Role Of Oxidative Stress In The Protective Effects Of Zingiber Zerumbet Smith Ethyl-Acetate Extract Against Paracetamol-Induced Hepatotoxicity In Sprague-Dawley Rats

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Abstract: Zingiber zerumbet is known to possess antioxidant, anti-inflammatory and anticancer activities. The aim of this study was to investigate the hepatoprotective effects of ethyl acetate extract of Z. zerumbet rhizome against paracetamol-induced hepatotoxicity. Fifty male Sprague-Dawley rats were divided into five groups consisted of control, 750 mg/kg paracetamol, 400 mg/kg Z. zerumbet extract, paracetamol plus 200 mg/kg Z. zerumbet extract and paracetamol plus 400 mg/kg Z. zerumbet extract. Paracetamol were administered orally for seven days concurrent with Z. zerumbet extract intraperitoneally. Administration of ethyl acetate Z. zerumbet extract at doses of 200mg/kg and 400mg/kg protected paracetamol-induced hepatotoxicity as evidenced by significantly reduced (p<0.05) activities of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP). Treatment with Z. zerumbet at similar doses were also able to significantly increased (p<0.05) the superoxide dismutase (SOD) activities and reduced glutathione (GSH) levels in liver homogenate. The increment of malondialdehyde (MDA) and protein carbonyl in liver homogenate were significantly inhibited (p<0.05) by administration of ethyl acetate extract of Z. zerumbet. Administration of Z. zerumbet at the dose of 400 mg/kg were found showed better hepatoprotective effects as compared to 200 mg/kg. In conclusion ethyl acetate extract of Z. zerumbet have the potential in preventing paracetamol-induced hepatotoxicity and this hepatoprotective effects was probably mediated through the reduction in oxidative stress.

Key words: Hepatotoxicity, antioxidants, oxidative stress, paracetamol, Zingiber zerumbet.

INTRODUCTION

Paracetamol (PCM) is an excellent antipyretic and analgesic drug and is proven safe when taken in therapeutic doses, however overdoses can causes hepatotoxicity (Larson, 2007). Hepatic injury in paracetamol toxicity is induced by reactive metabolite, N-acetyl-p-benzo-quinoneimine (NAPQI) (Nelson, 1990). The increment of NAPQI decreased intracellular reduced glutathione (GSH) which enable NAPQI to bind with cellular protein and leads to hepatocellular injury (Jollow et al., 1973). Aminotransferase enzymes (alanine aminotransferase: ALT, aspartate aminotransferase: AST) and alkaline phosphatase (ALP) which significantly elevated in hepatotoxicity condition are considered as a good marker of hepatocellular injury (Yanpallewar et al., 2003).

Depletion of GSH in paracetamol induced-hepatotoxicity is also a consequence of high reactive oxygen species formation (Mourelle et al., 1991). Generation of reactive oxygen species (ROS) and depletion of GSH in the early stage of hepatic metabolism of paracetamol has been proposed as the possible mechanism mediating hepatocellular injury process (Manov et al., 2002).

Recently the use of herbal natural product gains active research interest among researcher to study the effects and implication of various natural products in human life. To date, a number of herbs have been proven to have high medicinal value that beneficial for improvement of health status (Fakurazi et al., 2008). These include Kigelia africana, Hibiscus sabdariffa, Alchornea cordifolia and Moringa oleifera which shown to have high antioxidant properties and hepatoprotective effects (Fakurazi et al., 2008, Olaleye & Rocha 2008). Previously, Curcuma longa has been reported to show hepatoprotective effects against paracetamol-induced toxicity by reducing the formation of pro-inflammatory cytokines and upregulation of its antioxidant activities (Donatus et al., 1990). The role of antioxidants derivatives from natural products in mediating hepatoprotective effects has been shown in M. oleifera which hepatoprotective activities were achieved by restoring the level of GSH during paracetamol toxicity (Fakurazi et al., 2008).

