UNIVERSITI TEKNOLOGI MARA

PHYTOCHEMICAL STUDIES ON ALKALOIDS FROM *FISSISTIGMA LATIFOLIUM* (DUNAL) MERR.

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Thesis submitted in fulfillment of the requirement
for the degree of
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Candidate's Declaration

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the result of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non academic institution for any other degree or qualification.

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ABSTRACT

Fissistigma latifolium is a climbing shrub found in low land forest of Sumatera, Borneo, Philippines and Malaysia. Several species of the genus *Fissistigma* have been used as folk medicine for the treatment of tumors, inflammatory disease, diarrhea, ulcers and rheumatism. Previous phytochemical work on *Fissistigma* species has revealed presence of aporphine, oxoaporphine and phenanthrene alkaloids. Although the genus *Fissistigma* is well known as a source of alkaloids, *Fissistigma latifolium* has not been well studied. In the present work, phytochemical studies were conducted on *Fissistigma latifolium* collected from Dungun, Terengganu with the aim of isolating and identifying the alkaloid content from the bark of the plant. The phytochemical procedures adopted were acid-base extraction followed by solid-phase extraction, column chromatography and preparative thin layer chromatography. The structural elucidation was accomplished by spectroscopic methods such as ID-NMR (^{1}H, ^{13}C, DEPT), 2D-NMR (COSY, HMQC, HMBC), UV, IR and MS and comparison with published data. Isolation and purification of alkaloids from the bark of *Fissistigma latifolium* afforded nine alkaloids with one most probably new. The known alkaloids are; liriodenine, oxoxylophine, asimilobine, dimethyltryptamine, *N*-methylanonaine, anonaine, columbamine, lysicamine and alkaloid FL7. Dimethyltryptamine is reported for the first time from *Fissistigma* species. The crude extracts and selected alkaloids were screened for antioxidant assays using ferric thiocyanate (FTC), thiobarbituric acid (TBA) and diphenylpicrylhydrazyl (DPPH). The methanol extract showed the highest percent of inhibition while asimilobine has the strongest antioxidant activity observed from FTC and TBA assays. The DPPH radical scavenging assay indicated petroleum ether extract was a good radical scavenger with the percent of inhibition of 86.4%. However, the selected alkaloid compounds showed weak radical scavenging activity with the percent of inhibition in range 48.8 - 61.5%. Five selected alkaloids have been tested for cytotoxic activity. Liriodenine was found to be strongly cytotoxic towards WEHI, HL60 and CEMSS cell-line with CD_{50} values less than 23.0 μg/ml while oxoxylophine showed weak cytotoxicity towards WEHI cell-line with CD_{50} 27.4 μg/ml. In addition, four selected alkaloids have been tested for antimicrobial bioassay against twelve bacteria, *Bacillus subtilis*, *Enterococcus feacalis*, *Eschericia coli*, *Klebsiella pneumonia*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella typhnimurium*, *Serratia marcescens*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumonia* and *Streptococcus pyogenes*. Anonaine showed moderate activities against *Bacillus subtilis*, *Enterococcus feacalis, Staphylococcus aureus, Staphylococcus epidermidis* and *Streptococcus pneumonia*. Oxoxylopine showed moderate activities against *Bacillus subtilis* and *Streptococcus pneumonia* while liriodenine showed moderate activities against the same bacteria but weak activities against *Enterococcus feacalis, Staphylococcus aureus* and *Staphylococcus epidermidis.* The results of these test indicated that some of the isolated compounds showed interesting biological activity that indicated enough evidence to support the potential of *Fissistigma latifolium*.

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CHAPTER 1

INTRODUCTION

Natural products are chemical constituents or substances produced by living organisms that usually possess pharmacological activity useful as lead compound in drug discovery programme. Therefore, since the 1990s, interest in natural products for pharmaceutical industries has increased rapidly (Sticher, 2008) resulting in the discovery of many drugs. Many higher plants contain secondary metabolites with biological properties (Achmad, 2005) provide opportunity for some medicines to be obtained directly from natural sources. This gift from nature which consist of diverse chemical structures with various biological properties has made natural product chemistry research very attractive. Various useful and important compounds may be isolated from various species plants and animals. The isolation of natural products from tissues of terrestrial plants, marine organisms or microorganism fermentation has provided diverse chemical compounds with positive impact for advancement of research in natural products (Newman and Cragg, 2007).

Natural products compound possessing biological activity is known as active principle structure or lead compound (eg: cocaine **1**, quinine **2**, heroin **3**, morphine **4**, vincristine **5**) that maybe useful drugs in themselves or they may become the basis for synthetic drugs. This lead compound can act as a precursor for semisynthetic compounds or can be produced by total synthesis. Pharmaceutical products may be easily developed if the natural constituents which it is based on, can be prepared by total synthesis (Newman and Cragg, 2007). However some natural compounds with very complex structures are difficult to synthesize (Newman and Cragg, 2007) because various specific techniques and methods need to be employed. As a result, simpler analogues are easily designed through organic synthesis but the more complex compound still need to be obtained from natural resources.