

Original Research Article

A Review of Potential Combination of Clove and Orange peel Oil that Dispersed into Hydrogel as Herbal Medicine for Stomatitis Aftosa Recurrent

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Abstract

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Stomatitis Aftosa Recurrent (SAR) is one of recurrent abnormalities that occurred in oral mucosa including opportunistic infection of microbes. Sweet Orange production in Indonesia reaches 2 million ton each year and donated of orange peel waste. Orange peel contain β -pinen and limonene that have antibacterial activity. Clove oils contain high levels of eugenol that have activities as antibacterial, antifungal, anti-inflammatory. The aim of this review is to study the potential effectiveness of clove and orange peel oil combination into matrix hydrogel for SAR treatment. Antibacterial and antifungal activity were determined using agar dilution method. Antibacterial activity of essential oils was determined against bacterial strains (*Staphylococcus aureus*, *Staphylococcus mutans*, *Escherichia coli*). Antifungal activity was determined against *Candida albicans*. The results of literature study shows that clove and orange peel oil have high microbial inhibition for oral bacteria and fungi, and also shows anti-inflammatory activity. Steam distillation provides an efficient yield of clove and orange peel oil. Combination of both oils that dispersed into hydrogel preparation has potential for herbal medicine to treat SAR and making it easier to apply.

Keywords: Antimicrobial, Clove oil, Hydrogel, Orange peel oil, SAR

INTRODUCTION

Stomatitis Aftosa Recurrent (SAR) known as 'Sariawan' by Indonesian people is one of disorders that often occurs in the oral mucosa. The causes of SAR are diverse, one of which is caused by opportunistic infections by microbial fluctuations on the surface of the oral mucosa. Every year this disease has increased. An average of SAR prevalence in the world population is 20% (Darmanta, 2013). SAR lesions are painful at first, then after 24 hours a grey-yellow circle with erythema will appear on the oral mucosa. SAR lesions based on their clinical characterization can be divided into minor, major, and herpes. Among the three lesions, minor lesions that have the highest prevalence (70%) will recover within 7 to 14 days, while mayor Lesions will recover within 7 days and herpes lesions will recover within 7 to 10 days (Hamedi et al., 2016). Some people prefer to treat SAR with drugs that apparently contain policresulen, but this active

substance had been withdrawn from market by Badan Pengawas Obat dan Makanan Republik Indonesia (BPOM RI) since February 2018. Policresulen was reported to have side effects in 38 cases, two of them are enlargement of SAR and oral mucosal injury that causes infection, also 6 cases reported that the drugs which contain policresulen cause burn on the oral mucosa (Wardhany *et al.*, 2016).

Herbal medicine is widely developed to prevent and treat disease in Indonesia. Clove contains high eugenol which has antimicrobial activity for gram-negative and gram-positive bacteria, one of them is *Staphylococcus aureus*. Clove oil has been traditionally used as dental care, analgesic, and antiseptic. Eugenol was shown to have antifungal activity against *Candida albican* (Alfauziah and Budiman, 2016). Eugenol of clove also have strong antibacterial activity against Cariogenic (MIC

0.1-0.8 $\mu\text{g}/\text{mL}$; MBC 0.2-1.6 $\mu\text{g}/\text{mL}$) and against periodontal pathogens (MIC 0.1-1.6 $\mu\text{g}/\text{mL}$) (Moon *et al.*, 2011).

In Indonesia, the production of orange fruits reaches 2 million tons per year, and the orange peel waste has not been fully utilized. Orange peel has the potential to be used as an abundant and sustainable raw material. Especially because orange peel has essential oils contains β -pinene (Jamaludin *et al.*, 2017) and limonene which has antibacterial activity (Ambrosio *et al.*, 2020). *Citrus hystrix* essential oils contains a major chemical component of β -pinene, which has antibacterial activity (Jamaludin *et al.*, 2017). *Citrus sinensis*, *Citrus Maxima*, and *Citrus reticulate* essential oils contain a major component of Limonene. The antibacterial activity test can be carried out by the agar diffusion method using Mueller Hinton Agar (MHA) media which has been smeared with *Streptococcus mutans* (Mardiah *et al.*, 2019). The results show that the largest average diameter of the inhibition zone is at a concentration of 35% (11.3 mm) with the strong category, while the smallest average diameter of inhibition zone is concentration of 5% (8.4 mm) with the medium category.

Matrix hydrogel is selected as a delivery system because it has advantages as a recurrent abnormalities drug carrier system, high adhesion, can provide a cold affect or sensation, good drug release, and can facilitate drug application (Nakhil *et al.*, 2019). Hydrogel also dries easily, forms a washable film layer and gives a cool sensation to the mucosa, so that is expected to deliver the combination of clove and orange peel oil at oral mucosa as target of action and making it easier to use. Hydrogel preparation provide another pleasant option for people to treat SAR caused by opportunistic infections by microbial fluctuations on the surface of the oral mucosa.