Zingiberaceae family which is widely distributed in Southeast Asia region contains important natural resources for various products development and well known for its medicinal properties (Tushar et al., 2010).
Zingiber zerumbet Smith which belongs to the Zingiberaceae family is a herb commonly found in Malaysia and known locally as lempoyang (Ruslay et al., 2007). Traditionally, the fresh rhizome of Z. zerumbet is used as an appetizer and to treat swelling sores, stomach ache and worm infestation. Furthermore, the use of Z. zerumbet as an anti-inflammatory (Sulaiman et al., 2010) and anticancer agent (Syarifah Sakinah et al., 2007) has been also documented. Recently, ethyl acetate extract of Z. zerumbet has been found to contain high antioxidant properties (Ruslay et al., 2007). However no study has been done on its hepatoprotective effect. Considering the above facts, we embarked on the present study to determine the protective effects of ethyl acetate extract of Z. zerumbet rhizome against paracetamol-induced hepatotoxicity in rats.

MATERIALS AND METHODS

Plant Materials:

The rhizomes of Z. zerumbet were collected from Temerloh, Pahang, Malaysia and authenticated by a plant taxonomist at Department of Botany, Faculty of Science and Technology Universiti Kebangsaan Malaysia and was deposited as a voucher specimen at the herbarium of UKM, Bangi, Selangor. The specimen was cleaned and chopped into small pieces and then air-dried in room temperature for 3 days.

Extraction:

The air-dried rhizomes of Z. zerumbet (7 kg) was sequentially soaked at room temperature in n-hexane, ethyl acetate and followed by methanol for 72 hours. The resultant extracts were filtered and evaporated to dryness in vacuo to yield crude extracts of hexane, ethyl acetate, and methanol. The ethyl acetate crude extract (3.2 g) obtained were stored at 4ºC until tested for bioassay. Prior to use, the Z. zerumbet ethyl acetate extract was dissolved in DMSO and diluted in Phosphate Buffer Solution (PBS) pH 7.4.

Animal Preparation And Treatment Regime:

Male Sprague-Dawley rats (230 to 250g) were obtained from Laboratory Animal Resource Unit, Universiti Kebangsaan Malaysia (UKM). The animals were allowed to adapt to laboratory condition for 7 days prior to the experiments, kept in polypropylene cages with wood shavings at an ambient room temperature with 12 h light/dark cycle and access to food and water ad libitum without restriction. Animals handling procedure were in accordance with the rules and regulations by the UKM Animal Ethics Committee.

The animals were randomly divided into five groups consisting of 10 rats each. The first group was control group (Control) and only received distilled water, the second group was given 400 mg/ kg Z. zerumbet extract (Control 400) and the 3rd group was received oral PCM (20% suspension in distilled water) at the dose of dose of 750 mg/kg for seven consecutive days (PCM group). The 4th and 5th groups were paracetamol plus 200 mg/ kg of Z. zerumbet extract (PCM + 200) and paracetamol plus 400 mg/kg of Z. zerumbet extract (PCM + 400) respectively in which the extract were given intraperitoneally and concurrently with PCM administration for seven consecutive days. 24 hours after the last treatment body weight were measured and the animals were sacrificed to obtain blood and liver. Livers were quickly excised, washed in ice-cold saline, dried and weighed.

Biochemical Assays:

Blood was centrifuged for 15 min at 1000 g and the obtained serum was stored at −40 ºC until further used. Liver homogenate was prepared by homogenizing the tissue in cold KCl (1.15%, pH 7.4, 1:4 w/v) using homogenizer (Ultra Turrax T25). Serum aminotransferases (ALT and AST) were determined using the method by Reitman & Frankel (1957), and serum ALP activities were measured by the method of Boomers & McComb (1975). Serum and liver protein were determined following Bradford assay (Bradford, 1976).

Oxidative Stress Evaluation:

In vivo lipid peroxidation was determined by measuring malondialdehyde (MDA) spectrophotometrically according to the procedure of Stock et al., (1976) using various concentration of 1.1.3.3.-tetaethoxypropane (TEP) as a standard curve. Measurement of protein carbonyl was done according to the method of Levine et al., (1994) based on their reaction with 2,4- dinitro-phenylhydrazine (DNPH) to form hydrazones which was measured spectrophotometrically at 370 nm. Superoxide dismustase (SOD) activity was assayed according to the method of Beyer and Fridovich (1987) and one unit of SOD is considered as amount of enzymes caused 50 % inhibition of nitro blue tetrazolium (NBT) reduction. Reduced glutathione (GSH) was determined by the method of Ellman (1959) using 5,5,-dithiobis-2-nitrobenzoic (DTNB) as substrate whereby the homogenate and plasma were precipitated with perchloric acid (5%), centrifuged at 1000 g and the GSH in the supernatant were determined colourimetrically at 412 nm.
Statistical Analysis:

The data was expressed as mean ± standard error of mean (S.E.M.) Statistical analysis was performed using statistical Package for the Social Sciences (SPSS) version 18. The significant differences between groups were determined using one-way analysis of variance (ANOVA) followed by Post-hoc Tukey test with p<0.05 considered as statistically significance different.

