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ANTIMICROBIAL STUDIES OF BETA-CARYOPHYLLENE AND 1,8-CINEOL AGAINST GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA

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ANTIMICROBIAL STUDIES OF BETA-CARYOPHYLLENE AND 1,8-CINEOL AGAINST GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA

By

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The discovery and introduction of antibiotics to treat bacterial infections have almost successfully eradicated the threats posed by infectious bacteria. However, the misuse of antibiotics such as over-prescription of antibiotics and patient's non-compliance in completing the antibiotic course have led to the development of resistance in microorganisms due to the natural selection process. Consequently, novel antibiotics or alternatives have to be developed and discovered in order to mitigate this resistance. In this study, two compounds, beta-caryophyllene (BCP) and 1,8-cineol (CN), were first screened against several bacteria such as *Bacillus cereus*, *Escherichia coli* as well as multidrug-resistant strains *Klebsiella pneumoniae* to assess the antibacterial effects, followed by a few assays to evaluate the modes of action of the two mentioned compounds. We found that BCP and CN exhibited antibacterial effect against *B. cereus* and *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-KP) with the minimum inhibitory concentration (MIC) of 2.50 % (v/v) and 3.13 % (v/v) respectively. Time-kill analysis was performed to evaluate the killing kinetics of the compounds. Results show that BCP and CN was bactericidal against *B. cereus* and KPC-KP based on the reduction number of ≥ 3 log10 in CFU/mL. Subsequently, zeta-potential measurement, measurement of UV-absorbing materials, ethidium bromide influx/efflux assay, outer membrane permeability assay, scanning and transmission electron microscopies, oxidative stress evaluation and lipid peroxidation were performed to evaluate the modes of action of the compounds. The results obtained from various assays showed increased in membrane permeability and leakage of UV-absorbing materials (protein and nucleic acid) in BCP and CN-treated cultures, showing that both BCP and CN played a role in disrupting the bacterial membrane. Ethidium bromide influx/efflux assay showed that the influx of compounds into the bacterial cells was due to damaged membrane caused by BCP and CN. In addition, measurement of reactive oxygen species (ROS) and lipid peroxidation in CN-treated KPC-KP cells revealed that CN caused increase in ROS and malondialdehyde levels. The morphology of KPC-KP cells treated

with CN showed corrugated surfaces and irregular rod-shaped forms under scanning electron microscopic analysis, as well as cytoplasmic clear zones due to intracellular leakage and damaged membrane in transmission electron microscopic analysis. In conclusion, BCP causes increase in membrane permeability, intracellular leakage and membrane disruption. CN induced oxidative stress which leads to lipid oxidation, affecting the membrane permeability, intracellular leakage and eventually disruption in the bacterial membrane, resulting in cell death. This study investigated the mechanisms of action of BCP and CN in bacterial membrane disruptions. The findings of this study could be helpful in the future employment of BCP and CN as novel alternatives for existing antibacterial agents in the clinical setting.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

KAJIAN ANTIMIKROBIAL BETA-CARYOPHYLLENE DAN 1,8-CINEOL TERHADAP BAKTERIA GRAM-POSITIF DAN GRAM-NEGATIF

Oleh

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Penemuan dan pengenalan antibiotik untuk merawat jangkitan bakteria hampir berjaya membasmi ancaman yang ditimbulkan oleh bakteria berjangkit. Walau bagaimanapun, penyalahgunaan antibiotik seperti preskripsi antibiotik yang berlebihan dan ketidakpatuhan pesakit dalam menyelesaikan kursus antibiotik telah menyebabkan perkembangan daya tahan dalam mikroorganisma kerana proses pemilihan semula jadi. Oleh itu, antibiotik atau alternatif baru perlu dikembangkan untuk mengurangkan daya tahan ini. Dalam kajian ini, dua sebatian, beta-caryophyllene (BCP) dan 1,8-cineol (CN), dinilai terhadap beberapa bakteria seperti *Bacillus cereus*, *Escherichia coli* serta strain daya tahan terhadap pelbagai ubat *Klebsiella pneumoniae* untuk menilai kesan antibakteria, diikuti oleh beberapa ujian untuk menilai kaedah tindakan kedua sebatian tersebut. Kami mendapati bahawa BCP menunjukkan kesan antibakteria terhadap *B. cereus* sedangkan CN berkesan terhadap *K. pneumoniae* strain daya tahan pelbagai ubat penghasil karbapenemase (KPC-KP) dengan kepekatan perencatan minimum 2.50 % dan 3.13 % (v/v) masing-masing. Analisis pembunuhan masa dilakukan untuk menilai kinetik membunuh sebatian. Hasil kajian menunjukkan bahawa BCP dan CN dapat membunuh bakteria *B. cereus* dan KPC-KP berdasarkan pengurangan bilangan ≥ 3 log10 dalam CFU/mL. Selepas itu, ujian pengukuran potensi zeta, pengukuran bahan penyerap UV, pengujian influx/efflux etidium bromida, ujian kebolehtelapan membran luar, mikroskop elektron imbasan dan transmisi, penilaian tekanan oksidatif dan peroksidasi lipid dilakukan untuk menilai mod tindakan sebatian. Hasil yang diperoleh dari pelbagai pengujian menunjukkan peningkatan kebolehtelapan membran dan kebocoran bahan penyerap UV pada kultur yang dirawat dengan BCP dan CN, menunjukkan bahawa kedua BCP dan CN berperanan dalam mengganggu membran bakteria. Uji influx/efflux etidium bromida menunjukkan bahawa kemasukan sebatian ke dalam sel bakteria disebabkan oleh membran yang rosak, disebabkan oleh BCP dan CN. Selain itu, pengukuran spesies oksigen reaktif dan peroksidasi lipid pada sel KPC-KP yang dirawat dengan CN menunjukkan bahawa CN menyebabkan peningkatan kadar

spesies oksigen reaktif dan malondialdehid. Morfologi sel KPC-KP yang dirawat dengan CN menunjukkan permukaan bergelombang di bawah analisis mikroskopik elektron imbasan, manakala mikroskopik elektron transmisi menunjukkan zon jelas sitoplasma kerana kebocoran intraselular dan membran yang rosak. Secara ringkas, BCP menyebabkan peningkatan kebolehtelapan membran, kebocoran intraselular dan gangguan membran. CN menyebabkan tekanan oksidatif yang membawa kepada pengoksidaan lipid, mempengaruhi kebolehtelapan membran, kebocoran intraselular dan akhirnya gangguan pada membran bakteria, mengakibatkan kematian sel. Kajian ini meneliti mekanisme tindakan BCP dan CN dalam gangguan membran bakteria. Penemuan kajian ini dapat membantu dalam penggunaan BCP dan CN di masa depan sebagai alternatif baru agen antibakteria yang ada dalam keadaan klinikal.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

