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EFFECTS OF *Zingiber zerumbet* ON PARACETAMOL-INDUCED HEPATOTOXICITY IN SPRAGUE DAWLEY RATS

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ABSTRACT

Zingiber zerumbet is a wild ginger, known worldwide for its traditional medicinal values, and the constituents present in its rhizome suggest that it has potent antioxidant and anti-inflammatory activities. This study aimed to investigate the possible curative effects of *Zingiber zerumbet* rhizome ethanolic extract against Paracetamol (PCM) induced hepatotoxicity. The plant was obtained from Sendayan, Negeri Sembilan and identified by the Biodiversity Unit of Universiti Putra Malaysia (UPM), Malaysia. Its rhizomes were collected, cut into smaller pieces and shade dried before being extracted with 80% ethanol. The chemical profile of the ZREE extract determined through Gas Chromatography-Mass Spectrometry (GC-MS) analysis revealed three major compounds which may have contributed to the bioactivity of the plant. After that, an initial analysis to determine the minimum effective dose of PCM to induce hepatotoxicity in rats without causing necrosis was done. Three doses of PCM were tested (300, 400, 750 mg/kg bwt) and through liver function test (LFT) and histological observation, 750 mg/kg bwt was found to be the most effective dose. After PCM-induction, the hepatotoxic rats were treated orally with different doses of the extract (250, 350, 450 mg/kg bwt) for a week and N-acetyl-L-cysteine (NAC) was used as a reference drug. Upon the end of the treatment period, sera samples, livers and other selected organs were collected for liver function tests (LFT), histological analysis and measurement of superoxide dismutase (SOD) and reduced glutathione (GSH) activity. Significant improvements in all LFT parameters were observed in group ZREE 350 (ALP= 125.25 ±20.35 U/L, ALT= 59.75 ±3.09 U/L, AST= 147.50 ±12.78 U/L and TP= 66.45 ±6.96 G/L) while significant improvements in only ALP, ALT and TP were observed in group ZREE 450 (ALP= 127.25 ±12.53 U/L, ALT= 59.29 ±5.78 U/L and TP= 64.93 ±6.56 G/L) in comparison to the negative control group. The oxidative stress parameters (SOD and GSH contents) in liver, kidney and heart of hepatotoxic rats were also found to improved significantly in groups treated with ZREE 350 and ZREE 450. Although there was no significant difference between the outcome of LFT and oxidative parameters of ZREE 350 and ZREE 450 treated groups, the 350 mg/kg bwt of ZREE appeared to be the most effective dose in reducing liver enzyme markers and restoring SOD and GSH contents in the PCM-induced hepatotoxic rats. This was in correlation to the histological analysis result, whereby the qualitative observation of the liver tissue sections from ZREE 350 group scored 3/18 on Hepatic Activity Index which showed minimal damage and identical to the control. Zerumbone (a monocylic sesquiterpene known for its antioxidant activities) was found as the highest component concentration (95%) in ZREE in this study. Overall, ZREE exhibited the most optimum hepatocurative potential in improving liver functions, antioxidant levels and histological appearance in PCM-induced hepatotoxic rat at 350 mg/kg bwt dose.

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CHAPTER ONE
INTRODUCTION

1.1 Background of Study

In Malaysia, the use of herbal and dietary supplements is becoming highly prevalent (Shim, 2016). Among the supplements in demand are the ones that promise a remedy to diseases, promote better health and physical beautification which includes skin lightening and slimming. These supplements are usually food products with added active ingredients and due to their popularity, they have been listed under Food-Drug Interphase (FDI) by the National Pharmaceutical Control Bureau (NPCB) of Ministry of Health of Malaysia in 2014.

The public has a general belief that herbal and dietary supplements must be safe as they have already been marketed. This is a misconception as these products often go unregistered. As reported by the Adverse Drug Reaction (ADR) Monitoring Centre, 70% out of 730 adverse drug reaction reports were caused by unregistered products (National Pharmaceutical Regulatory Agency, (NPRA), 2015). These products usually contain hepatotoxicants such as drugs like steroids and ibuprofen and impurities such as toxic metals (Shaban *et al*., 2016). Due to this, the occurrence of hepatotoxicity associated with consumption of various supplements is emerging (Seeff *et al*., 2013) and according to the National Pharmacy News from the Malaysian Pharmaceutical Society (MPS) in 2017, 20% of hepatotoxicity cases are currently caused by dietary supplements.

Hepatotoxicity is defined as liver damage caused by hepatotoxicants which include overdoses of industrial chemicals, medicinal drugs, herbal remedies and dietary supplements (Willet *et al*., 2004; Papay *et al*., 2009). The liver is a vital organ that plays a role in controlling critical biochemical and physiological activities including homeostasis, growth, energy and nutrient supply. It has a central role in the clearance and transformation of chemicals that the body is exposed to, making it susceptible to being damaged by hepatotoxic agents (Saukkonen *et al*., 2006). Rimonabant, propylthiouracil and corticosteroids are newly developed drugs that have been used for the treatment of liver diseases. However, they may cause side effects such as insomnia, vomiting, constipation, and depression (Mahmood *et al*., 2014). For that reason, further