

EFFECTIVENESS OF THE NATURAL-BASED PRODUCTS AND MUCOADHESIVE FOR RECURRENT APHTHOUS STOMATITIS THERAPY: A SYSTEMATIC REVIEW

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ABSTRACT

The objective was to describe and recommend the most effective combination of Natural-Based Product (NBP) and mucoadhesive for Recurrent Aphthous Stomatitis (RAS) treatment. This systematic review writing was based on PRISMA guidelines. The articles published in the last 10 y were selected using PubMed and Google Scholar database carried out during May 2021. The keywords were: natural-based product, mucoadhesive, and Recurrent Aphthous Stomatitis. The risk of bias was assessed using the Oxford Quality Scoring System. Six articles of Randomized Controlled Trial were selected. The NBP were: *Aloe vera*, Myrrh, *Curcuma longa*, propolis, ginger, *Punica granatum* flower, and sesame oil. The drug's formulation was: gel, film, and spray. The mucoadhesive polymers as vehicles were Hydroxy Propyl Ethyl Cellulose (HPEC), Hydroxy Propyl Methylcellulose (HPMC), Benzocaine, Tragacanth Gum, Carbomer 934, Sodium CMC (carboxymethyl cellulose), and chitosan. *Curcuma longa* 10 mg/g with HPMC was the most effective to relieve pain, while *Punica granatum* flower extract with Carbomer 934 and Sodium CMC was the most effective to reduce the ulcer size in RAS. Both of the formulations were in gel form.

Keywords: RAS, Natural-based product, Mucoadhesive

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INTRODUCTION

Recurrent Aphthous Stomatitis (RAS) is the most common oral mucosal ulceration found in society, causing pain, recurrence, and can decrease the patient's quality of life [1, 2]. Clinically, RAS is divided into 3 types i.e., minor RAS (>70%), major RAS (10%) and *Herpetiform Stomatitis* (10%) [1, 3]. RAS prevalence was 20% of the general population in the world and found higher in females than male, while the etiology of RAS was still uncertain [1, 4]. However, several studies concluded that the cause of RAS was multifactorial such as local trauma, hereditary, stress, nutritional deficiency, virus, bacteria, allergy, hormone disorders and the like [1, 3, 5]. Therefore, management of RAS was very specific, using steroid in topical or systemic drug form. Unfortunately, this treatment sometimes caused side effects to the patients.

Natural-Based Products (NBP) was used in several countries in Asia for traditional medicine for several diseases since a very long time ago [6-8]. However, it was only in the last few decades that its scientific research for medical treatment has begun. Nowadays, the usage of NBP in society was increasing as long as the better efficacy and without side effects. This was also shown by data from the World Health Organization (WHO) in which about 88% of countries in the world have used traditional medicines [9].

Even though NBP was proven to be effective and safe for RAS therapy [6-8], the challenge in RAS therapy was the oral mucosa which is always wet and moist so that reducing the drug penetration. Mucoadhesive as a vehicle can prolong the contact time between the drug and mucous surface and increase the therapeutic effectiveness of therapy [10]. Therefore, the proper combination of NBP and mucoadhesive could be used for an alternative in RAS therapy. Unfortunately, up to now, there is no study that discusses the effectiveness of the combination of NBP and mucoadhesive for RAS therapy. This systematic review will become a complement and updating of scientific information data related to the treatment of RAS.

METHODS

The article's searching method was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [11], using 2 (two) electronic databases i.e.,

PubMed and Google Scholar. The keywords used were "(Recurrent Aphthous Stomatitis) AND (Mucoadhesive)". In addition, manual searching was also carried out on the topics and subjects related to the specified themes or based on the references of the selected articles. The data search was carried out during May 2021. Theme arranged on this Systematic Review used PICO (Population, Intervention, Comparison, and Outcome) framework, according to the objective. The population was patient with Recurrent Aphthous Stomatitis (RAS); the interventions was the combination of Natural-Based Product (NBP) and Mucoadhesive; the comparison was control materials/drug; while the outcome was a reducing of ulcer size and relieve of pain as the clinical parameters of the therapy.