UPM	Universiti Putra Malaysia
°C	degree Celsius
MDR	Multidrug resistant
BCP	Beta-caryophyllene
BSA	Bovine serum albumin
EO	Essential oil
CN	1,8-cineol
AMR	Antimicrobial resistance
MRSA	Methicillin resistant *Staphylococcus aureus*
ESBL	Extended-spectrum β-lactamases
PBP	Penicillin binding proteins
ABC	ATP-binding cassette
MATE	Multidrug and toxic compound extrusion
MFS	Major facilitator superfamily
SMR	Small multidrug resistance family
OM	Outer membrane
MIC	Minimum inhibitory concentration
CRISPRs	Clustered regularly interspaced short palindromic repeats
SEM	Scanning electron microscopy
TEM	Transmission electron microscopy
KPC-KP	*Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae*
CLF1	3β,6β,16β-trihydroxylup-20(29)-ene
LPS	Lipopolysaccharides
MPM	Meropenem

REMA	Resazurin microplate assay
MHB	Mueller-Hinton broth
EtBr	Ethidium bromide
SDS	Sodium dodecyl sulfate
DCF-DA	2′, 7′–dichlorofluorescin diacetate
DCFH	2′,7′-dichlorodihydrofluorescein
PBS	Phosphate buffered saline
MDA	Malondialdehyde
FIC	Fractional inhibitory concentration
ROS	Reactive oxygen species

CHAPTER 1

INTRODUCTION

1.1 Background of study

Antibiotics have saved millions of lives over the last century. However, the efficacy of existing antibiotics has been compromised due to the progressive emergence and spread of multidrug resistant (MDR) bacteria. The overdosing and non-judicious use of antibiotics are believed to be the main factors causing the rise in MDR detection. The current focus bacteria are ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pnemoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobactor* species) which are responsible for a wide range of infections. Moreover, the emergence of extended-spectrum β-lactamase-producing bacteria has caused the treatment of infections to become challenging, leading to substantial increased illnesses and death rate.

The development of novel antimicrobials is a daunting task and takes considerable amount of time, hence, the shift in research towards alternative therapies to lower the resistance of pathogenic organisms towards existing antimicrobial agents is a crucial aspect. There has been a resurgence in the use of natural products worldwide (Moo et al., 2019). Natural products are compounds that can be obtained from different natural sources such as plants, animals, and microbes. These compounds are secondary metabolites, derived from primary metabolism (Perveen, 2012). Terpenes, the largest class of secondary metabolites fundamentally consists of five carbon isoprene units linked to each other in many different ways, made up of simple hydrocarbons. The modified version of terpenes, termed terpenoids, carry the difference in functional groups, either oxidized methyl group removed or changed at different positions (Du Fall et al., 2011; Perveen, 2012; Mahizan et al., 2019). The number of carbon units categorises terpenoids into hemiterpenes, monoterpenes, diterpenes, sesquiterpenes, sesterpenes and triterpenes (Yazaki et al., 2017).

Terpenoids are used globally as antibacterial agents. Most of the monoterpenes exhibit strong antibacterial activities (Perveen, 2012). Zacchino et al. (2017) has reported that among the potentiators of antibacterial drugs streptomycin, gentamicin, nafcillin, tobramycin and amikacin, 75 % were monoterpenes and diterpenes (Zacchino et al., 2017). Besides that, α-terpineol, α-pinene and linalool were claimed to have antibacterial activities in *E. coli* O157:H7 (Zengin & Baysal 2014). Another study by Silva et al. (2015) demonstrated linalool possessed antibacterial activity against *S. aureus* and *P.aeruginosa* with the MIC of 1024 µg/mL (Silva et al., 2015). The sensitivity of bacteria towards terpenoids are determined by the composition, charge of the outer structures and membrane permeability of the bacteria. Monoterpenes alter the bacterial membrane permeability and increase membrane fluidity which causes the

change in the topology of membrane proteins, giving rise to the interruption in the respiratory process. Besides that, it is most likely that the lipophilicity and/or hydrophobicity together with the presence of hydroxyl group in the terpenes affect the antibacterial mechanism (Zengin & Baysal 2014).

Beta-caryophyllene (BCP) is a sesquiterpene with two fused rings, and a cyclobutane ring, normally found in essential oils (EOs) of oregano, cinnamon and black pepper (Gertsch et al. 2008). Studies shown that BCP has significant potential as an antimicrobial agent in food industry because of its low toxicity (Pieri et al., 2016). BCP is known for its anti-inflammatory, antioxidant and anticancer attributes (Dahham et al., 2015). Earlier on, a study conducted using plant extracts consisting BCP have identified antimicrobial activity against pathogens such as *Spiranthera odoratissima*, *Lantana* sp., *Lippia gracillis Thymus kotschyanus, Vernonia remotiflorae, V. brasiliana* and *Syzygium cumini* (Pieri et al., 2016).

1,8-cineol (CN), commonly known as eucalyptol, is a bicyclic monoterpene that can be found in various EOs such as the eucalyptus oil, rosemary oil, *C. longepaniculatum* leaf essential oil, just to name a few (Brown et al., 2017; Li et al., 2014). CN is used in the treatment of inflammatory diseases of the respiratory system such as sinusitis, chronic obstructive pulmonary disease and bronchial asthma due to its anti-inflammatory property (Sudhoff et al., 2015). Other than anti-inflammatory property, several studies reported that CN also exhibits antibacterial activity against *E. coli*, *Salmonella enteritidis*, *S. aureus* with MIC ranging from 0.781-6.25 µL/mL (Li et al., 2014). Besides that, according to Soković et al. 2010, CN was effective against human pathogenic bacteria strains, namely *Bacillus subtilis*, *E. coli* O157:H7, *Enterobacter cloacae*, *Micrococcus flavus*, *P. aeruginosa*, *Proteus mirabilis*, *S. aureus*, *S. enteritidis*, *Staphylococcus epidermidis*, and *Salmonella typhimurium* with the MIC value ranging from 4.0-7.0 µg/mL (Sokovicḱ et al., 2010). Despite the known anti-inflammatory property and antibacterial activity of CN against a few types of these bacteria, scientific data regarding the antibacterial mechanism of CN against bacteria is limited, especially with reference to antibiotic resistant bacteria.

