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EFFICACY OF BASIL LEAF EXTRACT (OCIMUM Spp.) AGAINST MICROBES THAT CAUSES DENTAL AND ORAL DISEASES: A LITERATURE REVIEW

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ABSTRACT

Background: Infection is one of the most common dental and oral health problems experienced by the community. Most infections in the oral cavity are caused by *Candida albicans* and bacteria such as *Streptococcus mutans*. Currently, there is a tendency to use natural ingredients that are believed to be antifungal and antibacterial as a substitute for chemicals. One of the natural ingredients that have the potential as antifungal and antibacterial that is easily obtained by the community is basil leaves *(Ocimum spp.)*.
Objective: This study aims to determine the efficacy of basil leaf extract *(Ocimum spp.)* on the growth of *C. albicans* and *S. mutans* in vitro.
Methods: A systematic literature review study using the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) method was conducted to find scientific evidence of the efficacy of basil leaves *(Ocimum spp)*.
Result: Extracts from most basil leaf species *(Ocimum spp.)* contain flavonoids, alkaloids, saponins, tannins, steroids, triterpenoids, which are expected to have activity as antifungal and antibacterial agents. The minimum inhibitory concentration (MIC) of basil leaf extract from various species, solvents and extraction methods varied with a range of 0.0025 – 25% w/v.
Conclusion: The most effective basil leaf species in inhibiting the growth of *C. albicans* was *Ocimum basilicum* which was extracted using maceration method with methanol solvent (MIC 0.01%). Meanwhile, the most effective basil leaf species in inhibiting the growth of *S. mutans* was *Ocimum sanctum L.* which was extracted using the soxhletation method with 96% ethanol solvent (MIC 0.0025%).

INTRODUCTION

Dental and oral health problems are one of the most common health problems experienced by the community. Based on Riskesdas data in 2018, the national prevalence of dental and oral health problems reached 57.6%[1]. Dental and oral health problems that are often encountered are infections, the entry of pathogenic microorganisms into the body that can cause illness. The most common causes of infection in the oral cavity are fungi and bacteria[2,3]. Candidiasis is one of the most common oral cavity diseases. Oral candidiasis is most often caused by over-colonization of the *Candida albicans*,

which is a normal flora in the oral cavity of healthy individuals. *Candida albicans* is estimated to be present in 45-65% of healthy infants and 30-55% of healthy adults[4]. Oral candidiasis has varied clinical manifestations depending on the causes of local and systemic risk factors[5].

Other than fungi, one of the microbes that causes dental and oral disease is *Streptococcus mutans*. These bacteria are the cause of caries in teeth, because they can produce acid from the fermentation of carbohydrates which damage the mineral balance of teeth[6]. *Streptococcus mutans* is a normal flora found in the oral cavity but can turn into a pathogen if the normal flora balance is disturbed[7].

Currently, antifungal and antibacterial therapy that can be used for the treatment of dental and oral infections is topical or systemic antibiotics. Most of the drugs used for the treatment of candidiasis are fungistatic and have developed resistance. In addition, the formation of dental plaque due to *S. mutans* also increases treatment failure. This raises the need for alternative medicine[8]. Currently, there is a tendency to use natural ingredients that are believed to be antibacterial and antifungal as a substitute for chemicals. Traditional medicines derived from plants have relatively no side effects, cheap, and easy to obtain[7].

One of the natural ingredients that have the potential as antifungal and antibacterial is basil leaves (*Ocimum spp.*)[9,7]. Basil leaves can contain compounds such as flavonoids and tannins that act on fungal cell membranes which can further inhibit or kill fungal cells[10]. Other compounds such as steroids and triterpenoids can also inhibit fungal growth by interfering the development of fungal spores through the cytoplasmic membrane[11]. In addition, essential oil from basil leaves also has antibacterial and antifungal activity by interfering the cell membrane formation [12].