Based on that description, a literature study has been conducted to observe the potential effectiveness of clove and orange peel oil combination into hydrogel preparation as herbal medicine that is a safe and comfortable alternative to treat SAR. The data collection is done through *Google Scholar*, *PubMed*, and *Scopus* with time range about 2010 to 2020. This review is expected to be based on the development of herbal medicine as an alternative treatment besides modern medicine and to overcome the side effect of modern medicine.

MATERIAL AND METHOD

This research is observational studies as narrative review, data that was collected from research papers from *Google Scholar*, *PubMed*, and *Scopus* with time range around 2010-2020. Studies were examined from paper related to antimicrobial activity of clove oil, antimicrobial activity of orange peel oil, hydrogel formulation, and SAR. Collected research data about antimicrobial activity of clove and orange peel oil is

formulated into a hydrogel preparation then evaluated the physical and chemical properties of the hydrogel and its antimicrobial activity.

RESULTS AND DISCUSSION

Distillation of Clove and Orange peel Oil

Generally, essential oil isolation of clove flower and orange peel carried out using steam distillation and water distillation methods. Both methods are easy and safe for the environment because they do not use harmful organic solvents. Steam distillation produced clove oil with a higher eugenol content than water distillation. Isolation of clove oil by steam distillation for 6 hours resulted in a yield of 7.04% (Ratri *et al.*, 2020) while using water vapor distillation for 4 hours resulted in a yield of 4.2% (Hossain *et al.*, 2012). Also, it can use the microwave steam distillation method. This method gave a higher yield of 5.43% in 6 minutes, while in conventional steam distillation gets yield of 5.45% in 2 hours (Sahraoui *et al.*, 2011). So it can be concluded that the distillation method that produces a high percentage of clove and orange peel oil is steam distillation.

Antimicrobial Activity of Clove Oil

Eugenol is the main component in clove oil. The strong antibacterial activity of clove oil is due to the high content of eugenol in clove oil. Eugenol is able to destroy the protein, and also able to influence phospholipid of membrane cells thus it triggers alteration in current permeability (Mardiyaningsih and Aini, 2014). These results are in line with previous research that reported includes antimicrobial, anti-inflammatory, analgesic, antioxidant and anticancer activities of cloves oil from Maluku, Indonesia (Kamatou *et al.*, 2012; Khalil *et al.*, 2017). Natural resources are potential as new sources of antibacterial and antifungal agents as herbal medicine to overcome the side effects of modern medicine. In this case, Eugenol was shown to have antifungal activity against *Candida albican* (Alfauziah and Budiman, 2016). Eugenol in clove oil also shown to have strong antibacterial activity against cariogenic (MIC 0.1-0.8 $\mu\text{g}/\text{mL}$; MBC 0.2-1.6 $\mu\text{g}/\text{mL}$) and against periodontal pathogens (MIC 0.1-1.6 $\mu\text{g}/\text{mL}$) (Moon *et al.*, 2011). Clove oil from clove flowers is widely used and has been known for medication purposes. The chemical components of clove oil can be seen in table 1.

Antimicrobial Activity of Orange Peel Oil

Citrus aurantiifolia contain essential oils which has strong antimicrobial activity (Ladytama *et al.*, 2014). *Citrus*

Table 1. Essential oil components of Clove Oil

Source	Clove Oil Components	Major Component
(Alshaikh and Perveen, 2017)	<i>Eugenol</i> (74.6%), <i>chavibetol</i> (19.7%), <i>caryophyllene</i> (3.5%), <i>trisiloxane, 1, 1, 1, 5, 5, 5-hexamethyl-3, 3-bis [(trimethylsilyl) oxy]</i> (1.7%) and <i>caryophyllene oxide</i> (0.5%)	<i>Eugenol</i>
(Hossain <i>et al.</i> , 2012)	<i>Eugenol</i> (51.51%), <i>caryophyllene</i> (36.2%), α - <i>caryophyllene</i> (4.26%), <i>eugenol acetate</i> (2.64%), and <i>carvacrol</i> (2.42%)	<i>Eugenol</i>
(Ratri <i>et al.</i> , 2020)	<i>Eugenol</i> (85.0%), <i>eugenol acetate</i> (13.06%), <i>caryophyllene</i> (1.14%), and <i>caryophyllene oxide</i> (0.32%)	<i>Eugenol</i>

