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Research Article
Antibacterial Potential of Kemangi (*Ocimum basilicum* L.) Against Pathogenic Oral Bacteria: An *in vitro* Study

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Abstract

Background and Objective: Natural products are potential source of new bio-actives that can be used as promising antibacterial compounds. The edible vegetable of Kemangi (*Ocimum basilicum* L.) has been empirically used as a spice and herb to treat various medical conditions, including infectious diseases caused by pathogenic bacteria. This study was aimed to determine the potency and investigate the antibacterial effects of the edible plant Kemangi against the oral bacteria of *Enterococcus faecalis*, *Streptococcus mutans* and *Streptococcus sanguinis*. **Materials and Methods:** Kemangi was extracted using different solvents to yield n-hexane, ethyl acetate, methanol and H_2O extracts for antibacterial assays, the concentrations of single and combination extracts were adjusted and assayed against bacteria of *E. faecalis* ATCC 29212, *S. mutans* ATCC 25175, *S. sanguinis* ATCC 10566 strains by agar well diffusion assays. Chlorhexidine, fosfomycine and quercetin were used as positive controls. **Results:** The Kemangi extracts in single and combination formulas showed significant and different antibacterial activities against different bacteria, thus indicating the important synergistic and antagonistic effects of their active constituents. **Conclusion:** Extracts from the edible herbal plant of Kemangi presented *in vitro* antibacterial activity against pathogenic oral bacteria of *E. faecalis*, *S. mutans* and *S. sanguinis*. This discovery is important information that can be used in further *in vivo* clinical studies to determine the exact dosages as well as assess its effectiveness in practical and clinical application. In this study, the potential antimicrobial and antifungal properties of Kemangi extract were revealed. This offers an alternative treatment backed by scientific basis consisting of a natural product has synergistic effects with conventional antibacterial treatment.

Key words: Kemangi, *Ocimum basilicum* L., antibacterial compound, oral bacteria, *S. sanguinis*, *S. mutans*, *E. faecalis*

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Oral disease is one of the major human health problems. It includes dental caries and periodontitis caused by bacterial infection from *Streptotococcus mutans*, *Enterococcus faecalis* and *Streptococcus sanguis*[1,2]. The increasing prevalence of antibiotic resistance against bacteria have led to the discovery of new antibacterial agents to overcome this problem. Dental caries is a transmissible bacterial disease process caused by acids from bacterial metabolism diffusing into the enamel and dentine[3]. Periodontitis is defined as an inflammatory disease affecting the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation[4]. Regarding antibiotic resistance from an evolutionary perspective, bacteria use two major genetic strategies to adapt to antibiotic attacks. These are mutations in genes often associated with the mechanism of action of the compound and the acquisition of foreign DNA coding for resistance determinants through horizontal gene transfer (HGT)[5].

The rationale of the root canal treatment is to debride and sterilize the root canal to eliminate pathogens causing tooth infection and thorough controlled root canal sterilization is required for predictable treatment outcomes[6]. After a root canal preparation, the canal should be considerably clean with diminished number of pathogens. Oral pathogens such as *E. faecalis* are seldom found in failed endodontic treatments where infection of the root canal and periapical tissue re-occurs. The bacterium are able to survive in unfavorable conditions, forming a biofilm which enables it to penetrate dentinal tubules[7,8]. The *E. faecalis* is not only found in the root canals, but can also exist in both the root canals and in the saliva[9]. Even though root canal treatment has a considerably high success rate of 85% some can fail over the long term to become reinfected[10].

Bioactive compounds from natural products are an enormous source of promising new antimicrobial agents with diverse structures of active secondary metabolites; these can be used to treat oral disease caused by pathogenic oral bacteria[11,12]. In continuous search for new bioactive compounds from natural sources, explored potential active constituents as such as the antibacterial agent from the interesting medicinal plant of Kemangi (*Ocimum basilicum* L.) were explored. Kemangi is an edible spice plant commonly known as sweet basil including Lamiaceae[13,14]. It contains monoterpene and diterpenoid as its major components, making it a well-known source for essential oil (basil oil) and an important component of fragrances. Phytochemical analysis of leaf extracts have shown that it contains the secondary metabolites of phenolic, terpenoid, steroid and flavonoid compounds[15]. Besides essential oil as its major component, two compounds were isolated from the non-essential oil part, namely diterpenoids of 2-(2-vinylcyclohexa-1,5-dienyl)propan-1-ol and 1-(2-vinylcyclohexa-1,4-dienyl) propan-2-ol[13].

