ANTI ACNE-CAUSING BACTERIA AND PHYTOCHEMICAL STUDIES OF JAMBU BATU (Psidium guajava Linn.) LEAF

KHAIRUL NAIM BIN MD PADZIL

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By

KHAIRUL NAIM BIN MD PADZIL

Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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Chairman : Assoc. Prof. Yaya Rukayadi, PhD
Institute : Bioscience

Acne vulgaris is a noticeable skin disorder in human that can be found on the face, on either back or on chest. Four main factors causing acne are bacteria, excess oil production, hair follicles clogged by oil and dead skin cells, and excess activity of a type of androgen hormone. The medicines to treat acne vulgaris mostly focused on its efficacy of antibacterial and antioxidant activities. Recently, there is increasing interest to use natural product from plant extracts to inhibit the growth of acne-causing bacteria. The aims of this study were to determine the antibacterial activity of *Psidium guajava* Linn. extracts and fractions against three major acne-causing bacteria, namely *Staphylococcus aureus* KCCM12255, *Staphylococcus epidermidis* KCCM40003 and *Propionibacterium acnes* KCTC3314, to determine the antioxidant of *P. guajava* Linn. of the extracts and its fractions and to identify the potential anti-acne metabolites in *P. guajava* Linn. The antibacterial activities were determined using standard methods of Clinical and Laboratory Standard Institute (CLSI), in term of disc diffusion assay, minimal inhibitory concentrations (MICs), minimum bactericidal concentrations (MBCs) and time kill assay. Total phenolic content (TPC) and antioxidant activity of *P. guajava* Linn. were determined using Folin-Ciocalteau assay and 2,2-diphenyl-1-picrylhydryzyl (DPPH) assay, respectively. The active compounds anti-acne in fractions were identified by using Gas Chromatography-Mass Spectrometry (GS-MS), Liquid Chromatography-Mass Spectrometry (LS-MS) and Proton Nuclear Magnetic Resonance (^{1}H NMR). The leaves of *P. guajava* Linn. was extracted into crude extract using four different solvents, namely methanol, ethanol, hexane and water. Moreover, methanolic extract was fractionated using four different solvents: hexane, chloroform, ethyl acetate and aqueous methanol. The results showed that disc diffusion assay of crude extracts and fractions showed that the range of inhibition zone were 8.50 ± 0.17 to 12.50 ± 0.41 mm and 8.45 ± 0.15 to 12.65 ± 1.55 mm, respectively. The *P. guajava* Linn. leaves extracts and its fractions have been able to inhibit the bacterial growth at MICs ranged from 0.31 ± 0.00 to 2.08 ± 0.59 mg/mL and 0.21 ± 0.07 to 4.17 ± 1.18 mg/mL, respectively. The extracts or fractions have been able to kill the bacteria with MBCs at values ranged from 0.63 ± 0.00 to 4.17 ± 1.18 mg/mL and 0.63 ± 0.00 to 4.17 ± 1.18 mg/mL, respectively. Time-kill curve analysis showed that bactericidal endpoint of all tested bacteria can be killed completely

with ranged concentration of 4× MIC (0.21 mg/ml – 4.16 mg/ml) for four hours. Total phenolic content of the extracts ranged from 441.18 ± 18.21 to 147.1 ± 4.27 mg of GAE/g of dried weight material. The DPPH assay showed IC_{50} of the extracts at the range from 124.66 to 217.87 µg/mL. The ten volatile compounds were found, as determined using GC-MS, are E-caryophyllene, β-selinene, α-selinene, α-humulene, globulol, aromadendrene, p-cymene, pyrogallol, 2,4-bis(tert-butyl)-phenol and oleic acid. Moreover, LC-MS has identified fifteen non-volatile compounds, namely α-linolenic acid, stearic acid, betulinic acid, ursolic acid, lupeol, myricetin, epicathecin, quercetin, syringic acid, 4-coumaric acid, luteolin, maslinic acid, asiatic acid, γ-tocopherol and caryophyllene oxide. An active metabolite has been identified based on the ^{1}H NMR, which is quercetin. In conclusion, *P. guajava* Linn. extracts and its compounds showed a promising potential of antibacterial activity against the acne-causing bacteria and antioxidant activity, thus it might be developed as natural anti-acne agents.