Results and Discussion

Throughout the study there was no mortality noted in all rats in the experimental groups. PCM group showed a significant decreased in body weight as compared to the control (p<0.05) and Z. zerumbet supplementation caused significantly higher body weight as compared to the PCM group (p<0.05) (Table I). No significant difference in total weight of the liver between all groups was observed. However, PCM groups exhibit significantly higher (p<0.05) in relative weight of liver as compared to control group. Treatment with 200 mg/kg and 400 mg/kg Z. zerumbet extract, both groups showed a significant reduction (p<0.05) in relative weight of the liver as compared to PCM group. Furthermore, the administration of 400 mg/kg Z. zerumbet extract alone, was able to maintain the relative weight of liver to the value of control group (p>0.05).

Liver enzymes namely ALP, ALT, AST were determined to indicate hepatic function. Administration of PCM alone at the dose of 750 mg/kg for seven consecutive days caused a significant increased the levels of serum ALT, AST and ALP in PCM group as compared to the control group (p<0.05) (Table II). Administration of Z. zerumbet ethyl acetate extract at 200 mg/kg and 400 mg/kg however prevented the liver injury as indicated by significant reduction (p<0.05) in the levels of liver enzymes activities. In addition, administration of extract at higher dose (PCM + Z. zerumbet 400 mg/kg) showed greater hepatoprotective effects as demonstrated with significantly reduced (p<0.05) activities of ALT, AST and ALP as compared to PCM + Z. zerumbet 200 mg/kg group. PCM administration significantly lowered the levels of serum and liver protein and significant increased (p<0.05) of protein levels was also observed in PCM groups treated with both doses of the extract.

The results of oxidative stress markers of liver homogenate showed in Table III. The liver MDA and protein carbonyl was found to be significantly higher (p<0.05) in PCM group as compared to the control group. Although the administration of Z. zerumbet extracts at both doses were able to significantly inhibit (p<0.05) the elevation of MDA and protein carbonyl during PCM toxicity, the levels were still significantly higher (p<0.05) as compared to the control group. In addition, treatment with higher dose of Z. zerumbet extract was significantly more effective in reducing (p<0.05) the production of liver homogenate MDA and protein carbonyl as compared to PCM + 200 mg/kg group-administered rats.

Meanwhile the GSH levels in the hepatic tissue homogenate of PCM group was significantly (p<0.05) decreased as compared to the levels measured in the control group and treatment with Z. zerumbet extract at both doses prevent the PCM-induced GSH reduction. In addition, group treated with Z. zerumbet at the dose of 400 mg/kg showed significantly higher GSH levels than in 200 mg/kg group. Results showed that SOD activities were not altered in PCM treated group and administration of Z. zerumbet also did not give any significant changes compared to control group.

According to the biochemical analyses, interestingly we found that rats treated with 400 mg/kg of Z. zerumbet ethyl acetate extract at the dose of 400 mg/kg did not cause any toxic effects to the experimental animals.

Discussion:

PCM induced-hepatocellular damage is mediated through its reactive metabolite, namely NAPQI which cause acute centrilobular hepatic necrosis that lead to loss of cell function and structural integrity of hepatocellular membrane (Lee et al., 1996). Leakage of cellular enzymes into the plasma is a hallmark of hepatic injury or damage and measurement of serum liver enzyme such as ALT, AST and ALP are commonly used as marker enzymes in assessing PCM induced hepatotoxicity (Ashta et al., 2004; Yen et al., 2007). In this study, administration of PCM at a dose of 750 mg/kg for seven consecutive days was able to induce hepatic damage as indicated with the substantial increased in serum liver enzymes and this finding is in accordance with other reported studies (Abdel-Zaher et al., 2007; Gardher et al., 2002). In addition, marked reduction of serum and protein levels were observed in PCM-treated rat. These events could be mediated through the covalent binding of NAPQI to proteins which has been reported as the causative factors for oxidative damage, proteins denaturation and changes in protein structures that contribute to the reduction of serum and liver protein levels (Hazai et al., 2002).

