris=Berberis vulgaris, C. pepo=Cucurbita pepo, R. officinalis=Rosmarinus officinalis, C. annuum=Capsicum annuum, A. millefolium=Achillea millefolium,* LV=Longo vital, *G. glabra=Glycyrrhiza glabra, A. pichinchensis=Ageratina pichinchensis, A. vulgaris=Alchemilla vulgaris, N. tabacum=Nicotiana tabacum, L. angustifolia=Lavandula angustifolia,* , ↓=Decrease, ↑=Increase

acids, and a water-soluble gum, is an anti-inflammatory, antibacterial, antifungal, antidiabetic, anti-infectious, and wound-curer agent that has been claimed to normalize mucous membrane activity.[33-35] It has been applied to treat diarrhea, coughs, inflammation, intestinal disorders, wounds, and chest ailments.[35] Experimentally, various studies have demonstrated antioxidative, cytotoxic, antigastric ulcer, and nonmutagenic properties of myrrh.[36] In the Mansour *et al.*'s study conducted on 90 patients with minor RAU, safety and clinical potency of two novel oral mucoadhesive gels based on *A. vera* gel or myrrh in a concentration of (0.5% w/w) were investigated in the treatment of RAU. In patients using aloe gel, mean ulcer size was remarkably smaller than that of myrrh and placebo groups at day 6 ($P < 0.05$), whereas pain intensity scores showed to be minimum in myrrh-treated patients at day 6 ($P < 0.05$). Furthermore, erythema and exudation levels were significantly lower in both aloe and myrrh groups in comparison with placebo but aloe was superior. No adverse effects were found with the use of any of the gels during the clinical trial.[12]

Glycyrrhiza glabra

Glycyrrhiza glabra (licorice) has been used in medicine for treating various diseases in many countries for years. Several studies have demonstrated that *G. glabra* extract or glycyrrhizin (active component existence in roots) possesses diuretic, expectorant, sedative, antipyretic, antidiabetic, laxative, antidepressive, spasmolytic, antiviral, antimicrobial, antioxidant, anti-inflammatory, and antiulcer activities.[37,38] Anti-inflammatory effect of methanolic extract of *G. glabra* is done by inhibiting of cyclooxygenase-2, inducible nitric oxide synthase (iNOS), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 productions.[39] Moghadamnia *et al.* conducted a placebo-controlled, observer-blind, consecutive group clinical trial on 15 patients (5 women and 10 men, age 22–35 years) with a history of RAU and recently suffering from lesions of the anterior region of the mouth to evaluate the efficacy of licorice hydrogel patches to manage the pain and decline the improvement time of aphthous ulcer. Bioadhesive patches containing licorice 1% were applied four times a day each time for 20 min, and the results showed that time of complete pain relief significantly decreased in patients using licorice containing biopatch in comparison no-treatment group ($P < 0.01$), but in complete healing time of ulcers, no significant difference was observed between no-treatment, placebo, and licorice biopatch groups ($P = 0.180$). Moreover, licorice patch application made a significant reduction in the diameter of the inflammatory halo and necrotic center of the ulcer as compared to the placebo group ($P = 0.03$).[40,41]

Alchemilla vulgaris

Alchemilla vulgaris (Lady's Mantle) belong to the family *Rosaceae* has traditionally been applied to remedy in several conditions such as inflammation, eczema, diarrhea, ulcers, skin rashes, bleeding, menstruation disorders, hypertension, and diabetes among the folk in Europe. It was shown that bioactive ingredients of *A. vulgaris* extract include flavonoid glycosides built of quercetin derivatives and gallic acid.[42] Ulcer-healing properties of *A. vulgaris* extract in glycerin was evidenced whereas it may enhance premitotic activity in the myofibroblasts and epithelial cells.[43] In an open-label study on 48 male and female patients with minor mouth ulcers, Shrivastava and John reported that topical utilization of a standard 3% extract of *A. vulgaris* in glycerin (Aphtarine®) three times daily led to complete healing in 75% within 3 days compared to 33.3% without treatment and 40% with an over-the-counter treatment. In addition, the majority of patients approved taste, ease of application, and texture of Aphtarine® gel but was found slight irritation in 18.2% and moderate irritation in 13.6%.[44]