Keywords: anti-acne, *P. guajava* Linn., acne vulgaris, metabolite isolation, medicinal plant.

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ANTI BAKTERIA PENYEBAB JERAWAT DAN PENGKAJIAN FITOKIMIA DALAM DAUN JAMBU BATU (*Psidium guajava* Linn.)

By

KHAIRUL NAIM BIN MD PADZIL

Oktober 2020

Penyelia : Prof. Madya Yaya Rukayadi, PhD
Institut : Biosains

Jerawat adalah gangguan kulit yang ketara pada manusia yang boleh didapati di muka, di belakang atau di dada. Empat faktor utama penyebab jerawat adalah bakteria, pengeluaran minyak berlebihan, folikel rambut yang tersumbat oleh minyak dan sel kulit mati, aktiviti berlebihan hormone androgen. Kebanyakan ubat-ubatan untuk merawat jerawat tertumpu pada keberkesanan aktiviti antibakteria dan antioksidan. Baru-baru ini, terdapat peningkatan minat terhadap penggunaan produk semula jadi dari ekstrak tumbuhan untuk menghalang pertumbuhan bakteria penyebab jerawat. Tujuan kajian ini adalah untuk mengetahui aktiviti antibakteria *Psidium guajava* Linn. ekstrak dan fraksi terhadap tiga bakteria penyebab jerawat utama, iaitu *Staphylococcus aureus* KCCM12255, *Staphylococcus epidermidis* KCCM40003 dan *Propionibacterium acnes* KCTC3314, untuk mengenal pasti aktiviti antioksidan *P. guajava* Linn. ekstrak dan fraksi dan untuk mengenal pasti potensi metabolit anti jerawat di *P. guajava* Linn. Kegiatan antibakteria ditentukan menggunakan kaedah *Clinical and Laboratory Standard Institute* (CLSI) dari segi ujian penyebaran cakera, kepekatan perencatan minima (MIC), kepekatan bakterisida minima (MBC) dan ujian pembunuhan masa. Jumlah kandungan fenolik (TPC) dan aktiviti antioksidan *P. guajava* Linn. ditentukan menggunakan ujian Folin-Ciocalteau dan ujian *2,2-diphenyl-1-picrylhydryzyl* (DPPH). Bahan aktif anti jerawat dalam fraksi dikenal pasti dengan menggunakan *Gas Chromatography-Mass Spectrometry* (GS-MS), *Liquid Chromatography-Mass Spectrometry* (LS-MS) dan *Proton Nuclear Magnetic Resonance* (^{1}H NMR). Daun *P. guajava* Linn. diekstrak menjadi ekstrak kasar dengan menggunakan empat pelarut yang berbeza iaitu metanol, etanol, heksana dan air. Selain itu, ekstrak methanol dipecahkan mengikut kelompok dengan menggunakan empat pelarut berbeza iaitu, heksana, kloroform, etil asetat dan methanol berair. Hasil ujian penyebaran cakera daripada ekstrak dan fraksi menunjukkan julat zon perencatan dengan diameter antara 8.50 ± 0.17 hingga 12.50 ± 0.41 mm dan 8.45 ± 0.15 hingga 12.65 ± 1.55, masing-masing. *P. guajava* Linn. ekstrak daun dan fraksi telah menghalang pertumbuhan bakteria pada MIC antara 0.31 ± 0.00 mg/mL hingga 2.08 ± 0.59 mg/mL dan 0.21 ± 0.07 mg/mL hingga 4.17 ± 1.18 mg/mL, masing-masing. Ekstrak dan fraksi dapat membunuh bakteria dengan MBC pada nilai antara 0.63 ± 0.00 mg/mL hingga 4.17 ± 1.18 mg/mL dan 0.63 ± 0.00 mg/mL

