FORMULATION AND CHARACTERISATION OF POLYHERBAL ANTI-ACNE GEL CONTAINING *Citrus aurantifolia* (Christm.) Swingle AND *Aloe barbadensis* Mill. EXTRACTS

By

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Chairman : Professor Ir. Yus Aniza binti Yusof, PhD
Institute : Halal Products Research

Acne vulgaris or common acne affects teenagers the most. Acne vulgaris is a skin disorder that occurs when dead cells, oil, and bacteria including *Propionibacterium acnes*, *Staphylococcus aureus* and *Staphylococcus epidermidis* clog hair follicles. Medicinal plants are used to treat acne and are safer with less side effects, such as skin irritation. Furthermore, the demand for halal herbal formulations is currently very high on the global market. However, prior research had shown that treating acne by applying *Citrus aurantifolia* (Christm.) Swingle juice, also known as key lime juice to the skin immediately would flow off upon application. In addition, only a single plant, *C. aurantifolia*, was employed in an anti-acne gel formulation to treat acne has no synergistic therapeutic effect and does not boost up effectiveness due to the inadequacy of their active bioactive compounds. Moreover, the effects of applying modern treatments (thermal and non-thermal) on anti-acne gel formulation are still unknown. Therefore, the objective of this study is to formulate a polyherbal anti-acne gel containing *C. aurantifolia* and *Aloe barbadensis* Mill., also known as *Aloe vera*. This study is also to characterise the formulated polyherbal anti-acne gel for its physicochemical properties, to investigate the efficacy of the best formulated gel in-vitro permeation study as well as the effects of modern processing treatments on the best formulated polyherbal anti-acne gel storage stability. The phytoconstituents found in plant extracts and their antibacterial activity against *S. aureus* were also analysed. After plant extracts discovery, gel formulations with varying concentration of plant extracts, and excipients were prepared along with compatibility studies. Various parameters like colour, odour, homogeneity, phase separation, consistency, washability, pH, spreadability, viscosity, extrudability, drug content, antibacterial activity, stability, particle size, in-vitro permeation and compared with a commercial herbal formulation were investigated. Subsequently, the best formulated polyherbal anti-acne gel had been given modern treatments using high-pressure processing and microwave pasteurisation. The results showed that gel formulation containing plant extracts of *C. aurantifolia* and *A. barbadensis* as well as the excipients Carbopol 940, methylparaben, propylparaben,

propylene glycol-400, triethanolamine and water was found optimum for all the parameters. It has a synergistic effect on antibacterial activity and was comparable to the commercial herbal formulation. However, high-pressure processing and microwave pasteurisation are not preferable treatments options to substitute the paraben in gel formulation. It is concluded that the formulation of a washable and skin-permeable polyherbal anti-acne gel containing *C. auranfolia* and *A. barbadensis* has high potential for halal cosmetics product development.

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

FORMULASI DAN PENCIRIAN GEL ANTI-JERAWAT POLIHERBA MENGANDUNGI EKSTRAK *Sitrus aurantifolia* (Christm.) SwingleDAN *Aloe barbadensis* Mill.

Oleh

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Jerawat vulgaris atau jerawat biasa paling banyak memberi kesan kepada remaja. Acne vulgaris ialah gangguan kulit yang berlaku apabila sel mati, minyak, dan bakteria termasuk *Propionibacterium acnes*, *Staphylococcus aureus* dan *Staphylococcus epidermidis* menyumbat folikel rambut. Tumbuhan ubatan yang digunakan untuk merawat jerawat adalah lebih selamat daripada pelbagai kesan sampingan. Tambahan pula, permintaan terhadap formulasi herba halal adalah sangat tinggi di pasaran global kini. Walau bagaimanapun, kajian lepas telah menunjukkan bahawa merawat jerawat dengan menggunakan jus *Citrus aurantifolia* (Christm.) Swingle, juga dikenali sebagai jus limau nipis pada kulit dengan segera akan mengalir apabila digunakan. Di samping itu, hanya satu tumbuhan, *C. aurantifolia*, digunakan dalam formulasi gel anti-jerawat untuk merawat jerawat tidak mempunyai kesan terapeutik sinergistik dan tidak meningkat keberkesanan kerana ketidakcukupan sebatian bioaktif yang aktif. Selain itu, kesan penggunaan rawatan moden (terma dan bukan terma) terhadap formulasi gel anti-jerawat masih tidak diketahui.

