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Halal Formulation of Antimicrobial Cream Containing *Melicope ptelefolia* Leaves Extract

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Abstract

Halal pharmaceuticals refer to drugs that are formulated with acceptable ingredients consistent with Islamic principles and conditions. In the pharmaceutical industry, the standard of halal pharmaceuticals is the crucial document that should be followed to standardize the quality and the safety of the products. *Melicope ptelefolia (M. ptelefolia)*, known as tenggek burung was claimed to have many health benefits, including antioxidant, anti-inflammatory and antimicrobial properties. This study aims to formulate halal cream containing *M. ptelefolia* extract. All the ingredients used were evaluated for their halal and safety status based on four supporting documents: Halal Certificate, Certificate of Analysis (CoA), International Nomenclature of Cosmetic Ingredients (INCI) and Material Safety Data Sheet (MSDS). The leaves of *M. ptelefolia* was extracted using methanol solvent and diluted into four different concentrations, 25% w/v, 50% w/v, 75% w/v, and 100% w/v. The extractwas then tested for *S. aureus* and *P. aeruginosa* antimicrobial screening using disk diffusion method. Based on the antimicrobial screening, four types of creams were formulated namely MP0, MP2, MP4 and MP6. It was then evaluated by its color, homogeneity, appearance, phase separation, effect on pH and temperature. The cream formulation was then evaluated for its antimicrobial activities against *S. aureus*. All the *M. ptelefolia* extract concentration demonstrates antimicrobial properties against *S. Aureus* but not *P. aeruginosa*.*M. ptelefolia* extract was then incorporated into the cream formulation with different concentration. Based on the evaluation, all the cream formulations are stable at various temperatures. The results showed that MP6 and storage temperature at 25°C has the highest inhibition zone. In conclusion, stable halal formulation of *M. ptelefolia* as antimicrobial cream was successfully formulated for treatment against *S. aureus*.

Keywords: Halal, *Melicope ptelefolia*, *Staphylococcus aureus,* Antimicrobial cream

Introduction

Halal is an Arabic word that implies "lawful," "permissible" under Islamic law, and it is frequently used in the context of Islamic consumption (Wilson, 2014). Consuming halal items was highlighted in numerous articles of the Qur'an and other sources of Islamic doctrine. Regardless of their geographic or cultural variety, muslims will always adhere to their principles and the Islamic religion. Whenever the concept of halal is mentioned, the concept of Tayyib is expressly mentioned as well. Tayyib means clean, pure, and in accordance with Shari'ah (Alzeer *et al.,* 2020). The Malaysian Standard was created by the National Industrial Standardization Committee and approved by the Department of Standardization Malaysia (DSM) (Azam *et al.,* 2021) are the guidelines that are compulsory to be follow by the manufacturers and distributers in order promote or sell their products in the market.

Pharmaceutical products are rarely halal-certified, especially medicines. As a result, the halal status of certain products remains unknown. Pharmaceutical products

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are made up of active substances and excipients (Aziz *et al.,* 2014). Both the active substance and the excipients must be halal. There must be no non-halal materials used in the manufacturing process (Khan *et al.,* 2013). A pharmaceutical product containing alcohol would be considered halal if there were no adequate alternatives. If any medicine does not have a label and the illness is critical, it can only be used if there are no other options (Halim *et al.,* 2014).

Melicope ptelefolia(*M. ptelefolia*) is a member of the Rutaceae family, and locally known as 'tenggekburung', 'pepauh', 'medangbeberas', 'tapakitik' and 'cabangtiga'. Additionally, *M. ptelefolia* leaves have grown in favor as a traditional fresh vegetable among Malaysians over the years (Abbas*et al.,* 2009). *M. ptelefolia* leaf extract claimed to possess anti-inflammatory, antipyretic, analgesic, antioxidant, and antibacterial effects (Mahadi *et al.,* 2016). 2,4,6-trihydroxy-3geranylacetophenone (tHGA) are the compounds reported to show anti-inflammatory activity (Kabir *et al.,* 2017). Meanwhile, melicolones A and B, isolated from the leaves of *M. ptelefolia*, have been shown to prevent glucose-induced oxidative damage in HUVEC cells (Kabir *et al.,* 2017). Other chemical constituents found in *M. ptelefolia* include p-O-geranylcoumaric acid, various polyprenylated acetophenones and benzylisoquinoline alkaloids (Shaari *et al.,* 2006; Shaari *et al.,* 2011). These secondary metabolites offer the potential of *M. ptelefolia*as an anti-microbial agent, hence this study was conducted to evaluate the effectiveness of *M. ptelefolia* extract incorporated into halal cream formulation against selective bacterial; *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa.*