Myrtus communis

Myrtus communis (MC) L. (myrtle) is an famous fragrant evergreen shrub indigenous North Africa, West Asia, and Southern Europe.[45,46] It has been reported that myrtle has antibacterial,[47,48] analgesic,[49] antihyperglycemic,[50] anticancer,[45] antifungal, antiviral, antioxidative, and anti-inflammatory properties.[51] Leaves are used as a mouth wash to cure candidiasis in among public[50] and also traditionally used for diarrhea and abdominal pain in Iranian, Turkish, Pakistanian, and Indian traditional medicine.[46] As recently reported, myrtle also has antioxidant activity suggesting that the plant could be useful for inflammatory and allergic diseases.[52,53] In a randomized, double-blind, controlled trial, clinical efficacy and safety of an oral paste containing myrtle in the control of RAU were assessed. Forty-five individuals suffering from RAU participated in the study received myrtle oral paste or placebo paste for 6 days rather after oral hygiene. The data revealed a statistically significant diminution of pain intensity ($P < 0.05$), ulcer diameter ($P < 0.001$), and erythema and exudation level ($P < 0.001$). In addition, there was a significant difference in terms of oral health impact factor ($P < 0.001$) between treatment and placebo groups. No side effects such as acute hypersensitivity reactions, infection, and pain were observed in any of the patients.[54]

Melissa officinalis

Melissa officinalis (MO) L., also known as lemon balm, is a medicinal herb that has traditionally been used to treat various cancers, cardiovascular and respiratory problems, mental and CNS diseases in Middle East countries, Mediterranean region, and European countries.[55] MO possesses antispasmodic, potent antioxidant, gastroprotective, antiulcer,[56] neuroprotective, antihyperlipidemic, and hepatoprotective effects.[57] Saberi *et al.* showed that methanolic extract of MO (150 and 300 mg/kg) significantly reduced the ulcer index (UI) in both water immersion-restraint stress and indomethacin groups as compared to the control rats that received the equal volume of saline ($P < 0.01$). Significant difference was not found in the UI between MO extract-treated rats (150 and 300 mg/kg) and ranitidine-treated rats ($P > 0.05$). Likewise, MO extract considerably enhanced superoxide dismutase and glutathione peroxidase levels and decreased malondialdehyde serum levels that lead promoting antioxidant defense and preventing lipid peroxidation.[56] In other study, Eslami Raveshty and Eslami Raveshty evaluated the efficacy of an herbal medicine composed of MC and MO plants in the treatment of RAU. A total of 137 patients suffering from aphthous lesions randomly received 5% solution of MC and MO essential oils in ethanol 80 or 10% solution of MC and MO essential oils in ethanol 80 or placebo (ethanol 80), five or six times a day. Finding displayed that treatment with 5% solution of MC and MO essential oils can significantly lessen the average complete healing time of ulcers for minor aphthous in comparison with 10% solution of MC and MO essential oils and placebo ($P < 0.0005$).[58]

Rhizophora mangle

Rhizophora mangle, which is a great source of phenolic compounds,[59] has been used as a traditional remedy in many Caribbean countries. The aqueous extract of bark contains large quantities of tannins, especially condensed tannins, and in traditional medicine used for treating bacteriological inflammation, wounds, and fungal diseases. It has been reported that its bark has antiulcer, antiseptic, antioxidant, wound-healing, antihemorrhagic, antifungal, and astringent activities.[59-61] A randomized, single-blinded, placebo-controlled trial was designed to estimate the effectiveness of aqueous bark extract of *R. mangle* in improving minor oral aphthous ulcers. Thirty-two male and female individuals (age range 35–45 years) with oral aphthous ulcer were enrolled in this study and applied *R. mangle* aqueous bark extract or placebo as medicine topically once a day. According to the results, the average time of complete ulcer improvement significantly decreased ($P < 0.0001$) so far as by 7 days in 71% of the patients in treatment group healed completely, in comparison to 7% in the placebo group ($P < 0.0001$). Furthermore, lesions and its symptoms were worsened in 33% patients the placebo group. No adverse side effect was evidence.[62]

Matricaria chamomilla (chamomile)

