

# Evidence-based effectiveness of herbal treatment modality for recurrent aphthous ulcers – A systematic review and meta-analysis

## ABSTRACT

Recurrent Aphthous Ulcers (RAU) has affected mankind through time immemorial. It is the most commonly prevalent oral mucosal lesion manifesting as painful ulcers involving non – keratinised oral mucosa. This review was done to assess herbal intervention in RAU patients for outcomes of ulcer size and pain intensity. Literature search of published articles in Medline, Scopus, Ovid and Journal of Web upto August 2020 were reviewed for the pre-described outcomes. Revman 5.4 software was used for study analysis. Total 9 articles were finally chosen for qualitative analysis. Meta analytic comparison demonstrated the ulcer reduction (CI = -2.22 to - 0.09; p <0.001) and pain intensity (CI = -4.60 to - 0.08; p <0.001) was reduced in the herbal group as compared to the controls. A definite evidence of herbal intervention was noted in alleviating RAU signs and symptoms.

**Keywords:** Erythema, exudates, herbal formulations, pain intensity, recurrent aphthous ulcers, ulcer size

## INTRODUCTION

A solitary/multiple aphthous ulcers, occurring at different intraoral sites have recurrent tendency leading to recurrent aphthous ulcers/Stomatitis (RAU), is/are the most common oral mucosal lesion, with a prevalence rate of 25%.<sup>[1]</sup> It manifests as a painful, shallow ulcer with a very well-defined erythematous margin and has a yellowish-gray pseudomembranous center. It has a predilection for affecting women and higher socioeconomic status individuals.<sup>[2,3]</sup>

The lesion manifests clinically as a recurrent, painful ulcer with a necrotic base. The lesion presents as three clinical subtypes depending on the severity, number, and frequency of outbreaks into minor, major, and herpetiform types.<sup>[4,5]</sup> Minor RAU presents itself as small, recurrent, and round ulcers that heal in 10–14 days without scarring. Major RAU are painful ulcers that are >5 mm in diameter and take a longer time to heal (6 weeks), leaving behind scars. Herpetiform RAU is characterized by numerous clusters of pinpoint ulcers that heal within 10 days.

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The etiology of the lesion is diverse. Various predisposing factors such as food allergens, trauma, genes, hormonal fluctuations as in menstrual cycles and pregnancy, periods of stress, and exposure to certain chemicals and microbes are reported in the literature.<sup>[6,7]</sup> Most of the time, the outbreak is self-limiting.<sup>[8]</sup> As the causative factors and pathogenesis of RAU remain ambiguous, no definite treatment protocol exists. Conventionally, the treatment is provided to alleviate pain and lessen lesion duration.<sup>[9]</sup> Commonly recommended are topical anesthetics, analgesics, and corticosteroids for recalcitrant lesions.<sup>[10]</sup> Frequent exposure and long-term therapy to these medications can result in fungal pathologies and drug resistance, which further can lead to adverse effects and even life-threatening risks.<sup>[11]</sup>

Alternative therapy in the form of herbal formulations for RAU treatment is widely employed across the globe for decades. A Plethora of Herbal mixtures is used in treating RAU. Literature evidence of such treatment has reported favorable effects in decreasing discomfort and ulcer duration. Hence, this analysis was undertaken to evaluate and reaffirm the efficacy of alternative herbal therapy in RAU.

## METHODS

### Protocol and registration

The PRISMA checklist, used for reporting systematic reviews and meta-analysis (Moher *et al.*, 2009)<sup>[12]</sup> was employed for this analysis. The review was registered in PROSPERO bearing the registration number CRD42020213755.

### Eligibility criteria

The research question was focused using the “PICOS” framework. The research question formulated was used to determine the inclusion and exclusion criteria.

- Population – Adult patients affected with recurrent aphthous ulcer condition
- Intervention – Herbal formulation in any form (toothpaste, solution, mucogel)
- Comparison – Population-free from RAU infection formed the comparison group
- Outcome – The primary outcome assessed was ulcer reduction and pain intensity. Secondary outcomes of the level of exudate and erythema were also taken into consideration wherever mentioned
- Setting – Private practice or hospital or cases reported in the normal population
- Inclusion criteria – Randomized Control Trials and Controlled Clinical Trial studies assessing the outcome of herbal formulation treated RAU patients were included. Studies which recruited RAU patients based on “The diagnosis and management of recurrent aphthous

stomatitis: A consensus approach,” which met the RAU diagnostic criteria. The experimental group received herbal medications used singly without any allopathic medicine. Control groups were recognized as those who were either placebo-treated or chlorhexidine rinse treated

- Exclusion criteria – Editorials, case reports, commentaries, animal studies, and articles written in a language other than English were excluded. Even randomized controlled trials (RCTs) done without a control group was not included.