The inclusion criteria were limited to: clinical trial study design, human studies, articles published in the last 10 y (2011 to 2021), and available full text. The articles were excluded if not relevant to the topic of mucoadhesive, NBP, and RAS; articles were duplicated between both databases; Literature Review articles; and if not presented in English. Furthermore, a risk of bias and quality assessment was carried out for each selected article in order to know the level of evidence-based medicine and the quality of the articles to be reviewed. The instrument used to assess the risk of bias and quality was the Oxford Quality Scoring System [12], which consisted of 5 (five) questions. It can assess the randomization of the subject's study, the blinding process during the study, the suitability of randomization and blinding methods, as well as any dropouts or withdrawals that occurred. The conclusion of risk of bias and quality assessment to the article was referring to the total score of each article. The maximum score was 5 (five), while the minimum score was -2 (minus two). An article was considered to have a high bias and low range of quality if the score was between -2 (minus two) until 2 (two) and it would be considered to have a low bias and high range of quality if the score was between 3 (three) and 5 (five).

The titles and abstracts of the reviewed articles were screened by IH in regard to checking the relevance with the aim of the study. The information related to population and problem (country, number of subjects), intervention (NBP, mucoadhesive and drug formulation), comparator group, and outcome were also extracted by IH. Both of the authors (IH and ISH) discussed the extracted data and made a decision to construct the final recommendation in this study, as well

as assessing the risk of bias or quality of the articles. If there were disagreements, discussions and decision-making were carried out in accordance to reach a mutual agreement. There was no difference in deciding the eligible articles for review, the extracted data, and the risk of bias assessment.

RESULTS

Articles identification process found 409 articles and 4 articles from manual searching, resulting in 413 total articles to be filtered. Taking into consideration the inclusion and exclusion criteria for each article, it was found that 407 articles were excluded as the articles did not meet the criteria and left 6 suitable articles for further review. All of the six articles were using Randomized Controlled Trial (RCT) study design. Therefore, the level of evidence for these six articles to be reviewed was at high level [13]. Fig. 1 shows a flowchart of the article searching process based on PRISMA guidelines.

Based on the risk of bias and quality assessment of the selected articles, it was concluded that all of the articles to be reviewed have a low risk of bias and a high range of quality. It was because the score for the risk assessment of bias and quality obtained was 3 for 3 articles [14-16] while the other articles scored 5 [17-19]. The details of the questions proposed in the risk of bias and quality assessment for 6 articles reviewed were presented in table 1.

The data and information from each article were extracted and compiled in a table. It presented the population (country of origin, number of patients), study design of the article, intervention (drug formula used and type), determination of the comparison group and also the results of the study i.e., the reduction of the ulcer size and pain relief, as well as the research funding source. General summary of the reviewed articles as seen in table 2, while the effectiveness of NBP and Mucoadhesive combination for RAS therapy as shown in table 3. The detailed results of clinical assessment on pain relief and reduction of the ulcer size was shown in table 4 and table 5.

Table 1: Assessment of the risk of bias and quality for the reviewed articles

| No | Risk assessment of bias and quality (Answer formulation) | Authors | | | | | |
|----|---|-----------------------------|---------------------------|---------------------------------|-------------------------------|------------------------------|-----------------------|
| | | Mansour, <i>et al.</i> [17] | Desmukh and bagewadi [14] | Stojanovska, <i>et al.</i> [15] | Haghpanah, <i>et al.</i> [16] | Tavangar, <i>et al.</i> [18] | Shao and Zhou [19] |
| 1 | Was the study described as random? (Yes: 1, No: 0) | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | Was the randomization scheme described and appropriate? (Yes: 1, No: -1) | 1 | 1 | -1 | -1 | 1 | 1 |
| 3 | Was the study described as double-blind? (Yes: 1, No: 0) | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | Was the method of double-blinding appropriate? (Yes: 1, No: -1) | 1 | -1 | 1 | 1 | 1 | 1 |
| 5 | Was there a description of dropouts and withdrawals? (Yes: 1, No: 0) | 1 | 1 | 1 | 1 | 1 | 1 |
| | Score | 5 | 3 | 3 | 3 | 5 | 5 |
| | Result | High range of quality | High range of quality | High range of quality | High range of quality | High range of quality | High range of quality |