Materials and Methods

Source of *Melicope ptelefolia*

The matured leaves of *M. ptelefolia* was chosen in this study. 1kg of matured leaves of *M. ptelefolia* were collected from the Institute of Bioscience, University Putra Malaysia (UPM), Serdang. The authentication of the plant was carried out by a qualified botanist from the faculty of Forestry, UPM where the vouchers (KM 0035/22) were obtained.

Identification of halal critical ingredient

Stearic acid has been identified to be the critical ingredient in formulation. Stearic acid was bought from Take It GlobalSdnBhd is halal certified by Jabatan Hal Ehwal Agama Islam Pulau Pinang that is recognized by JAKIM.Other ingredientfor cream formulation was checked via several documentsinclude Certificate of Analysis (CoA), International Nomenclature of Cosmetic Ingredients (INCI) and Material Safety Data Sheet (MSDS) to ensure the safety and the sources of ingredients was plant based.

Melicope ptelefolia methanolic extract

The extraction method was modified from Johari*et al.,* (2011). 1kg of freshly collected matured leaves of *M. ptelefolia* were cleaned, weighed and oven-dried for 48 hours at 40°C. The dried leaves were blended into a fine powder using an electrical blender. 50 g powder was extracted with 250 ml of methanol in five separate batches where the ratio of solvent to sample is 5:1. The macerated mixture was allowed to stand for 24 hours to ensure that all solvent and sample were completely homogenized. The macerated mixture was then filtered, concentrated and evaporated using a rotary evaporator under controlled temperature and reduced pressure. The resultant extract was then stored in a refrigerator at -20°C prior to use. Percentage yield of the extract was calculated in this study by using formula as below:

$$\text{Extraction yield (\%)} = \frac{\text{Mass of extract (g)}}{\text{Mass of dry matter (g)}} \text{ x } 100\%$$

Preparation of different concentration of *M. ptelefolia* extract

Four different concentrations of extract 25% v/v, 50% v/v, 75% v/v and 100% v/v were prepared from the concentration

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liquid extract for antimicrobial screening. Sterile distilled water was used as a solvent (Dahlan *et al.,* 2015). 6 mm filter paper discs were then impregnated with the various concentration of *M. ptelefolia*.

Antimicrobial screening of *M. ptelefolia* extract

Methanolic extract of *M.ptelefolia* leaves were evaluated for antimicrobial activity against *Staphylococcus aureus* (*S. aureus*) (ATCC 25923) and *Pseudomonas aeruginosa* (*P. aeruginosa*) (ATCC 9027) using disc diffusion method of various concentrations. Kirby-Bauer Disc Diffusion method was used as the antimicrobial testing protocol (Nassar *et al.,* 2019). *S. aureus and P. aeruginosa* inoculums were prepared using normal saline. 0.5 McFarland standard was used to ensure the number of bacteria in a suspension isequivalent.A 100 µl of inoculum suspension was withdrawn and transferred to the MH agar using the spreading plate technique. The impregnated disc was then appliedon the agar surface. The agar plate was then stored in an incubator of 37°C for 24 hours. The diameter of zones of inhibition was measured after 24 hours. Sterile distilled water was used as control negative, meanwhile gentamicin disk 10 µg used as control positive.

Physical evaluations of halal formulation of cream

The halal formulation of oil-in-water (o/w) emulsion-based cream was modified from Gidwani *et al.* (2010). Table 1 shows the halal cream formulation used.From the antimicrobial screening results, the extract concentration that gives the highest zone of inhibition will be chosen to formulate 60 g of cream with different *M. ptelefolia* extract weight. 2 g, 4 g and 6 g of *M. ptelefolia*extract was incorporated into the halal cream. The successfully cream formulated was then transferred into plastic container and labeled. Halal formulation of *M. ptelefolia* cream was