Table 2. Essential oil components of Orange peel Oil

Sources	Orange species	Volatile Oil	Major Component
(Megawati and Murniyawati 2016)	<i>Citrus sinensis</i>	<i>Limonene</i> (96.69%) and β - <i>pinene</i> (3.31%)	<i>Limonene</i>
(Megawati and Murniyawati 2016)	<i>Citrus Maxima</i>	<i>Limonene</i> (93.99%), β - <i>pinene</i> (3.2%), and <i>germacrene</i> (2.82%)	<i>Limonene</i>
(Jamaludin <i>et al.</i> , 2017)	<i>Citrus hystrix</i>	β - <i>pinene</i> (21.44%), <i>citronella</i> (20.91%), <i>limonene</i> (12.59%) and <i>terpinen-4-ol</i> (11.93%)	β - <i>pinene</i>
(Kamal <i>et al.</i> , 2011)	<i>Citrus reticulata</i>	<i>Limonene</i> (64.1%), <i>decanal</i> (7.71%), α - <i>sinensal</i> (5%) and β - <i>myrcene</i> (4.05%)	<i>Limonene</i>

sinensis, *Citrus Maxima*, and *Citrus reticulata* essential oils contains a major component of Limonene. Antibacterial mechanism of limonene is disturb on permeability which contributed in the lipid profile of bacterial capsule cells by increasing the amount of capric acid causing alteration in the surface of bacterial cells (Ambrosio *et al.*, 2020). The chemical components of orange peel oil can be seen in table 2.

Hydrogel Preparation for Delivery System of Clove and Orange peel Oil

Natural essential oils as medicine can be designed in various dosage forms, for example, hydrogel formulation. A gel is a semi-solid formulation as a drug transporter that can be used on the oral mucosa (Pertiwi *et al.*, 2016). Polymer hydrogels must be inert and not interact with active ingredients. Additional ingredients required include gelling agents, stabilizers, emulsifiers, flavorings, and preservatives specifically for oral use. The stabilizer

and gelling agent that usually used for oral administration such as Hydroxypropyl methylcellulose (HPMC), Carboxy methylcellulose (CMC), xanthan gum, and carbopol 940. CMC is a poly-anionic polymer derived from cellulose and has bioadhesive properties that can firmly adhere to biological surfaces, so potentially advantageous for transdermal and transmucosal use (Javanbakht and Shaabani, 2019). CMC also functions as a gelling agent and can control drug release. However, CMC has a sensitivity to pH. According to the Food and Drug Administration (FDA), the maximum oral use of CMC is 242 mg. Preservatives that are safe to use for oral use include the benzoic group such as benzoic acid and sodium benzoate. Sodium benzoate is more often used in the pharmaceutical dosage form because it has good solubility and stability (Ren *et al.*, 2014). The safe limit for using sodium benzoate as a preservative in food or oral use is 0.1% (Lennerz *et al.*, 2015). The design of hydrogel formula that suitable for clove and orange peel oil combination as active substance is shown in table 3. Evaluation of physical and chemical properties

Table 3. Hydrogel Preparation Design for clove and orange peel oil combination as active substance

Ingredients	Function
Orange peel oil	Active ingredients
Clove oil	Active ingredients
Amprotab®	Binder
Xanthan Gum	Gelling agent, stabilizer
CMC-Na	Gelling agent, thickening agent
Glycerin	Gelling agent, humectan
Stearyl alcohol	Emulsifier
Sodium benzoate	Preservative
Aquadest	Solvent

of hydrogel preparation includes:

Organoleptics

The hydrogel preparation of clove and orange peel oil combination has thick and clear honey with citrus and clove flavour. The resulting hydrogel color and thickness varies according to the amount of essential oil content, high concentration oil that can affect hydrogel consistency becomes diluted (Fardan and Harimurti, 2018).

pH value

pH value will increase following the increased concentration of essential oils that added in the hydrogel. Formulations that can be applied to the skin should have a pH range between 4.5 - 6.5 (Fardan and Harimurti, 2018).

Homogeneity

Hydrogel preparation meets the requirements of homogeneous if there is no separation between the oil phase and water phase for three months stored at room temperature.

Dispersibility

The increased concentration of oil was inversely related to the viscosity of the hydrogel preparation. Low viscosity of hydrogel can increase to dispersibility of the gel (Fardan and Harimurti, 2018). The dispersibility value of gel preparation that meets the requirements is between 5-7 cm.