Several studies on the effect of basil leaves on S. mutans and C. albicans microorganisms have been carried out. One of the studies suggested that basil leaf extract (*Ocimum sanctum L.*) dissolved in ethanol up to a concentration of 25% (w/v) could kill *C. albicans*. However, when dissolved in distilled water, the basil leaf extract with a concentration of 25% was only able to inhibit the growth of *C. albicans*[8]. Meanwhile, the effect of basil leaves on *S. mutans* has also been reported. Ethanol extract of basil leaves (*Ocimum basilicum*) has antibacterial effect against *S. mutans* bacteria with the most effective concentration 100%[12]. While in contrast to other studies, aquadest extract of basil leaves (*Ocimum basilicum*) had a stronger inhibitory effect on the growth of *S. mutans*, at concentrations of 7.5% and 15% (w/v)[6].

Based on the results of several *in vitro* studies on the efficacy of basil leaf extract, inconsistent results were still obtained in the inhibitory and bactericidal concentration against *C. albicans* and *S. mutans*. In addition, the solvent for extraction, the number of *C. albicans* and *S. mutans* colonies, and the type of susceptibility test method also seemed to have a role in causing differences in the efficacy

of the basil leaf extract. Therefore, literature review research conducted systematically is needed to answer the efficacy of basil leaves (*Ocimum spp.*) as antifungal and antibacterial.

MATERIAL AND METHODS

This research is a systematic review study using the PRISMA method. The data collection technique in this study was documentation method, which is data collection by finding data from the literature related to the problem. The data that has been obtained from various literatures is collected as a single document that is used to answer the problems that have been formulated.

This study focuses on articles related to the efficacy of basil leaf extract (*Ocimum spp.*) on the growth of *C. albicans* and *S. mutans*. The article searches were carried out using the search engines, among others Science Direct, PubMed, and Google Scholar with the inclusion criteria of articles published in 2011-2021. Article searches were conducted using the Indonesian keywords "daun kemangi" and "*Candida albicans*" and "*Streptococcus mutans*" and "*in vitro*", as well as the English keywords "Ocimum" and "*Candida albicans*" and "*Streptococcus mutans*" and "*in vitro*". The exclusion criteria included articles using the literature review research method, and articles excluded from the analysis of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (Figure 1).

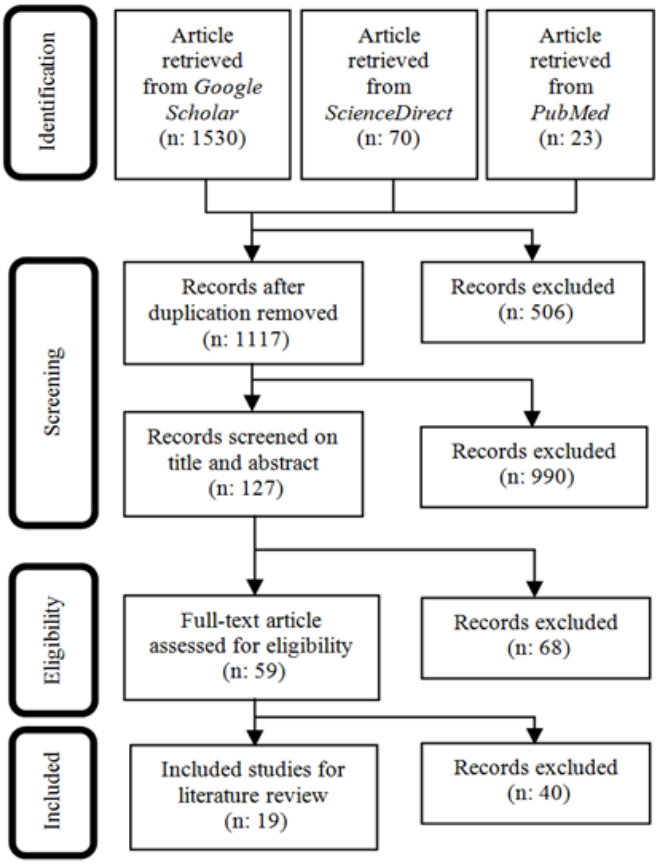

Figure 1. The process of selecting articles on the efficacy of basil leaves (Ocimum spp.) against Candida albicans and Streptococcus mutans using the PRISMA diagram method

