SYNTHESIS OF PIPERINE DERIVATIVES

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Special dedication to my:-

cherished husband and children;
Mohamed Syahrani b. Mat Nor
HafezulRahman b. Mohamed Syahrani
Abdullah Azam b. Mohamed Syahrani

adoring family and family-in-law;

and my trustworthy friends…

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ABSTRACT

The berries of black pepper (*P. nigrum*) are well known for its pungent smell and biting taste. Piperine which is one of the major amide present in *P. nigrum* contributes to the medicinal properties of the species. Extraction of the berries through maceration process followed by isolation of piperine *via* treatment with ethanolic potassium hydroxide successfully produced piperine (5-(1,3-benzodioxol-5-yl)-1-(1-piperidinyl)-2,4-pentadien-1-one). Several chemical modifications have been carried out to derivatize piperine. Acetal cleavage has afforded 5-(3,4-dihydroxyphenyl)-1-(1-piperidinyl)-2,4-pentadien-1-one. Basic hydrolysis of piperine then afforded piperic acid (5-(1,3-benzodioxol-5-yl)-2,4-pentadienoic acid) which had been used as the precursor to synthesize an aliphatic amide (5-(1,3-benzodioxol-5-yl)-1-(*n*-butylamine)-2,4-pentadien-1-one), an ester (5-(1,3-benzodioxol-5-yl)ethyl-2,4-pentadienoate) and an acid (1,3-benzodioxol-1-yl)-methanoic acid). The pure piperine and derivatives were characterized by using infrared spectroscopy (IR), nuclear magnetic resonance (NMR) and mass spectrometry (MS). The screening for antimicrobial properties of the compounds were also carried out by using disc diffusion, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) methods against Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). Piperine and all derivatives were found to be active towards Gram-positive bacteria with MIC value ranging from 225-900 µg/mL.

ABSTRAK

Bijiladahitam (*P. nigrum*) adalahdikenaliumumsebagaiherba yang mempunyaibau yang tajamdan rasa yang pahit.Piperinaadalahsalahsatuamidapenting yang wujud di dalam*P. nigrum* yang didapatimempunyaiciri-ciriperubatan.Pengekstrakanbiji*P. nigrum*secararendamandenganpelarutdiikutidenganpengasinganpiperinamelaluitindakbalasdengankaliumhidroksidaberalkoholtelahberjayamenghasilkanpiperina (5-(1,3-benzodioksol-5-il)-1-(1-piperidinil)-2,4-pentadien-1-on). Beberapatindakbalaspengubahsuaiankimiajugatelahdijalankanuntukmenghasilkanterbitanpiperina.Tindakbalaspemutusankumpulanasetaltelahmenghasilkansebatian5-(3,4-dihidroksifenil)-1-(1-piperidinil)-2,4-pentadien-1-on. Hidrolisisberalkalikeataspiperina pula berjayamenghasilkanasidpiperik (asid 5-(1,3-benzodioksol-5-il)-2,4-pentadienoik) yang seterusnyatelahdigunakansebagaisebatianpemulauntukmensintesisamidaberantailurus (5-(1,3-benzodioksol-5-il)-1-(*n*-butilamina)-2,4-pentadien-1-on), ester (5-(1,3-benzodioksol-5-il)etil-2,4-pentadienoat) danasid (asid 1,3-benzodioksol-1-il)-metanoik). Sebatianpiperinatulendansebatianterbitantelahdicirikandenganmenggunakankaedahspektroskopiinframerah (IM), resonans magnet nukleus (RMN) danspektrometrijisim (SJ).Saringanantimikrobkeatassemuasebatiantelahdijalankanmenggunakankaedahpembaurancakera, kepekatanperencatan minimum (KPM) dankepekatanbakteria minimum (KBM) keatasbakteria Gram-positif(*Bacillus subtilis* dan*Staphylococcus aureus*) dan Gram-negatif (*Escherichia coli* dan*Pseudomonas aeruginosa*).Piperinadankesemuasebatianterbitandidapatiaktifterhadapbakteria Gram-positifdengannilai KBM dalamjulat 225-900 µg/mL.