Stability Test

Hydrogel preparation was stored at a temperature of 4°C for 24 hours then placed at a temperature of 40°C. This process is counted as one cycle, and cycling test was carried out for six cycles. The physical and chemical properties of gel then compared before and after cycling tests. The gel was declared stable if there was no significant change after the cycling test. Table 3

Antimicrobial Activity Test

Oral Antibacterial Test

Based on Kouidhi et al. (2010) research, it is mentioned through the disk diffusion method that was tested on a large number of oral bacteria with a total of 104 strains. Clove oil was able to inhibit a large number of oral bacteria which are associated with dental caries. The concentration of Clove oil of 3.0 mg shows a clear zone inhibition with diameter value that is similar to erythromycin 15 µg. This shows that clove oil has antibacterial activity against a number of oral bacteria. The antibacterial activity of clove oil is related to the high concentration of eugenol compounds (Kouidhi *et al.*, 2010). In other literature it is also stated that clove oil can inhibit the activity of *Escherichia coli* by using the sterile disc diffusion method where Amoxicillin as a positive control and Tween 80 as a negative control. Amoxicillin as a positive control because it has broad-spectrum antibacterial activity. Tween 80 as a negative control acted as an emulgator.

Antibacterial activity of orange peel oil against *S. aureus* ATCC 29213 can be carried out by well diffusion method using MSA (Mannitol Salt Agar) media because it is selective against *S. aureus* bacteria (Cahyani and Artiyani, 2018). The largest average diameter of the inhibition zone is at a concentration of 35% (11.3 mm)

with the strong inhibition zone category, while the smallest average diameter of the inhibition zone is a concentration of 5% (8.4 mm) with the medium category.

Antifungal Activity

Clove oil can inhibit the activity of *C. albicans* using sterile disc diffusion method, where ketoconazole as a positive control and Tween 80 as negative control. Ketoconazole chosen as positive control because it is a broad spectrum antifungal in the imidazole class which mechanism action by inhibiting ergosterol biosynthesis which is an important component of the formation of fungal cell membranes. Ketoconazole activity as a positive control is smaller than the activity of clove oil. Based on these data, it can be concluded that the concentration of clove oil that is used affects antifungal activity. Each variation of clove oil concentration affects the diameter of clear zone inhibition. The concentration of 100% clove oil gave an average diameter of the highest clear zone of 14.2 mm. According to Mardiah *et al.* (2019), the clear zone diameter of 11-20 mm gave a strong growth inhibition response. In other literature, it is stated that through testing the disk diffusion method on 46 strains of oral fungi, it appears that clove oil is able to inhibit a number of oral fungi that are associated with dental caries. The concentration of Clove oil of 3.0 mg shows a clear zone inhibition with diameter value that equivalent with Amphoterin B 100 µg. It is stated that clove oil have antimicrobial activity against a number of fungal flora in the mouth (Kouidhi *et al.*, 2010).

Anti-inflammatory Activity

Eugenol can suppress Tumor Necrosis factor (TNF) signals and suppress Cyclooxygenase-2 (COX-2) expression so it has potential as an anti-inflammatory agent by involving the arachidonic acid metabolic pathway (Da Silveira E Sá *et al.*, 2014). Eugenol can reduce the incidence of infection and shorten the inflammatory period, thus supporting the start of the proliferation period, which stimulates the formation of new capillary blood vessels. Results of wound healing test in mice, clove oil is known to heal scratches in days. The concentration of clove oil in the preparation affects the duration of healing. Based on the research of Salmawati and Daesusi (2019) stated that the 100% concentration of clove oil can heal the wound after 7 days. The concentration of 75% can heal the wound after 8 days. The concentration of 50% can heal wound after 9 days, and at a concentration of 25% can heal wound after 10 days. Wound healing is a number that shows the average level of erythema and new tissue formation (Ordinal Scale).

Clove and orange peel oil combination can be used as

alternative herbal medicine to treat SAR caused by microbia such as *S. aureus* bacteria and *C. albicans* fungal in the mouth. The combination of clove and orange peel oil can induce the antimicrobial, anti-inflammatory, and antifungal activities. It can inhibit the growth of bacteria and fungi in the mouth. The combination of clove and orange peel oil as an active substance in the hydrogel preparation is expected to make it easier to apply for topical application for treatment of SAR. However, it is necessary to carry out a laboratory test and continue with an irritation test and an acute toxicity test to ensure the safety of oil combination and hydrogel preparation that contains essential oil as a first bioassay for natural product research.

CONCLUSION

Considerable attention is being given to the discovery of novel drugs capable of antibacterial, antifungal, and anti-inflammatory particularly those of plant origin. Essential oils and their active constituents, such as eugenol and limonene are a promising source of antibacterial, antifungal, and anti-inflammatory substances. The data presented in this review show the potential of clove and orange peel oil combination that dispersed into the hydrogel delivery system for treatment SAR. It is expected that further studies involving in vivo test, irritation test, acute toxicity test, and clinical trials will be carried out in order to ensure a safe use of these substances as a therapeutic agent against SAR diseases.

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