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DETECTION AND DETERMINATION OF ANTIBACTERIAL ACTIVITY OF CYMBOPOGON NARDUS (CITRONELLA) ETHANOLIC EXTRACT AGAINST ESCHERICHIA COLI AND STAPHYLOCOCCUS AUREUS

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ABSTRACT

Finding alternative treatments for bacterial infections due to the increase of antibiotic resistance is currently a major global challenge and discovery of phytochemicals with antibacterial potential is highly relevant. Cymbopogon nardus (Citronella) plant species has evidenced of having antibacterial property from previous research studies. This study was aimed to assess the antibacterial activity of phytochemical compounds of C. nardus ethanolic extract against Escherichia coli (ATCC 25922) and Staphylococcus aureus (ATCC 25923) bacterial strains. Antibacterial activity was assessed using in vitro antibacterial tests. Antibiotic susceptibility test (ABST) was the qualitative test conducted to determine zones of inhibition against bacterial species at 50 and 100 mg/ml concentrations. Highest zone diameters were exhibited against S. aureus as 15.67±0.58 mm and 16.67±0.58 mm respectively. Inhibition diameters detected against E. coli were 15.00±0.00 mm and 15.33 ±1.15 mm respectively. Antibacterial activity expressed by C. nardus was significantly different between bacterial species. Broth dilution method was conducted as quantitative antibacterial tests to detect Minimum Inhibitory Concentrations (MIC). Lowest concentration of C. nardus with bacteriostatic potential against S. aureus was detected as 12.50 mg/ml and against E. coli was detected as 25 mg/ml. Minimum Bactericidal Concentrations (MBC) for S. aureus and E. coli were detected as 50 and 100 mg/ml respectively. The data from present study confirmed the presence of antibacterial compounds and the promising aspect of C. nardus. The discovered therapeutic potential of C. nardus as an antibacterial agent against E. coli and S. aureus needs to be fully evaluated using further studies.

Keywords: Cymbopogon nardus (Citronella), Antibacterial activity, Antibiotic susceptibility test, bacteriostatic, Bactericidal

INTRODUCTION

Background

Antibacterial activity is killing or inhibiting the growth of bacteria without harming nearby tissues (Singh et al., 2019;Ventola, 2015). Antibiotics are drugs used for achieving this purpose. But due to the extensive use and misuse of antibiotics, bacteria can change their response to certain antibiotics. As a result, bacteria develop resistance against those antibiotics, which is posing a major global health care problem currently (Elisha et al., 2017; Ventola, 2015). Medicinal plants have been used in folk medicine to treat bacterial diseases (Cheesman et al., 2017). Therefore, some studies have been conducted to discover novel compounds with antibacterial properties from plant species as an alternative approach in the

wake of increasing antibiotic resistance. Treatments with medicinal plants have shown that they are less expensive with fewer side effects. Secondary metabolites of plants, such as tannins, alkaloids, flavonoids, lactones, terpenoids, steroids, glycoside, coumarins and quinones are identified as substances with antimicrobial potential (Abadallah and Ali, 2019; Cheesman et al., 2017; Elisha et al., 2017). However, medicinal plants could be more suited to treat non-severe infections because of the relatively weak defense activity and non-specificity(Cheesman et al., 2017).

Escherichia coli and Staphylococcus aureus bacterial species.