Oleh itu, objektif kajian ini adalah untuk memformulasikan gel anti-jerawat poliherba yang mengandungi *C. aurantifolia* dan *Aloe barbadensis* Mill., juga dikenali sebagai *Aloe vera*. Kajian ini juga adalah untuk mencirikan formulasi gel anti-jerawat poliherbal untuk sifat fizikokimianya, menyiasat keberkesanan kajian resapan dalaman vitro bagi formulasi gel yang terbaik serta kesan rawatan pemprosesan moden ke atas kestabilan penyimpanan bagi formulasi gel anti-jerawat poliherbal yang terbaik. Fitokonstituen yang terdapat dalam ekstrak tumbuhan dan aktiviti antibakteria ekstrak tumbuhan terhadap *S. aureus* juga telah dianalisis. Selepas penemuan ekstrak tumbuhan, formulasi gel dengan kepekatan ekstrak tumbuhan dan eksipien yang berbeza-beza telah disediakan dan diikuti oleh kajian keserasian. Pelbagai parameter seperti warna, bau, kehomogenan, pemisahan fasa, ketekalan, kebolehbasuh, pH, kebolehtebaran, kelikatan, kebolehsemperitan, kandungan dadah, aktiviti antibakteria, kestabilan, saiz zarah,

resapan dalam vitro dan dibandingkan dengan formulasi herba komersial juga telah disiasat. Selepas itu, formulasi gel anti-jerawat poliherba yang terbaik telah diberikan rawatan moden menggunakan pemprosesan tekanan tinggi dan pempasteuran gelombang mikro. Keputusan menunjukkan bahawa formulasi gel yang mengandungi ekstrak tumbuhan *C. aurantifolia* dan *A. barbadensis* serta eksipien Carbopol 940, methylparaben, propylparaben, propylene glycol-400, triethanolamine dan air didapati optimum untuk semua parameter. Formulasi gel mempunyai kesan sinergistik pada aktiviti antibakteria dan setanding dengan formulasi herba komersial. Walau bagaimanapun, pemprosesan tekanan tinggi dan pempasteuran gelombang mikro bukanlah pilihan rawatan yang lebih baik untuk menggantikan paraben dalam formulasi gel. Disimpulkan bahawa formulasi gel anti-jerawat poliherbal mengandungi *C. auranfolia* dan *A. barbadensis* dan bercirikan kebolehbasuhan dan ketelapan kulit mempunyai potensi tinggi untuk pembangunan produk kosmetik halal.

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LIST OF ABBREVIATIONS

°C	degree celsius
CFU/mL	colony-forming unit per milliliter
cm	centimetres
cm^2	centimetres square
cps	centipoise
d	diameter
g	gram
g/cm^3	gram per cubic centimetre
h	hour
M	mol
m	metre
mg	milligram
mg/L	milligram per litre
mg/mL	milligram per millilitre
min	minute
mL	millilitre
mm	millimetre
mm/sec	millimetre per second
nm	nanometre
p	Probability
PDI	polydispersity index
pH	power of hydrogen
q.s	quantum satis
rpm	rotation per minute

s	second
SAS	statistical analysis system
SD	standard deviation
UV	ultraviolet
V	volume
v/v	volume to volume
VIS	visible
w/o	without
μg/mL	microgram per litre
μL	microlitre
μm	micrometre