Hence, this study investigates the use of BCP and CN, as an antibacterial agent by assessing the antibacterial activity and its mechanism of action, aiming to provide information in potential alternative therapy to combat antimicrobial resistance (AMR) by the exploitation of plant secondary metabolites.

1.2 Objectives of the research

The objectives of this study were to:

1) Assess the potential of BCP and CN as an antimicrobial agent.
2) Determine the antimicrobial mechanisms of BCP and CN against Gram-positive and Gram-negative bacteria.

REFERENCES

Alves, C. S., Melo, M. N., Franquelim, H. G., Ferre, R., Planas, M., Feliu, L., Bardají, E., Kowalczyk, W., Andreu, D., Santos, N. C., Fernandes, M. X., & Castanho, M. A. (2010). *Escherichia coli* cell surface perturbation and disruption induced by antimicrobial peptides BP100 and pepR. *The Journal of biological chemistry*, *285*(36), 27536–27544.

Ambrosio, S. R., Tirapelli, C. R., da Costa, F. B., & de Oliveira, A. M. (2006). Kaurane and pimarane-type diterpenes from the Viguiera species inhibit vascular smooth muscle contractility. *Life sciences*, *79*(10), 925–933.

Aslam, B., Wang, W., Arshad, M. I., Khurshid, M., Muzammil, S., Rasool, M. H., Nisar, M. A., Alvi, R. F., Aslam, M. A., Qamar, M. U., Salamat, M., & Baloch, Z. (2018). Antibiotic resistance: a rundown of a global crisis. *Infection and drug resistance*, *11*, 1645–1658.

Ballhausen, B., Kriegeskorte, A., Schleimer, N., Peters, G., & Becker, K. (2014). The mecA homolog mecC confers resistance against β-lactams in *Staphylococcus aureus* irrespective of the genetic strain background. *Antimicrobial agents and chemotherapy*, *58*(7), 3791–3798.

Belley, A., Neesham-Grenon, E., Arhin, F. F., McKay, G. A., Parr, T. R., Jr, & Moeck, G. (2008). Assessment by time-kill methodology of the synergistic effects of oritavancin in combination with other antimicrobial agents against *Staphylococcus aureus*. *Antimicrobial agents and chemotherapy*, *52*(10), 3820–3822.

Blanco P, Hernando-Amado S, Reales-Calderon JA, et al. Bacterial Multidrug Efflux Pumps: Much More Than Antibiotic Resistance Determinants. *Microorganisms*. 2016;4(1):14. Published 2016 Feb 16. doi:10.3390/microorganisms4010014

Borges, A., Ferreira, C., Saavedra, M. J., & Simões, M. (2013). Antibacterial activity and mode of action of ferulic and gallic acids against pathogenic bacteria. *Microbial drug resistance (Larchmont, N.Y.)*, *19*(4), 256–265.

Borisy, A. A., Elliott, P. J., Hurst, N. W., Lee, M. S., Lehar, J., Price, E. R., Serbedzija, G., Zimmermann, G. R., Foley, M. A., Stockwell, B. R., & Keith, C. T. (2003). Systematic discovery of multicomponent therapeutics. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(13), 7977–7982.

Breijyeh, Z., Jubeh, B., & Karaman, R. (2020). Resistance of Gram-Negative Bacteria to Current Antibacterial Agents and Approaches to Resolve It. *Molecules (Basel, Switzerland)*, *25*(6), 1340.

Brown, S. K., Garver, W. S., Orlando, R. A (2017). 1,8-cineole: An underappreciated anti-inflammatory therapeutic. *Journal of biomolecular*

research & therapeutics, 6(01), 6–11.

Campbell, J., Singh, A. K., Santa Maria, J. P., Jr, Kim, Y., Brown, S., Swoboda, J. G., Mylonakis, E., Wilkinson, B. J., & Walker, S. (2011). Synthetic lethal compound combinations reveal a fundamental connection between wall teichoic acid and peptidoglycan biosyntheses in *Staphylococcus aureus*. *ACS chemical biology*, *6*(1), 106–116.

Carvalho, T. C., Simão, M. R., Ambrósio, S. R., Furtado, N. A., Veneziani, R. C., Heleno, V. C., Da Costa, F. B., Gomes, B. P., Souza, M. G., Borges dos Reis, E., & Martins, C. H. (2011). Antimicrobial activity of diterpenes from *Viguiera arenaria* against endodontic bacteria. *Molecules (Basel, Switzerland)*, *16*(1), 543–551.

Centers for Disease Control and Prevention, Office of Infectious Disease (2013). *Antibiotic resistance threats in the United States*. http://www.cdc.gov/drugresistance/threat-report-2013.

Chandra, H., Bishnoi, P., Yadav, A., Patni, B., Mishra, A. P., & Nautiyal, A. R. (2017). Antimicrobial Resistance and the Alternative Resources with Special Emphasis on Plant-Based Antimicrobials-A Review. *Plants (Basel, Switzerland)*, *6*(2), 16.

Chen, S., Liu, H., Liang, W., Hong, L., Zhang, B., Huang, L., Guo, X., & Duan, G. (2019). Insertion sequences in the CRISPR-Cas system regulate horizontal antimicrobial resistance gene transfer in Shigella strains. *International journal of antimicrobial agents*, *53*(2), 109–115.

Cos, P., Vlietinck, A. J., Berghe, D. V., & Maes, L. (2006). Anti-infective potential of natural products: how to develop a stronger in vitro 'proof-of-concept'. *Journal of ethnopharmacology*, *106*(3), 290–302.

