The Protective Effect of Curcuma longa in Thioacetamide-Induced Hepatic Injury in Rat

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Abstract: Curcumin derived from Curcuma longa was shown to have strong antioxidant, anti-inflammatory and hepatoprotective properties. This study determined the protective effect of curcumin in thioacetamide-induced hepatic injury in rats. Thirty two rats were divided into 4 equal groups. Control Group did not undergo any intervention and kept in their cages for 10 weeks. Sham Group received 1 ml of normal saline intraperitoneally. Thioacetamide (TAA) Group received 300 mg/kg of TAA intraperitoneally. Curcumin Group, 48 hours after intraperitoneal injection of 300 mg/kg of TAA received 4 mg/kg of curcumin per day for 10 weeks. All animals were bled after 10 weeks. The provided blood samples were tested for ALP, ALT, AST and total bilirubin serum levels. After bleeding, the animals were euthanized and their livers were removed for histological studies. AST, ALT, ALP and total bilirubin levels significantly increased after injection of thioacetamide. After administration of curcumin, a significant decline in these parameters was noticed. Histologically in TAA Group, inflammation in hepatic lobules was noticed. In Curcumin Group, even a moderate portal inflammation was still present but when compared to the TAA group, it was significantly less. As our findings demonstrated the hepatoprotective effect of curcumin in thioacetamide-induced liver injuries, it can be recommended in prevention and treatment of liver injuries.

Key words: Curcuma longa, Liver Injury, Liver Enzymes, Rat

INTRODUCTION

Liver diseases are still considered as the important causes of morbidity and mortality worldwide [1]. Oxidative stress was shown to be the mechanism contributing in initiation and progression of liver injury in several liver disorders [2]. An excess of reactive species from oxygen and nitrogen or deficiency of antioxidants results into cell damage [3]. Plants with antioxidant properties are considered as therapeutic strategy in treatment of liver diseases [4].

Curcumin is derived from Curcuma longa with biologically active phenolic compounds and is available as a strong antioxidant, anti-inflammatory and hepatoprotective herbal medicine [3]. Curcumin (diferuloylmethane) is an additive used as spice in China and India [5,6]. Due to its potent anti-inflammatory and anti-oxidative properties, it was used in a variety of diseases such as gallstones [7], cancer [8,9], cardio-pulmonary and neurological diseases [10,11] and autoimmunity states [12-14].

In liver diseases, it can inhibit the nuclear factor-kappa B which is a modulator of many pro-inflammatory and profibrotic cytokines [14]. Curcumin was shown to have potent hepatoprotective properties [15-17] and to attenuate hepatic damage in liver injury models [18,19]. In hepatic encephalopathy, neuroprotective potentials of curcumin were noted as central nervous system is injured secondary to hepatic insufficiency [14].
Thioacetamide (TAA) was shown to be appropriate in modeling of liver diseases depending on duration of administration and dosage [20,21]. Its use leads to oxidative stress in liver and brain in rat models and when high doses were administered [21-23].

Unfortunately, the studies of curcumin on hepatic diseases are not satisfactory and due to high mortality rates, more investigations in this area are needed. This study evaluated the protective effect of Curcuma longa in thioacetamide-induced hepatic injury in rat model.

RESULTS AND DISCUSSION

In TAA group, AST serum level significantly increased when compared to the control and sham groups ($p=0.03$). In curcumin group, AST level revealed a decrease ($p=0.03$) (Table 1). Regarding ALT liver enzyme

**MATERIALS AND METHODS**

Thirty two male Sprague Dawley rats with a weight of 200-250 g provided from Laboratory Animal Center of the university were divided into 4 equal groups. Group 1 (Control Group) did not undergo any intervention and kept in their cages for 10 weeks and just received their normal feeding. Group 2 (Sham Group) received 1 ml of normal saline intraperitoneally and kept similarly in their cages for 10 weeks. Group 3 (TAA Group) kept identically in their cages for 10 weeks and received 300 mg/kg of TAA intraperitoneally as described before [22]. Group 4 (Curcumin Group) 48 hours after intraperitoneal injection of 300 mg/kg of TAA received 4 mg/kg of curcumin per day for 10 weeks. All animals were bled after 10 weeks.

Blood sampling was performed under general anesthesia using 10% ketamine and 2% xylazine. The provided blood samples were sent to laboratory to determine the serum levels of alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin. After bleeding, the animals were euthanized and their livers were removed and transferred into 10% buffered formalin solution for histological studies.

Animal selection, experiments, animal care and the sacrifice protocol were adhered to the guidelines of the animal care of Iran Veterinary Organization. The study was approved by the ethics committee of the university. The animals were individually housed in one cage using a 12 hours light and 12 hours darkness condition under a humidity of 30% and temperature of 22°C. They were fed with a balanced diet with free access to water. All interventions were performed under aseptic conditions.