Table 1: Halal cream formulation of *M. ptelefolia*

	Cream with 2 g of *M. ptelefolia* extract (MP2)	Cream with 4 g of *M. ptelefolia* extract (MP4)	Cream with 6 g of *M. ptelefolia* extract (MP6)	Cream without *M. Ptelefolia* extract (MP0)
Components	Amount (g)			
Oily phase:				
Stearic acid	1.50	1.50	1.50	1.50
White beewax	0.90	0.90	0.90	0.90
Stearyl alcohol	3.00	3.00	3.00	3.00
Cetyl alcohol	3.90	3.90	3.90	3.90
Mineral oil	3.00	3.00	3.00	3.00
Aqueous phase:				
Propylene glycol	3.00	3.00	3.00	3.00
Triethanolamine	1.20	1.20	1.20	1.20
Methyl paraben	0.01	0.01	0.01	0.01
Propyl paraben	0.03	0.03	0.03	0.03
M. ptelefolia extract	2.00	4.00	6.00	0.00
Water	41.46	39.46	37.46	43.46
Total	60.00	60.00	60.00	60.00

Halal Formulation of Antimicrobial Cream

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inspected visually for its color, homogeneity, consistency and phase separation (Viswanad *et al.,* 2012).

pH test

Digital pH meter was used to determine the pH of various formulations of the cream. The pH meter was calibrated using standard buffer solution with pH 7 and pH 4.01. 0.5 g of o/w cream was weighed and dissolved in 50 ml of distilled water to obtain an even distribution of cream in the solution. pH measurement of various formulation of halal creams were carried out in triplicate and the average reading was recorded.

Effect of temperature on halal formulation of cream

Halal formulation of *M. ptelefolia* cream was stored in three different temperatures which were 4°C, 25°C and 37°C for one month period. Parameters such as physical characteristics, pH and antimicrobial activity were re-evaluated.

Antimicrobial screening of halal formulation of cream

Halal formulation of *M. ptelefolia* cream were screened for its antimicrobial activity against *S. aureus* by using agar disc diffusion method. 2g, 4g, 6g and blank cream was impregnated with the disc. The antimicrobial activity was evaluated by measuring diameter of "zone of inhibition". *M. ptelefolia* cream were not tested on *P. aeruginosa* as it did not show any antimicrobial activity in antimicrobial screening of *M. ptelefolia* extract.

Statistical analysis

Statistical analysis was performed by using the IBM Statistical Package for the Social Sciences (SPSS) Version 28. One-way ANOVA followed by post-hoc, Tukey's test was conducted to determined significance between groups. p value less than 0.05 was accepted as significant.

Results and Discussion

Preparation of *M. ptelefolia* extract

The percentage of *M.ptelefolia* yield extract is 16% as shown in Table 2. Study reported by Kadum et al., (2019), claimed that 16% of percentage yield is considered as a good average yield for many plants extract, however the optimal yield can vary depending on factors such as the plant species, the extraction method, and the intended use of the extract.Methanol was claimed to show a good solvent for plant extraction (Alo *et al.,* 2012). Plants that contain compounds of antimicrobial properties are reported to be soluble in methanol (Naz *et al.,* 2020). Hence, this study uses methanol as a solvent which in line with previous study reportedthat methanolic extract was very potent and has the strongest antimicrobial activity when compared to ethanol and ethyl acetate(Chauhan *et al.,* 2010).Study conducted by Borges *et al.,* 2020 mentioned that 80% methanol gave the highest extract yield during extraction due to solubility of active ingredients, which have polar character.

Evaluation of antimicrobial activities of *M. ptelefolia* methanolic extract

The concentration liquid of methanolic extract of *M. ptelefolia* was prepared and tested at four different concentrations which is 25% v/v, 50% v/v, 75% v/v and 100% v/v against gram-positive bacteria, *S. aureus* and gram-negative bacteria, *P. aeruginosa*. The

Table 2: Percentage yield of methanolic *M. ptelefolia* extract

Sample	Weight of dry plant before extract (g)	Weight of dry extract after solvents have been remove (g)	Percentage Yield (%)
M.ptelefolia	250.00	40.00	16.00

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different concentration of *M. ptelefolia* was proved to show antimicrobial activity as shown in Table 3.