Cowan M. M. (1999). Plant products as antimicrobial agents. *Clinical microbiology reviews*, *12*(4), 564–582.

Da Silva, G.J., Pereira, M., Da Salvador, J. (2017) Synthesis and antibacterial activity of novel semi-synthetic triterpenoids. *Federation of American societies for experimental biology journal*, 11(9), 1122–1126.

Dahham, S. S., Tabana, Y. M., Iqbal, M. A., Ahamed, M. B., Ezzat, M. O., Majid, A. S., & Majid, A. M. (2015). The Anticancer, Antioxidant and Antimicrobial Properties of the Sesquiterpene β-Caryophyllene from the Essential Oil of *Aquilaria crassna*. *Molecules (Basel, Switzerland)*, *20*(7), 11808–11829.

de la Fuente-Núñez, C., & Lu, T. K. (2017). CRISPR-Cas9 technology: applications in genome engineering, development of sequence-specific antimicrobials, and future prospects. *Integrative biology : quantitative biosciences from nano to macro*, *9*(2), 109–122.

de León, L., Beltrán, B., & Moujir, L. (2005). Antimicrobial activity of 6-oxophenolic triterpenoids. Mode of action against *Bacillus subtilis*. *Planta medica*, *71*(4), 313–319.

Dean, C. R., Visalli, M. A., Projan, S. J., Sum, P. E., & Bradford, P. A. (2003). Efflux-mediated resistance to tigecycline (GAR-936) in *Pseudomonas aeruginosa* PAO1. *Antimicrobial agents and chemotherapy*, *47*(3), 972–978.

Dhanasekaran, S., & Chopra, S. (2016). Getting a Handle on Smart Drug Delivery Systems – A Comprehensive View of Therapeutic Targeting Strategies. In (Ed.), Smart Drug Delivery System. IntechOpen.

Doménech-Sánchez, A., Martínez-Martínez, L., Hernández-Allés, S., del Carmen Conejo, M., Pascual, A., Tomás, J. M., Albertí, S., & Benedí, V. J. (2003). Role of *Klebsiella pneumoniae* OmpK35 porin in antimicrobial resistance. *Antimicrobial agents and chemotherapy*, *47*(10), 3332–3335.

Du, D., van Veen, H. W., & Luisi, B. F. (2015). Assembly and operation of bacterial tripartite multidrug efflux pumps. *Trends in microbiology*, *23*(5), 311–319.

Du, D., Wang, Z., James, N. R., Voss, J. E., Klimont, E., Ohene-Agyei, T., Venter, H., Chiu, W., & Luisi, B. F. (2014). Structure of the AcrAB-TolC multidrug efflux pump. *Nature*, *509*(7501), 512–515.

Du Fall, L.A., Solomon, P.S. (2011). Role of cereal secondary metabolites involved in mediating the outcome of plant-pathogen interactions. *Metabolites*, 1(1), 64–78.

Egorov, A. M., Ulyashova, M. M., & Rubtsova, M. Y. (2018). Bacterial Enzymes and Antibiotic Resistance. *Acta naturae*, *10*(4), 33–48.

El-Hosseiny, L., El-Shenawy, M., Haroun, M., Abdullah, F. (2014). Comparative evaluation of the inhibitory effect of some essential oils with antibiotics against *Pseudomonas aeruginosa*. *International journal of antibiotics*, 1–5.

Evaristo, F.F.V., Albuquerque, M.R.J.R., Dos Santos, H.S., Bandeira, P.N., Ávila, F.D.N., Da Silva, B.R., Vasconcelos, A.A., Rabelo, É.D.M., Nascimento-Neto, L.G., Arruda, F.V.S., et al (2014). Antimicrobial effect of the triterpene 3 β,6 β,16 β -trihydroxylup-20(29)-ene on planktonic cells and biofilms from gram positive and gram negative bacteria. *Biomed research international*, 1-7.

Farrag, H. A., Abdallah, N., Shehata, M., & Awad, E. M. (2019). Natural outer membrane permeabilizers boost antibiotic action against irradiated resistant bacteria. *Journal of biomedical science*, *26*(1), 69.

Fleming A. (1980). Classics in infectious diseases: on the antibacterial action of

cultures of a penicillium, with special reference to their use in the isolation of B. influenzae by Alexander Fleming, Reprinted from the British Journal of Experimental Pathology 10:226-236, 1929. *Reviews of infectious diseases*, *2*(1), 129–139.

Fortuna, A. M., Juárez, Z. N., Bach, H., Nematallah, A., Av-Gay, Y., Sánchez-Arreola, E., Catalán, C. A., Turbay, S., & Hernández, L. R. (2011). Antimicrobial activities of sesquiterpene lactones and inositol derivatives from *Hymenoxys robusta*. *Phytochemistry*, *72*(18), 2413–2418.

Gallucci, N., Casero, C., Oliva, M., Zygadlo, J., Demo, M. (2006). Interaction between terpenes and penicillin on bacterial strains resistant to beta-lactam antibiotics. *Journal of applied microbiology*, 10(1998):30–32.

Gertsch, J., Leonti, M., Raduner, S., Racz, I., Chen, J. Z., Xie, X. Q., Altmann, K. H., Karsak, M., & Zimmer, A. (2008). Beta-caryophyllene is a dietary cannabinoid. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(26), 9099–9104.

Giedraitienė, A., Vitkauskienė, A., Naginienė, R., & Pavilonis, A. (2011). Antibiotic resistance mechanisms of clinically important bacteria. *Medicina (Kaunas, Lithuania)*, *47*(3), 137–146.

Ginsberg, A. M., & Spigelman, M. (2007). Challenges in tuberculosis drug research and development. *Nature medicine*, *13*(3), 290–294.

Gomaa, A. A., Klumpe, H. E., Luo, M. L., Selle, K., Barrangou, R., & Beisel, C. L. (2014). Programmable removal of bacterial strains by use of genome-targeting CRISPR-Cas systems. *mBio*, *5*(1), e00928-13.

Gomes, F. I., Teixeira, P., Azeredo, J., & Oliveira, R. (2009). Effect of farnesol on planktonic and biofilm cells of *Staphylococcus epidermidis*. *Current microbiology*, *59*(2), 118–122.