The ethanol extracts showed antimicrobial activity against *Acinetobacter*, *Bacillus*, *Escherichia*, *Staphylococcus*, while the methanol extract was active against Acinetobacter, *Bacillus*, *Brucella*, *Escherichia*, *Micrococcus* and *Staphylococcus*[16]. The ethanol extract of Kemangi was reported to inhibit the bacterial growth of *S. epidermidis*, *S. aureus*, *B. paludis* and *B. subtilis* with inhibition zone values of 12, 12, 10 and 12 mm, respectively. Apart from that, the methanol extract of *O. basilicum* was found to have MIC values of 6040 and 80 g mL^{-1} against bacteria of *K. pneumoniae*, *S. typhii* and *S. aureus*, respectively[17,18].

As an alternative to antibacterial agents for root canal sterilization, new antibacterial and anti-inflammation agents, irrigants, medicaments and materials for endodontic treatment are in demand. Edible plants and herbs have emerged as a possible alternative, since screenings have shown that they contain significant active phytotherapy compounds[19,20].

Medicinal plants have been accepted as an alternative therapy to complement modern medicine. For this research, choosing an edible vegetable as the source for developing an antibacterial agent was performed with an assumption that the process for drug development would be simpler. The toxicity levels of vegetables are negligible as they are consumed on a daily basis.

Based on a continuous search for a new antibacterial agent from Indonesian plants, this paper describes the isolation, structure determination and activity of the edible plant Kemangi (*O. basilicum* L.) against particular pathogenic oral bacteria[21-23]. This study was primarily aimed to investigate the overall potency and antibacterial effects of the edible plant Kemangi against the oral bacteria of *Enterococcus faecalis*, *Streptococcus mutans* and *Streptococcus sanguinis*.

MATERIALS AND METHODS

The research was conducted since January, 2018 to June, 2019 at Laboratory of Natural Product and Synthesis, Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran, Bandung, Indonesia.

Fresh Kemangi (*Ocimum basilicum* L.) was collected on January, 2018 from local farmers in Ciwidey-Kabupaten Bandung, Jawa Barat, Indonesia. Extracts were obtained from the extraction method with organic solvents of methanol, n-hexane and ethyl acetate.

Instruments: Laminar airflow, incubator Memmert, autoclave machine HVE-50 Hirayama and jars.

Preparation of the kemangi extracts: All samples were extracted with methanolic extract (MeOH) for 3×24 h by subsequent partitioning between n-hexane-water and ethyl acetate-water[13,14,22].

Preparation of the combination extracts and reference compounds: All samples were carefully prepared and the concentrations were adjusted according to inhibition zone data values[13,14,22].

Preliminary phytochemical screening: Screening for the secondary metabolites of alkaloids, terpenoids and flavonoids was performed in methanol, n-hexane, ethyl acetate and water extracts, as previously mentioned in published papers[24,25].

Microorganism assay: *Enterococcus faecalis* ATCC 29212, *Streptococcus mutans* ATCC 25175, *Streptococcus sanguinis* ATCC 10566 were used for antibacterial testing with Muller Hinton broth and Muller Hinton agar as mediums, chlorhexidine (purchased from Merck Co. Ltd. and Sigma Aldrich) as a positive control and anaerobic jar antibacterial assay.