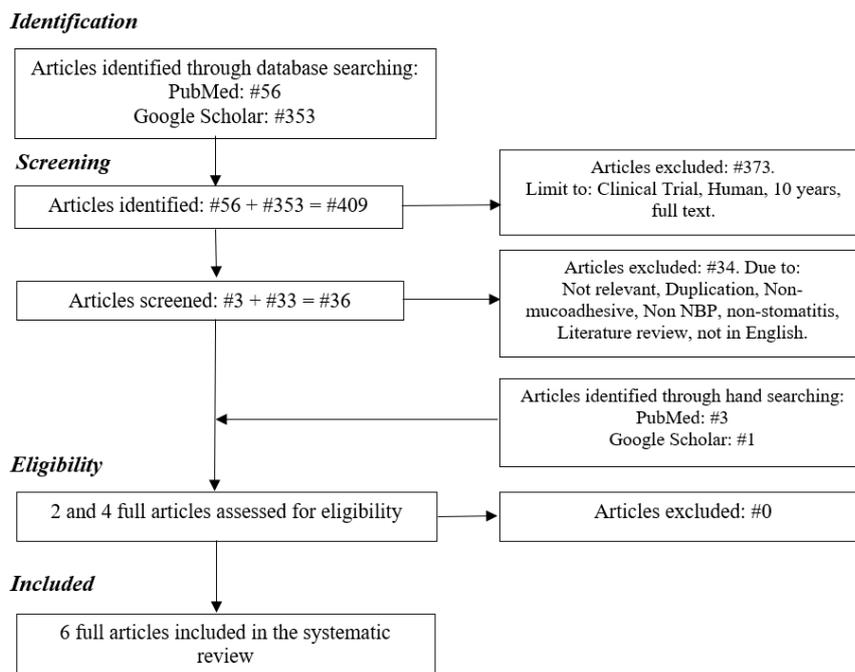


Fig. 1: Flowchart of article searching based on the PRISMA guidelines

Table 2: General summary of the reviewed articles

| No | Author (Year) | Country | Study design | Number of patient | Mucoadhesive form | NBP | | Comparison /Control | Funding |
|----|---|--------------|--------------|--|-------------------|-----------------------------|-------|------------------------------|--|
| | | | | | | 1 | 2 | | |
| 1 | Mansour <i>et al.</i> , (2014) [17] | Saudi Arabia | RCT | 90 (<i>Aloe Vera</i> : 30 Myrrh: 30 Placebo: 30) | Gel | <i>Aloe Vera</i> | Myrrh | Placebo | Deanship of Scientific Research (DSR) at King Abdulaziz University, Jeddah, Saudi Arabia |
| 2 | Deshmukh and Bagewadi (2014) [14] | India | RCT | 60 (Curcumin: 30 TA: 30) | Gel | Curcumin | | Triamcinolone Acetonide 0.1% | Not mentioned |
| 3 | Stojanovska <i>et al.</i> , (2014) [15] | Macedonia | RCT | 20 (Propolis: 10 Placebo: 10) | Spray | Proaftol (Propolis Extract) | | Placebo | Not mentioned |
| 4 | Haghpanah <i>et al.</i> , (2015) [16] | Iran | RCT | 30 (Ginger: 15 Placebo: 15) | Film | Ginger | | Placebo | Deputy of Research and Technology of Babol University of Medical Sciences |
| 5 | Tavangar <i>et al.</i> , (2019) [18] | Iran | RCT | 60 (PG: 20 TA: 20 Placebo: 20) | Gel | <i>Punica granatum</i> | | Triamcinolone Acetonide 0.1% | Vice-chancellor for Research and Technology, Isfahan University of Medical Sciences |
| 6 | Shao and Zhou (2019) [19] | China | RCT | 66 (SO: 34 PVA film: 32) | Film | Sesame Oil | | PVA Film | National Key R&D Program of China and National Construction Project of Clinical Key Specialized Department |

Notes: NBP = Natural-Based Product; RCT = Randomized Control Trial; PVA = Polyvinyl Alcohol.