Griffin, S.G., Wyllie, S.G., Markham, J.L., Leach, D.N. (1999). The role of structure and molecular properties of terpenoids in determining their antimicrobial activity. *Flavour and fragrrance journal*. 14 (5): 322-332.

Guimarães, A. C., Meireles, L. M., Lemos, M. F., Guimarães, M., Endringer, D. C., Fronza, M., & Scherer, R. (2019). Antibacterial Activity of Terpenes and Terpenoids Present in Essential Oils. *Molecules (Basel, Switzerland)*, *24*(13), 2471.

Gyawali, R., Hayek, S.A., Ibrahim, S.A. (2015) Plant extracts as antimicrobials in food products: Mechanisms of action, extraction methods, and applications. In: M. Taylor (Ed.), *Handbook of natural antimicrobials for food safety and quality* (pp. 49-68). Oxford: Elsevier Ltd.

Halder, S., Yadav, K. K., Sarkar, R., Mukherjee, S., Saha, P., Haldar, S., Karmakar, S., & Sen, T. (2015). Alteration of Zeta potential and membrane permeability in bacteria: a study with cationic

agents. *SpringerPlus*, *4*, 672.

Hamza, M., Nadir, M., Mehmood, N., & Farooq, A. (2016). *In vitro* effectiveness of triterpenoids and their synergistic effect with antibiotics against *Staphylococcus aureus* strains. *Indian journal of pharmacology*, *48*(6), 710–714.

Hasdemir, U. O., Chevalier, J., Nordmann, P., & Pagès, J. M. (2004). Detection and prevalence of active drug efflux mechanism in various multidrug-resistant *Klebsiella pneumoniae* strains from Turkey. *Journal of clinical microbiology*, *42*(6), 2701–2706.

Hille, F., & Charpentier, E. (2016). CRISPR-Cas: biology, mechanisms and relevance. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *371*(1707), 20150496.

Hong, Y., Zeng, J., Wang, X., Drlica, K., & Zhao, X. (2019). Post-stress bacterial cell death mediated by reactive oxygen species. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(20), 10064–10071.

Hullahalli, K., Rodrigues, M., Nguyen, U. T., & Palmer, K. (2018). An Attenuated CRISPR-Cas System in *Enterococcus faecalis* Permits DNA Acquisition. *mBio*, *9*(3), e00414-18.

Hullahalli, K., Rodrigues, M., & Palmer, K. L. (2017). Exploiting CRISPR-Cas to manipulate *Enterococcus faecalis* populations. *eLife*, *6*, e26664.

Handbook of anti-tuberculosis agents. Introduction. (2008). *Tuberculosis (Edinburgh, Scotland)*, *88*(2), 85–86.

Islam, M.S., Aryasomayajula, A., Selvaganapathy, P.R. (2017). A review on macroscale and microscale cell lysis methods. *Micromachines*, 8(3), 83.

Jana, S., & Deb, J. K. (2006). Molecular understanding of aminoglycoside action and resistance. *Applied microbiology and biotechnology*, *70*(2), 140–150.

Kapoor, G., Saigal, S., & Elongavan, A. (2017). Action and resistance mechanisms of antibiotics: A guide for clinicians. *Journal of anaesthesiology, clinical pharmacology*, *33*(3), 300–305.

Kaur, I. (2016). Novel strategies to combat antimicrobial resistance. *Journal of infectious diseases and therapy*, 4(4).

Keen E. C. (2012). Phage therapy: concept to cure. *Frontiers in microbiology*, *3*, 238.

King, T., Dykes, G., & Kristianti, R. (2008). Comparative evaluation of methods commonly used to determine antimicrobial susceptibility to plant extracts and phenolic compounds. *Journal of AOAC International*, *91*(6), 1423–

1429.

Koo, H., Pearson, S. K., Scott-Anne, K., Abranches, J., Cury, J. A., Rosalen, P. L., Park, Y. K., Marquis, R. E., & Bowen, W. H. (2002). Effects of apigenin and tt-farnesol on glucosyltransferase activity, biofilm viability and caries development in rats. *Oral microbiology and immunology*, *17*(6), 337–343.

Krause, K. M., Serio, A. W., Kane, T. R., & Connolly, L. E. (2016). Aminoglycosides: An Overview. *Cold Spring Harbor perspectives in medicine*, *6*(6), a027029.

Kumar, A., Sharma, V., & Dhawan, A. (2013). Methods for detection of oxidative stress and genotoxicity of engineered nanoparticles. *Methods in molecular biology (Clifton, N.J.)*, *1028*, 231–246.

Kuroda, M., Nagasaki, S., & Ohta, T. (2007). Sesquiterpene farnesol inhibits recycling of the C55 lipid carrier of the murein monomer precursor contributing to increased susceptibility to beta-lactams in methicillin-resistant Staphylococcus aureus. *The Journal of antimicrobial chemotherapy*, *59*(3), 425–432.

Lai, P. J., Ng, E. V., Yang, S. K., Moo, C. L., Low, W. Y., Yap, P. S., Lim, S. E., & Lai, K. S. (2020). Transcriptomic analysis of multi-drug resistant *Escherichia coli* K-12 strain in response to *Lavandula angustifolia* essential oil. *3 Biotech*, *10*(7), 313.

Lee, N., Yuen, K. Y., & Kumana, C. R. (2003). Clinical role of beta-lactam/beta-lactamase inhibitor combinations. *Drugs*, *63*(14), 1511–1524.

Li, L., Li, Z. W., Yin, Z. Q., Wei, Q., Jia, R. Y., Zhou, L. J., Xu, J., Song, X., Zhou, Y., Du, Y. H., Peng, L. C., Kang, S., & Yu, W. (2014). Antibacterial activity of leaf essential oil and its constituents from *Cinnamomum longepaniculatum*. *International journal of clinical and experimental medicine*, *7*(7), 1721–1727.

Li, X. Z., Plésiat, P., & Nikaido, H. (2015). The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. *Clinical microbiology reviews*, *28*(2), 337–418.

Lima, R., Del Fiol, F. S., & Balcão, V. M. (2019). Prospects for the Use of New Technologies to Combat Multidrug-Resistant Bacteria. *Frontiers in pharmacology*, *10*, 692.