From the study, all *M. ptelefolia* methanolic extract displayed antimicrobial activity against gram-positive *S. aureus* as shown in Table 3. *M. ptelefolia* 25% v/v has the lowest zone of inhibition (9.39 ± 0.43 mm) while *M. ptelefolia* 100% v/v has the highest zone of inhibition (14.18 ± 0.38 mm) for the extract. However, the positive control showed the highest zone of inhibition with 23.20 ± 0.52 mm compared to all group. According to Zainuddin *et al.,* (2010), the higher concentrations of the extract, the larger amounts of metabolite present andthismay lead to a greater potential in inhibiting the growth of the bacteria. In contrast, the lower concentration of plant extract maycontainless active metabolite hence lower the ability to inhibit the growth of microorganisms.Liu *et al*., (2012) reported that *Melicope patulinervia*, a difference species of *Melicope* originated from China, that belong to samefamily, Rutaceaefound to have phenol and flavonoid in the extract. Moreover, it also possessesanti-oxidant and antimicrobial activities against differences fungi species which include *Penicillium.sp, Oxytetracycline hydrochloride, Fusarium graminearum, Botrytis cinerea, Northern Leaf Blight of Corn, Lecannostictaacicula* and *Rhizoctonia solani.* Flavonoids have been reported to possess the antimicrobial activity against gram-positive bacteria, *S. aureus* and *S. epidermidis*via inhibiting nucleic acid synthesis, block the fatty acid synthesis, and inhibit peptidoglycan synthesis (Yuan *et al.,* 2022; Fialová *et al.,* 2021). Phenolic compounds are a type of molecule that contain one or more phenol units, predominantly derived from plants, although they can also be sourced from bacteria, fungi, and marine organisms. Research has indicated that phenolic and polyphenolic substances possess antimicrobial effects against a broad spectrum of microorganisms including methicillin-resistant *S. aureus* (MRSA) (Ecevit *et al*., 2022). In line with the previous study, the inhibition of *S. aureus*in *M. ptelefolia* methanolic extractmay be due to the present of flavonoid and phenol.

Study conducted by Eliaser *et al*., (2018) led to the discovery of two types of quinoline alkaloids – buchapine and 3-(3-methyl-2-butenyl)-4-[(3-methyl-2-butenyl)oxy]-2(1H)-quinolinone – as well as three furoquinoline alkaloids, known as roxiamines A, B, and C, fromflowers, leaves, and twigs of Melicopelunu-ankenda originated from Malaysia. The study revealed that quinoline alkaloids possess anti-viral activity against human immunodeficiency virus. Consistent with the previous study, Fialová *et al*., (2021) claimed that alkaloids present in the plants produce antimicrobial

Table 3: Zone of inhibition exhibited by various concentration of *M. ptelefolia* against *S. aureus* and *P. aeruginosa*

Concentration (% v/v)	Zone of inhibition ± SD (mm)	
	S. aureus	*P. aeruginosa*
Normal Saline	0 ± 0.00[a]	0 ± 0.00
M. ptelefolia 25	9.39 ± 0.43[b]	0 ± 0.00
M. ptelefolia 50	10.62 ± 0.42[b]	0 ± 0.00
M. ptelefolia 75	13.44 ± 0.45	0 ± 0.00
M. ptelefolia 100	14.18 ± 0.38	0 ± 0.00
Gentamicin 10µg	23.20 ± 0.52[a]	14.65 ± 0.19[a]

Note: ANOVA test with post hoc Tukey's test (P < 0.05) where:[a]Statistically significant when compared with all group at p<0.05; [b] Statistically significant when compared with *M. ptelefolia* 100 at p<0.05

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activity against skin pathogens including *S. aureus*. In this study, no zone of inhibition was observed in gram-negative bacteria, *P. aeruginosa*. Similarly, study conducted by Dahlan *et al*. (2015) claimed that methanolic extract of *M. ptelefolia* has no antimicrobial properties against *P. aeruginosa*. This may be due to the different composition or morphology of the cell wall between gram-positive and gram-negative bacteria. The protective and unique feature that distinguishes gram-negative bacteria and gram-positive is the outer membrane. This outer membrane is the main reason for the resistance because of its hydrophobic properties (Breijyeh *et al*., 2020).

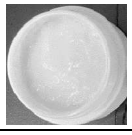
Halal cream formulation and preparation

Halal cream formulation was prepared by incorporating different volume of 100% v/v *M. ptelefolia* extract as an active ingredient. In this study, oil in water (o/w) cream were chosen to be incorporated with *M. ptelefolia* extract. According to Dahlan *et al.* (2015), o/w cream has the ability to release the flavonoids compound of the plant extract which is the constituent of the active compound in *M. ptelefolia*. Another study reported that o/w creams showed the highest ability to release active compounds such as flavonoids compared to other creams such as lipophilic or amphiphilic cream (Sawant *et al.,* 2021). The cream formulated is miscible in with water and skin secretion due to its hydrophilic properties and this results in effective interaction with skin and penetrates more readily through the membrane because of emulsified nature of the skin surface. When the cream is miscible with water and skin secretion, they are easy to be removed from the skin (Bernatoniene *et al.,* 2011).

