# ANTIOXIDANT, ANTIBACTERIAL ACTIVITY AND *IN SILICO* STUDY OF SELECTED MEDICINAL PLANTS AGAINST PATHOGENIC BACTERIA

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*I dedicate this to my mother and father, who taught me the best kind of knowledge*

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## ABSTRACT

An increase in the number of antibiotic resistant bacteria worldwide has necessitated new antibacterial agents, mainly by medicinal plants. For this, the antioxidant and antibacterial activities of four Malaysian medicinal plants; *Alpinia galanga*, *Centella asiatica*, *Clinacanthus nutans* and *Persicaria odorata* extracts were evaluated against gram-positive (*Bacillus subtilis*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus* (MRSA)) and gram-negative (*Escherichia coli*, *Pseudomonas putida*) in this study. The medicinal plants were extracted using solvents with different polarities and screened for the total phenolic contents via Folin-Ciocalteu method and antioxidant capacity by diphenyl-1-picrylhydrazyl (DPPH) activity. The antibacterial activities were conducted using disc diffusion, minimal inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) tests. The most effective plant extract was further fractionated by column chromatography and thin layer chromatography. The fractions were then characterized using antibacterial assays, Zeta potential measurements, followed by scanning electron microscopic (SEM) observations and Gas Chromatography Mass Spectrometry (GCMS) analysis. Compounds identified were docked with Penicillin binding protein (PBP) using Autodock 4.0 and simulate (MD) by Gromacs 5.0.4. The findings from this study showed that acetone plant extracts exhibited the highest antioxidant and antibacterial activities; significantly by *P. odorata* acetone extract. This extract was also chosen due to its comparable MIC and MBC values with both the positive controls respectively. A total of 12 fractions were separated from the extract, however only H05 fraction showed bactericidal action against all gram-positive bacteria. This fraction could also alter the magnitude of bacterial negativity, significantly against MRSA. This data was supported by morphological alterations induced in treated MRSA, through SEM images. The GCMS analysis of H05 fraction showed that the presence of seven major phenolic compounds derivatives that met the Lipinski's Rule of Five were present in the H05 extract. Among the seven compounds, the MD trajectory analysis showed that 6-hydroxy-8-methoxyoctanoic acid (tannins derivatives) shows strongest and most stable binding with PBP protein. The present study indicates that phenolics mainly tannins present in the *P. odorata* acetone extract were highly responsible for its antibacterial potential, especially for MRSA infection treatment.

# ABSTRAK

Pertambahan bakteria rintangan terhadap antibiotik di seluruh dunia telah menyebabkan perlunya ejen antibakteria yang baharu, terutamanya daripada tumbuhan ubatan. Oleh itu, dalam kajian ini, aktiviti antioksida dan antibakteria daripada empat tumbuhan ubatan Malaysia; ekstrak *Alpinia galanga*, *Centella asiatica*, *Clinacanthus nutans* dan *Persicaria odorata* telah diuji terhadap bakteria gram positif (*Bacillus subtilis*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus* (MRSA)) dan bakteria gram negatif (*Escherichia coli*, *Pseudomonas putida*). Tumbuh-tumbuhan ubatan diestrak dengan kekutuban larutan yang berbeza dan diuji untuk mengetahui jumlah kandungan fenol menggunakan kaedah Folin-Ciocalteu dan kemudiannya kapasiti antioksidan oleh aktiviti difenil-1-pikrilhidrazil (DPPH). Aktiviti antibakteria dijalankan dengan menggunakan serapan cakera, ujian kepekatan minima (MIC) dan ujian perencatan kepekatan minima bagi bakteria (MBC). Ekstrak paling berkesan telah difraksikan seterusnya dengan kromatografi turus dan kromatografi lapisan nipis. Fraksi tersebut kemudiannya dicirikan melalui ujian antibakteria, pengukuran potensi Zeta dan diikuti dengan pengimbasan mikroskop elektron (SEM) dan analisis Spektrometri Jisim Gas (GCMS). Sebatian yang dikenal pasti telah dipaut-tindih dengan protein pengikat Penicillin (PBP) menggunakan Autodock 4.0 dan simulasi (MD) dengan Gromacs 5.0.4. Keputusan menunjukkan bahawa tumbuhan yang diekstrak aseton mempamerkan aktiviti antioksida dan antibakteria yang sangat bagus iaitu ekstrak aseton *P. odorata*. Ekstrak tumbuhan ini juga dipilih kerana nilai aktiviti MIC dan MBC yang masing-masing setanding dengan dua kawalan positif. Sejumlah12 fraksi telah dipisahkan dari ekstrak tumbuhan ini, tetapi hanya fraksi H05 menunjukkan tindakan mematikan ke atas semua bakteria gram-positif. Fraksi ini juga boleh mengubah keadaan negatif bakteria, ketara terhadap MRSA. Data ini telah disokong dengan perubahan morfologi MRSA yang dilihat melalui imej SEM. Analisis GCMS fraksi H05 menunjukkan kehadiran tujuh sebatian fenolik utama, yang memenuhi Peraturan Lima Lipinski yang hadir dalam ekstrak H05. Antara tujuh sebatian, 6-hydroxy-8-methoxyoctanoic acid (derivatif tanin) menunjukkan pengikatan sebatian yang terkuat dan paling stabil dengan protein PBP, berdasarkan analisis unjuran MD. Kajian ini menunjukkan bahawa fenolik iaitu tanin hadir dalam ekstrak aseton *P. odorata* yang bertanggungjawab terhadap potensi antibakterianya, terutamanya untuk rawatan jangkitan MRSA.