RESULTS

The results of a literature review on the topic of the efficacy of basil leaf extract (*Ocimum spp.*) against microbes that cause dental and oral diseases (*Candida albicans* and *Streptococcus mutans*), were conducted on 19 articles. Three species of basil leaves (*Ocimum sanctum L*, *Ocimum micranthum*, and *Ocimum basilicum*) were investigated for their efficacy against *C. albicans* (Table 1). The strongest inhibition (Minimum Inhibitory Concentration-MIC of 0.01% w/v) was found from the species *Ocimum basilicum* which was extracted using methanol.

Table 1. Summary of literature review analysis regarding efficacy of *Ocimum spp.* extract againts *C. albicans*.

No	Plant Species	Author (Year)	ExtractionMethod	Solvent for Extraction	Description of Antifungal Susceptibility Testing	MIC Value (%)	MBC Value (%)	Inhibition Zone (mm)
1.	*Ocimum sanctum L.*	Sivareddy *et al.*, (2019)	Cold extraction	Ethanol 96%	- Broth dilution - Suspension concentration 0.1×10^7 CFU/mL - Temperature for incubation 28ºC during 48-72 hour - *Candida albicans* used are resistant to fluconazole	0.2 (b/v)	-	-
				Ethyl acetate		0.2 (b/v)		
				Ethanol 96%	- Disk diffusion - Potato Dextrose Agar (PDA) - Temperature for incubation 28ºC in 48 hour	0.05 (b/v)	-	7
				Ethyl acetate		0.1 (b/v)	-	13
		Parida *et al.*, (2018)	Hot extraction	Ethanol 96%	- Well-diffusion - Mueller Hinton Agar (MHA) - Suspension concentration Mc Farland 0,5 ($0,5\times10^8$ CFU/mL) - Temperature for incubation 37ºC during 24 hour	0,04 (b/v)	-	10,67
		Ornay *et al.*, (2017)	Cold extraction	Ethanol 96%	- Broth dilution - Sabouraud's Dextrose Broth (SDB) - Suspension concentration Mc Farland 0,5 ($0,5\times10^8$ CFU/mL) - Temperature for incubation 37ºC during 18-24 hour	12,5 (v/v)	25 (v/v)	-
		Silvia *et al.*, (2017)	Cold extraction	Aquadest	- Agar dilution - Sabouraud's Dextrose Agar (SDA) - Suspension concentration Mc Farland 0,5 ($0,5\times10^8$ CFU/mL) - Temperature for incubation 37ºC during 48 hour	25 (v/v)	-	-
		Sukmawati & Purnamasari, (2017)	Cold extraction	Ethanol 96%	- Microbroth dilution - Sabouroud Dextrose Broth (SDB) - Suspension concentration Mc Farland 0,5 ($0,5\times10^8$ CFU/mL) - Temperature for incubation 25ºC during 72 hour	0,1 (b/v)	-	-
		Subramanian *et al.*, (2014)	Cold extraction	Methanol	- Disk diffusion - Nutrien Agar (NA) - Temperature for incubation 28-30ºC during 18 hour	100% extract dissolved in 300 µl of aquadest	-	18,34
				Ethanol 96%				11,23
				Ethyl acetate				14,19
				Chloroform				17,13
2..	*Ocimum micranthum*	Caamal-Herrera *et al.*, (2018)	Hot extraction	Ethanol 96%	- Microdilution - Sabouraud Broth (SB) - Suspension concentration Mc Farland 0,5 ($0,5\times10^8$ CFU/mL) - Temperature for incubation 35ºC during 40-42 hour	0,5 (v/v)	-	-
				Aquadest		8 (v/v)		
			Hydro-distilation	Essential oil		12,5 (v/v)		
3.	*Ocimum basilicum*	Ahmad *et al.*, (2016)	Cold extraction	Methanol	- Agar dilution - Potato Dextrose Agar (PDA)	0,6 (b/v)	-	100% Inhibition