Liu, G., Song, Z., Yang, X., Gao, Y., Wang, C., Sun, B. (2016). Antibacterial mechanism of bifidocin A, a novel broad-spectrum bacteriocin produced by *Bifidobacterium animalis* BB04. *Food control*. 62, 309–316.

Lopez-Romero, J. C., González-Ríos, H., Borges, A., & Simões, M. (2015). Antibacterial effects and mode of action of selected essential oils components against *Escherichia coli* and *Staphylococcus*

aureus. *Evidence-based complementary and alternative medicine : eCAM*, *2015*, 795435.

Lu, T. K., & Collins, J. J. (2009). Engineered bacteriophage targeting gene networks as adjuvants for antibiotic therapy. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(12), 4629–4634.

Machado, D., Fernandes, L., Costa, S. S., Cannalire, R., Manfroni, G., Tabarrini, O., Couto, I., Sabatini, S., & Viveiros, M. (2017). Mode of action of the 2-phenylquinoline efflux inhibitor PQQ4R against *Escherichia coli*. *PeerJ*, *5*, e3168.

Mahfouz, T.M., Young, M.J. (2017). New bacterial targets and computational methods against bacterial resistance. *Archives of medical research*, 5(4).

Mahizan, N. A., Yang, S. K., Moo, C. L., Song, A. A., Chong, C. M., Chong, C. W., Abushelaibi, A., Lim, S. E., & Lai, K. S. (2019). Terpene derivatives as a potential agent against antimicrobial resistance (AMR) pathogens. *Molecules (Basel, Switzerland)*, *24*(14), 2631.

Marchese, A., Arciola, C. R., Barbieri, R., Silva, A. S., Nabavi, S. F., Tsetegho Sokeng, A. J., Izadi, M., Jafari, N. J., Suntar, I., Daglia, M., & Nabavi, S. M. (2017). Update on Monoterpenes as Antimicrobial Agents: A Particular Focus on p-Cymene. *Materials (Basel, Switzerland)*, *10*(8), 947.

Katsuyama, M., Kobayashi, Y., Ichikawa, H., Mizuno, A., Miyachi, Y., Matsunaga, K., & Kawashima, M. (2005). A novel method to control the balance of skin microflora Part 2. A study to assess the effect of a cream containing farnesol and xylitol on atopic dry skin. *Journal of dermatological science*, *38*(3), 207–213.

McGuinness, W. A., Malachowa, N., & DeLeo, F. R. (2017). Vancomycin Resistance in *Staphylococcus aureus*. *The Yale journal of biology and medicine*, *90*(2), 269–281.

Meletiadis, J., Pournaras, S., Roilides, E., & Walsh, T. J. (2010). Defining fractional inhibitory concentration index cutoffs for additive interactions based on self-drug additive combinations, Monte Carlo simulation analysis, and in vitro-in vivo correlation data for antifungal drug combinations against Aspergillus fumigatus. *Antimicrobial agents and chemotherapy*, *54*(2), 602–609.

Ministry of Health, Malaysia and Ministry of Agriculture & Agro-Based Industry Malaysia. (2017). *Malaysian action plan on antimicrobial resistance (MyAP-AMR) 2017-2021*. https://www.moh.gov.my/moh/resources/Penerbitan/Garis%20Panduan/Garis%20panduan%20Umum%20(Awam)/National_Action_Plan_-_FINAL_29_june.pdf.

Moo, C. L., Yang, S. K., Osman, M. A., Yuswan, M. H., Loh, J. Y., Lim, W. M., Lim, S. H., & Lai, K. S. (2020). Antibacterial activity and mode of action of β-caryophyllene on *Bacillus cereus*. *Polish journal of microbiology*, *69*(1), 1–6.

Moo, C. L., Yang, S. K., Yusoff, K., Ajat, M., Thomas, W., Abushelaibi, A., Lim, S. H., & Lai, K. S. (2020). Mechanisms of Antimicrobial Resistance (AMR) and Alternative Approaches to Overcome AMR. *Current drug discovery technologies*, *17*(4), 430–447.

Mosa, R.A., Nhleko, M.L., Dladla, T.V., Opoku, A.R. (2014). Antibacterial activity of two triterpenes from stem bark of *Protorhus longifolia*. *Journal of medicinal plants research*, 8(18), 686–702.

Munita, J. M., & Arias, C. A. (2016). Mechanisms of Antibiotic Resistance. *Microbiology spectrum*, *4*(2), 10.1128/microbiolspec.VMBF-0016-2015.

Nazari, M., Kurdi, M., & Heerklotz, H. (2012). Classifying surfactants with respect to their effect on lipid membrane order. *Biophysical journal*, *102*(3), 498–506.

Nazzaro, F., Fratianni, F., De Martino, L., Coppola, R., & De Feo, V. (2013). Effect of essential oils on pathogenic bacteria. *Pharmaceuticals (Basel, Switzerland)*, *6*(12), 1451–1474.

Nikaido H. (2003). Molecular basis of bacterial outer membrane permeability revisited. *Microbiology and molecular biology reviews : MMBR*, *67*(4), 593–656.

Nikaido H. (1994). Prevention of drug access to bacterial targets: permeability barriers and active efflux. *Science (New York, N.Y.)*, *264*(5157), 382–388.

Ormälä, A. M., & Jalasvuori, M. (2013). Phage therapy: Should bacterial resistance to phages be a concern, even in the long run?. *Bacteriophage*, *3*(1), e24219.

Pagès, J. M., James, C. E., & Winterhalter, M. (2008). The porin and the permeating antibiotic: a selective diffusion barrier in Gram-negative bacteria. *Nature reviews. Microbiology*, *6*(12), 893–903.

Palmer, J., Flint, S., & Brooks, J. (2007). Bacterial cell attachment, the beginning of a biofilm. *Journal of industrial microbiology & biotechnology*, *34*(9), 577–588.

Pelgrift, R. Y., & Friedman, A. J. (2013). Nanotechnology as a therapeutic tool to combat microbial resistance. *Advanced drug delivery reviews*, *65*(13-14), 1803–1815.

Perveen, S. (2012). Introductory chapter: terpenes and terpenoids. In S. Perveen & A. Al-Taweel (Eds.), *Terpenes and terpenoids* (pp.1-12). InTech.