Table 3: Effectiveness of NBP and mucoadhesive combination for RAS therapy

| No | Authors (Year) | NBP | Polimer mucoadhesive (vehicle) | Parameters and results | Conclusion | Safety aspect |
|----|---|--|--|--|--|----------------------------------|
| 1 | Mansour <i>et al.</i> , (2014) [17] | 1) Extract <i>Aloe Vera</i> 1.5g (0.5% w/w) 2) Extract Myrrh 1.5g (0.5% w/w) 3) Placebo HPEC | Hydroxy Propyl Ethyl Cellulose (HPEC) | 1) Visual Analog Score (VAS) Effect of <i>Aloe Vera</i> and Myrrh with HPEC as a mucoadhesive polymer on VAS score was significantly different than placebo, but the effect of Myrrh was better than <i>Aloe Vera</i> . 2) Ulcer size Effect of <i>Aloe Vera</i> and Myrrh with HPEC as a polymer mucoadhesive on reducing ulcer size was significantly different from placebo, but the effect of <i>Aloe Vera</i> was better than Myrrh. | Combination of Myrrh extract with HPEC was better in relieving pain, while the combination of <i>Aloe Vera</i> extract and HPEC was better in reducing the ulcer size. | No adverse effects were reported |
| 2 | Deshmukh and Bagewadi (2014) [14] | Extract <i>Curcuma longa</i> 10 mg/g (Curenex oral gel, Abbot Pharmac.) | Hydroxy Propyl Methyl Cellulose (HPMC) | 1) VAS Effect of <i>Curcuma longa</i> with HPMC as a mucoadhesive polymer on VAS score on day 0 until day 7 was significantly different and was as effective as Triamcinolone acetonide 0.1%. 2) Ulcer size Effect of <i>Curcuma longa</i> with HPMC as a mucoadhesive polymer on reducing ulcer size on day 0 until day 7 was significantly different and was as effective as Triamcinolone acetonide 0.1%. | Combination of <i>Curcuma longa</i> extract 10 mg/g with HPMC was as effective as Triamcinolone Acetonide 0.1% on relieving pain and reducing the ulcer size. | No side effects |
| 3 | Stojanovska <i>et al.</i> , (2014) [15] | Proaftol (Extract Propolis 25%) (Apimell-Dr Bacheff) | Benzocaine 0.3g | 1) VAS Effect of proaftol with benzocaine 0.3g as a mucoadhesive polymer on VAS score was significantly different than placebo. 2) Ulcer size Effect of proaftol with benzocaine 0.3g as a mucoadhesive polymer on reducing ulcer size was significantly different than placebo. | Combination of Proaftol spray (25% propolis extract) with Benzocaine 0.3g was better than placebo, i.e., Macedonian propolis 62.5µg/ml | Not mentioned |
| 4 | Haghpanah <i>et al.</i> , (2015) [16] | Extract Ginger Alcoholic | Tragacanth Gum | 1) VAS Effect of Ginger and Tragacanth gum as a mucoadhesive polymer on VAS score was significantly different than placebo 2) Ulcer size | Combination of an alcoholic Ginger extract with Tragacanth gum was better than | No side effects |

| No | Authors (Year) | NBP | Polimer mucoadhesive (vehicle) | Parameters and results | Conclusion | Safety aspect |
|----|--------------------------------------|--|--|---|---|--------------------|
| 5 | Tavangar <i>et al.</i> , (2019) [18] | Extract <i>Punica granatum</i> (PG) Flower | Carbomer 934 and Sodium Carboxy Methyl Cellulose (CMC) | Effect of Ginger and Tragacanth gum as a mucoadhesive polymer on reducing ulcer size was not significantly different from placebo. 1) VAS Effect of <i>Punica granatum</i> with Carbomer 934 and Sodium CMC as mucoadhesive polymers on VAS score was not significantly different than Triamcinolone Acetonide 0.1%. 2) Ulcer size Effect of <i>Punica granatum</i> with Carbomer 934 and Sodium CMC as mucoadhesive polymers on reducing ulcer size was significantly different than Triamcinolone Acetonide 0.1%. | placebo on relieving pain, but not better on reducing ulcer size. Combination of <i>Punica granatum</i> flower extract with Carbomer 934 and Sodium CMC was as effective as Triamcinolone Acetonide 0.1% in terms of relieving pain but better in term of reducing ulcer size. | No adverse effects |
| 6 | Shao and Zhou (2019) [19] | Sesame Oil | Chitosan | 1) VAS Effect of Sesame oil with Chitosan as a mucoadhesive polymer for VAS score on day 1 until day 6 was significantly different but was as effective as PVA film. 2) Ulcer size Effect of Sesame oil with Chitosan as a mucoadhesive polymer for reducing ulcer size on day 1 until day 6 was significantly different, but was as effective as PVA film. | Combination of Sesame Oil with Chitosan was as effective as PVA film on relieving pain and reducing ulcer size. | No side effects |

