Effect of Piperine on Liver Function of CF-1 Albino Mice


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Abstract: Background: Piperine is isolated from Piper nigrum popularly known as black pepper. Previous studies have demonstrated the beneficial effects of piperine in various health conditions. Additionally, it is a powerful bioenhancer for many drugs. Piperine extract is believed to potentiate the effect of drugs by several folds. The present study is focused on its individual effect on liver function. Materials and methods: A total of 30 CF-1 albino mice obtained from the animal house of faculty of Medicine, Benghazi University, Benghazi, Libya were included in the study. These mice were fed with high cholesterol diet and divided into 2 groups. Twenty mice were administered piperine at a dose of 5mg/kg body weight. Piperine was isolated in Department of Pharmacognosy, Faculty of Pharmacy, Benghazi University, Benghazi and 10 mice were not administered piperine but fed with high fat diet. These mice were anesthetized with ketamine and halothane and blood was drawn from each mouse before the study and after three weeks by cardiocentesis. Serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), alkaline phosphatase and total protein were measured by authenticated methods. Results: Serum alanine amino transferase was significantly elevated (p=0.0002) in group A mice after the administration of Piperine extract for three weeks compared to those of group B mice. Serum aspartate amino transferase was elevated significantly (p=0.046) and alkaline phosphatase (p= 0.0001) also was significantly increased after the administration of piperine. Serum total protein (p= 0.011) values were significantly decreased after the use of piperine for three weeks in group A mice. Conclusion: This study showed that there might have been a considerable damage to liver with piperine extract. Further research may be required to prove this damage to liver function.

Keywords: Liver, mice, piperine, toxicity.

BACKGROUND
Plant alkaloids have immense medicinal values, one of the best we can say is cardiac glycosides i.e. digitalis. Many plant alkaloids have been shown to have several anti-microbial functions [1, 2]. Piperine (1-peperoyl piperidine) is a pungent alkaloid found in piper nigrum, piper longum, piper retrofractum, piper crussi and piper genticum. It is supposed to have medicinal value with various beneficial effects. There are a lot of experimental data on piperine as an antidepressant and for its cognitive enhancing effects. It is also claimed to have a myriad of other activities including antioxidant, anti-inflammatory, antithyroid,
antihypertensive, anti-platelet, antitumor, hepatoprotective and antiasthmatic. Piperine enhances absorption of various drugs from the gastrointestinal tract and decreases their metabolism, thus increasing their bioavailability [3]. In a previous study conducted by our group, we observed that piperine reduced LDL cholesterol and triglyceride levels and increased HDL cholesterol levels [4, 5].

While most studies have shown a beneficial effect of piperine on liver function, some have shown contradictory results. We therefore undertook the current study to assess the effects of piperine on liver function.

MATERIALS AND METHODS

The study was conducted on 30 CF-1 albino (strain 023) mice, which were obtained from the animal house of the Faculty of Medicine, Benghazi University (former Garyounis University), Benghazi, Libya. These mice were fed with high fat diet with a composition of protein 24 g%, carbohydrate 41 g% and fat 24 g% with a caloric intake of 20% from proteins, 35% from carbohydrates and 45% from fats. The main ingredients of the diet were casein, corn starch and cellulose with sheep tail fat. The mice were divided into 2 groups A and B of 20 and 10 each respectively. Twenty mice i.e., group A mice were administered piperine at a dose of 5mg/kg body weight orally in the form of suspension mixed with corn oil for a period of three weeks. The purity of the piperine was ascertained by TLC and HPLC (94.6%) and was isolated in the Department of Pharmacognosy, Faculty of Pharmacy, Benghazi University, Benghazi. Ten mice were not administered piperine but fed only with a high fat diet considered in this study as controls. These mice were anesthetized with ketamine and halothane and blood was withdrawn by cardiocentesis from each mouse at baseline i.e., before administration of piperine and at the end of three weeks. Serum transaminases (ALT and AST), alkaline phosphatase, and total protein were measured by Cobas Integra 400 plus with kits supplied by Roche diagnostics [6-8]. Statistical analysis of the data was done by using student ‘t’ test with Graph pad software.