### Information sources

Search engines such as MEDLINE, Ovid, Scopus, and Journal on web databases were searched for literature. All searches were performed through EBSCO. All relevant articles identified, which were obtained in full, through electronic and other search methods were checked. Abstract and conference proceedings were used to search and identify unpublished studies.

### Search strategy

#### Keywords

Key terms were used for the search: (1) recurrent aphthous ulcers; (2) herbal formulation; (3) recurrent aphthous stomatitis; (4) herbal medicine; (5) ulcer reduction; (6) pain scale; (7) level of exudates; and (8) level of erythema

### Boolean operators

The Boolean operator ‘OR’ was employed to complement truncated synonyms in each search theme. The Boolean operator ‘AND’ makes up the sum of each four main search themes to specifically output papers that give at least one result for each time.

### Search limits

Searches incorporated the literature from the year 2000 up until 2020 as the concluding year for the search. Only sources in English were used.

### Process of study identification

Endnote X8 was used to import the results of the search data and to remove the duplicates. The screening of abstracts will be carried out by the use of the eligibility criteria and for those not excluded; full-text articles were searched for. These were, then, assessed for inclusion and upon acceptance, underwent data extraction, and quality assessment. Articles, failing to meet inclusion criteria, were omitted.

### Data collection

All the titles and the extracts were independently screened by the reviewers and on a meticulous review of the full-text articles, the data were extracted and documented in a data extraction table, which shows depicting data items evaluated for the review.

**Data items**

The data extraction table will include study ID, sample size, location, type of herbal formulation, outcome assessed, results, and adverse events.

**Risk of bias in individual studies**

Cochrane Handbook for Systemic Review of Interventions was used for assessing the quality of recruited studies.<sup>[13]</sup> Criteria assessed were random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias).

**Data synthesis**

Out of the 6 articles reviewed, 3 articles were processed for data synthesis as the rest did not provide data on the comparison group.

**Statistical analysis**

Data analysis was carried out using RevMan 5.4 software (Cochrane Review Group).

**RESULTS**

The search results yielded a total of 429 manuscripts, of which were excluded as they were in duplicate. 286 articles were

removed as only abstracts were available in search engines. Seventy-two articles were removed because of duplication. Further 72 articles had to be excluded as only abstracts were obtained of these articles. After assessing for the eligibility, 10 articles were included for qualitative evaluation and 9 analyzed quantitatively [Figure 1].

The systematic review evaluated 9 articles, all of which were RCTs in patients having recurrent aphthous ulcers, including both males and females. The herbal formulations reviewed were diverse, delivered in the form of mouthwashes, solution, toothpaste, essential oils, and gelatine preparations. Herbal formulation reviewed were *Zataria multiflora*, curcumin, pudilan extract, *Echinacea*, aloe vera, honey, myrrh, berberine, Yunnan Baiyao, and Camelthorn. Subjects assessed in the age range of 18–50 years in the analysis and were evaluated for 3–10 days (mean of 5.24 + 1.43). The study characteristics are summarized in Table 1.

**Meta-analysis results**

A total of 9 studies were included in the meta-analysis.

**Ulcer size reduction**

Ulcer reduction was reported in 9 studies, with 382 subjects in the herbal group and 367 in the control group. A highly significant reduction in ulcer (measured in mm) was observed in the experimental group than the control, with a mean