CHAPTER 1

INTRODUCTION

1.1 Research Background

Acne vulgaris is another name for common acne. It is a skin disorder that occurs when dead skin cells, bacteria, and oil clog hair follicles (Aini et al., 2018). This results in blackheads, whiteheads, nodules, papules, and pustules on the skin (Kusuma et al., 2018; Jain et al., 2018). Acne is caused by the bacteria *Propionibacterium acnes*, *Staphylococcus epidermidis* and *Staphylococcus aureus* (Borse et al., 2020). *S. epidermidis* causes superficial infections in the sebaceous unit, whereas the chemicals produced by *P. acnes* cause irritation, and *S. aureus* causes acne lesions (Borse et al., 2020), which affects the skin on the face, upper chest, and back (Mate et al., 2021).

Acne vulgaris was ranked eighth among the top ten most common skin diseases worldwide in 2010 (Hay et al., 2014). According to reports, around 85% of individuals between the ages of 12 and 24 years old, 8% of adults between the ages of 25 and 34 years old, 3% of adults between the ages of 35 and 44 years old, and 42.5% of males and 50.9% of women are impacted in their twenties (Prabu et al., 2017). Acne vulgaris is a skin disease that affects teenagers the most due to hormonal changes produced by the adrenal glands of both males and females throughout puberty (Jain et al., 2018) causing them to lose confidence due to their looks and interfering with their everyday activities (Fabbrocini et al., 2018). They are looking for a way to get rid of the acne.

Acne treatment can be topical and systemic treatment. Topical therapy is a mild acne treatment that can lead to acne remission. Retinoids, benzoyl peroxide and combinations of these drugs are commonly utilized (Keri, 2022). Retinoids can cause skin irritation such as redness, swelling, peeling, blistering, erythema, burning, and stinging if used excessively. Eczema can also be triggered by retinoids. Benzoyl peroxide is a powerful antibacterial, comedolytic, and anti-inflammatory agent (Sutaria, 2023). The side effects of benzoyl peroxide are dryness, peeling, stinging, burning, itching and erythema.

For moderate to severe acne vulgaris, systemic treatment such as oral antibiotics have been frequently employed (Yvette, 2023). This is because it can prevent bacteria from colonizing pilosebaceous glands. Antibiotic treatment for an extended period can result in antibiotic resistance and a variety of adverse effects, including erythema, photosensitivity, allergic dermatitis, urinary problem, joint and muscle pain, headache, depression and excessive skin irritation.

Long term usage of antibiotics has resulted in bacterial resistance and unanticipated adverse effects, medicinal plants should be considered as an alternate treatment for acne vulgaris (Prabhakar et al., 2020). Phytochemicals are well recognized in medicinal plants. Primary and secondary metabolites are two types of phytochemicals. Alkaloids, saponins, quinones, coumarins, steroids, phenols, flavonoids, tannins, and other

metabolites are examples of secondary metabolites (Kola-Mustapha et al., 2020). Secondary metabolites can perform the properties of antimicrobial and anti-inflammatory. When medicinal plants are combined, their secondary metabolites are enough to have a synergistic therapeutic effect (Kola-Mustapha et al., 2020). Furthermore, these medicinal plants are widely available, inexpensive, and have few side effects (Keshri, 2020).

1.2 Problem Statement

Prior research had shown that *C. aurantifolia* is also known as key lime juice was found to be an effective antibacterial in treatment of two acne-causing bacteria, *P. acnes* and *S. epidermidis* (Aini et al., 2018), but it is not practicable to apply *C. aurantifolia* juice to the skin immediately. It is both ineffective and inconvenient due to the property of low viscosity of juice would flow off the skin upon application. It had also been established previously that an anti-acne gel containing only *C. aurantifolia* juice was formulated to treat acne caused by *P. acnes* and *S. epidermidis* (Kusuma et al., 2018) may not be able to provide the desired synergistic therapeutic effects due to the inadequacy of their active bioactive compounds in the single plant (Kola-Mustapha et al., 2020). Therefore, a higher dosage is required for the treatment of acne. In addition, most cosmetics are produced by non-halal certified companies, whose production processes might not meet the standards of halal science. The development of halal cosmetics and the evaluation of their effectiveness as a product are still unsatisfied (Sugibayashi et al., 2019). To date, no processing technique in use, including modern treatments (thermal and non-thermal) using high-pressure processing and microwave pasteurisation has been investigated for its effects on the storage stability of anti-acne gel formulation.