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| | | |
|---|---|---|
| *A. galanga* | - | *Alpinia galanga* |
| *C. asiatica* | - | *Centella asiatica* |
| *C. nutans* | - | *Clinacanthus nutans* |
| *P. odorata* | - | *Persicaria odorata* |
| *B. subtilis* | - | *Bacillus subtilis* |
| *S. epidermidis* | - | *Staphylococcus epidermidis* |
| *S. aureus* | - | *Staphylococcus aureus* |
| MRSA | - | Methicillin-resistant *Staphylococcus aureus* |
| *E. coli* | - | *Escherichia coli* |
| *P. putida* | - | *Pseudomonas putida* |
| TPC | - | Total Phenolic Content |
| DPPH | - | 2,2-diphenyl-1-picrylhydrazyl |
| MIC | - | Minimal Inhibitory Concentration |
| MBC | - | Minimum Bactericidal Concentration |
| GCMS | - | Gas Chromatography Mass Spectrometry |
| TLC | - | Thin Layer Chromatography |
| SEM | - | Scanning Electron Microscopy |
| $IC_{50}$ | - | Inhibitory Concentration at 50% |
| AEAC | - | Ascorbic Acid Equivalent Antioxidant Capacity |

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# CHAPTER 1

# INTRODUCTION

## 1.1 Background of Study

Antibiotic-resistance is the ability of bacteria to withstand the effects of conventional antibiotics (Frieri *et al*., 2017). It is one of the biggest crises to global human health, as reported by World Health Organization (2018). Causing around 700,000 deaths each year, and estimated to increase to more than 10 million in 2050 (Dockrill, 2017). Besides, an estimation of $300 billion to more than $1 trillion per year will be lost globally for the healthcare costs, attributed by antibiotic resistance crisis (Founou *et al*., 2017). The overuse, inappropriate prescriptions and a lack of new drugs development are the main causes of this crisis (Crouch *et al*., 2015). Consequently, it has reduced the efficacy of antibiotics used to save millions of lives in the past decades. Therefore, new therapeutics is urgently needed.

For this reason, researchers have focused on medicinal plants to combat against resistant bacteria. They were initially used in traditional health care globally for centuries (Joshi *et al*., 2011). As example, diseases such as fever, diarrhoea, malaria, common cold, intestinal parasites and gastroenteritis were treated by the medicinal plants (Kumar *et al*., 2013; Li *et al*., 2015). Currently, many Malaysian medicinal plants are being extensively used in research for their wide pharmacological properties, including antioxidant and antibacterial activities.

Thus, in the present study, some of Malaysian medicinal plants were selected. The rhizome of *Alpinia galanga* (Langkuas) and the leaves of *Centella asiatica* (Pegaga), *Clinacanthus nutans* (Belalai Gajah) and *Persicaria odorata* (Kesum) were

used extensively in antioxidant, antimicrobial, anti-cancer and anti-inflammatory activities (Rao *et al*., 2010; Orhan, 2012; Yong *et al*., 2013; Yanpirat and Vajrodaya, 2015). These beneficial medicinal effects were detected due to the presence of phytochemicals (Godstime *et al*., 2014). According to a review by Compean and Ynalves (2014), phytochemicals are the chemicals produced by plants, which involved in their defence mechanisms. However, large percentages of these phytochemicals are still yet to be known. Their medicinal effects could be important strategies to understand the biological activities of medicinal plants to the well-being of humanity (Munita and Arias, 2016).

Therefore, the present study attempted to evaluate the antioxidant and antibacterial activities of *Alpinia galanga* (Langkuas), *Centella asiatica* (Pegaga), *Clinacanthus nutans* (Belalai Gajah) and *Persicaria odorata* (Kesum) extracts against antibiotic-resistant bacteria include gram-positive (*Bacillus subtilis*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus*) and gram-negative (*Escherichia coli*, *Pseudomonas putida*). Further possible mechanisms of antibacterial actions were also attempted based on *in vitro* and *in silico* studies.