Escherichia coli and Staphylococcus aureus are bacterial species of human normal flora (Bajaj, Singh and Virdi, 2016; Sannasiddappa et al., 2011). E. coli is gram-negative, rod-shaped bacterium located in human gastrointestinal tract (Tanih et al., 2015). Certain serotypes can cause infectious diseases including urinary tract infections, diarrheal diseases, septicemia, meningitis and pneumonia (Peirano et al., 2018; Lee, Lee and Choe, 2018; Fratamico et al., 2016; Kim, 2016; Jafri et al., 2014). β-lactams, fluoroquinolones and trimethoprim-sulfamethoxazole are the antibiotics used for E. coli infections. β-lactams, such as ampicillin, amoxicillin and cephalosporin bind with penicillin binding protein (PBP) to lead the inhibition of peptidoglycan cell wall synthesis (Stohr et al., 2020; Alanazi, Alqahtani and Aleanizy, 2018; Kapoor, Saigal and Elongavan, 2017; Vranic, and Uzunovic, A, 2016; Park et al., 2012). However, E. coli build up the ability to hydrolyze β-lactam ring with the production of β-lactamase enzyme (Zeng and Lin, 2013). Fluoroquinolones primarily targets enzyme DNA gyrase in E. coli which catalyzes DNA negative supercoiling (Terahara and Nishiura, 2019; Kapoor, Saigal and Elongavan, 2017). The increase in resistance is due to the development of mutations in gyrA subunit of gyrase and in addition, it induces mutation in parC subunit of topoisomerase IV, enzyme nicks and separate daughter DNA strand after the replication (Karczmarczyk et al., 2011; Stone et al., 2003). Trimethoprim-sulfamethoxazole is a combination of sulfonamide and trimethoprim involve in inhibition of distinct steps of tetrahydrofolic acid (THF) synthesis (Gangcuangco et al., 2015; Masters et al., 2003). Sulfonamide inhibits the enzyme dihydropteroate synthase (DHPS) which synthesize dihydropteroate from para-aminobenzoate (de Castro Spadari et al., 2020). Trimethoprim involves in the inhibition of the catalytic activity of dihydrofolate reductase (DHFR) and the production of THF from dihydrofolic acid (Fairhurst and Wellems, 2015; Capasso and Supuran, 2014). Resistance could be induced by overproducing DHFR and cause mutations in the target enzymes (Eliopoulos and Huovinen, 2001). In addition, drug efflux pump in E. coli contribute to the enhance of resistance (Soto, 2013; Webber and Piddock, 2003).

Staphylococcus aureus is gram-positive, opportunistic bacteria generally located in human nose and pharynx (Kuraitis and Williams, 2018; Brugger, Bomar and Lemon, 2016). It causes food poisoning and infections in pulmonary, endocarditis, osteoarticular, skin and soft tissues (Tong et al., 2015; Treangen et al., 2014; Parker and Prince, 2011). β-lactam penicillin was used to treat the infections. S. aureus showed the resistance to penicillin with the production of β-lactamase by showing the similar resistance mechanism of E. coli (Guo et al., 2020; Foster, 2017). Methicillin, β-lactamase resistant antibiotic was developed to reduce above resistance mechanism (Llarrull, Fisher and Mobashery, 2009). However, S. aureus developed the resistance to methicillin by encoding modified PBP by mecA gene,

known as PBP2a (Foster, 2017; Rağbetli et al., 2016; Llarrull, Fisher and Mobashery, 2009). Methicillin-resistant S. aureus (MRSA) causes nosocomial infections (Tong et al., 2015; Šiširak, Zvizdić and Hukić, 2010). Currently, methicillin has been superseded by glycopeptide antibiotic vancomycin (Schweizer et al., 2011). Novel researches have been shown the resistance development against vancomycin within S. aureus by altering cell wall biosynthesis and homeostasis (Gardete and Tomasz, 2014; Loomba, Taneja and Mishra, 2010).

Cymbopogon nardus (Citronella).

Cymbopogon nardus is perennial, aromatic, tropical plant belonging to Poaceae family. It is cultivated in tropical and subtropical regions and native to Southeast Asia, such as India, Burma, Sri Lanka, Indonesia and Java (Muttalib et al., 2018; De Toledo et al., 2016). C. nardus is categorized as a medicinal plant. It is used to cure intestinal parasite infections, digestive and menstrual problems, rheumatism and fever (Sabuna et al., 2018; Subramanian et al., 2015; Abena et al., 2008). Essential oil of C. nardus is commonly used as a repellent against Aedes aegypti and Culex quinquefasciatus (Sritabutra and Soonwera, 2013). Antimicrobial, Antibacterial, antifungal and antioxidant activities of C. nardus have been found from previous studies (Pontes et al., 2018; Kačániová et al., 2017; Subramanian et al., 2015). C. nardus is abundant with citronellal, geraniol and citronellol monoterpenes, elemol and naphthalene phytochemicals which have been recognized as antibacterial agents (Sabuna et al., 2018; Bhattamisra et al., 2018; Lopez-Romero et al., 2015). Wei and Wee (2013) has shown that essential oil of C. nardus has high potential to use as an antibacterial agent against systemic bacteria of aquatic animals. According to the study of Wibowo et al. (2018), C. nardus essential oil has antibacterial activity against both positive and negative bacteria. Pontes et al. (2018) discovered the antimicrobial activity and antibiofilm activity of C. nardus essential oil and geraniol. The research of Kamal et al. (2020) has proved the antimicrobial activity of C. nardus essential oil and its volatile compounds against oral pathogens.