to 4.17 ± 1.18 mg/mL, masing-masing. Analisis titik akhir bakteriasidal terhadap semua bakteria yang diuji dapat dibunuh sepenuhnya dengan kepekatan 4× MIC (0.21 mg/mL - 4.16 mg/mL) selama empat jam. Jumlah kandungan fenolik ekstrak antara 441.18 ± 18.21 hingga 147.1 ± 4.27 mg daripada GAE/g bahan berat kering diperolehi. Ujian DPPH menunjukkan IC_{50} ekstrak adalah antara 124.66 hingga 217.87 µg/mL. Sebanyak sepuluh bahan mudah meruwap telah dikesan, seperti yang ditentukan menggunakan GS-MS, adalah E-caryophyllene, β-selinene, α-selinene, α-humulene, globulol, aromadendrene, p-cymene, pyrogallol, 2,4-bis(tert-butil)-phenol and oleic acid. LC-MS telah mengenal pasti lima belas bahan utama yang tidak mudah menguap, iaitu α-linolenic acid, stearic acid, betulinic acid, ursolic acid, lupeol, myricetin, epicathecin, quercetin, syringic acid, 4-coumaric acid, luteolin, maslinic acid, asiatic acid, γ-tocopherol and caryophyllene oxide. Satu metabolit aktif telah dikenal pasti berdasarkan ^{1}H NMR, iaitu quercetin. Kesimpulannya ekstrak *P. guajava* Linn. dan bahan aktif menunjukkan potensi aktiviti antibakteria yang bagus terhadap bakteria jerawat dan aktiviti antioksidan, sehingga dapat dikembangkan sebagai agen anti-jerawat semula jadi.

Kata kunci: Anti-jerawat, *P. guajava* Linn., jerawat, pengasingan metabolit, tumbuhan perubatan.

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

Yaya Rukayadi, PhD
Associate Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Chairman)

Khozirah Shaari, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Member)

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ZALILAH MOHD SHARIFF, PhD
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Signature : _____

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LIST OF ABBREVIATIONS

CFU	Colony Forming Unit
CHX	Clorhexidine
CLSI	Clinical and Laboratory Standards Institute
DMSO	Dimethyl sulfoxide
DPPH	1,1-diphenyl-2-picryl-hydrazyl
FRAP	Ferric reducing antioxidant potential
GC-MS	Gas Chromatography – Mass Spectrometry
IBS	Institute of Bioscience
IC_{50}	Inhibition Concentration at 50 percent
KCCM	Korean Culture Center of Microorganisms
KCTC	Korean Collection for Type Cultures
LC-MS	Liquid Chromatography – Mass Spectrometry
MBC	Minimum Bactericidal Concentration
MHA	Mueller Hinton agar
MHB	Mueller Hinton broth
MIC	Minimum Inhibitory Concentration
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium Bromide
NIST	National Institute of Standards and Technology
PBS	Phosphate Buffer Saline
TLC	Thin layer chromatography
UV	Ultraviolet
VLC	Vacuum liquid chromatography
^{13}C NMR	Carbon Nuclear Magnetic Resonance
^{1}H NMR	Proton Nuclear Magnetic Resonance