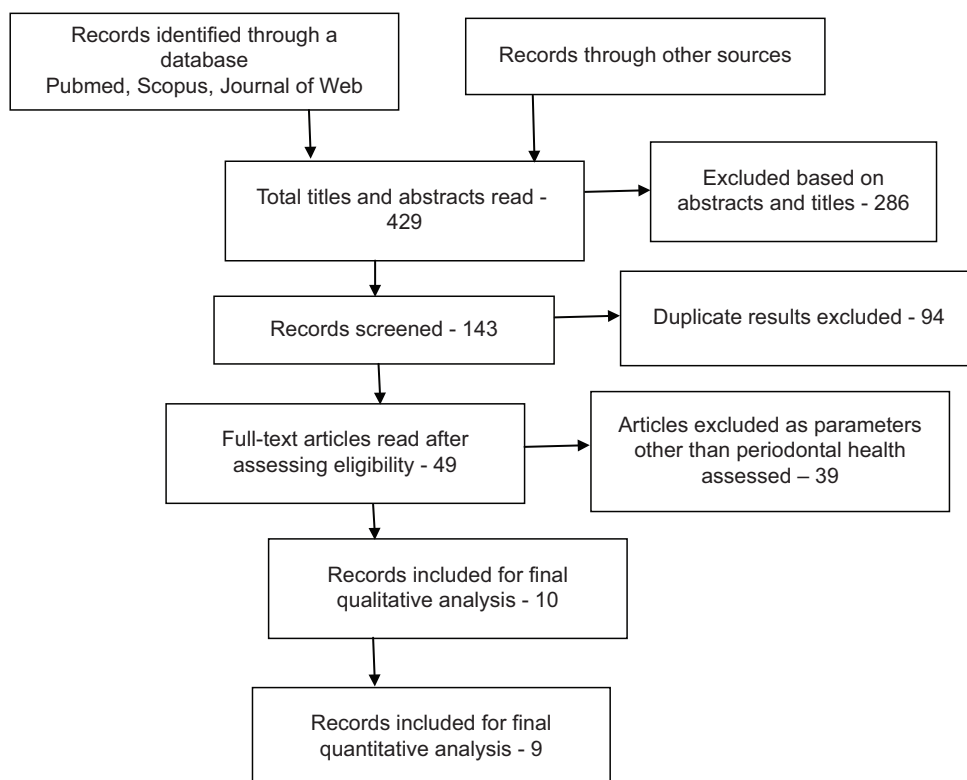


Figure 1: Flow chart diagram for article inclusion

**Table 1: Characteristics description of studies included**

Study	Location	Sample size	Herbal formulation - delivery route and ingredients	Outcome assessed	Results	Adverse events
Pandharipande et al. 2019 <sup>[14]</sup>	Swargiya Dadasaheb Dental college, India	105 patients of 18-45 years with 1-5 aphthous ulcer which occurred within 48 h duration	Group A - Curcumin extract; Group B - Honey extract; Group C - Orabase used as a control group	Pain intensity, ulcer size, erythema and exudates level	Curcumin showed a significant reduction in ulcer compared to orabase on 7 <sup>th</sup> day ( $P < 0.001$ ). Same was noted for size, VAS, exudate level	No adverse effect reported
Khozeimeh et al., 2018 <sup>[15]</sup>	Isfahan Iran	50 patients of minor recurrent ulcer	Tablets of Echinacea tablet (Immustim tablet) given for 5 weeks, 3 tablets daily	Number of lesions, duration of complete improvement, recurrent intervals, pain intensity	The improvement recorded in the study group Number of lesions 0+0.33 Pain intensity 0+2.19 Remission duration 0+6.60 Recurrent intervals 19+0.01	None recorded
Yang et al., 2016 <sup>[16]</sup>	West China Hospital Stomatology	80	Toothpaste containing Pudilan extract (conc - 0.8%-2.2%) and Baicalin extract	Primary rate - Healing rate Secondary outcome - Healing period, pain, area of target ulcer, degree of exudation, degree of hyperemia	Healing rate in the study group was 80% versus 50% of the control group at $P = 0.049$ Healing period was twice as early in the study group than the control group VAS score, exudation and hyperemia exhibited a significant difference between the groups	1 case was noted which was round-shaped exfoliation lesion of lower lip mucosa with a diameter of 1.5 cm
Mansour et al., 2014 <sup>[17]</sup>	King Abdulaziz University, Jeddah, South Arabia	90 patients with 1-3 minor fresh Recurrent Aphthous stomatitis	Mucoadhesive gel Group 1-30 patients treated with a mucoadhesive gel containing aloe vera Group 2-30 patients treated with gel with myrrh extract Group 3-30 patients treated WITH Plain gel	Ulcer size, pain scale (VAS), erythema, exudation levels	76.6% of patients of Aloe vera gel healed completely, while 86.7% and 80.0% demonstrated relief from erythema and exudation. 76.7% of myrrh treated cases reported absence of pain on 6 <sup>th</sup> day	No side effect
Babaei et al., 2015 <sup>[18]</sup>	Babool University of Medical Sciences in North of Iran	28 patients of 18-40 years	Zataria (0.5%) multiflora essential oil evaluated till 7th day	Healing time, pain intensity, aphthous zone diameter	The average complete healing time and duration of burning sensation were significantly lower in the ZM group ( $P < 0.05$ )	None reported
El-Haddad et al., 2014 <sup>[19]</sup>	Salman Bin Abdul Aziz University, Kingdom of Saudi Arabia	94 patients with 180 minor RAU in the age range of 20-29 years with male: female: 1:2 predilection	Group I - Honey treated group Group II - 0.1% triamcinolone acetonide treated group and Group III - Orabase as a control group	Pain score, reduction in ulcer size and erythema degree	Ulcer size reduced from 4 <sup>th</sup> day itself in the honey group as compared to other groups. A significant difference was noted amongst groups for ulcer size and erythema	None reported
Jiang et al., 2013 <sup>[20]</sup>	South University, China	84, in the age group of 18-50 years having only 1 ulcer	Group 1 - Berberine group (Berberine gelatine - 10 g containing 50 mg berberine Group 2 - control group	Reduction in ulcer size; Moderation of pain; Reduction in erythema and exudation	Berberine-treated erythema group showed a significant reduction in all evaluated parameters at $P < 0.05$	None
Liu et al. 2012 <sup>[21]</sup>	Nankai University, Peking University, Capital centre	240 patients	Test group - 113 patients given toothpaste containing Yunnan Baiyao extract Control group - 114 patients given a placebo	Ulcer size, Pain level	A significant amount of ulcer healing was noted in Yunnan Baiyao extract toothpaste by day 5 when compared to placebo (66.4% versus 50.0%, $P = 0.01$ ) Pain alleviation was significant in the test group (66.4% versus 51.8%, $P < 0.05$ )	Nil