According to the evidences of previous research studies, C. nardus has been shown positive results as an antibacterial agent against certain bacterial species. Therefore, ethanolic extracts of C. nardus could potentially show antibacterial activity against E. coli and S. aureus. This study is aimed to determine the antibacterial activity of ethanolic extract of C. nardus and detect its effectiveness against E. coli and S. aureus.

METHODOLOGY

Bacterial strains.

Stock cultures of bacterial strains Escherichia coli (ATCC 25922) and Staphylococcus aureus (ATCC 25923) were obtained from Medical Research Institute, Sri Lanka and subcultures were maintained in BMS laboratory under refrigeration. Fresh overnight cultures were prepared from subcultures before conducting each experiment.

Plant sample preparation.

C. nardus plant was collected from the cultivation of 'Citro' essential oil (Pvt) LTD, Katuwana, Hambanthota.

Aerial part of C. nardus was washed using mineral water, distilled water and disinfected using 70% ethanol. It was dried under the shade with exerted pressure continuously for 7 days.

Dried C. nardus sample was pulverized into fine powder by using electric spice grinder (Panasonic) and was refrigerated by storing in red cap vials.

Plant extract preparation.

About 20g of the powdered form of C. nardus sample was macerated with 50ml of 95% ethanol. Sample was placed on the roller mixer (KJMR-II) for 48hrs with constant shaking. It was filtered and filtrate was kept in the fume hood (BIOBASE, FH1000) for the ethanol evaporation. Dried extract was weighed and reconstituted to 200 mg/ml concentration using Dimethyl sulfoxide (DMSO) prior to the experimentation procedures (Abdulla et al.,2019; Abadallah and Ali, 2019; Sabuna et al., 2018).

Preparation of bacterial subcultures and diluted suspension of bacterial cultures.

Luria-Bertani (LB) broth was prepared according to the manufacturer's instructions (HiMedia). Approximately 15ml of LB broth was introduced to two 150 ml conical flasks. Three loops of the bacterial culture taken from certain stock culture were inoculated to each media and were incubated at overnight at 370C.

Diluted bacterial suspensions were prepared by inoculating bacteria taken from overnight cultures into distilled water by visually comparing the turbidity with 0.5 McFarland standard.

Antibacterial susceptibility testing using well diffusion technique.

The protocol is modified from Abadallah and Ali, 2019. Mueller Hinton agar plates were prepared, based on the manufacturer's instructions (HiMedia). Diluted bacterial suspension was inoculated onto the surface of the plates using a sterile swab stick. Four wells of 8mm diameter were bored into the media by using sterilized 1000 µl of micropipette tips. About 50 µl of 50 and 100 mg/ml concentrated reconstituted samples, Negative Control-Distilled water and positive control-1 mg/ml Gentamicin were added into four wells as shown in figure 1. Plates were incubated overnight at 37 0C. Zones of inhibition were observed and diameters were measured.

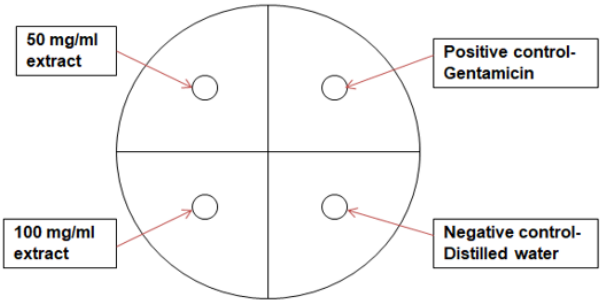

Figure 1. Layout of prepared petri dishes for the well diffusion. 50 mg/ml and 100 mg/ml concentrated ethanolic extract, Gentamicin as positive control and distilled water as negative control were introduced to the wells.

Determination of Minimum Inhibitory Concentration (MIC).