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LIST OF ABBREVIATIONS

mg	milligram
mL	millilitre
µL	microlitre
µg/mL	microgram per mililitre
ppm	part per million
m.p	melting point
R_f	retention factor
TLC	Thin Layer Chromatography
UV	Ultraviolet
IR	Infrared
FTIR	Fourier Transform Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
MS	Mass Spectrometry
EIMS	Electron Ionized Mass Spectrometry
KBr	potassium bromide
ν_{max}	maximum absorbance
^{1}H	proton
^{13}C	carbon-13
δ	chemical shift
$CDCl_3$	deuterated chloroform
J	coupling constant
s	singlet
d	doublet
t	triplet
q	quartet

dd	doublet of doublets
qd	quartet of doublets
m	multiplet
m/z	mass-to-charge ratio
amu	atomic mass unit
$CHCl_3$	chloroform
KOH	potassium hydroxide
EtOH	ethanol
PE	petroleum ether
CH_3COOH	acetic acid
$NaHCO_3$	sodium bicarbonate
Et_2O	diethyl ether
DMSO	dimethyl sulfoxide
$NaOCH_3$	sodium methoxide
HCl	hydrochloric acid
BBr_3	boron tribromide
DCM	dicholoromethane
N_2	nitrogen
$NaBH_4$	sodium borohydride
THF	tetrahydrofuran
I_2	iodine
MeOH	methanol
Et_3N	triethylamine
CH_3SO_2Cl	methane sulfonylchloride
KF	potassium fluoride
Al_2O_3	alumina
Pd	palladium
C	carbon
H_2	hydrogen
HBr	hydrogen bromide
mCPBA	*meta*-chloroperoxybenzoic acid
NaOH	sodium hydroxide
Na_2SO_4	sodium sulphate

$KMnO_4$	potassium permanganate
H_2SO_4	sulphuric acid
$BaCl_2$	barium chloride
SS	streptomycin sulphate
MIC	Minimum Inhibitory Concentration
MBC	Minimum Bactericidal Concentration
B. subtilis	*Bacillus subtilis*
S. aureus	*Staphylococcus aureus*
E. coli	*Escherichia coli*
P. aeruginosa	*Pseudomonas aeruginosa*

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CHAPTER 1

INTRODUCTION

1.1 Natural Plants and their Benefits

Malaysia has wide varieties of natural resources of flora and faunawith high biological diversity [1, 2]. Its natural plants have lots of uses and benefits. The plants' part that are very useful to us are the seeds, flowers, leaves, stems, barks, roots, and rhizomes, which mostly act as spices that can be used in culinary preparations, perfumery and cosmetics [3].

Plants can also contribute to the development of medicinal field. Human beings really rely on herbs and spices for medicines and they act in different ways in curing diseases as they have different medicinal properties [4],and a few examples are listed in **Table 1.1**.

Table 1.1: Various medicinal properties of spices

Medicinal properties	Details	Examples
Anti-gas activity	Help expel gas and relieve flatulence	Aniseed, caraway seeds, cinnamon, clove, dill, fennel seeds, garlic, ginger, mint
Anticoagulant activity	Discourage platelets from clumping together or aggregating	Chilli pepper, clove, garlic, ginger, onion
Antidepressant activity	Influencing serotonin, thus helping in elevating moods by changing brain chemistry	Cardamom, chilli, garlic, pepper
Painkilling activity	Alleviate pain	Asafoetida, bishop's weed, clove, garlic, ginger, mustard seeds, nutmeg, onion, pepper, poppy seeds
Mucus-clearing activity	Activate nerve endings in the oesophagus and stomach, causing watery reactions. Thinning mucus and encouraging it to move along	Aniseed, asafoetida, basil, bishop's weed, chilli pepper, clove, fennel, garlic, ginger, onion, tamarind, turmeric
Antibacterial activity	Kill bacteria	Clove, cumin seeds, garlic, ginger, onion, turmeric
Anti-diabetic activity	Lowering blood sugar or stimulating insulin production	Cinnamon, curry leaves, fenugreek seeds, garlic, onion
Anti-diarrhoeal activity	Contain tannins and astringent compounds that can fight bacteria in intestines and thereby exert soothing effect	Dill, fenugreek seeds, garlic, ginger, mint, nutmeg, turmeric
Anti-inflammatory activity	Help in manipulating prostaglandins system to block process of inflammation	Garlic, ginger, onion, tamarind, turmeric
Anti-viral activity	Fight various types of viruses that enter body	Basil, cinnamon, dill, garlic, ginger, onion, turmeric
Calming and sedative property	Work as sedatives by stimulating the activity and levels of neurotransmitters	Aniseed, cumin seeds, dill, nutmeg, poppy seeds

Sex stimulating property	Serve as aphrodisiacs, which help in correcting sexual inadequacy and dysfunction. Help building up health of various sex glands and organs	Asafoetida, bishop's weed, cardamom, fenugreek seeds, garlic, ginger, nutmeg, onion, pepper

1.2 Background of Study

Nowadays, development of research on natural products are on demand. Researches are looking forward in isolating new compounds from the natural products, and some even heading towards expanding the research into production of derivatives from the compounds isolated, especially for structure-activity relationships (SAR)investigations purposes. This can be achieved *via* chemical modifications using organic synthesisreactions. Therefore, organic synthesis has play an important role in organic chemistry.