Chamomile is a well-known medicinal plant with various properties, which is used as a therapeutic herb for many years.[63] It has been reported that its essential oil constituents have antispasmodic, antiallergic, antipyretic, ulcer-protective, anti-inflammatory, antibacterial, antifungal, sedative, analgesic, and antioxidant properties.[63-67] Oxidant/antioxidant activity was studied in patients with RAU, and it was shown that their enzymatic and nonenzymatic antioxidant defense systems are destroyed in patients with RAU.[68] However, the antioxidant activity of chamomile may have some positive effects on the ulcers.[69] In addition, due to anti-inflammatory effects, chamomile can be useful in recovery of ulcers.[63] In a randomized, double-blind placebo-controlled study on 45 individuals with oral mucosal minor aphthous who received chamomile extract in Orabase or triamcinolone in Orabase or placebo resulted in a significant pain relief similarly at chamomile and triamcinolone in Orabase in comparison to placebo, however, no significant difference was observed in chamomile and triamcinolone in Orabase ($P > 0.05$). In addition, triamcinolone in Orabase reduced ulcer size and time of complete healing very more than two other groups. According to the study findings, chamomile extract caused satisfaction of the patients for their treatment and diminished pain intensity of the ulcers.[70]

Rosa damascena

Rosa damascena (*Rosaceae*) is a plant which grows in Andalusia, Morocco, and the Middle East, especially in Iran.[71] In traditional medicine, *R. damascena* flowers and petals have been used for the treatment of gastrointestinal disorders, reduction of inflammation, ulcers skin, abdominal pain, polymenorrhea, and heart reinforcement.[72] Antioxidant, analgesic, anti-inflammatory, hepatoprotective, antispasmodic, antiulcer, and antibacterial properties have been considered for this plant.[73-76] In Zaidi *et al.*'s study, extracts of *R. damascena* (100 μg/ml) represented strong inhibitory activity against IL-8 secretion and demonstrated its anti-inflammatory effects.[77] Furthermore, other study by Mansouri *et al.* indicated that topical application of hydroalcoholic extract of *R. damascena* mill in combination with 0.1% tretinoin lotion dramatically accelerated wound healing in diabetic rats.[72] In a randomized, double-blind, placebo-controlled study, clinical efficacy of a mouthwash-containing aqueous extract of *R. damascena* as a treatment for 50 patients with RAU was observed. It has been affirmed that ulcer diameter, pain score, and number of aphthous ulcers were dramatically lower ($P < 0.05$) than placebo on days 4 and 7, but there were no significant difference on days 11 and 14. However, 48% and 96% of patients receiving *R. damascena* extract experienced complete healing by days 4 and 7, respectively; whereas only 4% and 32% of patients in placebo completed the healing process up to this time, respectively. In the end, authors concluded that *R. damascena* extract can be effective in management of RAU.[78]

Nicotiana tabacum

Nicotiana tabacum (tobacco) is a thick herbal plant belonging to *Solanaceae* which grows throughout the world.[78,79] In Chinese medicines, people consume aerial parts of the tobacco as anesthetic, sedative, emetic, and diaphoretic agent.[80] Tobacco leaves are very rich

of bioactive components such as polyphenols, aromatic compounds, nicotine, malic and citric acids, coumarins, enzymes, polysaccharides, and proteins. While antioxidant and antimicrobial activities of polyphenols have been investigated, therapeutic properties such as anti-inflammatory, immunomodulating, antitumor, antipathogens, and antioxidant effects have been attributed to polysaccharides.[81,82] In a systematic review performed by Tsouh Fokou *et al.,* the ethnobotanically use of crushed leaves of tobacco for treatment wounds or disinfectant or as pomade was pointed out in three West African countries.[82] In a randomized double-blinded placebo-controlled study designed by Vaziri *et al*., potential of decoction of *N. tabacum* leaves on 60 patients with minor recurrent aphthous was determined. Patients applied 10 ml of tobacco mouthwash three times a day for 5 days and the results showed that the mean pain score and ulcer size in the treatment group were significantly lower than placebo ($P < 0.01$). Meanwhile, in the tobacco group, reduction of pain score of ulcer was by 79.2% and 93.8% and ulcer size was by 69.1% and 92.2% (days 3 and 5, respectively). In safety evaluation, natural tobacco mouthwash was considered as a safe and tolerable remedy for the management of recurrent aphthous.[83]