							compared to growth control
	Issazadeh *et al.*, (2012)	Cold extraction	Methanol	- Well-diffusion - Mueller Hinton Agar (MHA) plate - Suspension concentration (10^6 CFU/mL) - Temperature for incubation 25ºC during 96 hour	0,01 (b/v)	-	6

Meanwhile, the efficacy of several species of basil leaves (*Ocimum basilicum*, *Ocimum sanctum L*, and *Ocimum americanum)* against *S. mutans* has been investigated. Based on the results of the analysis, various MIC values and minimum bactericidal concentration (MBC) were obtained from the various species of *Ocimum spp*. Different types of solvents and extraction methods also affect the efficacy of *Ocimum spp.* against *S. mutans* (Table 2).

Table 2. Summary of literature review analysis regarding efficacy of *Ocimum spp.* extract againts *S. mutans*.

No	Plant Species	Author (Year)	Extraction Method	Solvent for Extraction	Description of Antibacterial Susceptibility Testing	MIC Value (%)	MBC Value (%)	Zone Inhibition (mm)
1.	*Ocimum basilicum*	Syahrul & Syahriel, (2021)	Cold extraction	Methanol	- Disk diffusion - Mueller Hinton Blood Agar (MHBA) - Suspension concentration Mc Farland (1×10^8 CFU/mL) - Temperature for incubation 37ºC during 18-24 hour.	3,5 (v/v)	-	7
		Evangelina *et al.*, (2021)	Cold extraction	Ethyl acetate	- Microdilution - Microplate 96 well - Temperature for incubation 37ºC during 48 hour - Growth inhibition of *Streptococcus mutans* was measured using an ELISA reader spectrophotometer	0,3125 (b/v)	0,625 (b/v)	-
					- Disk diffusion - Mueller Hinton Agar (MHA) - Suspension concentration 0,5 Mc Farland (1×10^8 CFU/mL) - Temperature for incubation 37ºC during 48 hour	5 (v/v)	-	7,6
		Aminah S. *et al.*, (2020)	Cold extraction	Ethanol 96%	- Well-diffusion - Nutrien Agar (NA) - Suspension concentration Mc Farland (1×10^8 CFU/mL) - Temperature for incubation 37ºC during 24 hour	20 (v/v)	-	6,97
		Usman *et al.*, (2019)	Cold extraction	Ethanol 70%	- Disk diffusion - Nutrien Agar (NA) - Suspension concentration 0,5 Mc Farland (3×10^8 CFU/mL) - Temperature for incubation 37ºC during 24 hour - The *Streptococcus mutans* bacteria used are already resistant to tetracycline	7 (v/v)	-	7,9
		Paksi *et al.*, (2018)	Cold extraction	Aquadest	- Broth dilution - Brain Heart Infusion (BHI) Broth - Suspension concentration 10^8 CFU/mL - Temperature for incubation 37ºC during 24 hour - Measurement of inhibition using spectrophotometry at 550 nm wavelength	7,5 (v/v)	-	-
2.	*Ocimum Sanctum L.*	Rai *et al.*, (2020)	Hydrodistilation	Essential oil	- Well-diffusion - Blood agar plate - Suspension concentration 0,5 Mc Farland - Temperature for incubation 37ºC during 24-72 hour	0,7 (v/v)	-	22,7
		Parida *et al.*, (2018)	Hot extraction	Ethanol 96%	- Broth dilution - Nutrien Broth	0,0025 (b/v)	0,0025 (b/v)	-