Antibacterial activity: Antibacterial effects of Kemangi extract against *E. faecalis* ATCC 29212 *Streptococcus mutans* ATCC 25175, *Streptococcus sanguinis* ATCC 10566 were observed using the Kirby-Bauer disk diffusion method. The sensitivity or resistance of *E. faecalis*, *S. mutans* and *S. sanguinis* to compounds were determined based on CLSI protocols[26,27]. All samples were diluted with methanol except for chlorhexidine (control) which was diluted with water. The concentrations used in all samples and control were1, 2, 3, 4 and 5%, with 2% of chlorhexidine. Paper discs (6 mm) were impregnated with 20 µL of each sample and then placed on the surface of the agar. Tests were performed in duplicate.

RESULTS

Phytochemical screening of kemangi (*Ocimum basilicum* L.) extracts: Phytochemical screening data in Table 1 suggests that the secondary metabolite constituents of phenolic, flavonoid, steroid, triterpenoid, saponin and tannin compounds were found in all extracts, except that steroid and triterpenoid were not found in H_2O and n-hexane and ethyl acetate extracts, respectively. On the other hand, alkaloid was only found in the H_2O extracts.

Antibacterial activity

Antibacterial activity of the extracts: In order to predict the potential of Kemangi (*Ocimum basilicum* L.) as a natural source of antibacterial activity, extracts to inhibit bacterial growth were assayed against *E. faecalis*, *S. mutans* and *S. sanguinis*. The susceptibility of Kemangi extracts against bacteria were evaluated from their sample inhibition zones on bacteria growth by the Kirby-Bauer method and the samples were conducted at concentrations of 1, 2, 3, 4 and 5%, with 2% chlorhexidine as a positive control and methanol and water as negative controls. As shown in Table 2, the reported assay data confirms that all extracts inhibited bacterial growth for all tested bacteria with different levels of activity based on their inhibition zone values. For testing against *E. faecalis*, all extracts had the highest activity at 5% with inhibition zone values of 10.4, 8.8 and 10, 3, while the H_2O extract was inactive. For the *S. mutans* bacterium, only n-hexane and ethyl acetate extracts were active at 5% with inhibition zone values of 9.4 and 7.5, respectively, while the methanol and H_2O extracts were inactive. On the other hand, interesting antibacterial activity against *S. sanguinis* was found. All extracts showed highest activity at 5% with inhibition zone values of 11.4, 13.5, 16.2 and 10.1 mm, respectively. Then, the

Table 1: Phytochemical analysis of Kemangi (*Ocimum basilicum* L.) extract

		Extracts			
Compounds	Reagent	H_2O	n-Hexane	Ea	MeOH
Phenolic	$FeCl_3$ 5%	+	+	+	+
Flavonoid	HCl (p.a)+Mg	+	+	+	+
	H_2SO_4 2 N	+	+	+	+
	NaOH 10%	+	+	+	+
Steroid	Lieberman-Burchard	-	+	+	+
Triterpenoid	Lieberman-Burchard	+	-	-	+
Saponin	HCl+H_2O	+	+	+	+
Tannin	$FeCl_3$ 1%	+	+	+	+
Alkaloid	Dragendorff	+	-	-	-
	Wagner	+	-	-	-

MeOH: methanol, Ea: Ethyl acetate, H_2O: Water, +: Positive results according to procedure, -: Negative results not according to procedure

Table 2: Antibacterial activity of kemangi (*O. basilicum* L.) extract against pathogenic oral bacteria *E. faecalis* ATCC 29212, *S. mutans* ATCC 25175 and *S. sanguinis* ATCC 10556

	Inhibition zones (mm) at concentration (%)				
Extracts	1	2	3	4	5
E. faecalis					
Methanol	6.9	7.4	7.7	8.9	10.4
n-Hexane	0.0	0.0	0.0	8.2	8.8
Ethyl acetate	0.0	0.0	8.6	9.6	10.3
Water	0.0	0.0	0.0	0.0	0.0
Chlorhexidine 2%	15.5	15.0	14.8	15.5	15.2
S. mutans					
Methanol	0.0	0.0	0.0	0.0	0.0
n-Hexane	0.0	0.0	0.0	8.3	9.4
Ethyl acetate	0.0	0.0	0.0	0.0	7.5
Water	0.0	0.0	0.0	0.0	0.0
Chlorhexidine 2%	10.4	10.6	10.8	10.8	10.9
S. sangunis					
Methanol	0.0	7.8	8.6	9.4	11.4
n-Hexane	7.2	8.6	10.1	10.3	13.5
Ethyl acetate	10.6	11.5	13.3	14.6	16.2
Water	0.0	0.0	0.0	0.0	10.1
Chlorhexidine 2%	17.3	17.6	17.8	17.8	17.9