The procedure was performed according to protocols by Abdulla et al., 2019; Abadallah and Ali, 2019; Subramanian et al. 2015. Minimum Inhibitory Concentration (MIC) was determined by two-fold broth dilution method. Test tubes were labeled and 1 ml of Mueller Hinton Broth (HiMedia), prepared according to manufacturer's instructions was introduced into each tube. 100 µl of diluted bacterial suspension was inoculated into the broth (Six tubes were prepared for broth dilution test of each bacterial strain). About 1 ml of 200, 100, 50, 25, 12.50 and 6.25 mg/ml concentrated reconstituted ethanol extract was added to the tube series respectively to final concentrations of 100, 50, 25, 12.50, 6.25 and 3.125 ml. Positive controls were prepared for each bacterium by adding 250 µl of 1mg/ml gentamicin into seeded broth. Negative controls were prepared with only seeded broth. In addition, a media control was prepared containing only the broth to check sterility. Prepared tubes were incubated overnight at 37 0C.

Turbidity of each tube was observed with controls and detected the lowest concentration of extract which had shown absence of turbidity.

Determination of Minimum Bactericidal concentration (MBC).

The experiment was performed according to protocols explained by Abdulla et al., 2019; Abadallah and Ali, 2019; Subramanian et al., 2015. Tryptone soy agar (HiMedia) plates were prepared according to manufacturer's instructions. Above MIC test samples with higher concentrations than the MIC value were selected and were streaked on agar media by using quadrant streaking method. Plates were incubated overnight at 370C. The plates which had shown absence of growth of colonies or one or two colonies were selected and the respective concentrations were determined as the MBC.

Statistical analysis.

All the results of ABST were recorded and were statistically analyzed using IBM SPSS statistics version 21. The data was expressed as mean ± standard deviation. The significant differences between bacterial species and concentrations and interaction between bacterial species and concentrations were determined by using Two-way ANOVA test.

RESULTS

Results of Antibiotic Susceptibility Test (ABST).

Inhibition zones were detected from C. nardus ethanolic extract against both E. coli and S. aureus bacterial species. Following table 1 shows the zones of inhibition as mean ± standard deviation of C. nardus ethanolic extract against each bacterial species.

Table 1. Zones of inhibition of C. nardus ethanolic extract for each bacterial species.

Concentrations (mg/ml)	Zones of inhibition (mean ± standard deviation) of bacterial species (mm).	
	E. coli	*S. aureus*
50	15.00±0.00	15.67±0.58
100	15.33 ±1.15	16.67±0.58

Below figure 2 shows the plate pictures of three replicates of ABST test against each bacterial species.

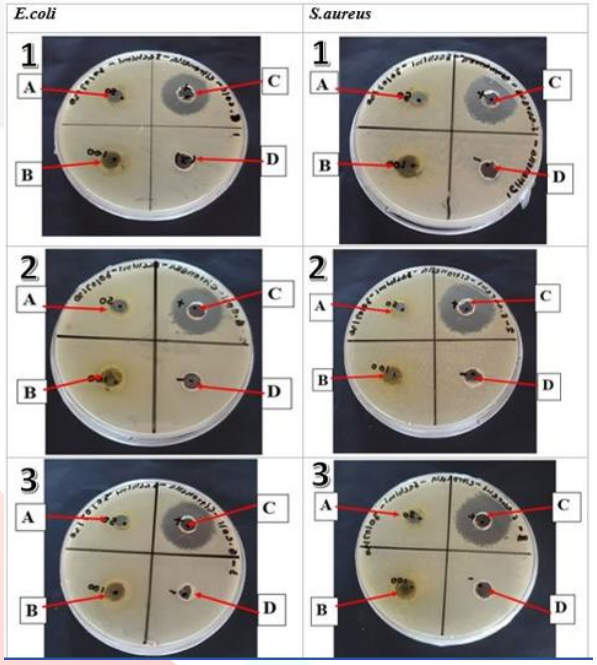

Figure 2. ABST results of three replicates of C. nardus ethanolic extract against both E. coli and S. aureus. Inhibition zones of all three replicates, conducted for E. coli and S. aureus species were presented as mean ± standard deviation. 1, 2, 3- replicate number. A-50 mg/ml, B-100 mg/ml, C-Positive control and D-Negative control. Mean value of positive controls of E. coli was 24.00± 2.00 mm and S. aureus was 26.00± 1.73 mm. Inhibition zones were absent in negative controls.