Punica granatum var. *pleniflora*

Punica granatum L. (pomegranate) is a small tree or shrub of the *Punicaceae* family and is considered to be native from the Himalayas in northern India to Iran and Afghanistan.[84,85] Male abortive flowers of *P. granatum* that are known locally as "Golnar-e-farsi" have antibacterial, antifungal, hemostatic, astringent, and antiviral properties and are used for the treatment of bronchitis, diarrhea, digestive problems, diabetes, hemorrhage, cut wound, and dermal infected wounds in the traditional Persian medicine.[86,87] The topical use of pomegranate preparations is shown to be effectively useful for controlling oral inflammation, as well as bacterial and fungal infections in periodontal disease and *Candida*-associated denture stomatitis.[85] In a double-blind method study, alcoholic and water extracts of *Punica granatum* var. pleniflora, *Punica granatum* var. Sweet Alak, and *Punica granatum* var. Saveh Black were tested on 210 participants (females 32% and males 68%) suffering from minor aphthous ulcers, four times a day and for 10 days. According to the results, the highest level of pain relief and satisfaction of individual was seen in alcohol and water extracts of *P. granatum* var. pleniflora and water extract of *P. granatum* var. Sweet Alak ($P < 0.0001$); naturally patients' satisfaction of the water extract was more than the alcoholic extract because of some irritation in them. Results also indicated that water and alcohol extracts of *P. granatum* var. pleniflora and *P. granatum* var. Sweet Alak significantly decreased lesion size, but the best effect on aphthous amelioration and the shortest complete healing period of lesions were observed in water extract of *P. granatum* var. pleniflora.[88]

Ageratina pichinchensis

Ageratina pichinchensis (Schauer) King and H. Rob. (*Asteraceae*) is a medicinal herb and indigenous of Mexico. It is utilized to treat gastric ulcers and pain in the one of Mexican states.[89] Furthermore, this plant has been used for many years in the treatment of vaginitis, skin wounds, fungal infections, and chronic venous leg ulcers.[90,91] In a pharmacological and chemical study, the most active compounds in aqueous extract of *A. pichinchensis,* which has an ability to prompt reproduction of cellular, were isolated and identified as flavonoids 7-O-(β-d-glucopyranosyl)-g alactin. Furthermore, in assessment of anti-inflammatory effect of this plant, it was demonstrated that aqueous extract reduces inflammation induced by carrageenan in mice and does not have any acute (2 g/kg) and subchronic (1 g/kg for 28 days) toxic effect in oral administration.[92] In another study in an animal model of diabetes, hexane–ethyl acetate and aqueous extracts of *A. pichinchensis* showed wound-healing activity *in vivo*.[90] In a double-blind, randomized, controlled pilot study, a phyto-pharmaceutical formulation made with 5% hexane–ethyl acetate extract of *A. pichinchensis* administered in 56 patients with minor RAU, the therapeutic achievement was evidence and no case of therapeutic failure was observed. Furthermore, no statistically significant differences in pain, clinical effectiveness, and ulcer evolution were detected in patients included in the study in both groups.[93]

Norwegian LongoVital

LongoVital (LV) is a supplement tablet composed of vitamins in recommended daily doses and a variety of dried and ground herbs. The herbal ingredients of the tablets change a little between the countries as Norwegian LV contains pumpkin seeds (*Cucurbita pepo*), rosemary leaves (*Rosmarinus officinalis*), paprika (*Capsicum annum*), and milfoil flowers (*Yarrow Achillea millefolium*).[94,95] LV has been noticed to have immunostimulatory, antimicrobial, and immunomodulatory properties.[95,96] Previous studies have evidenced preventive and therapeutic effects of the tablets on aphthous stomatitis, gum bleeding, periodontal disease, Sjogren's syndrome, and herpes labialis.[95-97] In a clinical, prospective, placebo-controlled, double blind, 10-month trial (introduction period [IP] 60 days, tablet period [TP] 4 months, followed up period [F-UP] 4 months), the prevented effect of Norwegian LV tablet on patients with at least one attack of minor recurrent aphthous ulceration per 2 months was investigated. After IP, in TP, patients received LV or herbal component of LV or placebo, three tablets in the morning with breakfast. Clinical data revealed that the number of ulcer-free days significantly increased within all three groups in the first 60 days of TP (TP1) in comparison to IP ($P < 0.05$). In the LV group, a further increase was demonstrated in ulcer-free days in later 2 months of TP compared with the first 2 months of TP. Furthermore, the number of new ulcers was reduced within both the LV and the herbal groups in F-UP, in comparison to TP ($P < 0.05$), but no statistically significant differences were shown between the three groups in both number of new ulcers and ulcer-free days in F-UP compared with TP ($P < 0.05$).[98]