Table 3: Antibacterial activity of the combination extracts of kemangi (*O. basilicum* L.) at 5% concentration against pathogenic oral bacteria *E. faecalis* ATCC 29212, *S. mutans* ATCC 25175 and *S. sanguinis* ATCC 10556

	Inhibition zones (mm) at concentration (%)		
Samples	*E. faecalis*	*S. mutans*	*S. sanguinis*
M+Hex	6.8	0	0
M+Ea	0.0	0	0
M+H_2O	0.0	0	0
n-Hex+Ea	6.9	0	0
n-Hex+H_2O	0.0	0	0
Ea+H_2O	0.0	0	0

M: Methanol, Ea: Ethyl acetate, Hex: n-hexane, H_2O: Water

Table 4: Antibacterial activity of the combination extracts of kemangi (*O. basilicum* L.) and reference compounds at 10% concentration against pathogenic oral bacteria *E. faecalis* ATCC 29212, *S. mutans* ATCC 25175 and *S. sanguinis* ATCC 10556

	Inhibition zones (mm) at concentration (%)		
Samples	*E. faecalis*	*S. mutans*	*S. sanguinis*
M+Chx	12.00	0.00	0.00
M+F	20.15	30.85	30.85
M+K	0.00	0.00	0.00
Hex+Chx	11.25	0.00	0.00
Hex+F	23.30	27.80	27.80
Hex+K	0.00	0.00	0.00
Ea+Chx	12.75	0.00	0.00
Ea+F	22.95	31.20	31.20
Ea+K	0.00	0.00	0.00
H_2O+Chx	17.15	0.00	0.00
H_2O+F	21.90	31.85	31.85
H_2O+K	0.00	0.00	0.00

M: Methanol, Ea: Ethyl acetate, Hex: n-hexane, H_2O: Water, Chx: Chlorhexidine, F: Fosfomycin, Q: Quercetin

data represented very promising potential antibacterial activity in n-hexane and ethyl acetate extracts against *S. sanguinis*, as they were active until the smallest assay concentrations at 1% with inhibition zone values of 7.2 and 10.6 mm, respectively.

Antibacterial activity of the combination extracts: To predict the synergistic effects of active constituents in the single and combination extracts, formulated mixture extracts were made and their activities were evaluated against bacteria of *E. faecalis* ATCC 29212, *S. mutans* ATCC 25175 and *S. sanguinis* ATCC 10556, respectively.

As shown in Table 3 containing data on the antibacterial activity of combination extracts, only two combination extracts of M+Hex and n-Hex+Ea were active with inhibition zone values of 6.8 and 6.9 mm, respectively, while other extracts were inactive.

Antibacterial activity of the combination extracts and references compounds: For advanced analysis to determine antibacterial activity produced by the active constituents of extracts in combination with the reference compounds, mixture extracts were made and their antibacterial activity were re-evaluated against *E. faecalis* ATCC 29212, *S. mutans* ATCC 25175 and *S. sanguinis* ATCC 10556, respectively.

The results of antibacterial activity are shown in Table 4, only four combination extracts of M+F, Hex+Chx, Ea+F and H_2O+F actively inhibited the growth of all bacteria including *E. faecalis*, *S. mutans* and *S. sanguinis* with different inhibition zone values, while four combination extracts of M+Chx, Hex+Chx, Ea+Chx, H_2O+Chx were active only against *E. faecalis*. On the other hand, four other combination extracts were inactive.