SPSS software (Version 14, Chicago, IL, USA) was used for statistical analysis. ANOVA, t test and Duncan tests were used to determine any differences between groups. Levels of significance were set at $p<0.05$. 

![Fig 1: Control group receiving distilled water (x200, H and E).](image1)

![Fig 2: Extensive necrosis and inflammation of hepatic lobules after administrating. (x200, Masson trichrome) 300 mg/kg of TAA](image2)

![Fig 3: Moderate inflammation in the portal space and focal necrosis of hepatocytes at periportal spaces after administrating 100 mg/kg of curcumin (x200, H and E).](image3)
Table 1: A comparison for liver enzyme changes in different groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>AST level (IU)</th>
<th>ALT level (IU)</th>
<th>ALP level (IU)</th>
<th>Bilirubin (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>Control</td>
<td>27.3±180</td>
<td>39.7±97.7</td>
<td>79.1±455.7</td>
<td>0.1±0.5</td>
</tr>
<tr>
<td>Sham</td>
<td>49.6±187</td>
<td>27.9±84</td>
<td>141.1±354.2</td>
<td>0.1±0.5</td>
</tr>
<tr>
<td>Thioacetamide</td>
<td>75.0±321</td>
<td>27.1±112.3</td>
<td>163.7±356.7</td>
<td>0.3±0.7</td>
</tr>
<tr>
<td>Curcumin</td>
<td>36.9±244</td>
<td>57.0±99.3</td>
<td>231.9±486</td>
<td>0.3±0.5</td>
</tr>
<tr>
<td>P value</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.007</td>
</tr>
</tbody>
</table>

in TAA group, it significantly increased in comparison to the control and sham groups ($p=0.03$). In curcumin group, the enzyme level decreased in comparison to the control group ($p=0.03$) (Table 1).

Table 1 denotes to a significant increase in ALP serum level in TAA group in comparison to control and sham groups ($p=0.03$). In curcumin group, there was a significant decrease in the enzyme level too ($p=0.03$). As Table 1 represents in TAA group, a significant increase in total bilirubin was noticed in comparison to the control and sham groups ($p=0.007$). Regarding curcumin group, it resulted into a significant decrease in total bilirubin in comparison to other groups ($p=0.007$).

In Control and Sham groups, no histological changes were visible (Figure 1). In TAA Group, inflammation in hepatic lobules was noticed (Figure 2). In Curcumin Group, even a moderate portal inflammation was still present but when compared to the TAA group, it was significantly less (Figure 3).

It was shown that oxidative/nitrosative stress played a major role in pathophysiology of acute liver injuries [24]. Curcumin was shown to have neuroprotection [25] and hepatoprotection properties [26] due to involvement in antioxidation [27], inhibition of kinases [28], interference with the activity of transcription factors such as nuclear factor-kB and activator protein-1 [29] and suppression of expression of the enzyme COX-23 [30].

Intake of oxygen radical scavengers as antioxidants present in plants may be a good defense for hepatoprotection, as it contain antioxidant and anticarcinogenic compounds, including phenolics, caretenoids, thiols and tocoherols, which may protect against different diseases [31]. Curcumin is yellow phenolic compound present in tumeric; *Curcuma longa L.* (Family Zingiberaceae) and used as a food preservative [31]. It has been shown to act as antioxidant through modulation of glutathione (GSH) levels and possesses anti-inflammatory properties through interleukin-8 inhibition [31].

Zheng and Chen, 2007 recently reported that curcumin elevated the level of cellular GSH and induced de novo synthesis of GSH in HSC by stimulating the activity and gene expression of GCL, a key rate-limiting enzyme in GSH synthesis [32]. They further demonstrated that de novo synthesis of GSH was a prerequisite for curcumin to inhibit HSC activation [32]. Results of Yumei et al. (2008) indicated that oral administration of curcumin not only increased the level of total hepatic GSH but also significantly improve the ratio of GSH/GSSG in the liver. These observations are supported by other studies [33].

Treatment with 100 mg/kg curcumin prevented the drop in the content of hepatic GSH, diminished lipid peroxidation and minimized hepatocarcinogenesis in rats [34]. It bears emphasis that our results do not exclude any other mechanisms involved in the antioxidant capacity of curcumin and in the curcumin elevation of the level of hepatic GSH. The level of cellular GSH is mainly determined by GSH synthesis (GSH supply) and GSH consumption (GSH demand). This current report focused on the effect of curcumin on GSH synthesis [34].

The decrease in ALT, AST and ALP liver enzymes by administration of curcumin in our rats can be interpreted as its hepatoprotective effect. The level of total bilirubin was also lower in curcumin group in comparison with the control and sham groups. Higher doses could also be tested in further studies. A few other researches emphasizing on acute liver failure [35] suggesting that curcumin is a good pharmacologic agent for treatment of the fatal disease state, Acute HE. Our findings showed that curcumin could successfully prevent liver injury induced by TAA, it can be recommended in prevention and treatment of liver injuries.

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**Conflict of Interest**

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REFERENCES