1.3 Principles of Organic Synthesis

The tremendous improvements in understanding the structure and reaction mechanisms, and with the aid of increasing powerful instrumentation and analytical tools, had enabled the organic synthesis extended to virtually all of science. These included studies on the reactive intermediates, organometallic chemistry,photochemistry, natural products chemistry, catalysis,solid-phase synthesis, chemical libraries, electrochemistry,novel materials, enzyme-mediated transformations,biochemistry, medicinal chemistry, biologyand virology[5].

Majority of the organic reactions at first seemed to be highly complex which included extensive reorganization of the bonds of the reactants. However, they actually comprise of a comparatively small number of basic processes and each reaction is a combination of these, and five such processes may be recognized as the

bond-breaking, bond-forming, synchronous bond-breakage and bond-formation, intramolecular migration and electron-transfer. These unit processes when combined in the overall reaction will lead to organic reactions that can be classified as the addition reaction, elimination reaction, substitution reaction, condensation reaction, rearrangement reaction, pericyclic reaction and oxidation-reduction reaction [6]. The classification of reactions and their subdivision reactions are shown in **Table 1.2**.

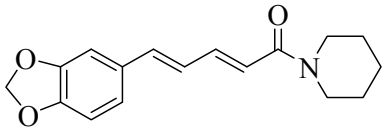
Table 1.2: Classification of reactions and their subdivision reactions

Classification of reactions	Subdivision
Addition	Electrophilic addition, nucleophilic addition, radical addition
Elimination	β-elimination, α-elimination
Substitution	Synchronous substitution, elimination-addition, addition-elimination
Condensation	-
Rearrangement	Intramolecular rearrangements, intermolecular rearrangements
Pericyclic	Cycloadditions, electrocyclic reactions, cheletropic reactions, sigmatropic reactions, ene-reactions
Oxidation-Reduction	-

The interconversions of functional groups are one of the important aspects of organic synthesis. Several transformations can be made to the functional group present in a molecule, and such examples are the transformation of the hydroxyl group, transformation of the amino group, transformation of the halogeno compounds, transformation of the nitro compounds, transformation of the aldehydes and ketones, and the transformation of the acids and acid derivatives [7]. All these transformations experiments can be carried out in the laboratory by using appropriate materials and conditions to obtain the desired product.

1.4 Black Pepper *(P. nigrum)*

*P. nigrum***(Figure 1.1)**is one of the examples ofwidely investigated plant for phytochemicals, and its phytochemical investigationshave led to the isolation of alkaloid,amides, propenylphenols, lignans, neolignans, terpenes, steroids, kawapyrones, piperolides, chalcones, dihydrochalcones, flavones and flavanones. The fruits of *P. nigrum* is known as the 'King of Spices', and is one of theimportant spices of India[8]. The ripened fruit of *P. nigrum*is the source of white pepperwhile the unripe ones**(Figure 1.2)**is thesource of black pepper [9]. One of *P. nigrum* major constituents is the piperine**(1)**, which is very abundant in the plant and being extracted from the dry fruits with a yield of 3–7% [10].



(1)

Piperine **(1)**can be modified into new compounds through several chemical reactions, and these reactions have played an important role especially in producing derivatives of piperine. These derivatives then can be used in treatment of various human disorders. Organic synthesis therefore opens up new paths for research in medicinal chemistry to evolve better drugs [11].

Figure 1.1: *P. nigrum* tree

Figure 1.2:*P. nigrum* fruits before ripened

1.5 Problem Statement

Piperine **(1)** is apiperamide which contribute to the pungent principle of *P. nigrum*, and lots of researches have demonstratedthe superior potential of such amide as insecticides, molluscicides, and antifungal agents[12]. There are already lots of researches done to piperine **(1)**. However, very little researches reported on the direct derivatization of piperine **(1)** to produce piperine derivatives. This may bebecause of piperine **(1)** is an amide which is known as theleast reactive of the acyl compounds [13]. Therefore there is a need to carry out derivatization of piperine **(1)** especially in evaluating their medicinal properties.