Various medicinal plants have been evaluated for their potential effects as hepatoprotective agent (Ahmed & Khater 2001; Kumar et al., 2004). To our knowledge, no studies have been done to investigate the protective role of ethyl acetate extract of Z. zerumbet rhizome in PCM-induced hepatocellular damage. Results from the present study demonstrated that concurrent administration of Z. zerumbet at 200 mg/kg and 400 mg/kg with
750mg/kg PCM for seven consecutive days was able to suppress PCM induced hepatocellular injury as evidenced by the significant reduced in the levels of serum hepatic enzymes and elevation in protein levels. This indicates that _Z. zerumbet_ was able to maintain the structural integrity and functional capacity of the hepatocyte thus preventing enzymes leakage into the plasma and suggest the potential used of _Z. zerumbet_ rhizome as hepatoprotective agents during PCM toxicity. Furthermore, administration of _Z. zerumbet_ at 400 mg/kg alone showed no significant alteration of the levels of theses liver enzymes which were almost similar as in control group.

Our results are in agreement with previous study which showed that plant extract have the potential in preventing the hepatocellular damage thus inhibit the leakage of hepatic enzymes into the circulation (Ahmed and Khater 2001). In addition, similar effect was also observed when _Moringa oleifera_ Lam that was given prior to PCM administration was able to restore plasma liver enzymes to almost normal levels and the hepatoprotective effects were confirmed by reduced histopathological changes with less hepatic cell damage were observed (Fakurazi et al., 2008).

GSH is one of the most important non-enzymatic biological antioxidant that present in the liver which responsible for the removal of free radical species such as hydrogen peroxide and superoxide radicals (Prakash et al., 2001). GSH is also the main water-soluble cellular antioxidant that serves as the first line of defence mechanism in combating against free radicals species and plays as an important role in the detoxification activities in liver (Kaplowitz, 2000). GSH is essential to maintain the redox environment by detoxifying electrophiles and scavenging free radicals (Ibrahim et al., 2010). In PCM toxicity, NAPQI will bind to GSH and being converted to the oxidized form (GSSG) and thus exacerbated the oxidative membrane damage. Furthermore, the generation of reactive nitrogen and oxygen species appears as an early event, which exacerbates intracellular GSH depletion (Manov et al., 2002).

**Table 1:** Effects of _Z. zerumbet_ ethyl acetate extract on mean body weigh total and relative weight of liver in rats given 750 mg/kg/day PCM for 7 consecutive days.

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>Total weight of liver (g)</th>
<th>Relative weight of liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>255.33 ± 5.47</td>
<td>10.53 ± 0.26</td>
<td>0.043 ± 0.001</td>
</tr>
<tr>
<td><em>Z. zerumbet</em> (400 mg/kg)</td>
<td>251.17 ± 4.92</td>
<td>10.28 ± 0.41</td>
<td>0.039 ± 0.002</td>
</tr>
<tr>
<td>PCM</td>
<td>210.33±20.22*</td>
<td>10.71 ± 0.17</td>
<td>0.051 ± 0.002*</td>
</tr>
<tr>
<td>PCM + <em>Z. zerumbet</em> (200 mg/kg)</td>
<td>232.17 ± 7.57**</td>
<td>10.48 ± 0.13</td>
<td>0.045 ± 0.002*</td>
</tr>
<tr>
<td>PCM + <em>Z. zerumbet</em> (400 mg/kg)</td>
<td>244.17±7.34*</td>
<td>10.50 ± 0.16</td>
<td>0.043 ± 0.002**</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM, n=10 animals for each group. * significantly different compared to the control group, # significantly different compared to PCM groups, * significantly different compared to PCM + 200 mg/kg _Z. zerumbet_ (all significant value is at p<0.05).

**Table 2:** Effect of _Zingiber zerumbet_ ethyl acetate extract on liver enzymes and total protein levels in rats given 750 mg/kg/day PCM for 7 consecutive days.