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Acne vulgaris is a noticeable skin disorder in human that can be found on either on the face, back or chest and even though the life-threatening condition case is unlikely occurred however, it becomes a crucial struggle for health care provider (Zaenglein *et al.*, 2016). Clinically, acne is characterized by seborrhea, the formation of open and closed comedones, erythematous papules, and pustules and in more severe cases nodules, deep pustules and pseudocysts (George and Sridharan, 2018). It is depending on these four key pathogenic processes lead to the formation of acne lesions: alteration of follicular keratinization that leads to comedones; increased and altered sebum production under androgen control; follicular colonization by *Propionibacterium acnes*; and complex inflammatory mechanisms that involve both innate and acquired immunity. Genetics (family history of severe acne), diet (glycemic index), chocolate and dairy consumption and environmental factors (smoking), occlusive cosmetics, occupational exposures also contribute to the pathogenesis of acne (Tan *et al.*, 2018; Nasri *et al.*, 2015)

People are vulnerable to acne disease at any stage of life and may continue into 30s and 40s, which around 20% of young peoples those are affected with the severe acne correlated with pubertal maturity (Admani and Barrio, 2013). A previous study reported that in 2015, acne was estimated to affect 633 million people globally, making it the 8th most common disease worldwide (Hay *et al.*, 2014). Approximately 85% of people between the ages of 12 and 24 experience at least minor acne (Bhate and Williams, 2013). Among Malaysian adolescents, the prevalence of facial acne occurrence was 67.5% with higher commonness among males than females (Hanisah *et al.*, 2009).

There are several different therapy methods for acne treatment, which are topical, systemic, complementary and alternative medicine and physical. The individual patient factors must be taken into account when determining a regimen for the treatment of acne (Fox *et al.*, 2016). However, a combination treatment that targets more than one of the methods of treatment is highly costly as in a recent report in USA, the cost of acne treatment is estimated to be 3 billion dollars per year in terms of treatment and loss of productivity (Sinha *et al.*, 2014). Furthermore, it has been suggested that the uses of medicinal plant as an alternative approach due to its low side effect in treating the acne lesion compared to the chemical approach (Nasri *et al.*, 2015).

A previous study suggests resolution by using antibiotic compounds which can be integrated into therapy method for acne treatment, intended to complement the prevention of acne formation such as tetracycline, erythromycin, clindamycin, retinoid, isotretinoin, salicyclic acidchlorhexidine and benzoyl peroxide (Bettoli *et al.*, 2015; Rathi, 2011). A previous study conducted in Japan by Yamakoshi *et al.* (2012) suggested that chlorhexidine gluconate ointment is a useful topical medicine for the treatment of

early-stage acne and for preventing acne. However, periodic usage of acne antibiotic often correlates with the potentially arise of side effect such as antibiotic resistance, skin's sun sensitivity (Garett and Margolis, 2012), liver function abnormalities, teratogenic side effects (Tripathi *et al.*, 2012) or common side effect included skin dryness, irritation, itching, redness and peeling (Mosler *et al.*, 2018). With these issues arise, therefore, imply that discovering a new, safe, less corrosive, skin loving, cost effective and compelling anti acne compounds are still required. For many years, nature has been of great resources for medicinal agents and a significant number of current medications have been isolated, many of which based on their utilization in conventional medicine. Only 1% of the natural resources have been phytochemically examined out of approximately 500,000 plant species existing worldwide (Palombo, 2011).

In skin environment, the bacteria associated with acne formation are often referred to as acne-causing bacteria. If left untreated, acne-causing bacteria can give rise to comedone, papule, pastule and nodule or cyst, a disease related to an inflammation of the acne on skin. Therefore, to prevent acne formation, the study about plants with active anti acne properties with includes both antibacterial and antioxidant activities are required. In this current study, the antibacterial activity of dried leaves of *Psidium guajava* Linn. extracts with different solvents extraction and its fractions against acne-causing bacteria primarily *Staphylococcus aurues, Staphylococcus epidermidis* and *Propionibacterium acnes* and antioxidant activity are determined. The active anti acne metabolites are also identified using Gas Chromatography-Mass Spectrometry (GC-MS), Liquid Chromatography-Mass Spectrometry (LC-MS) and proton nuclear magnetic resonance (^{1}H NMR).