Contd...

Table 1: Contd...

Study	Location	Sample size	Herbal formulation - delivery route and ingredients	Outcome assessed	Results	Adverse events
Pourahmad et al., 2010 <sup>[22]</sup>	Jahron university of medical sciences, Iran	93 RAU patients	Test group (49 patients) treated with a solution of camel thorn distillate - Daily 40-millilitre solution administered for 4 times in a day The control group (44 patients) - treated with distilled water	Diameter reduction, pain intensity from 0 to 14 days	Complete resolution time was 4.02 days in camel thorn group versus 8.09 days in the control group	None reported

RAU: Recurrent aphthous ulcer, VAS: Visual analog scale

difference of  $-1.16$  (confidence interval [CI] =  $-2.22$  to  $-0.09$ ;  $P < 0.001^{**}$ ;  $Z = 2.13$ ) from the treatment initiation to pre-fixed follow-up period [Figure 2].

#### Pain scale intensity

Pain intensity was reported in 5 studies, with 221 subjects in the herbal group and 205 in the control group. A statistically significant reduction in the intensity of the pain (measured by visual analog scale) was found in the study group as compared to the control, with a mean difference of  $-2.26$  (CI =  $-4.60$  to  $-0.08$ ;  $P < 0.001^{**}$ ;  $Z = 1.90$ ) from the start of the treatment to the end of follow-up period. Four studies had to be excluded as they reported the percentage reduction of pain in participants [Figure 3].

#### Level of erythema

Erythema level was reported in 3 studies, with 132 subjects in the herbal group and 121 in the control group. A statistically significant reduction in the level of erythema (considered at level 3) was seen in the study group as compared to the control group, with a mean difference of  $-1.35$  (CI =  $-1.86$  to  $-0.84$ ;  $P < 0.001^{**}$ ;  $Z = 5.20$ ) from the beginning of the trial to the end of follow-up period. Only those studies that reported erythema levels were included [Figure 4].

#### Level of exudate

The level of exudate was analyzed in 2 studies, with 65 subjects in each of the groups. A highly significant reduction in the level of exudates was observed in the study group as compared to the control population, with a mean difference of  $-1.30$  (CI =  $-1.69$  to  $-0.91$ ;  $P < 0.001^{**}$ ;  $Z = 6.50$ ) from baseline to the end [Figure 5].

## DISCUSSION

Since ancient times, natural products have been utilized to prepare curative agents for every possible ailment. They are either used in medicinal form or as food supplements. In the current era too, patients prefer natural or alternative

medicine therapy to avoid the adverse effects associated with synthetic medications. Natural herbs possess least to no cytotoxic properties. Literature reports favorable results when efficacious herbal formulations are used as therapy. Results of our study are in similar lines to the review of Heydarpour et al.<sup>[23]</sup> and Philips et al.<sup>[24]</sup> evaluating herbal interventions for RAU and found a significant reduction in signs and symptoms. Herbs have exhibited antibacterial, anti-inflammatory, immunomodulatory, and antiviral benefits.