Notes: VAS = Visual Analog Scale for pain; PVA = Polyvinyl Alcohol Film

Table 4: Comparison on VAS reduction in RAS therapy using the natural based product and mucoadhesive combination

| No | Author (Year) | Material study | | VAS Score and Percentage (%) on day. | | | | | | | | |
|----|--|--|---|--------------------------------------|--------------|---------------|--------------|---------------|--------------|---------------|--------------|--------|
| | | NBP | Polymer mucoadhesive (Vehicle) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 1 | Mansour, <i>et al.</i> (2014) [17] | Extract <i>Aloe Vera</i> 1.5g (0.5% w/w) | Hydroxyl Propyl Ethyl Cellulose (HPEC) | 4.67 (100%) | | | | 2.6 (55.67%) | | 1.1 (23.55%) | | |
| 2 | | Extract <i>Myrrh</i> 1.5g (0.5% w/w) | Hydroxyl Propyl Ethyl Cellulose (HPEC) | 4.61 (100%) | | | | 2.2 (47.72%) | | 0.72 (15.62%) | | |
| 3 | Deshmukh and Bagewadi (2014) [14] | Extract <i>Curcuma longa</i> 10 mg/g | Hydroxyl Propyl Methyl Cellulose (HPMC) | 4.7 (100%) | 3.3 (70.2%) | 2.1 (44.68%) | 1.1 (23.40%) | 0.4 (8.51%) | 0.06 (1.28%) | 0 (0%) | 0 (0%) | |
| 4 | Stojanovska, <i>et. al</i> (2014) [15] | Proaftol (Extract Propolis 25%) | Benzocaine 0.3g | | 3.0 (100%) | | 1.4 (46.67%) | | 1.0 (33.33%) | | | 0 (0%) |
| 5 | Haghanah, <i>et. al</i> (2015) [16] | Extract Ginger Alcoholic | Tragacanth Gum | 4.2 (100%) | 4.0 (95.24%) | | 3.1 (73.81%) | | 2.8 (66.67%) | | 2.7 (64.29%) | |
| 6 | Tavangar, <i>et. al</i> (2019) [18] | Extract <i>Punica granatum</i> (PG) Flower | Carbomer 934 and Sodium CMC | 9.7 (100%) | | 8.2 (84.54%) | 6.0 (61.86%) | 2.2 (22.68%) | 1.6 (16.49%) | 0 (0%) | 0 (0%) | |
| 7 | Shao and Zhou (2019) [19] | Sesame Oil | Chitosan | | 3.86 (100%) | 3.36 (87.05%) | | 2.02 (52.33%) | | 0.76 (19.69%) | | |

Table 5: Comparison of the ulcer size reduction in RAS therapy using natural based product and mucoadhesive combination

| No | Author (Year) | Material study | | Ulcer size (mm) and percentage (%) on day ... | | | | | | | | |
|----|------------------------------------|--|--|---|---|---|---|--------------|---|--------------|---|---|
| | | NBP | Polymer mucoadhesive (Vehicle) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 1 | Mansour, <i>et al.</i> (2014) [17] | Extract <i>Aloe Vera</i> 1.5g (0.5% w/w) | Hydroxyl Propyl Ethyl Cellulose (HPEC) | 6.2 (100%) | | | | 4.0 (64.52%) | | 2.5 (40.32%) | | |
| 2 | | Extract <i>Myrrh</i> 1.5g (0.5%) | Hydroxyl Propyl Ethyl Cellulose | 6.0 (100%) | | | | 4.3 (71.67%) | | 2.5 (55.0%) | | |

| No | Author (Year) | Material study | | Ulcer size (mm) and percentage (%) on day ... | | | | | | | | |
|----|-----------------------------------|--|---|---|--------------------|----------------------|---------------------|----------------------|-----------------|-----------------|----------------------|----------------|
| | | NBP | Polymer mucoadhesive (Vehicle) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 3 | Deshmukh and Bagewadi (2014) [14] | w/w) Extract <i>Curcuma longa</i> 10 mg/g | (HPEC) Hydroxyl Propyl Methyl Cellulose (HPMC) | %) 3.8 (100 %) | | | | 1.0 (26.32 %) | | 0.07 (1.84%) | | 0 (0%) |
| 4 | Stojanovska, et al. (2014) [15] | Proaftol (Extract Propolis 25%) | Benzocaine 0.3g | | 5.7 (10 0%) | | 3.4 (59.65 %) | | 1.1 (19.30%) | | | 0 (0%) |
| 5 | Haghpanah, et al. (2015) [16] | Extract Ginger Alcoholic | Tragacanth Gum | 3.0 (100 %) | 3.0 (10 0%) | | 2.8 (93.33 %) | | 2.1 (70.00%) | | | 1.8 (60.0%) |
| 6 | Tavangar, et al. (2019) [18] | Extract <i>Punica granatum</i> (PG) Flower | Carbomer 934 and Sodium CMC | 5.0 (100 %) | | | 2.6 (52.00 %) | | 0 (0%) | | | |
| 7 | Shao and Zhou (2019) [19] | Sesame Oil | Chitosan | | 8.07 (10 0%) | 7.98 (98.8 8%) | | 6.45 (79.93 %) | | | 3.53 (43.7 4%) | |