According to the graph of figure 3, mean values of inhibition zones were increased from 50-100 mg/ml concentrations. Mean values of both 50 and 100 mg/ml concentrations of S. aureus were higher than mean values of E. coli.

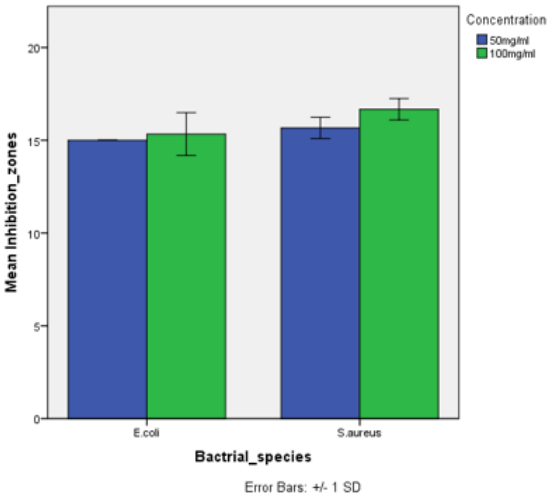

Figure 3. Antibacterial activity of C. nardus ethanol extract against E. coli and S. aureus. The blue bars indicate 50 mg/ml and the green bars indicate 100 mg/ml. The data represent mean ± SD for three replicates.

Statistical analysis of the plant extracts.

Table 2 shows the Two-way ANOVA analysis of C. nardus ethanolic extract against E. coli and S. aureus at 50 and 100 mg/ml concentrations.

Table 2. Two-way ANOVA analysis of C. nardus extract.

Dependent Variable: Inhibition zones

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	4.667[a]	3	1.556	3.111	.089
Intercept	2945.333	1	2945.333	5890.667	.000
Bactrial_species	3.000	1	3.000	6.000	.040
Concentration	1.333	1	1.333	2.667	.141
Bactrial_species* Concentration	.333	1	.333	.667	.438
Error	4.000	8	.500		
Total	2954.000	12			
Corrected Total	8.667	11			

a. R Squared = .538 (Adjusted R Squared = .365)

Profile plot of figure 4 shows the statistical significance and interaction of concentrations and bacterial strains on estimated marginal means of inhibition zones.

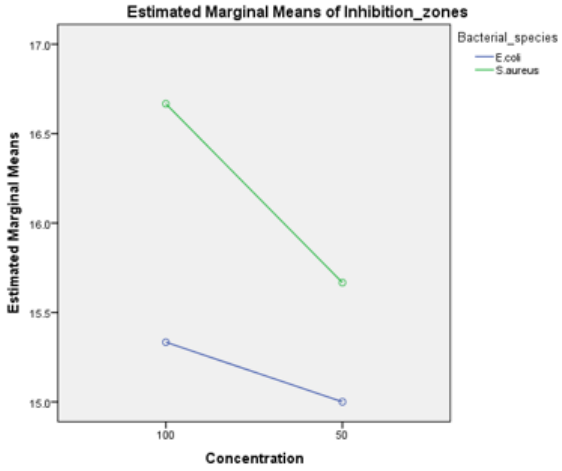

Figure 4. Profile plot of the Two-way ANOVA analysis of C. nardus.

According to the analysis, antibacterial activity of C. nardus extract showed significant difference ($P<0.05$) between bacterial species but did not show any significance between concentrations and interaction between concentrations and bacterial species. The bacterial strains used have an observable main effect in relation to the plant samples.

Results for Minimum Inhibitory Concentrations (MIC).

Minimum inhibitory concentrations (MIC) were detected C. nardus ethanolic extracts against for both E. coli and S. aureus. Following table 3 shows the MIC results of C. nardus ethanolic extract against each bacterial species.

Table 3. Detected MIC results of C. nardus ethanolic extracts against each E. coli and S. aureus species.

Bacterial species	Concentrations (mg/ml)					
	100	50	25	12.50	6.25	3.125
E. coli	-	-	-	+	+	+
S.aureus	-	-	-	-	+	+

Key - No visible growth + Visible growth

According to the results of MIC test, 25 mg/ml concentration was detected as MIC against E. coli and 12.50 mg/ml concentration was detected as the MIC against S. aureus.