Physical evaluation

Halal formulation of *M. ptelefolia* cream were characteristically dark greenish in color. Based on this study, the color of the cream increased in intensity as the volume of the *M. ptelefolia* extract increased. Table 4 shows the evaluation of color, homogeneity, appearance and phase separation.From the result, all the halal cream formulation showed

Table 4: Physical evaluation of halal formulation *M. ptelefolia* creams

Formulation	Color	Homogeneity	Appearance	Phase Separation
MP0	White 	Homogenous	Smooth, opaque, greasy on application	No
MP2	Olive green 	Homogenous	Smooth, opaque, greasy on application	No
MP4	Dark olive green 	Homogenous	Smooth, opaque, greasy on application	No
MP6	Dark moss green 	Homogenous	Smooth, opaque, greasy on application	No

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are homogenous cream and no phase separation. The halal cream has the appearance of smooth, opaque and greasy on application for all the formulation. The formulations also are easily removed from the skin when washedwith water. Cream formulation that is not stable will cause the breakdown of the emulsion. The ideal cream should have emollient properties and a smooth texture (Sawant *et al.,* 2021). Another study has shown that cream that is stable are homogenous, almost constant in pH, emollient and easily removed after application (Sharma *et al.,* 2013). Due to emulsified nature of skin surface, drugs formulated as cream are more effectively interact with skin. It is also more readily penetrated through biological membranes (Handali *et al.,* 2011).

Effect on pH and temperature

Halal formulation cream of *M. ptelefolia* were stored at the different storage temperature conditions which is 4°C, 25°C and 37°C for a month. All the cream formulation evaluation of color, homogeneity, appearance and phase separation does not change after a month. This indicates the formulation is stable. Cream that is stable in various temperature conditions will exhibit longer shelf-life. Table 5 and Table 6 show the effect of temperature, pH and zone of inhibition in different temperatures. Based on the study, almost all pH of the formulations increases when the *M. ptelefolia* were added to the bases as the nature of the extract is acidic. pH value after one month for MP2 and MP4 at 37°C is lower than the freshly prepared cream compared to others that increase in pH (Table 7). However, the pH of the skin normally ranges from 4 to 7 (Saptarini *et al.,* 2020). The pH value of the cream ranges from 5.32 to 7.08 was almost similar to the skin's normal pH. Too-alkaline pH preparations will cause scaly skin, whereas too acid pH will cause skin irritation (Viswanad, 2012). This value was acceptable as the pH of the cream will not interfere with normal skin physiology. Studies by Pakzad *et al.,* (2022) stated that there was a slight variation in the pH when the cream stored in different temperature and the rate of

Table 5: pH value of halal formulation *M. ptelefolia* creams after a month of different storage condition

Formulation	pH of freshly prepared cream	pH (mean ± SD)		
		4°C	25°C	37°C
MP0	6.84 ± 0.01	6.91 ± 0.02	7.08 ± 0.03	7.02 ± 0.01
MP2	5.78 ± 0.02	6.57 ± 0.04	5.94 ± 0.01	5.76 ± 0.12
MP4	5.32 ± 0.01	5.73 ± 0.01	5.57 ± 0.13	5.41 ± 0.10
MP6	5.30 ± 0.02	5.57 ± 0.01	5.40 ± 0.01	5.23 ± 0.04

Table 6: Zone of inhibition of halal formulation of *M. ptelefolia* cream *against S. aureus* after a month of different storage condition

Formulation	Inhibition of freshly prepared cream (mm)	Zone of inhibition ± SD (mm)		
		4°C	25°C	37°C
MP0	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00
MP2	6.59 ± 0.08	6.64 ± 0.07	7.57 ± 0.12	7.23 ± 0.12
MP4	7.30 ± 0.36	8.25 ± 0.09	8.33 ± 0.13	8.19 ± 0.10
MP6	8.83 ± 0.33	8.76 ± 0.21	9.21 ± 0.08	9.10 ± 0.04