1.6 Objectives of Study

The objectives of this research are as listed below:-

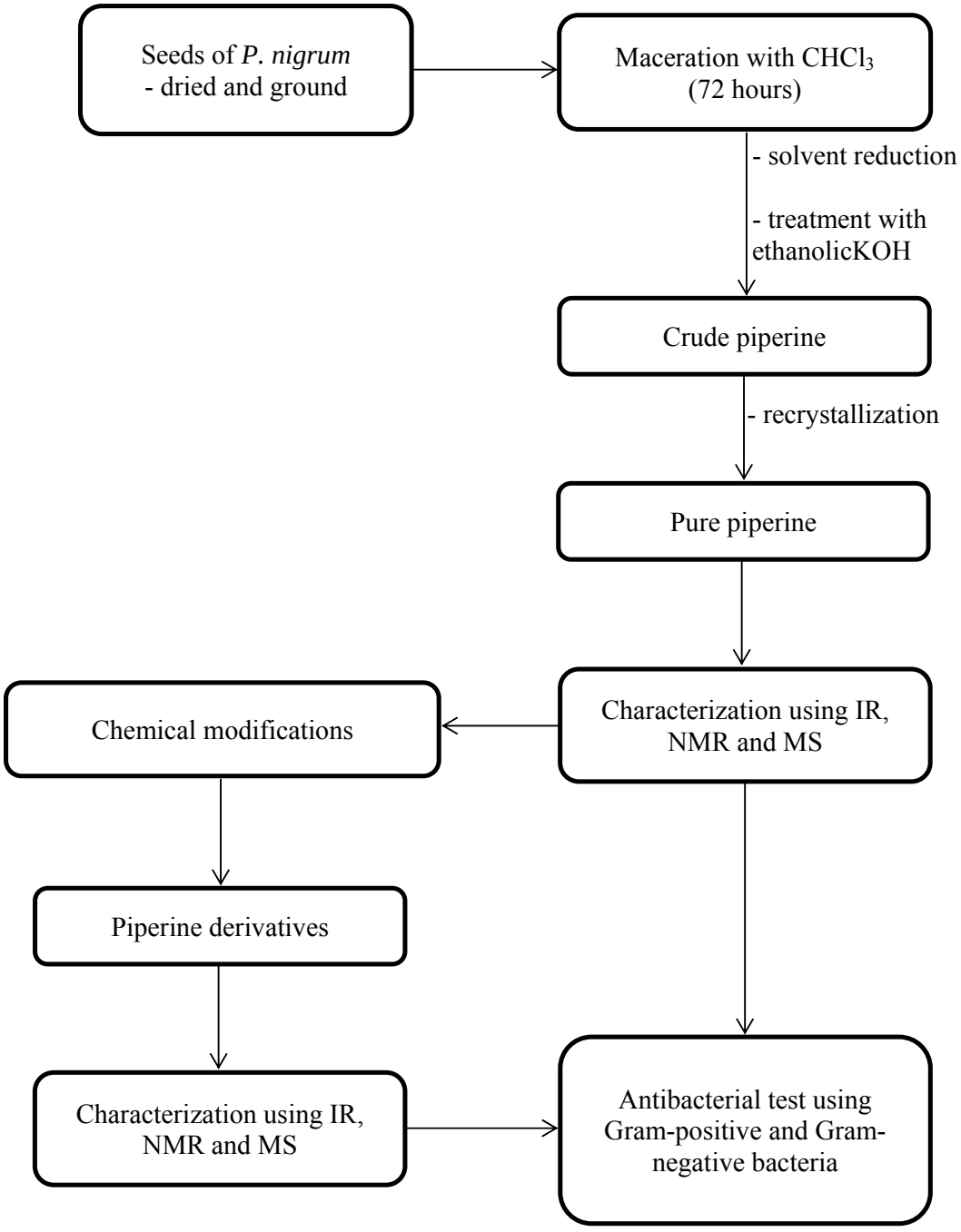
a. To isolatepiperine **(1)** from the $CHCl_3$ extract of *P. nigrum*, andderivatize it through several chemical reactions.
b. To characterize the piperine **(1)** and its derivatives using IR, NMR andMS spectroscopies.
c. To screen the antibacterial activity of piperine **(1)** and the derivatives.

1.7 Scope of Study

The *P. nigrum* berries will be extracted by maceration using $CHCl_3$. The solid piperine **(1)** will be purified either by column chromatography or recrystallization and analyzedspectroscopically. The characterized piperine **(1)**will be subjected to various chemical reactions such asacetal cleavage, reduction and epoxidation, while the basic hydrolysis product of piperine **(1)**will then be derivatized toformamide, ester and acid. All products will be characterized by using several spectroscopy

techniques such as IR, NMR and MSspectroscopies. The piperine **(1)**and its derivatives will be screened for antibacterial test using Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria.

1.8 Flow Chart of Studies



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