## 1.2 Problem Statement

The year 1950s to 1970s were considered as the golden era of antibiotics. The antibiotics were known as a magic bullet that selectively targeted the bacteria, without affecting the host (Govindappa *et al*., 2011). However, due to their irresponsible usage, resistant strains have rapidly increased (Barbieri *et al*., 2017). Recently, the development of resistant bacteria was directly proportional to the production of new antibiotics (Zaman *et al*., 2017). Every year, around 25,000 patients die in Europe, while others resulted in extra healthcare and losses of productivity (Crouch *et al*., 2015). The major antibiotic-resistance bacteria, *S. aureus* were the main cause of bacteraemia and infective endocarditis (Tong *et al*., 2015). The diseases could cause heart damage, infections in various organs, especially in the kidneys, and also leads to death (Rosa *et al*., 2014). A more serious

infection was associated with the resistant strain of *S. aureus*, known as MRSA (Salvador *et al*., 2017). In 2011, 80,000 serious MRSA diseases, with 11,285 deaths were reported (Centers for Disease Control and Prevention, 2015).

Medicinal plants possess strong pharmacological activities, economic viability and low toxicity (Arya and Mehta, 2017). Previous literatures by Chomnawang *et al*. (2009), Jarrar *et al*. (2010) and Oskay *et al*. (2009) found that plant sources has significant antioxidant and antibacterial activities. Responding to the need for evidence regarding medicinal plants, the antioxidant and antibacterial properties of selected Malaysian medicinal plants were evaluated in this study. Therefore, medicinal plants could be used as new sources in designing potential antibacterial drugs.

## 1.3 Objectives of Study

1. To isolate and determine the antioxidant capacities of *A. galanga*, *C. asiatica*, *C. nutans* and *P. odorata* extracts by total phenolic, total tannins and DPPH-free radical scavenging activity.
2. To evaluate the antibacterial activities of plant extracts by disc diffusion, minimal inhibitory concentration (MIC) followed by minimum bactericidal concentration (MBC) assays.
3. To isolate and identify the bioactive compounds of the most effective plant extract by bioassay-guided fractionation and Gas Chromatography Mass Spectrometry (GCMS).
4. To determine the antibacterial effect of fractions on bacterial cell membrane by Zeta potential measurement and scanning electron microscopic (SEM) observations.
5. To visualize the interactions between the modelled bioactive compounds of plant extracts with receptor protein of human pathogenic bacteria by using bioinformatic tools.

## 1.4 Scope of Study

As referred to the objectives, the study was started with the plant extraction in 80% of hexane, 80% of acetone, 80% of ethanol and 100% of aqueous solvents. The crude extracts were screened for their total phenolic and tannins content of plant extracts using Folin-Ciocalteu method and antioxidant capacity by DPPH-free radical scavenging activity. The correlation of TPC with the antioxidant activity of plant extracts were demonstrated by Pearson's Correlation Coefficient. Then, the antibacterial activities were conducted by disc diffusion assay, minimal inhibitory concentration (MIC) assay which followed by minimum bactericidal concentration (MBC) test against gram-positive (*B. subtilis*, *S. epidermidis*, *S. aureus*, MRSA) and gram-negative (*E. coli*, *P. putida*). Further studies on the bioactive compounds of the most effective plant extract were determined by bioassay-guided fractionation involving the column chromatography and thin-layer chromatography (TLC) techniques. Fractionates selected based on the weight of yield were evaluated by conducting a series of antibacterial assay. The bacterial surface charge of untreated and treated bacteria were measured by Zeta potential, followed by the visualization of membrane permeability by Scanning Electron Microscopy (SEM). SHIMADZU QP2010 Gas Chromatography Mass Spectrometry (GCMS) was used to identify the bioactive compounds of the most effective plant extract based on NIST Standard Reference Database. The sequence of identified bioactive compounds were then obtained from ChemSpider webpage in PDB format, or modelled by using ChemSketch free software. The same format of bacterial receptor protein, Penicillin binding protein (PBP) was obtained by RCSB webpage (PDB code: 1CEF). Further molecular docking and molecular dynamics (MD) simulations of the protein-ligand interactions were conducted by using a series of bioinformatic tools.

## 1.5 Significance of Study

The emergence of bacterial resistance to commonly available antibiotics has necessitated the search for new antibacterial agents. In Malaysia, there were many medicinal plants were reported to pose potential antibacterial activities. Hence, in this study, their phytochemicals were explored further. It was done to highlight the mechanisms and mode of antibacterial actions based on *in vitro* and *in silico* analyses. The study could provide a significant finding of the antibacterial potential, and explore their additional values as highly beneficial herbs.

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