DISCUSSION

Previous published systematic review articles [6, 8], stated that several herbal medicines and natural products for the RAS therapy in various formulas were effective and safe; however, both of them did not discuss the regarding the mucoadhesive vehicles and its effects in RAS therapy. Many studies only explored herbal or natural products for RAS therapy but did not consider the role of mucoadhesive as a vehicle. Actually, mucoadhesive materials are easy to synthesize and if used for RAS therapy together with herbs or NBP, it is estimated that they are better in reducing pain and more effective in accelerating the healing of lesions.

Based on table 3 and referring to the origin of the country, 2 studies were conducted in Iran [16, 18], and each 1 study in Saudi Arabia [17], India [14], Macedonia [15], and China [19]. Previous and this study proved that NBP and mucoadhesive in RAS therapy, mostly carried out in Asia, but still few conducted in Europe, and no study found in Americas, Africa, or other else. This was related to the geographical condition and climates of the countries in Asia to grow the plants, so that can produce various herbal or natural products as basic ingredients in drugs manufacture. In several Asia countries such as Indonesia, Malaysia, Thailand, India, China, Iran, Saudi Arabia, and others, herbal medicines have been used as a traditional medicine for years [6].

NBPs for RAS therapy in this review were *aloe vera* and myrrh [17], curcumin [14], propolis (proaftol) [15], ginger [16], *Punica granatum* flower [18], and sesame oil [19]. They have been explored and proven good results. These studies were supported by the mucoadhesive application in various formulas so that the anti-inflammatory properties of these NBP act more optimal, as the drug attached longer on the oral mucosa.

Aloe Vera was known to contain a lot of acemannan and glucomannan as painkillers and antibiotics [20-22]. Glucomannan plays a role in fibroblast growth factor and stimulates the activity and proliferation of cells so it would increase the production and secretion of collagen at the ulcer site [20]. On the other, Myrrh was biologically an oleo-gum resin that contains anti-inflammatory properties. Myrrh has historically been used to treat inflammation [23]. The myrrh and *Aloe vera* used in the reviewed study was equal, 1.5 g or 0.5% w/w with the same HPEC mucoadhesive polymer in the gel formula used as the vehicle [17].

Curcumin was found in curcuma as a secondary metabolite [14]. Curcumin has many pharmacological effects like an anti-inflammatory and inhibits lipoyxygenase and cyclooxygenase enzymes. These enzymes increase their expression during inflammatory conditions [24,25]. In the reviewed study, *Curcuma longa* 10 mg/g or 10% w/w was used with Hydroxypropyl

Methylcellulose (HPMC) in the gel form as the mucoadhesive polymer [14].

Propolis also had anti-inflammatory therapeutic properties in the form of flavonoid as a secondary metabolite [26,27]. Likewise, with the *Punica granatum* flower extract which contains high levels of flavonoids [28,29]. Flavonoids can inhibit pain and also have anti-inflammatory properties. The flavonoids mechanism of action through the inhibitory effect on the enzymes involved in the production of inflammation chemical mediators. The Caffeic Acid Phenethyl Ester (CAPE) in the flavonoids was an active compound that can inhibit the production of the inflammatory cytokines such as: IL-1, IL-6, TNF- α and TGF- β 12 through the NF- κ B pathway [26].

The mechanism of action of flavonoids contained in propolis and *Punica granatum* is a little different but still in line with the mechanism of action of secondary metabolites in ginger. The nanoparticles from the ginger derivatives could prevent intestinal inflammation by increasing levels of anti-inflammatory cytokines such as IL-10 and IL-12 and also reducing proinflammatory cytokines such as TNF- α , IL-6 and IL-1 β [30]. However, the anti-inflammatory properties in ginger are phenolic compounds in the form of gingerol and shogaol [31].