1.3 Objectives

The aims of this study are:

1. To formulate a polyherbal anti-acne gel containing *C. aurantifolia* and *A. barbadensis*, also known as *Aloe vera*, along with qualitative and quantitative analysis on phytoconstituents in plant extracts and compatibility studies.
2. To analysed the physicochemical properties, antibacterial activity, stability, particle size of formulated gels and as comparison to a commercial herbal formulation.
3. To investigate the efficacy of the best formulated gel via in-vitro permeation study.
4. To investigate the effects of high-pressure processing and microwave pasteurisation on the storage stability of anti-acne gel formulation.

1.4 Research Hypothesis

The hypotheses of this study are as follow: -

1. The polyherbal anti-acne gel formulation containing *C. aurantifolia* and *A. barbadensis* can treat mild acne vulgaris.
2. The best formulated gel is clear, no odour, uniform, without lumps, consistent and easily washed. It also has a pH that is closer to that of the skin, good spreadability, viscosity, extrudability, as well as a high percentage of drug content and good stability. It has a synergistic effect with the largest diameter of inhibition zone. The mean particle size and the polydispersity index are regarded as acceptable in drug delivery applications. It is comparable to the commercial herbal formulation.
3. The best formulated gel shows good drug release and permeation characteristics.
4. The modern treatments using high-pressure processing and microwave pasteurisation provide storage stability to the treated gel formulation.

1.5 Significance of Study

Direct application of *C. aurantifolia* juice to treat acne is problematic. The juice would run off the skin upon application. The juice is formulated in the form of anti-acne gel which can increase bioavailability and allows active substances to be released freely. In addition, the chosen combination of plant extracts, *C. aurantifolia* and *A. barbadensis* are formulated in the form of anti-acne gel is synergistically therapeutic against microorganisms like *P. acnes*, *S. epidermidis* and *S. aureus*, which cause acne inflammation. *C. aurantifolia* and *A. barbadensis* contain phytoconstituents such as alkaloids, flavonoids, phenol, tannic and ascorbic acid which have antibacterial properties. These plant extracts are also safe with minimal side effects.

Moreover, the gel formulation can boost patients with acne compliance by providing additional cold sensations on the skin, is quickly absorbed, and forms a film that is easy to wash. Furthermore, there has not been any research done on the effects of modern treatments using high-pressure processing and microwave pasteurisation on gel formulation as an alternative for the excipient, paraben in the gel formulation. The storage stability of gel formulation may be improved by high-pressure processing and microwave pasteurisation.

1.6 Scope of the Study

In the present study, attention was mainly focused on the usage of plant extracts, *C. aurantifolia* and *A. barbadensis* to develop a formulation based on gel. The excipients such as Carbopol 940, propylene glycol-400, methylparaben, propylparaben, triethanolamine and required amount of water in a sufficient quantity were added to

prepare 50 g of gel. Meanwhile, the total amount of phytoconstituents, such as phenol, tannins, flavonoid, and ascorbic acid were determined in plant extracts.

The parameters like colour, odour, homogeneity, phase separation, consistency, washability, pH, spreadability, viscosity, extrudability, drug content, antibacterial activity, stability studies, particle size and in-vitro permeation of the formulations were evaluated and compared with a commercial herbal formulation. Furthermore, the best formulated gel undergoes two processing methods, both of which are modern treatments using high-pressure processing and microwave pasteurisation on the storage stability of gel formulation were examined.

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