					- Suspension concentration Mc Farland 0,5 ($0,5\times10^8$ CFU/mL) - Temperature for incubation 37ºC during 24 hour			
					- Well-diffusion - Mueller Hinton Agar (MHA) - Suspension concentration Mc Farland 0,5 ($0,5\times10^8$ CFU/mL) - Temperature for incubation 37ºC during 24 hour	0,04 (b/v)	-	7,3
		Gadiyar *et al.*, (2017)	Cold extraction	Ethanol 96%	- Broth dilution - Brain Heart Infusion (BHI) Broth - Suspension concentration 0,5 Mc Farland ($1,5\times10^8$ CFU/mL) - Temperature for incubation 37ºC during 24 hour	2,5 (b/v)	-	-
		Kochikar Pai *et al.*, (2015)	Hot extraction	Ethanol 90%	- Well-diffusion - Brain Heart Infusion (BHI) agar - Temperature for incubation 37ºC during 48 hour	2,5 (v/v)	-	12
3.	*Ocimum Americanum*	Herdiyati *et al.*, (2020)	Cold extraction	Methanol	- Microdilution - Mueller Hinton Broth (MHB) - Microplate 96 well - Temperature for incubation 37ºC during 24 hour	0,125 (b/v)	0,25 (b/v)	-
					- Disk diffusion - Mueller Hinton Broth (MHB) - Temperature for incubation 37ºC during 24 hour	20 (b/v)	-	8

Phytochemical screening has been carried out on several species of basil leaves such as *Ocimum sanctum L*., *Ocimum basilicum*, and *Ocimum americanum*. The three species of basil leaves were all positive for the content of flavonoid compounds, alkaloids, saponins, tannins, steroids and terpenoids (Table 3).

Table 3. Results of phytochemical screening analysis on basil leaf species (*Ocimum spp.*)

No	Plant Species	Chemical Compound						References
		Flavonoid	Alkaloid	Saponin	Tannin	Steroid	Terpenoid	
1	*Ocimum sanctum L.*	+	+	+	+	+	+	(Silvia *et al.*, 2017) (Balakumar *et al.*, 2011)
2	*Ocimum basilicum*	+	+	+	+	+	+	(Issazadeh *et al.*, 2012) (Usman *et al.*, 2019) (Kumalasari & Andiarna, 2020)
3	*Ocimum americanum*	+	+	+	+	+	+	(Pasaribu *et al.*, 2018)

DISCUSSION

Based on the results previously presented, there are differences in the effectiveness of basil leaf species (*Ocimum spp.*) to inhibit or kill *C. albicans* or *S. mutans*. The solvent used for the extraction and also the extraction method is the most influential factor to the antifungal and antibacterial efficacy of basil leaves.

Solvent is one of the chemical factors that can affect the quality of the extract. Solvents are selected based on differences in polarity in order to obtain large amounts of extract[29]. Based on the results in tables 1 and 2, it can be concluded that ethanol is better than aquadest. This is caused by the difference in polarity level between aquadest and ethanol. Aquadest has the highest level of polarity among other solvents, so it produces the lowest total phenol yield compared to other solvents[30]. Meanwhile, methanol was concluded to be stronger than ethanol to attract more flavonoids. Methanol is a universal solvent that can attract most polar and non-polar compounds[31].

The concentration of the solvent extraction also affects the quality of the basil leaf extract produced. Extracting 70% ethanol can produce stronger activity rather than 96% ethanol, because polar flavonoid compounds tend to dissolve more in 70% ethanol. Ethanol has an OH group (hydroxyl group) which can form a hydrogen bond with the hydroxyl group (OH) of flavonoid compounds, futhermore increase the solubility of flavonoid compounds[32].