Sesame oil was made of sesame seeds and was popular in many countries in the world such as China, Japan and other regions in the Middle East. Specifically, a main content of sesame oil was lignans and tocopherols [32]. Lignans and tocopherols have an inhibitory activity on oxidative stress by modulating the concentration of antioxidant enzymes or inflammatory mediators.

Study on the use of NBP and mucoadhesive combination for RAS therapy, intended to find the right formulation, optimum effect and safety. RAS therapy on the oral mucosa had its own challenges because the oral mucosa was always moist and wet with saliva, produced by the major and minor salivary glands. Natural mucoadhesive materials or synthetic polymers are needed to hold the drug in order to stick longer to the surface of the oral mucosal lesion and allow optimal drug penetration [33, 34].

In our review, the mucoadhesive were in gel, film, and spray formula. The gel form has the advantage of being able to expand, absorb liquids well, and be more stable. However, the water content in this formula can increase microbial attack and slower in releasing the drugs [35, 36]. The film formula has the advantage of being easily soluble, more stable, and durable, but it is fragile and hygroscopic; thus, it must be stored in a dry place and requiring special packaging for product stability [37]. The spray formula has the advantage of having a large coverage area and the dosage was adjustable based on the needs, while the disadvantage was lack of stability [38].

The mucoadhesive in this review consist of: HPMC, HPEC, Benzocaine, tragacanth gum, Carbomer 934 and Sodium CMC, and also chitosan. HPMC is a hydrophilic polymer that can form a hydrogel layer (gelling agent). It has good resistance, able to expand when in contact with water, and increases adhesion to the oral mucosa [39]. HPEC in the gel form has the characteristics as bio-adhesive, emulsifier, suspension agent, and also as a matrix in release modification [17]. On the other side, Benzocaine (Anesthesine 0.3 gr) in the spray form was a clear crystalline compound, odorless, and tasteless. It is also an anesthetic agent and can relieve pain [15]. Tragacanth gum in the film form has stable properties against microbial, heat and acid degradation [16, 40]. Another mucoadhesive polymer, namely Carbomer 934 and Sodium CMC were used together in gel formula [18], and also showed a good adhesion property. Chitosan is also used in the film formula. It was an N-deacetylated derivative of chitin which a naturally abundant polysaccharide and containing β (1-4)-linked D-glucosamine and N-acetyl-D-glucosamine units which could be ionized into active carboxyl ions and amines then producing hydrogen that bonds on oral mucosal glycoproteins [19].

The use of the NBP and mucoadhesive combination compared with positive control drugs, Triamcinolone Acetonide 0.1%, showed equivalent effectiveness [14,18]. Whilst the other four studies (*Aloe vera*, myrrh, propolis, and ginger) compared with negative control in the form of PVA film [19] and Placebo [15-17], also showed better effectiveness. This means that the NBPs had a good activity for RAS therapy. The results in tables 5 and 6 also show that the overall NBP and mucoadhesive combination have significant results in RAS therapy outcomes since the first until the last day of the study.

Therefore, to determine the best recommendation, the authors consider that the combination of *Curcuma longa* 10 mg/g with HPMC [14] and the combination of *Punica granatum* flower extract with carbomer 934 and sodium CMC [18], has been proven to be effective as RAS therapy. It is based on the same effectiveness outcomes compared with the positive control which is a drug that has been established all this time in RAS therapy. Both combinations [14, 18], also showed better results in relieving pain and reducing the ulcer size when compared to others.

This review presents the proper combination of NBP and mucoadhesive for RAS therapy and could be used as a basis for further research or for clinical application in patients with RAS. The limitation of this review was several reviewed articles were conducted on a limited number of patients.

CONCLUSION

The most effective NBP in relieving pain in RAS therapy was *Curcuma longa* 10 mg/g combined with HPMC as a mucoadhesive gel form. Meanwhile, the most effective NBP in reducing ulcer size was the combination of *Punica granatum* flower extract with Carbomer 934 and Sodium CMC also in gel form. The other NBPs such as *Aloe vera*, myrrh, propolis, ginger, and sesame oil, with their mucoadhesive polymers, basically also had very good prospects in RAS therapy. However, they still need to be researched.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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