DISCUSSION

As the use of antibiotics has increased markedly over the last decade, the problem of antimicrobial drug resistance has emerged. This opens the challenge and opportunity for sustainable modern research of drugs. Among the bacteria that cause infection in oral disease, antibacterial treatment for *E. faecalis*, *S. mutans* and *S. sanguinis* has attracted the attention of many researchers. Current treatment for pulpal and periapical lesionsuses2% chlorhexidine as the gold standard, but this may result in discoloration of the teeth and drug resistance[28,29]. Therefore, there is a need to find and develop new antibacterial compounds which are more selective, effective and efficient with zero or very limited side effects.

Natural products are a source of therapeutically viable antibacterial agents. Higher plants can synthesize diverse bioactive compounds that act as antifungal and antibacterial agents. This study presented preliminary data on the antibacterial activity of some edible vegetables and fruits selected because they are consumed daily by humans[30-32].

As the process of drug discovery is long and expensive, the selection of natural antibacterial sources is an important starting point. The edible vegetable plant selected in this study is assumed to contain phytochemical active constituents that have antibacterial activity, no side effects and is not toxic to the human body because it is consumed as a food source[33]. The preliminary phytochemical screening described in Table 1 shows that all extracts of Kemangi contain important secondary metabolites of phenolic, flavonoid, steroid, triterpenoid, saponin, tannin and alkaloid compounds; these have been reported as antibacterial compounds[34]. The data from the phytochemical analysis describes the potency of the Kemangi, as it contains important phytochemical constituents. Thus, it can be used as a promising natural source to find new antimicrobial compound[35].

In order to evaluate the antibacterial activity, the extracts were tested against *E. faecalis*, *S. mutans* and *S. sanguinis*. The assay data in Table 2 states that extracts have different sensitivities to different bacteria, thus suggesting that their mechanisms of inhibiting bacterial growth are different. Based on the antibacterial data, most extracts were active against *S. mutans.* Three extracts of methanol, n-hexane and ethyl acetate were active from all assay concentrations of 1-5%, with inhibition zone values of 7.2-16.2 mm. The activity of ethyl acetate at 5% of 16.2 mm was nearly the same as the activity of 2% chlorhexidine as the gold standard at 17.9 mm. Previous data have reported on the activity of the extracts against *S. mutans*[30].

Further antibacterial data analysis showed that the extract was also active against *E. faecalis*, especially methanol which was active at 1-5% with inhibition zones values of 6.9-10.4 ppm, while n-hexane and ethyl acetate extracts was only active from 4-5 and 3-5%, respectively. The antibacterial activities of the extract against *E. faecalis* were lower than the gold standard of 2% chlorhexidine. Some extracts active against *E. faecalis* have been reported in previous data[31]. On the other hand, antibacterial activity against *S. mutans* was only present in *n*-hexane and ethyl acetate extracts at 4 and 5%, but this data is important because the inhibition value of n-hexane at 5% of 9.4 mm was the nearest to10.9 mm at 2% chlorhexidine which is the gold standard. On the other hand, some extracts active against *E. faecalis* have been reported in previous data[31].

The prediction values of the antibacterial activities of single and combination extracts were then evaluated against all bacteria. Using the same assays, sample formulations were used to determine the synergistic effects of the extracts. As shown in Table 3, the antibacterial activity of the combination extracts described that only two combination extracts of M+Hex and n-Hex-Ea were active; this suggested that active constituents of extracts had antagonistic effects which each other while tire when combined. This data is supported by published reports; previous researchers have reported some extracts to have synergistic and antagonistic effects[32]. The observed data can be used as important information and a guide to further determine the most appropriate separation and purification methods to isolate the active compounds from the extracts.

As the main aim of this study was to discover a new antibacterial agent to complement or substitute antibacterial drugs, the effect combinations between extracts and references compounds against their antibacterial activity were also evaluated. In this study, chlorhexidine, fosfomycine and quercetin were used as reference compounds. Chlorhexidine has substantivity for a period of 10-12 h as well as long lasting antibacterial activity with a broad spectrum of action[34]. Fosfomycin is a bactericidal with putative activity against several bacteria, including multidrug-resistant gram-negative bacteria and it works by irreversibly inhibiting an early stage in cell wall synthesis[34]. Quercetin is a polyphenolic flavonoid with potential chemoprotective properties and recent studies have shown the effectiveness of quercetin as an antibacterial agent on selected organisms[35].