Berberine

Berberine, a isoquinoline alkaloid isolated from stem bark, rhizomes, and roots of many plants, such as *Coptis chinensis* (coptis or golden thread), *Berberis vulgaris* (barberry), *Hydrastis canadensis* (goldenseal), *Berberis aquifolium* (Oregon grape), and *Berberis aristata* (tree turmeric), is being beneficial for the treatment of congestive heart failure, cancer, inflammation, obesity, atherosclerosis, neurodegenerative diseases, cardiovascular diseases, rheumatoid arthritis, and metabolic disorders in the traditional Chinese medicine. Furthermore, berberine exerts several pharmacological activities, including antiurolithiatic, anti-inflammation, antitumoral, antimicrobial, immunomodulatory, and glucose- and cholesterol-lowering.[99-101] In an animal study conducted by Pan *et al*. in the evaluation of the protective effects of berberine on ethanol-induced gastric lesions and proving of nitric oxide (NO) role, it was exhibited that UI in the berberine-treated groups (5 mg/kg and 50 mg/kg) was lower than the control group. NO amount in the berberine-treated groups (5 mg/kg and 50 mg/kg) was greater than the control group at 1 h after the oral administration of ethanol ($P < 0.05$) and was lesser at 6 h ($P < 0.05$). On the other hand, berberine can protect the gastric mucosa and hasten the healing of peptic ulcers via improving endothelial NO synthase mRNA expression and low expression of iNOS mRNA.[102] In a randomized, double-blind, placebo-controlled, clinical trial on 84 subjects with minor RAU, berberine gelatin (10 g) containing 50 mg berberine was administrated four times daily for 5 days. Results demonstrated that the pain score of lesions was significantly lower in the berberine group on day 2 ($P < 0.05$), day 4 ($P < 0.02$), and day 6 ($P < 0.03$)

than that in the control group. The ulcer diameter in the berberine group significantly decreased on day 2 ($P < 0.01$), day 4 ($P < 0.03$), and day 6 ($P < 0.005$) in comparison to placebo. The differences in erythema and exudation levels between two groups were not significant on days 1 and 2 of the visits ($P > 0.05$, $P > 0.05$, respectively), but on day 4 and 6, these parameters were significantly lower in the treatment group ($P < 0.01$, $P < 0.01$, respectively, for erythema and $P < 0.04$, $P < 0.05$, respectively, for exudation) than the control group.[4]

Lavender oil

Lavandula angustifolia (lavender; *Labiatae*) has been used as a traditional medicine worldwide. It has been proved that the oil has antibacterial and antifungal properties and exerts positive effects on burns and insect bites.[103,104] It has also been shown that silexan (standardized essential oil of *L. angustifolia* flowers) can act as an anxiolytic agent in generalized anxiety disorder patients and possesses beneficent effects on typically associated symptoms of anxiety disorders including somatic complaints, decreased quality of life, impaired sleep, and comorbid depression.[105,106] In a clinical study performed by Altaei in 115 subjects with aphthous ulcers, topically treated with the formulation of standard lavender oil (2%) in glycerin or placebo, lavender oil revealed anti-inflammatory and analgesic activity. The peak intensity of pain reduction of lavender oil was shown after the 5 min of application and was completely invisible after 20 min, but the placebo group experienced the pain until the end of experiment. Furthermore, in lavender oil-treated group, individuals experienced reduction of ulcer size and complete ulcer healing after 4 days. In this study, no patient showed signs of side effects or irritation.[107]

Perilla oil

Common *Perilla* (*Perilla frutescens* (L.) Britton) is an edible plant of family *Lamiaceae*, native to East Asia, which is traditionally used in the treatment of common cold, cough, asthma, influenza prevention, lung afflictions, abdominal pain, food poisoning, constipation, cancers, morning sickness, depression, anxiety-related disorders, fish- and crab-poisoning symptoms, and mental stress.[108-110] Furthermore, the seed oil of *Perilla* is an edible drying oil and is rich in linolenic acid.[108] Several *in vitro*, animal, and human nutritional researches have shown that *Perilla* oil improves membrane stability, lowers plasma triacylglycerol levels, increases glucose-6-phosphatase activity, and controls liver fatty acid composition as well as regulates glucose metabolism in rats and control serum lipid concentrations.[109] Thirty patients with minor RAS (at least once a month) were randomly divided to two groups including subjects asked to use soybean oil (group 1) or a perilla oil (group 2) as a cooking oil for 8 month. According to the results, there were no significant differences in the prevalence of minor RAU or complete healing time between two groups in experimental phase. However, average monthly occurrences of minor RAU significantly reduced in the experimental phase in both groups in comparison to run-in phase in which patients received a 50/50 mixture of soybean oil and rapeseed oil ($P < 0.05$ and $P < 0.005$ for *Perilla* and soybean groups, respectively).[111]