Phillips, M. A. , Stewart, M. A. , & Xie, D. L. W. a. (2018). Has Molecular Docking Ever Brought us a Medicine?. In (Ed.), *Molecular docking*. IntechOpen.

Pieri, F. A., Souza, M. C., Vermelho, L. L., Vermelho, M. L., Perciano, P. G., Vargas, F. S., Borges, A. P., da Veiga-Junior, V. F., & Moreira, M. A. (2016). Use of β-caryophyllene to combat bacterial dental plaque formation in dogs. *BMC veterinary research*, *12*(1), 216.

Plésiat, P., & Nikaido, H. (1992). Outer membranes of gram-negative bacteria are permeable to steroid probes. *Molecular microbiology*, *6*(10), 1323–1333.

Podoll, J. D., Liu, Y., Chang, L., Walls, S., Wang, W., & Wang, X. (2013). Bio-inspired synthesis yields a tricyclic indoline that selectively resensitizes methicillin-resistant *Staphylococcus aureus* (MRSA) to β-lactam antibiotics. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(39), 15573–15578.

Poole K. (2005). Efflux-mediated antimicrobial resistance. *The Journal of antimicrobial chemotherapy*, *56*(1), 20–51.

Pourahmad Jaktaji, R., & Mohiti, E. (2010). Study of Mutations in the DNA gyrase gyrA Gene of *Escherichia coli*. *Iranian journal of pharmaceutical research : IJPR*, *9*(1), 43–48.

Qi, G., Li, L., Yu, F., & Wang, H. (2013). Vancomycin-modified mesoporous silica nanoparticles for selective recognition and killing of pathogenic gram-positive bacteria over macrophage-like cells. *ACS applied materials & interfaces*, *5*(21), 10874–10881.

Quinn, J. P., Dudek, E. J., DiVincenzo, C. A., Lucks, D. A., & Lerner, S. A. (1986). Emergence of resistance to imipenem during therapy for *Pseudomonas aeruginosa* infections. *The Journal of infectious diseases*, *154*(2), 289–294.

Ramalingam, B., Parandhaman, T., & Das, S. K. (2016). Antibacterial effects of biosynthesized silver nanoparticles on surface ultrastructure and nanomechanical properties of gram-negative bacteria viz. *Escherichia coli* and *Pseudomonas aeruginosa*. *ACS applied materials & interfaces*, *8*(7), 4963–4976.

Rice, L. B., Bellais, S., Carias, L. L., Hutton-Thomas, R., Bonomo, R. A., Caspers, P., Page, M. G., & Gutmann, L. (2004). Impact of specific pbp5 mutations on expression of beta-lactam resistance in *Enterococcus faecium*. *Antimicrobial agents and chemotherapy*, *48*(8), 3028–3032.

Rocha, A.J., de Oliveira Barsttini, M.R., Rocha, R.R., Laurindo, M.V., de Moraes, F.L.L., da Rocha, S.L. (2019). *Pseudomonas aeruginosa*: Virulence

factors and antibiotic resistance genes. *Brazilian archives of biology and technology*. 62, e19180503.

Shao, S., Hu, Y., Cheng, J., & Chen, Y. (2018). Research progress on distribution, migration, transformation of antibiotics and antibiotic resistance genes (ARGs) in aquatic environment. *Critical reviews in biotechnology*, *38*(8), 1195–1208.

Sharma, A., Kumar Arya, D., Dua, M., Chhatwal, G. S., & Johri, A. K. (2012). Nano-technology for targeted drug delivery to combat antibiotic resistance. *Expert opinion on drug delivery*, *9*(11), 1325–1332.

Sieradzki, K., & Tomasz, A. (1997). Suppression of beta-lactam antibiotic resistance in a methicillin-resistant *Staphylococcus aureus* through synergic action of early cell wall inhibitors and some other antibiotics. *The Journal of antimicrobial chemotherapy*, *39 Suppl A*, 47–51.

Silva, V.A., Sousa, J.P., Guerra, F.Q.S, Pessôa, H.L.F., Freitas, A.F.R., Coutinho, H.D.M., Alves, L.B.N., Lima, E.O. (2015). Antibacterial activity of the monoterpene linalool: Alone and in association with antibiotics against bacteria of clinical importance. *International journal of pharmacognosy and phytochemical research*, 7(5),1022–1026.

Singh, K. V., Weinstock, G. M., & Murray, B. E. (2002). An *Enterococcus faecalis* ABC homologue (Lsa) is required for the resistance of this species to clindamycin and quinupristin-dalfopristin. *Antimicrobial agents and chemotherapy*, *46*(6), 1845–1850.

Soares, A.C.F., Matos, P.M., Da Silva, K.F., Martins, C.H.G., Veneziani, R.C.S., Ambrósio, S.R., Dias, H.J., Dos Santos, R.A., Heleno, V.C.G. (2019). Antimicrobial potential of natural and semi-synthetic ent-kaurane and ent-pimarane diterpenes against clinically isolated gram-positive multidrug-resistant bacteria. *Journal of the Brazilian chemical society*, 30(2),333–341.

Soković, M., Glamočlija, J., Marin, P. D., Brkić, D., & van Griensven, L. J. (2010). Antibacterial effects of the essential oils of commonly consumed medicinal herbs using an in vitro model. *Molecules (Basel, Switzerland)*, *15*(11), 7532–7546.

Souza, A. B., Martins, C. H., Souza, M. G., Furtado, N. A., Heleno, V. C., de Sousa, J. P., Rocha, E. M., Bastos, J. K., Cunha, W. R., Veneziani, R. C., & Ambrósio, S. R. (2011). Antimicrobial activity of terpenoids from *Copaifera langsdorffii* Desf. against cariogenic bacteria. *Phytotherapy research : PTR*, *25*(2), 215–220.

Sudhoff, H., Klenke, C., Greiner, J. F., Müller, J., Brotzmann, V., Ebmeyer, J., Kaltschmidt, B., & Kaltschmidt, C. (2015). 1,8-cineol reduces mucus-production in a novel human ex vivo model of late rhinosinusitis. *PloS one*, *10*(7), e0133040.

