UNIVERSITI TEKNOLOGI MARA

CHEMICAL CONSTITUENTS AND NEUROPROTECTIVE EFFECT OF THE SELECTED PLANTS OF SARAWAK, *CALOPHYLLUM GRACILENTUM* AND *CALOPHYLLUM RECURVATUM*

NURR MARIA ULFA BINTI SERUJI

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ABSTRACT

Calophyllum species is well known due to its abundance of potentially beneficial phytochemicals, such as xanthones, coumarins, and others. Despite the extensive report on the rich source of phytochemicals and their biological activities from *Calophyllum*, *Calophyllum gracilentum* and *Calophyllum recurvatum* from the Sarawak Forest is relatively unknown due to the limited information available. A phytochemical study conducted on the stem bark extracts of *Calophyllum gracilentum* successfully afforded two new xanthones, namely marixanthone I **(CG9)** and marixanthone II **(CG10)** together with ten other known xanthones namely brasixanthone B **(CG1),** trapezifolixanthone **(CG2)**, bracteaxanthone XII **(CG3)**, caloxanthone I **(CG4)**, pyranojacareubin **(CG5)**, 5-methoxytrapezifolixanthone **(CG6)**, caloxanthone A **(CG7)**, brasilixanthone B **(CG8**), 9-hydroxycalabaxanthone **(CG11),** pancixanthone B **(CG12)** and, three chromanone acids, isocalolongic acid **(CG13),** isoblanchoic acid **(CG14)** and apetalic acid **(CG15)** also two triterpenoids, friedeline **(CG16)** and lupeol **(CG18)** and a phytosterol, *β*-sitosterol **(CG17).** Meanwhile, a total of six compounds were isolated from *C. recurvatum*, namely trapezifolixanthone **(CR1)**, 6-deoxyjacareubin **(CR2)**, ananixanthone **(CR3)**, thwaitesixanthone **(CR4)**, friedeline **(CR5)** and stigmasterol **(CR6)**. The total phenolic content and total flavonoid content tests showed that both species contain high to moderate levels of phenolic and flavonoid content and antioxidant free radical scavenging assay showed that the extracts exhibited significant activity. Moreover, the evaluation of their neuroprotective properties has been the least studied. Hence, this study is aimed to find and investigate potential therapeutic agents especially for Alzheimer's and Parkinson's disease treatment derived from *Calophyllum gracilentum and Calophyllum recurvatum* in accordance with the goal. Overall, the findings have highlighted the therapeutic potential of **CR4, CR5, CR6, CG3,** and **CG12** as neuroprotective agents as supported by the molecular docking analysis and the structure-activity relationship (SAR) analysis has led to structural features underlying the positive interactions of the tested compounds with specific protein receptors, providing further insight into the mechanisms underlying their biological activities.

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CHAPTER 1

INTRODUCTION

1.1   Research Background

The ancient cultures including the Egyptians, Greeks, and Chinese have used plants as medicine for thousands of years. Several ancient literature and archaeological discoveries provide comprehensive documentation of the use of plants in traditional medical systems including Ayurveda, Traditional Chinese Medicine, and Unani (Cragg *et al*., 2014). A significant field of research in drug development today is the investigation of natural compounds which are the secondary metabolites in plants as potential sources of therapeutic molecules. Secondary metabolites are organic substances that play significant roles in interactions with the environment and other living things but are not directly engaged in the growth or development of an organism. Since many natural products have demonstrated significant biological activities, including antimicrobial, anticancer, anti-inflammatory, and antioxidant properties, the isolation, structural identification, and chemical characterization of natural products are essential steps in the discovery and development of new drugs.

Due to the advancement of technology and the development of new techniques for extraction, isolation, and characterization, natural product chemistry has become a rapidly growing field of research. A wide variety of phenolic compounds, which are potent antioxidants, can be found in plants, including fruits, vegetables, and medicinal plants. Numerous phytochemicals, such as polyphenolic flavonoid compounds, found in a number of plant sources have been shown to possess a variety of bioactivities, including substantial antioxidant, autophagy, and DNA repair activities (Franco *et al*., 2019; Martel *et al*., 2019) as well as a strong anti-inflammatory effect (Franco *et al*., 2019; Martel *et al*., 2019; Zhu *et al*., 2018) effective defence against oxidative cell damage, avoidance of Alzheimer's disease, and prevention from a variety kind of cancer (Custódio *et al*., 2015; Kumari & Jain, 2012; Shivapriya *et al*., 2015).

As people live longer, the prevalence of age-related neurodegenerative disorders (ND) will rise globally (Borgesius *et al*., 2011). According to research, a huge number of fatalities caused by these neurodegenerative disorders (Hussain *et al*., 2018).