Following figure 5 includes the three replicates of broth dilution test.

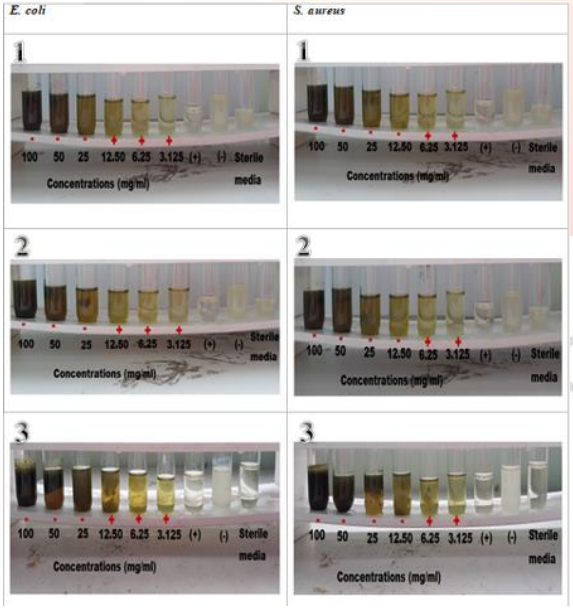

Figure 5. Results of three replicates of broth dilution test, conducted to detect MIC values against E. coli and S. aureus. MIC of C. nardus ethanolic extract against E. coli and S. aureus was detected from the 2-fold serial dilution with 100, 50, 25, 12.50, 6.25 and 3.125 mg/ml concentrations. 1, 2, and 3 represent the replicate number. (+) - Positive control and (-) – Negative control. Sterile media was used to detect media sterility. + represents the tubes with visible bacterial growth and – represents the tubes with non-visible bacterial growth. According to the replicates, 25 mg/ml concentration was detected as MIC against E. coli and 12.50 mg/ml concentration was detected as MIC against S. aureus from all three replicates.

Results for Minimum Bactericidal concentration (MBC).

MBCs of C. nardus ethanolic extract were determined against both E. coli and S. aureus species. Table 4 shows the MBC results of both E. coli and S. aureus.

Table 4. Detected MBC results of C. nardus ethanolic extract against each E. coli and S. aureus species.

Bacterial species	Concentrations			
	100	50	25	12.50
E.coli	-	+	+ (MIC)	
S. aureus	-	-	+	+ (MIC)

Key + more than two colonies – no growth of colonies or 1 or 2 colonies

According to the table 4, 100 mg/ml concentration was observed as the MBC against E. coli. The MBC against S. aureus observed as 50 mg/ml.

Figure 6 includes images of plates detected as MBC against E. coli and S. aureus.

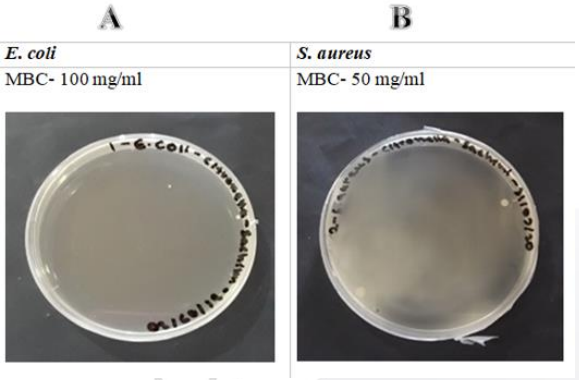

Figure 6. Plates detected MBC of C. nardus ethanolic extract against E. coli and S. aureus. A- Plate of 100 mg/ml detected as MBC against E. coli. B -Plate of 50 mg/ml detected as MBC against S. aureus

DISCUSSION

The ethanolic extract of C. nardus exhibited antibacterial property against both E. coli and S. aureus from all in vitro antibacterial tests. The results showed that S. aureus was most susceptible towards C. nardus ethanolic extracts compared to E. coli.