<table>
<thead>
<tr>
<th>Groups</th>
<th>ALT (U/L)</th>
<th>AST (U/L)</th>
<th>ALP (U/L)</th>
<th>Total serum protein (mg/ml)</th>
<th>Total liver protein (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>24.02 ± 8.79</td>
<td>20.70 ± 4.23</td>
<td>61.03 ± 4.96</td>
<td>109.38 ± 18.85</td>
<td>122.38 ± 20.76</td>
</tr>
<tr>
<td><em>Z. zerumbet</em> (400 mg/kg)</td>
<td>20.37 ±1.83</td>
<td>22.93 ±2.07</td>
<td>68.72 ±3.09</td>
<td>107.38 ±17.65</td>
<td>121.88 ±24.34</td>
</tr>
<tr>
<td>PCM</td>
<td>64.17 ±4.60*</td>
<td>110.20±12.14*</td>
<td>127.88 ±8.59*</td>
<td>54.88 ±10.95*</td>
<td>55.21 ±6.60*</td>
</tr>
<tr>
<td>PCM + <em>Z. zerumbet</em> (200 mg/kg)</td>
<td>52.07±3.92**</td>
<td>98.40±13.32**</td>
<td>119.60±6.46*</td>
<td>109.54±13.74*</td>
<td>96.69±15.90*</td>
</tr>
<tr>
<td>PCM + <em>Z. zerumbet</em> (400 mg/kg)</td>
<td>24.93±2.40*</td>
<td>81.23±13.64**</td>
<td>79.10±7.12**</td>
<td>113.54±14.69*</td>
<td>119.88±23.08**</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. n=10 animals for each group. * significantly different compared to the control group, # significantly different compared to PCM groups, * significantly different compared to PCM + 200 mg/kg _Z. zerumbet_ (all significant value is at p<0.05).

**Table 3:** Effect of _Zingiber zerumbet_ ethyl acetate extract on oxidative stress status of liver homogenate in rats given 750 mg/kg/day PCM for 7 consecutive days.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Protein carbonyl (mmol/g protein)</th>
<th>MDA (nmol/g protein)</th>
<th>SOD (u.e/min/g protein)</th>
<th>GSH (mmol/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.14 ± 0.02</td>
<td>8.27 ± 0.73</td>
<td>14.1 ± 1.29</td>
<td>4.28 ± 0.10</td>
</tr>
<tr>
<td><em>Z. zerumbet</em> (400mg/kg)</td>
<td>0.10 ± 0.01</td>
<td>8.04 ± 0.53</td>
<td>13.6 ± 1.49</td>
<td>3.65 ± 0.38</td>
</tr>
<tr>
<td>PCM</td>
<td>0.41 ± 0.04*</td>
<td>25.58 ± 1.10*</td>
<td>13.33 ± 1.61</td>
<td>2.72 ± 0.14*</td>
</tr>
<tr>
<td>PCM + <em>Z. zerumbet</em> (200mg/kg)</td>
<td>0.22 ± 0.01**</td>
<td>19.02 ± 0.83**</td>
<td>13.57 ± 0.81</td>
<td>5.22 ± 0.38*</td>
</tr>
<tr>
<td>PCM + <em>Z. zerumbet</em> (400mg/kg)</td>
<td>0.20 ± 0.02**</td>
<td>14.59 ± 0.84**</td>
<td>14.67 ± 0.69</td>
<td>6.24 ± 0.11**</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SEM. n=10 animals for each group. * significantly different compared to the control group, # significantly different compared to PCM groups, * significantly different compared to PCM + 200 mg/kg _Z. zerumbet_ (all significant value is at p<0.05).
From this study, the decreased level of GSH has been observed in paracetamol-treated group, hence were in favour of the possibility that the overproduction of NAPQI in PCM hepatotoxicity, and excess generation of free radical species lead to oxidative stress condition with subsequent depletion in GSH levels. However, Z. zerumbet administration appeared to cause less oxidative stress condition as evidenced in this study showing that ethyl acetate extract of Z. zerumbet did increase the levels of GSH. According to Chan et al., (2001), Nrf2 (nuclear factor erythroid 2-related factor 2) played an essential role for detoxification of acetaminophen. In addition a study conducted by Nakamura et al., (2004) revealed that Zerumbone (ZER), a sesquiterpene compound from Z. zerumbet could boost Nrf2 function which plays an essential role in the defense against oxidant and electrophilic chemical insults. Nrf2 will mediate glutathione (GSH) synthesis pathway as it binds to antioxidant response element (ARE) of the phase II enzymes genes. In agreement with these findings, a study conducted by Ibrahim et al., (2010) revealed that rats treated with Zzerumbet had elevated level of renal GSH in cisplatin induced nephrotoxicity in rats models.