Tooke, C. L., Hinchliffe, P., Bragginton, E. C., Colenso, C. K., Hirvonen, V., Takebayashi, Y., & Spencer, J. (2019). B-lactamases and β-lactamase inhibitors in the 21st century. *Journal of molecular biology*, *431*(18), 3472–3500.

Tripathi, K. (2004). Antimicrobial drugs. *MCQs pharmacol*, 8(8),318–318.

Trombetta, D., Castelli, F., Sarpietro, M. G., Venuti, V., Cristani, M., Daniele, C., Saija, A., Mazzanti, G., & Bisignano, G. (2005). Mechanisms of antibacterial action of three monoterpenes. *Antimicrobial agents and chemotherapy*, *49*(6), 2474–2478.

Tyagi, A. K., & Malik, A. (2012). Morphostructural damage in food-spoiling bacteria due to the lemon grass oil and its vapour: SEM, TEM, and AFM investigations. *Evidence-based complementary and alternative medicine : eCAM*, *2012*, 692625.

UN News. (2019). *Global health agencies sound alarm on drug-resistant infections; new recommendations to reduce 'staggering number' of future deaths*.

Urzúa, A., Rezende, M. C., Mascayano, C., & Vásquez, L. (2008). A structure-activity study of antibacterial diterpenoids. *Molecules (Basel, Switzerland)*, *13*(4), 882–891.

Vaara M. (1992). Agents that increase the permeability of the outer membrane. *Microbiological reviews*, *56*(3), 395–411.

Vakulenko, S. B., & Mobashery, S. (2003). Versatility of aminoglycosides and prospects for their future. *Clinical microbiology reviews*, *16*(3), 430–450.

Van der Paal, J., Neyts, E. C., Verlackt, C., & Bogaerts, A. (2016). Effect of lipid peroxidation on membrane permeability of cancer and normal cells subjected to oxidative stress. *Chemical science*, *7*(1), 489–498.

Visalli, M. A., Murphy, E., Projan, S. J., & Bradford, P. A. (2003). AcrAB multidrug efflux pump is associated with reduced levels of susceptibility to tigecycline (GAR-936) in *Proteus mirabilis*. *Antimicrobial agents and chemotherapy*, *47*(2), 665–669.

Viswanathan V. K. (2014). Off-label abuse of antibiotics by bacteria. *Gut microbes*, *5*(1), 3–4.

Wilson D. N. (2014). Ribosome-targeting antibiotics and mechanisms of bacterial resistance. *Nature reviews. Microbiology*, *12*(1), 35–48.

Woldringh, C. L., & van Iterson, W. (1972). Effects of treatment with sodium dodecyl sulfate on the ultrastructure of *Escherichia coli*. *Journal of bacteriology*, *111*(3), 801–813.

Wong-Ekkabut, J., Xu, Z., Triampo, W., Tang, I. M., Tieleman, D. P., & Monticelli, L. (2007). Effect of lipid peroxidation on the properties of lipid bilayers: a molecular dynamics study. *Biophysical journal*, *93*(12), 4225–4236.

World Health Organization. (2014). *Antimicrobial resistance: Global report on surveillance*, https://apps.who.int/iris/bitstream/handle/10665/112642/9789241564748_eng.pdf;jsessionid=76592BB49CA1313582F06ED6E3C62B2D?sequence=1

Yang, S.K., Yap, P.S.X., Krishnan, T., Yusoff, K., Chan, K.G., Yap, W.S., Lai, K.S., Lim, S.H.E. (2018). Mode of action: Synergistic interaction of peppermint (*Mentha x piperita* L. Carl) essential oil and meropenem against plasmid-mediated resistant *E. coli*. *Records of natural products*, 12(6), 582–594.

Yang, S. K., Yusoff, K., Ajat, M., Thomas, W., Abushelaibi, A., Akseer, R., Lim, S. E., & Lai, K. S. (2019). Disruption of KPC-producing *Klebsiella pneumoniae* membrane via induction of oxidative stress by cinnamon bark (*Cinnamomum verum* J. Presl) essential oil. *PloS one*, *14*(4), e0214326.

Yang, S.K., Yusoff, K., Ajat, M., Yap, W.S., Lim, S.H.E., Lai, K.S. (2020). Antimicrobial activity and mode of action of terpene linalyl anthranilate against carbapenemase-producing *Klebsiella pneumoniae*. *Journal of pharmaceutical analysis*. doi:10.1016/j.jpha.2020.05.014

.

Yang, S. K., Yusoff, K., Mai, C. W., Lim, W. M., Yap, W. S., Lim, S. E., & Lai, K. S. (2017). Additivity vs synergism: Investigation of the additive interaction of cinnamon bark oil and meropenem in combinatory therapy. *Molecules (Basel, Switzerland)*, *22*(11), 1733.

Yang, S.K., Yusoff, K., Thomas, W., Akseer, R., Alhosani, M.S., Abushelaibi, A., Lim, S.H.E., Lai, K.S. (2020). Lavender essential oil induces oxidative stress which modifies the bacterial membrane permeability of carbapenemase producing *Klebsiella pneumoniae*. *Scientific reports*, 10, 819.

Yap, P.S.X., Yang, S.K., Lai, K.S., Lim, S.H.E. (2017). Essential oils: The ultimate solution to antimicrobial resistance in *Escherichia coli*? In: A. Samie (Ed), *Escherichia coli* - Recent advances on physiology, pathogenesis and biotechnological applications.(pp.299-313). InTech.

Yazaki, K., Arimura, G. I., & Ohnishi, T. (2017). 'Hidden' terpenoids in Plants: Their biosynthesis, localization and ecological roles. *Plant & cell physiology*, *58*(10), 1615–1621.

Zacchino, S. A., Butassi, E., Cordisco, E., & Svetaz, L. A. (2017). Hybrid combinations containing natural products and antimicrobial drugs that interfere with bacterial and fungal biofilms. *Phytomedicine : international journal of phytotherapy and phytopharmacology*, *37*, 14–26.

Zengin, H., & Baysal, A. H. (2014). Antibacterial and antioxidant activity of essential oil terpenes against pathogenic and spoilage-forming bacteria and cell structure-activity relationships evaluated by SEM microscopy. *Molecules (Basel, Switzerland)*, *19*(11), 17773–17798.