1.2 Justification of Study

Acne vulgaris is a noticeable skin disorder in human that can be found on either on the face, back or chest and even though the life-threatening condition case is unlikely occurred however, it becomes a crucial struggle for health care provider. People are vulnerable to acne disease at any stage of life and may continue into 30s and 40s, which around 20% of young peoples those are affected with the severe acne correlated with pubertal maturity. There are several different therapy methods for acne treatment but it is highly cost. For many years, nature has been of great resources for medicinal agents including anti acne. In skin environment, the acne-causing bacteria are associated with acne formation. Therefore, to prevent acne formation, the study about plants with active anti acne properties with includes both antibacterial and antioxidant activities are required.

1.3 Significance of Study

The significance of the research study is to help better understand the effect of medicinal plants toward fighting acne lesion formation. This research was needed to be done as there are lacks of sufficient information regarding *P. guajava* Linn. as anti acne treatments. This study also gives insight on future anti-acne natural product development in combating acne lesion to the phytopharmaceutical industries.

1.4 Limitation of Study

A limitation of this study was the anti-inflammatory effect of *P. guajava* Linn. Emerging data indicate that acne vulgaris is a primary inflammatory disease, with histological, immunological, and clinical evidence suggesting that inflammation occurs at all stages of acne lesion development. The immunochemical pathways underlying the initiation and propagation of the inflammation in acne are complex and still being elucidated and involved *P. acnes*. Thus, because inflammation is critical to all types of acne lesions and is multifactorial, anti-inflammatory effect on *P. guajava* Linn. can be expected to exert effects against all lesion stages.

1.5 Hyphothesis of Study

Different type of solvent extraction of *Jambu batu* (*P. guajava* Linn.) leaf has different anti-acne activities. The phytochemical studies will reveal the active metabolites that responsible for the active anti acne activities. The active compound/s which has anti-acne activities in *Jambu batu* (*P. guajava* Linn.) leaf extracts can be isolated and identified.

1.6 Problem Statements

Acne problem are related to various factor including over chemical usage, uncontrolled drying of skin, food consumption, environment, unhygienic system and genetic (Ayer and Burrows, 2006). The finding of suitable natural resources with fewer side effects for consumer is another alternative solution for acne problem. For many years, *Jambu batu* (*P. guajava* Linn.) leaf has been used in the prevention of acne formations as well as for medicinal purposes in Malaysia. Currently, our screening studies of antibacterial activity, the methanolic of *P. guajava* Linn. leaves extract inhibit the growth of some skin bacteria. Despite the previous studies about (*P. guajava* Linn.) leaf extract, there are some limitation in aspect of types of solvent used for extraction, concentrations of extract and types of bacteria. An approach of using different solvents for extraction with different concentrations of extract might be useful in understanding the antibacterial activity at its best. Solvents with different polarities and concentrations will yield extracts with different compounds thus vary in aspect of antimicrobial activity and antioxidant. Even natural products have been widely accepted, consumer are searching for a less corrosive and skin loving product that are safe for daily usage but the issues regarding the safety of natural products are still rising. Thus, active anti-acnes metabolites-rich extract (fraction) and its compound/s which have potential anti-acne activity (antibacterial and antioxidant) need to be evaluated and identified for further application in any acne care products.

1.7 Objectives

The objectives of this study are:

1. To determine antimicrobial activity of *Jambu batu* (*P. guajava* Linn.) leaf extracts and fractions of different solvents, extracts and fractions concentrations

against *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Propionibacterium acnes* using disc diffusion, minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and time-kill curve assays.

2. To determine the antioxidant activity of *Jambu batu* (*P. guajava* Linn.) leaf extracts and fractions with different solvents, extracts and fractions concentrations using total phenolic content (TPC) and 2,2-diphenyl-1-picrylhydryzyl (DPPH) assay.

3. To identify and isolate the active anti-acne metabolites in *Jambu batu* (*P. guajava* Linn.) leaf extracts using bioassay guided approach.

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