Previous study reported that the ROS mediated hepatotoxicity can be effectively prevented by administration of compound possessing antioxidants (Fakurazi et al., 2008; Olaleye & Rocha 2008; Hemabarathy et al., 2002). Family Zingiberaceae was known to possess highly antioxidant activity and highly medicinal value (Tushar et al., 2010). In support with our finding, previously study also reported that the extract of Alpania galangal, a member of zingiberaceae family also possess hepatoprotective effects by reducing the oxidative stress in paracetamol induced toxicity rats (Hemabarathy et al., 2009). Z. zerumbet treatments were able to ameliorate the PCM induced hepato cellular damage and therefore the hepatoprotective effects were most probably due antioxidant activities of its compound. Previous finding reported that ethyl acetate extract of Z. zerumbet rhizome rich with flavonoid glycosides, the derivatives of kaempferol, and possess antioxidant property (Ruslay et al., 2007). Ruslay et al., (2007) had measured the total antioxidant activity from rhizome of Zzerumbet using ferric thiocyanate (FTC) assay and thiobarbituric acid (TBA) assay which revealed that the antioxidant activity of ethyl acetate extract from rhizome of Zzerumbet was the most significant.

Excess production of free radicals attack the biological molecules such as DNA, proteins and lipid and in which lipid and protein oxidation has been suggested as a mechanism that lead to hepatocellular injury (Genet et al., 2000). In addition, the depletion in intracellular GSH in PCM toxicity condition, causes high levels of reactive electrophilic metabolites bind massively to the biological molecules (Kaplowitz, 2000). PCM toxicity led covalent binding of NAPQI with sulphhydryl group of proteins results in the protein oxidation and cell necrosis (Lin et al., 1997). MDA is one of the main products of lipid peroxidation that is widely used as a biomarker of oxidative stress in determination of the total lipid peroxidation in cell and tissues (Yagi, 1998). In agreement with the previous study (Gamal et al., 2003), the present study shows that the depletion of hepatic GSH leads to oxidation damage of lipid, and protein, and also failure of the antioxidant defense system as evidence by increased in MDA and protein carbonyl levels in the liver and plasma together with reduced SOD activities in PCM treated rats and these finding suggested that tissue injury had occurred.

The ethyl acetate extract of Z. zerumbet rhizome used in the present study able to minimize the oxidative damage in plasma and liver of Z. zerumbet-treated PCM group. These results suggested the hepatoprotective effect of Z. zerumbet against paracetamol-induced hepatotoxicity which most probably mediated through its antioxidant properties. The ability of Z. zerumbet to reduce protein and lipid oxidation and to increase the antioxidant defense mechanism are believed as the possible mechanism that preserve the cell function through inhibition of oxidative cellular damage through oxidative stress. Furthermore the probable mechanism by which Z. zerumbet exerts its protective effect against paracetamol-induced hepatocellular injury is also could be mediated by its ability to accelerate detoxification and excretion of hepatotoxic reactive metabolite products.

The Z. zerumbet used in this study shows the hepatoprotective effects in dose dependent manner as evident with better hepatoprotective effects was demonstrated at higher dosage (400mg/kg) of Z. zerumbet than in rats received lower dosage (200mg/kg). In addition, administration of Z. zerumbet ethyl acetate extract at 400mg/kg that was given alone in the absence of paracetamol showed no hepatotoxicity effects as indicated by the levels of hepatic enzymes and oxidative stress markers that were almost similar to the control group. This finding is believed to be mediated through its higher antioxidant properties that prevent PCM-induced liver damage.

Conclusion:

Present results suggested that oral administration of ethyl acetate extract of Z. zerumbet protects rats from PCM-induced hepatotoxicity and the effect is most probably mediated through the reduction of oxidative stress. These observations suggest that Z. zerumbet could be applied in clinical application in which cellular damage is a consequence of oxidative stress.

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Declaration of Interest:
The authors report no conflicts of interest. All the authors are responsible in writing and contents of this article.

REFERENCES