In addition to the type of solvent, the extraction method also affects the efficacy of *ocimum spp*. If using the same solvent, the soxhletation method is better than the maceration method for extracting secondary metabolites from *Ocimum spp*. Extraction using the soxhletation method is one of the best methods used to separate bioactive compounds from nature[33]. Maceration and soxhletation are extraction methods with immersion techniques, but have differences in the temperature used during the extraction process[34]. The soxhletation method has several advantages over other methods, one of them is the use of more efficient solvents. The continuous extraction and the condensation process in soxhletation resulted in higher yields than the maceration method. The temperature factor or solvent heating in the soxhletation extraction process can increase the transfer of metabolites into the solvent[33].

In general, the antifungal and antibacterial susceptibility testing of an agent can be done using several methods such as the dilution and the diffusion method. The dilution method is divided into broth and agar dilution. The broth dilution method is carried out by growing the test microbes in a broth medium containing an antimicrobial agent that has been diluted into various concentration. Meanwhile, the agar dilution method is carried out by inoculating the test microbes on agar media contain diluting antimicrobial agents[35,36]. The microdilution method itself is a development of the broth dilution method with the smaller in the amount of media, bacteria, and antimicrobial agents[37]. The diffusion method can be divided into well diffusion and disc diffusion methods. The well diffusion method is carried out by making holes perpendicular to the solid agar medium that has been inoculated with the test bacteria[38]. While the disc diffusion method is an antimicrobial test using a disc containing an antimicrobial agent[20,38].

Based on the results of a literature review on the efficacy of basil leaves (*Ocimum spp.*), the use of the well diffusion method can produce greater antibacterial activity than the disc diffusion method.

This is because the basil leaf extract which is inserted into the well can more easily undergo osmosis and be mixed homogeneously throughout the agar media[39].

In general, *Streptococcus mutans* and *C. albicans* used for the efficacy test of basil leaf extract (*Ocimum spp.*) were still sensitive to antibiotics and antiseptics. However, there are several articles showing the pattern of resistance of *S. mutans* and *C. albicans* to antibiotics (Tables 1 and 2). This is in line with other studies which state that only 83% of *Candida sp.* still sensitive to fluconazole (Mursinah, (2016). Meanwhile, the resistance pattern of *Streptococcus sp.* against tetracycline reached 100%[41].

Efficacy of *Ocimum spp.* against *C. albicans*

Based on the results in table 1, it can be concluded that the most effective species of *Ocimum spp*. in inhibiting the growth of the *C. albicans* was *Ocimum basilicum* which was extracted using maceration method with methanol solvent. The antifungal susceptibility test method used to assess the efficacy of the *Ocimum basilicum* was the well diffusion test method, and the MIC value was 0.01% to form an inhibition zone diameter of 6 mm.

Other basil leaf species such as *Ocimum sanctum L*. were extracted using the maceration method, but they have different efficacy due to the different extraction solvents used. The extraction solvent that was able to produce the strongest *C. albicans* inhibition zone was methanol, followed by chloroform, ethyl acetate, 96% ethanol, and aquadest. However, the inhibitory strenght of *Ocimum sanctum L* (MIC of 0.05% w/v) which was extracted using methanol was weaker than *Ocimum basilicum* [13,16]. Meanwhile, for the species *Ocimum micranthum*, the strongest MIC value (0.5% w/v) was obtained in the extraction using 96% ethanol as solvent. Furthermore, the activity of the 96% ethanol extract prepared by the soxhletation method was better than the essential oil processed using the hydrodistillation method[17].

Efficacy of *Ocimum spp.* against *S. mutans*

The most effective *Ocimum spp*. in inhibiting the growth of *S. mutans* was the *Ocimum sanctum L.* which was extracted using the soxhletation method with 96% ethanol as solvent. The antibacterial susceptibility test method used to assess the efficacy of *Ocimum sanctum L*. was the broth dilution test method, with the MIC value of 0.0025% w/v.