RESULTS

After the administration of piperine for 3 weeks, in group A, we observed a significant increase in serum ALT (p=0.0002), serum AST (p=0.046) and alkaline phosphatase (p=0.0001). There was also a significant decrease in serum total protein (p=0.011) in this group, compared to group B. Tables 1 and 2 describes the changes in the results of the liver function tests done at baseline and at the end of three weeks. Among controls also there is significant elevation of all three enzymes i.e ALT (p=0.0071), AST (p=0.0001) and ALP (p=0.0008) but there is no reduction of total proteins (p=0.2233). Changes in the LFT in the two groups are shown in Tables 1 and 2.

DISCUSSION

In our study, we found a significant detrimental effect of piperine extract on all the parameters of liver function. All the mice that received piperine extract for a period of three weeks showed a significant increase in their ALT, AST and alkaline phosphatase levels and also showed a significant decrease in the total protein levels.

Previous studies have shown contradictory results of piperine on liver function. P. nigrum has been shown to have hepatoprotective effect in both animal models as well as in humans in some studies [9]. Matsuda et al. reported that in mice

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<th>Baseline</th>
<th>After 3 weeks of piperine administration</th>
<th>p-Value</th>
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<tr>
<td>ALT</td>
<td>59.44±22.35</td>
<td>189.19±86.47</td>
<td>0.0002</td>
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<tr>
<td>AST</td>
<td>268±93.70</td>
<td>392±251.77</td>
<td>0.046</td>
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<tr>
<td>ALP</td>
<td>259.28±58.89</td>
<td>681.75±64.70</td>
<td>0.0001</td>
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<tr>
<td>TP</td>
<td>5.33±1.06</td>
<td>4.55±0.91</td>
<td>0.011</td>
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Table 1. Results of changes in LFT in mice fed with high fat diet and piperine.
with D-galactosamine induced liver toxicity, piperine inhibited an increase in serum ALT and AST levels [10]. Koul and Kapil demonstrated that piperine inhibited the hepatotoxicity of carbon tetrachloride in rodents [11]. Diwan et al. state that supplementation with piperine (375 mg/kg food; approximately 30 mg/kg/day) in high carbohydrate high fat (HCHF)-fed rats not only attenuated hepatic inflammatory cell infiltration and fibrosis, but also improved liver function [12]. In another recent study by Choi et al., administration of piperine reversed preexisting high fat diet (HFD)-induced hepatic steatosis and insulin resistance in mice [13]. Sahu et al. also reported a beneficial effect of piperine on liver function, when administered as microspheres (targeted drug delivery), where it significantly reduced the serum AST and ALT levels [14].

However, da Silva Cardoso et al. in their study found that at concentrations of 120 and 180 mg/kg, piperine increased AST, indicating hepatocyte damage caused due to alterations in cellular membrane permeability [15]. Similarly, Piachaturawat et al. showed that piperine potentiated the hepatotoxicity of carbon tetrachloride [16]. Our study has shown a significant deleterious effect of piperine on the liver function of all these albino mice. There were two studies showing that piperine inhibits both the drug transporter P-glycoprotein and the drug metabolizing enzyme CYP3A4. Because both proteins are expressed in enterocytes and hepatocytes can contribute to a major extent to first-pass elimination of many drugs, data indicate that dietary piperine could affect plasma concentrations of P-glycoprotein and CYP3A4 substrates in humans, in particular if these drugs are administered orally [17, 18].

This study has shown hepatic dysfunction caused by piperine extract based on a significant increase in the serum AST, ALT, alkaline phosphatase; the established biomarkers of liver function and this effect is reinforced by a significant decrease in the total protein levels. However, this a small preliminary study that needs to be confirmed by larger studies to establish the role of piperine extract on the metabolic function of liver as a hepatotoxic or a hepatotoxic agent.

**CONFLICT OF INTEREST**

The authors confirm that this article content has no conflict of interest.

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**REFERENCES**