Inhibitory effect of C. nardus ethanolic extract determined by ABST showed distinctly higher antibacterial effect for S. aureus than E. coli. However, the inhibitory effect was not distinctly increase between 2-fold increases of concentration values. The research of Kamari et al. (2018), had found zones of inhibition as 14±0.3 mm against S. aureus and 18± 0.5 mm against E. coli for the concentration of 15µl/disk of C. nardus essential oil. Brugnera, Oliveira and Piccoli (2011) had detected 5.37± 1.16 and 8.03± 1.92 mm zones of inhibition respectively for 500 µl/ml concentration. Similar study had discovered minimum concentration of C. nardus with bacteriostatic potential (MIC) as 3.90 µl/ml and 7.81 µl/ml concentrations against E. coli and S. aureus respectively. Research of Wibowo et al. (2018) had observed 500 µg/ml concentration as MIC against E. coli, whereas MIC against S. aureus was detected as 1000 µg/ml. Additionally, the study had discovered the MIC against Methicillin-resistant S.aureus (MRSA) as 2000 µg/ml. Pontes et al. (2018) had conducted a study to observe the antibiofilm activity of C. nardus essential oil. According to the study, C. nardus had expressed 41± 0.94 mm of inhibitory activity against biofilms of S. aureus at the concentration of 18mg/ml. However, the study had not showed the inhibitory effect against the biofilms of E. coli. Furthermore the study was discovered the bacteriostatic effect of C. nardus against S. aureus biofilm at the concentration of 0.5 mg/ml and bactericidal effect at the concentration of 4 mg/ml. Bacteriostatic and bactericidal activity against biofilms of E. coli was determined as higher than 8 mg/ml. Present study proved the antibacterial activity of C.nardus ethanolic extract is relatively lower than its essential oil. Low yield of phytochemical extraction than essential oil could be the reason for lesser activity observed (Wei and Wee, 2013). In addition, composition of phytochemical compounds often differs according to the climate changes, soil composition and extraction methods (Kamal et al. 2020; De Zoysa et al., 2019; Kamari et al. 2018).

Monoterpenes (Citronellal, geraniol and citronellol) found from C. nardus show toxic effect for the structural and function of bacterial cell membrane. Monoterpenes interact with the cell membrane of bacteria due to its lipophilic character. This leads expansion of cell membrane, increase of membrane permeability and fluidity, disturbance of membrane-embedded proteins, respiratory inhibition and abnormality of ion transport process (Bouyahya et al., 2019; Trombetta et al., 2005).

Causes of showing lower susceptibility of gram-negative bacteria (E. coli) than gram-positive bacteria (S. aureus) could be inherent tolerance, structure of bacteria and how the chemical composition of plants affects above parameters. Previous studies have found outer peptidoglycan layer of gram-positive bacterial cell wall makes more permeable for phytochemicals than outer lipopolysaccharide layer of gram-negative bacterial cell wall. Due to the above reason, most of the antimicrobial substances have failed to penetrate through lipopolysaccharide layer of gram-negative bacteria. However, some have displayed the ability to penetrate by breaking the lipopolysaccharide layer (Breijyeh, Jubeh and Karaman, 2020; Koohsari et al., 2015; Brugnera, Oliveira and Piccoli, 2011).

CONCLUSION

The study revealed ethanol extract C. nardus possess effective antibacterial property against both E. coli and S. aureus strains. According to the results of this study, C. nardus contains compounds that can be used as antibacterials which serve as alternative treatments for less severe bacterial infections.

As future works, optimization of the extraction of phytochemicals could be done by altering the solvent such as aqueous, methanol, acetone, petroleum ether, benzene and chloroform with different percentages or essential oil synthesis according to the polarity difference (Abiramasundari, Devi and Jeyanthi, 2017). Identification and isolation of phytochemical could be performed by using qualitative phytochemical analysis, high-performance liquid chromatography (HPLC), gas chromatography (GC) or gas chromatography-mass spectrometry (GC-MS) (Ezeonu and Ejikeme, 2016; Subramanian et al., 2015; Chai et al., 2014). Analysis of the antibacterial activity using other in vitro studies, such as conducting MTT assay to asses bacterial cell viability after treated with the extract (Rai et al, 2018).In addition, studies to evaluate antibiofilm activity of extract could be proceeded (Aka, 2015). All the studies can also be performed for other bacterial strains and clinical isolates to verify the full antibacterial spectrum (Balouiri, Sadiki and Ibnsouda, 2016).

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