Meanwhile, *Ocimum basilicum* had the strongest activity (MIC of 0.3125% w/v) when extracted using maceration method and ethyl acetate as solvent[21]. For *Ocimum americanum*, maceration extraction method using methanol produced the strongest MIC value (0.125% w/v). Furthermore, the microdilution test method was better to assess the strength of *Ocimum americanum*, when compared to the disc diffusion method[26].

Phytochemical analysis of *Ocimum spp.*

Basil leaf extract (*Ocimum spp.*) contains antibacterial and antifungal compounds such as flavonoids, alkaloids, saponins, tannins, steroids, and triterpenoids. Flavonoid can work as antioxidants and eventually damage bacterial cell walls. In addition, flavonoids can also damage and inhibit the formation of cell membranes, cell walls, and bacterial nucleic acids[6]. As antifungals, phenol flavonoids can inhibit the process of forming fungal cell walls and lysing cell walls[9].

Alkaloids are also compounds that have antibacterial activity that can interfere with the integrity of the peptidoglycan constituent components, prevent cell wall formation, and lead to cell death[42]. Alkaloids are also able to inhibit the formation of protein and bacterial DNA[6]. Alkaloids also have antifungal activity by inhibiting the proliferation of protein formation and respiration in cells which can cause fungal death[9].

Other compounds such as saponins are soap-like compounds that are antiseptic and have antibacterial effects. Saponins work by lowering the surface tension of bacterial cell membranes. Saponins act on the phospholipid phosphate groups of cell membranes, so that they can finally enter the cell and denature cell proteins[6]. Saponins as antifungals are surfactants in a polar form, then they can break down lipids in cell membranes resulting in impaired permeability of fungal cell membranes. It will cause interference with the diffusion process of substances needed by fungi[43].

Tannins are compounds that have antibacterial and antifungal properties. As an antibacterial, tannins work by denaturing bacterial cell proteins and inhibiting the process of nucleic acid synthesis[42]. The activity of tannins as antifungals can cause shrinkage of fungal cell walls and then cause fungal cell death[9].

Meanwhile, steroids and terpenoids in general have a mechanism of action by causing leakage from liposomes and capable of disrupting the integration of lipid membranes of bacteria and fungi[44]. Steroids interact with cell phospholipid membranes which are permeable to lipophilic compounds so that the integrity of the cell membrane decreases and eventually the cell becomes brittle and lyses. Terpenoids have a mechanism of action that can react with transmembrane proteins on the outer membrane of the bacterial cell wall and cause the formation of strong and damaging polymer bonds. Damaged transmembrane proteins can reduce the permeability of the bacterial cell wall which can result in reduced nutrients. It can inhibit the growth or kill the bacteria [45].

In addition, basil leaf species such as *Ocimum sanctum L*. and *Ocimum micranthum* can produce essential oil. This essential oil has various pharmacological activities such as analgesic, antiseptic, antipyretic, and has strong antifungal and antibacterial activities. Basil essential oil is composed of hydrocarbon compounds, esters, alcohols, phenols, phenolic ethers, ketones and oxides[34]. Essential

oils can interfere with the process of forming cell membranes and cell walls of fungi and bacterial cells[9,46].

CONCLUSIONS

Based on the results of the literature review, it can be concluded that basil leaf extracts from various species have antibacterial activity againts *S. mutans* and antifungal activities againts *C. albicans*. The most effective in inhibiting the growth of *C. albicans* was *Ocimum basilicum* which was extracted using maceration method with methanol solvent (MIC 0.01% w/v). Meanwhile, the most effective in inhibiting the growth of *S. mutans* was *Ocimum sanctum L.* which was extracted using soxhletation method with etanol 96% solvent (MIC of 0.0025% b/v). In addition to the different types of basil leaf species, differences in the extraction method, solvent type, and antibacterial/antifungal susceptibility test methods can affect the efficacy of basil leaves against *C. albicans* dan *S. mutans*.

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