DISCUSSION AND CONCLUSION

RAU is an oral painful mucosal condition which has unknown etiological factors. Regardless of the term of the disease in various therapeutic systems, the main goal of treatment of ulcers is alleviating pain, inflammation, as well as period and recurrence of the disease.[112]

Several therapeutic approaches are used for the treatment of RAU and its complications. Although these treatments are sometimes effective, there is a necessity for discovering new pharmacological agents. The short effects of topical anesthetics, simply washing the topical drug from the mucosa, and drug-related side reactions such as secondary fungal infections as well as creating the oral ulcers are the main limitation of conventional treatments.[113,114] Therefore, scientists are investigating to find the medications with higher efficacy and lower side effects and are focusing on agents which have high protective effects on mucosa and potential to relief the pain and inflammation, as well as wound-healing ability. Medicinal plants possess a crucial role in traditional and alternative therapeutic approaches. Plant-derived natural products provide an enormous resource which considered as potential drugs for managing a wide range of diseases.[115]

In the present review article, we summarized the current evidence on the effectiveness of the extracts of medicinal plants and their bioactive phytochemicals in the treatment of RAU. The question is whether anti-aphthous natural drugs are effective in treating the clinical signs of RAU or not. Therapeutic approaches of RAU are symptomatic and depend on the type of ulceration; however, the aim of treatment is reducing healing time, number, and size of lesions as well as pain level. A wide range of scientific evidence has approved the therapeutic benefits of natural medicaments in the management of RAU. Patients with RAU suffer from different slight and extensive ulcers on the buccal and labial mucosa, soft palate, the floor of mouth, tongue, and tonsillar areas. Several factors predispose individuals to RAU including genetic factors, food hypersensitivity, trauma, smoking cessation, and hormonal disturbances. Mounting evidence demonstrated that the medicinal plants and their phytochemical components perform their therapeutic beneficial in patients with RAU through several cellular mechanisms including immunoregulatory effect, inhibition of pro-inflammatory cytokines TNF-α, antibacterial, antiviral, analgesic effects mediated by regulating opioid pathway, as well as anti-inflammatory response effects.[69,116]

This review calls attention to medicinal plant extracts and phytochemical compounds, whose role in the management of RAU deems crucial. In comparison with control group, topical herbal drugs or their derived natural products significantly improved the patients' symptoms by alleviating ulcer pain, decreasing ulcer size, as well as restricting ulcer duration, with no major adverse effects. Several animal experiments have suggested different candidates as natural anti-aphthous agents; however, only a restricted number of these medicines could find their way into clinical trials. Acemannan and berberine are among these natural phytochemical molecules which are the most studied ones in animal model of oral inflammations and ulcers. One clinical trial on berberine and another assessing on acemannan were successful in demonstrating the anti-aphthous effects of these natural products in human subjects.[4,32]

Result obtained from clinical trials evaluating anti-aphthous effects of bioactive compounds, derived from medicinal plants, showed the need for conducting further well-designed clinical trials to assess the efficacy of other natural products in patients with RAU. In addition, performing *in vivo* or *in vitro* studies is suggested to understand the main cellular and molecular mechanisms of action of natural drugs in treating RAU and its symptoms.

Regarding toxicity and adverse effects in clinical trials of these medicinal plants and their active phytochemical compounds, no patient of the trials showed significant side effects such as sense malfunctions, hypersensitivity, pain, and infection. Reviewing the clinical studies revealed slight side effects including mild burning sensation and slight-to-moderate irritation, which spontaneously relieved.

Plant-derived natural products can be considered as future pharmaceutical drugs or adjuvant treatment with conventional therapeutic approaches to improve their efficacy and alleviate the side effects in the management of oral disorders, including RAU.

Assessing the structure–activity relationship of highly potent anti-aphthous phytochemicals is suggested to find the future natural,

semi-synthetic, or synthetic drugs based on the backbone of these natural phytochemicals. Further clinical studies are also necessary to confirm the efficacy and safety of natural products with potential effects in treating RAU. The present review revealed that further preclinical researches are required to recognize the absorption, metabolism, bioavailability, and bioefficacy of phytochemical compounds in the pathogenesis of aphthous stomatitis diseases.

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Conflicts of interest

There are no conflicts of interest.

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