Overall 749 patients in a total of 9 clinical trials were evaluated for the current analysis. In comparison to the control group, the herbal formulation group statistically facilitated the recovery of RAU lesions measured by reduction in ulcer diameter, pain alleviation, level of exudates, and erythema.

Pudilan extract is a mixture of dandelion, Isatis root, Bunge corydalis herb, *Scutellaria baicalensis*, gallnut, and propolis. It exhibits significant anti-inflammatory effects mediated by tumor necrosis factor-alpha inhibition and secretion of interleukin along with a decrease in nitric oxide and prostaglandin E2 inflammatory mediators.<sup>[25]</sup> It inhibits bacterial growth through ATP synthesis interference; analgesic and antipyretic action by decreasing production of arachidonic acid and exudates reduction by protein precipitation promotion.<sup>[26,27]</sup> Myrtus communis or myrtle found commonly in North Iran is a perennial shrub widely employed for candidiasis treatment in Persia. This extract has shown antibacterial, analgesic, and anti-inflammatory properties.<sup>[28,29]</sup> Camel thorn can preserve even in the challenging non-favorable ecological oral conditions and exhibits anti-inflammatory and protective membrane characteristics. It inhibits histidine decarboxylase thus facilitating the prevention of ulcer formation.<sup>[22]</sup> Turmeric is found as a dry rhizomatous plant possessing anti-inflammatory and antioxidative effects preventing and

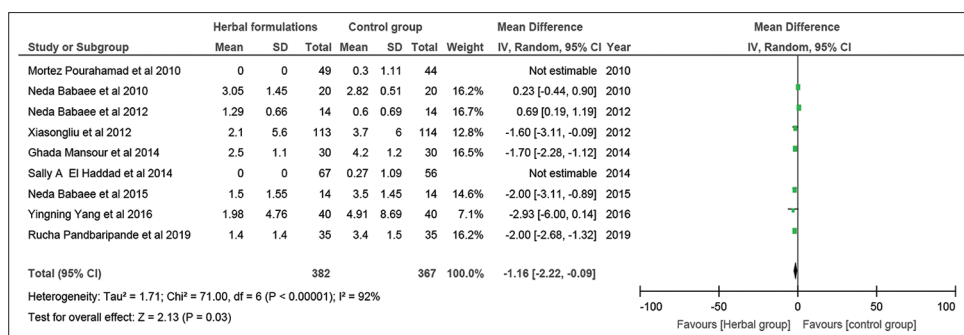


Figure 2: Forest plot depicting ulcer size reduction between herbal and control group

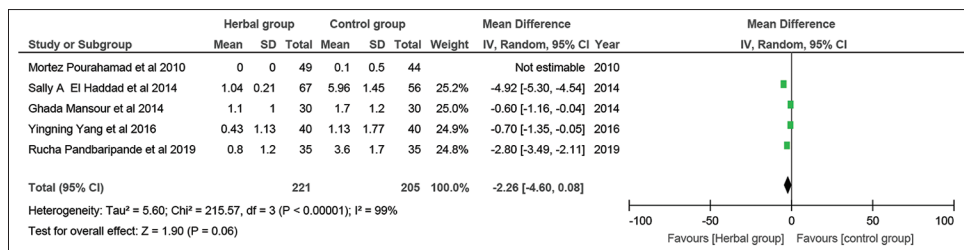


Figure 3: Forest plot depicting pain scale intensity between herbal and control group

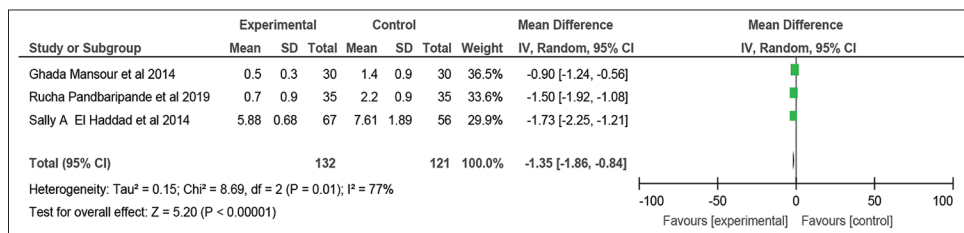


Figure 4: Forest plot depicting the level of erythema between herbal and control group