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Table 7: Zone of inhibition of halal formulation of *M. ptelefolia* cream and control	
Formulation	Zone of Inhibition ± SD (mm)
Negative control	0 ± 0.00
MP2	6.59 ± 0.08
MP4	7.30 ± 0.36
MP6	8.83 ± 0.33
Positive control	24.12 ± 1.77[a]
Note: ANOVA test with post hoc Tukey's test (P < 0.05) where:[a]Statistically significant when compared with all group at p<0.05	

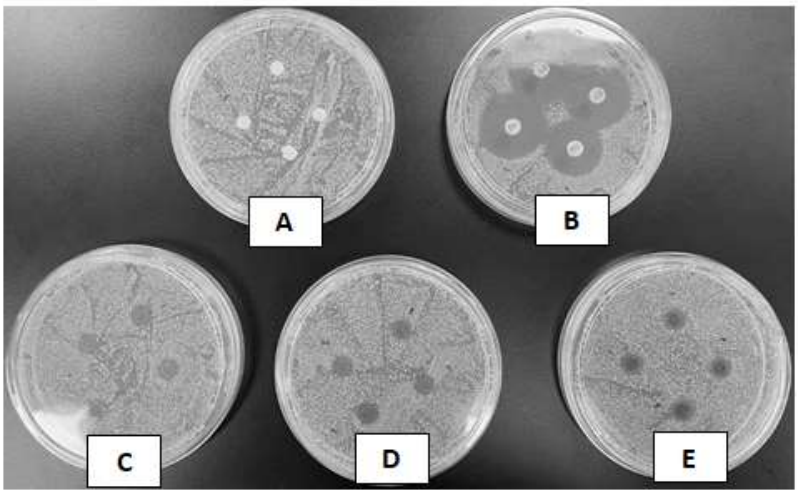

Figure 1: Inhibition zone of *M. ptelefolia* cream against *S. aureus A) MP0 B) Positive control C) MP2 D) MP4 E) MP6*

degradation of cream depends upon two parameters pH and temperature.All types of cream in three conditions showan increasing trend of inhibition. This study found that the halal formulation still exhibits antimicrobial properties after being stored for one monthin three different conditions. This indicates that the halal cream was stable. In comparison between those three conditions, it appears that the best temperature to store cream was in the 25°C condition. This because storage condition of 25°C has the highest zone of inhibition when compared to other storage condition which is 4°C and 37°C. Similar with the pH, study has documented the rate of degradation of cream depends on the temperature (Pakzad *et al.,* 2020). The reduction of antimicrobial activity of natural products by heating may be due to volatilization or the chemical or physical changes that occur during heating (Durairaj *et al.,* 2009).

Evaluation of antimicrobial activity of halal formulation of *M. ptelefolia* cream

Three different formulation of halal *M. ptelefolia* cream were prepared with 2g, 4g and 6g of the 100% v/v extract. The cream was tested on *S. aureus* by using agar disc diffusion method. The zone of inhibition is shown in Table 5. Figure 1 shows the inhibition zone of *M. ptelefolia* cream against *S. aureus.* Based on the studies, all the halal formulation cream containing different

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amount of 100% v/v extract *of M. ptelefolia* shows antimicrobial activity against *S. aureus*. MP6 has the highest inhibition zone compared to others. On the other hand, MP2 that containsthe lowest amount of extract has the lowest inhibition. This result is consistent with earlier antimicrobial test of the extract whereby the higher the amount of extract, the higher the active metabolite that leads to higher inhibition growth of bacteria. According to Dahlan *et al.,* (2015), different amount of *M. ptelefolia* was incorporate into semisolid dosage form or gel formand display edits antimicrobial activity. This show that *M. ptelefolia* extract is a promising source of active ingredient to be added and use for the treatment of infection caused by *S. aureus*.

Conclusion

Methanolic extract of *M. ptelefolia* leaves has shown good antimicrobial activity against *S. aureus*. Concentration of extract plays animportant role in antimicrobial activity. The higher the concentration of extract, the higher the antimicrobial activity. Halal formulation *M. ptelefolia* cream show the similar antimicrobial activity against *S. aureus* as in the extract. Hence, *M. ptelefolia* is a potential active ingredient to be cooperated into pharmaceutical product such as gel or cream and can be used as alternative to treat infection. Further study such as *in-vivo* could be more interesting to conduct to identify the effectiveness of the cream produce.

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