The results of antibacterial activity are tabulated in Table 4. Only four combination extracts of M+F, Hex+Chx, Ea+F and H_2O+F actively inhibited the growth of all bacteria including *E. faecalis*, *S. mutans* and *S. sanguinis* with different inhibition zone values, while four combination extracts of M+Chx, Hex+Chx, Ea+Chx, H_2O+Chx were active only against *E. faecalis*. Conversely, four other combination extracts were inactive.

As shown in Table 4, extract addition into reference compounds has various effects on their antibacterial activity; different combinations resulted in varying increases in antibacterial activity against different bacteria. The highest antibacterial activity against *E. faecalis*, *S. mutans* and *S. sanguinis* were found in the combinations of Hex+F,H_2O+F, H_2O+F with inhibition values of 23.3, 31.85 and 31.85, respectively. This fact suggested that the bioactive constituents in n-hexane and H_2O extract together with fosfomycine were significantly synergistic combined to increase their activity to inhibit bacterial growth of *E. faecalis*,

S. mutans and *S. sanguini*. Other important data showed that the extracts of M+F and Ea+f also had similarly high activity against *S. mutans* and *S. sanguinis* of 30.85 and 31.2 mm, respectively. Both extracts were less active against *E. faecalis* which suggested that the extract contained active constituents with the ability to treat bacteria *S. mutans* and *S. sanguinis* but not *E. faecalis.* Since the antibiotic fosfomycine was known as the inhibitor enzyme MurA, it was suggested that the Hex+F,H_2O+F, H_2O+F and M+F extracts were active as antibacterial agents by inhibiting the formation of bacterial cell walls of *E. faecalis* and *S. mutans.* Then, the increase in the highest antibacterial activity against *E. faecalis* by the addition of M+F extracts presented the possibility of inhibiting formation bacterial cell wall of *E. faecalis*, similar to fosfomycine[36]. Despite the lack of thorough research into the underlying mechanisms supporting the antibacterial activity of extracts, previous research has suggested that different compounds target components of bacterial cells differently[36]. Based on the data in this study, the results showed that the edible plant of Kemangi (*Ocimum basilicum* L.) has potential as an antibacterial agent. The different activity values of single and combination extracts together with the additional effect of reference antibacterial drugs have provided important biomarkers as antibacterial constituents according to oral bacteria species. The structure and identity of antibacterial lead compounds in active extracts could be determined in single or pure compounds by using the guidance of combination phytochemical screening and antibacterial activity data. The data obtained further supports a previous study stating that important antibacterial compounds are derived from secondary metabolites[37].

CONCLUSION

The edible plant of Kemangi (*Ocimum basilicum* L.) has shown *in vitro* activity as an antibacterial agent against the pathogenic oral bacteria of *E. faecalis* ATCC 29212, *S. mutans* ATCC 25175 and *S. sanguinis* ATCC 10556. This discovery is an important finding that can be utilized in further *in vivo* clinical studies to determine the exact dosages and its effectiveness in practical and clinical applications. Since the plant is consumed daily, toxicity studies should be conducted to determine the safety profile of the plant. Apart from that, future work is required to isolate and characterize the structures of lead antibacterial compounds that play an important role in inhibiting or eliminating bacteria. The discovery a new antibacterial agent from an edible plant may lead to the possibility of finding new antibacterial compounds with clinical effectiveness against dental caries and other bacterial oral pathogens.

SIGNIFICANCE STATEMENT

This study discovers the possible synergistic effect interactions between extracts of Kemangi (*O. basilicum*) and gold standard of chlorhexidine that can be beneficial for antibacterial formulation against oral bacteria such as *E. faecalis*, *S. mutans* and *S. sanguinis*. This study will help the researcher to find good formulation dose for *in vivo* and clinical studies. Thus, a new theory of structure activity relationship (SAR) of bioactive constituents in Kemangi (*O. basilicum*) may be suggested.

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