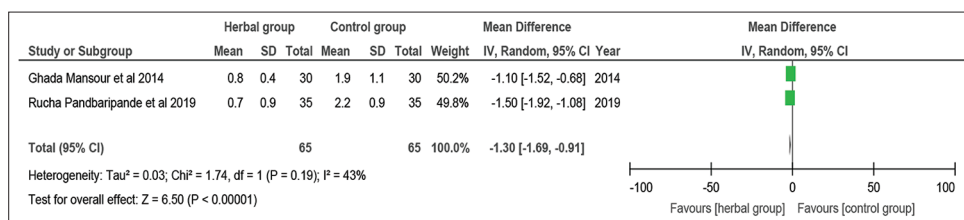


Figure 5: Forest plot depicting the level of exudate between herbal and control group

suppressing the process of inflammation.<sup>[30]</sup> Yunnan Baiyao is widely employed for treating RAU.

An attempt to reduce heterogeneity was made by the inclusion of only those articles which evaluated RAU patients receiving herbal formulations without any combinations and placebo groups. Yet, some elements of heterogeneity cannot be overlooked as the studies did not employ a consistent approach in RAU diagnosis. Further, the time duration of follow-up for all the outcomes assessed was also not the same.

The risk assessment of the studies was mostly of unknown type, owing to poor study design and greater risks in

the performance, detection, attrition, and reporting bias [Table 2]. These calls for multi-centered clinical trial analysis designed with precise criteria and standardized methodology to assure high-quality studies.

All the included studies in this analysis employed clinical trial design-making for Grade A (Level 1) level of evidence-based on the criteria given by the Oxford Center for Evidence-Based Medicine.<sup>[31]</sup> Incorporation of Randomised control trial in meta – analysis ranks it to be of highest evidence, when designed and implemented correctly. This is the best design to be employed to elicit causal relationship.<sup>[31]</sup>

**Table 2: Risk of bias of studies included**

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Rucha Pandbaripande <i>et al.</i> , 2019	?	-	-	-	+	?
Yingming Yang <i>et al.</i> , 2016	+	+	+	+	+	?
Neda Babaei <i>et al.</i> , 2015	+	+	+	?	+	+
Ghada Mansour <i>et al.</i> , 2014	+	?	+	+	+	?
Sally A El Haddad <i>et al.</i> , 2014	+	?	+	?	+	?
Faezeh Khozeimeh <i>et al.</i> , 2018	-	-	-	-	+	+
Jiang <i>et al.</i> , 2103	+	?	-	-	+	?
Xiasongliu <i>et al.</i> , 2012	+	?	+	?	-	?
Morteza Pourahamad 2010	+	+	+	?	+	?

+: Low bias, -: High bias, ?: Uncertain bias

The main outcome measured in all the studies were the size of the ulcer and the pain intensity scale. An inconsistency in studies was noted with regards to the ulcer size in terms of size, duration time, and level of pain. A standard manner of measurement was lacking especially with ulcer size. RAU can present as a single ulcer, multiple ulcers of various shapes in the mucosa, making it nonsuitable to measure ulcer diameter accurately. Hypothetically, calculating ulcer diameter may sound better, but calculating it precisely in clinics is questionable. Liu *et al.*,<sup>[21]</sup> hence in their study, proposed that the specific way to address this is to measure maximum and vertical diameter, which is also convenient.

Till date, a definitive treatment choice is not available for prevention or to cure aphthous ulcers. The existing options aim for symptomatic improvement such as reduction in lesion count or extension of lesion-free intervals. A thorough consideration for all predisposing factors must be given such as testing of blood samples for iron, folate, ferritin, and Vitamin B12.<sup>[5]</sup>

Visual analog scale was used for pain assessment in all the included studies, which measured a range of “no pain” to “unbearable pain” on a 100 mm horizontal line. The use of this scale demonstrated greater reliability.

Herbal formulations seemed to be effective in RAU therapy, but still, further research in this arena is needed placing stress on specific protocols, type of intervention, and standard measures of assessment. In addition, homogenizing the dose and application technique will help provide a better picture. Although the present analysis yielded favorable results, the applicability of these results clinically is yet not clear.

Herbal formulations provide a broader range of therapeutic choices for both practitioners and patients. Owing to their

minimal adverse effects, it is of great utility as alternative to chemical medicine.

## CONCLUSION

Owing to the complex pathogenesis of RAU lesions and the unpredictable outcome associated with the existing intervention modalities, coupled with the potential risk of adverse effects of systemic medications, herbal formulations are preferred. They offer the advantage of producing less adverse effects and are significantly efficacious.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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