THE HEPATOPROTECTIVE AND ANTIFIBROTIC POTENTIAL OF ROOT EXTRACT OF ALOCASIA INDICA LINN. AGAINST CCL4 INDUCED HEPATIC INJURY AND FIBROSIS IN WISTAR RATS

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ABSTRACT:
The hepatoprotective activity of hydro-alcohol extract of roots of Alocasia indica Linn. (AI-E) was evaluated against carbon tetrachloride (CCL4) induced hepatic damage in rats. The AI-E at dose of 400 mg/kg is administered orally once daily for fourteen days. The substantially elevated serum enzymatic levels of serum glutamate oxaloacetate transaminase (AST), glutamate pyruvate transaminase (ALT), alkaline phosphatase (ALP), total lipoprotein (TP), total cholesterol (TC), triglyceride (TG), albumin (ALB), hepatic malondialdehyde (MDA) content, superoxide dismutase (SOD), hyaluronic acid (HA) and liver index were restored towards normalization significantly by the AI-E at dose of 400 mg/kg. AI-E 400mg/kg dose exhibited significant hepatoprotective activity against carbon tetrachloride induced hepatotoxicity in rats. The biochemical observations were supplemented with histopathological examination of rat liver sections. The results of this study strongly indicate that roots of Alocasia indica have potent hepatoprotective activity against carbon tetrachloride induced hepatic damage in experimental animals. This study suggests that possible mechanism of this activity may be due to the presence of flavonoids and phenolics compound in the AI-E which may be responsible to hepatoprotective activity.

Keyword: Hepatoprotective, Alocasia indica, Carbon tetrachloride, Roots.

INTRODUCTION
The medicinal plants were a common link between modern and traditional medical sciences as they were the main source of drugs and medicaments1. The liver is a vital organ of paramount importance involved in the maintenance of metabolic functions and detoxification from the exogenous and endogenous challenges, like xenobiotics, drugs, viral infections and chronic alcoholism. If during all such exposures to the above mentioned challenges the natural protective mechanisms of the liver are overpowered, the result is hepatic injury2. Liver diseases remain one of the serious health problems3. In spite of tremendous strides in the modern medicine, there are not much drugs available for the treatment of liver diseases. There are a number of medicinal preparations recommended in the Indian traditional system of medicine “Ayurveda” for the treatment of liver diseases. There are scientific claims to offer significant relief as hepatoprotective4.

The Alocasia indica Linn. (Family- Araceae) commonly known as Giant Taro is a perennial herb found throughout greater part of India. According to ayurvedic literature survey, different parts of this plant are traditionally used in jaundice, antioxidant, analgesic, antiarthritic, disease of abdomen, spleen inflammation5. It has also reported to use in the treatment of piles6. The leaves juice is used as digestive, astringent, laxative, diuretic and rheumatic arthritis and antifungal properties7,8. This plant contains flavonoids, cyanogenic glycosides, ascorbic acid, gallic acid, malic acid, oxalic acid, alocasin, amino acids, succinic acid, and B-lectines. Silymarin, one of these compounds, was used as a standard reference and exhibited significant hepatoprotective and antioxidant activity against CCl4-induced haptotoxicity in rat models9,10. Carbon tetrachloride accumulates in hepatic parenchyma cells and is metabolised to C-Cl by liver cytochrome P450-dependent monoxygenases11. One of the principal causes of CCl4- induced liver injury is lipid peroxidation induced and accelerated by free radical derivatives of CCl412.

The roots of Alocasia indica are used for the treatment of jaundice in traditional system of medicine. However, there is lack of scientific report regarding the hepatoprotective activity of Alocasia indica. The present investigation is an endeavor to validate the scientific use of hydro-ethanolic extract of the Alocasia indica (AI-E) against carbon tetrachloride induced hepatic damage in experimental animals.

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MATERIALS AND METHODS

Plant material

The fresh roots of *Alocasia indica* Linn. used in the present study were collected from local areas of Ibrahimpatnam, Hyderabad, India in the month of February (winter) 2013. The plant species was authenticated by Prof. B. Amarendhar Reddy, M.sc (Botany), Sai Gouthami College, Ibrahimpatnam, R.R. District, India and the voucher herbarium specimen was deposited in the institute's herbarium. The fresh roots of *Alocasia indica* Linn. were separated from plant, washed under running tap water and then with isopropyl alcohol (5%) followed by distilled water. Roots were cut into small pieces and allowed it to shed dry (temperature 30°C, relative humidity 45-55%) for 15 days and then homogenized to get a coarse powder. This powder was stored in an air tight container and used for further successive extraction.

Preparation of Extract: Hydro-alcoholic extract (by cold maceration method)

About 250 g of the powder was extracted with hydro-alcohol (ethanol-95% and water in 1:1 proportion) at room temperature by cold maceration method. The filtrate was collected and concentrated on heating mantle at 45°C till a syrupy mass was obtained. Then the extract was again dried by using rotary evaporator under controlled condition of temperature and pressure. The extract thus obtained was preserved at -4°C. The percentage yield was found to be 6.14 g.

Chemicals

Silymarin was used as the reference drug (positive control); carbon tetrachloride (CCl₄), purchased from Merck Specialities Pvt. Ltd. Mumbai, (India); total cholesterol (TC), triglyceride (TG), total lipoprotein (TP), serum albumin (SA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), hepatic malondialdehyde (MDA), and superoxide dismutase (SOD) commercial assay kits were purchased from Erba Diagonostics Mannheim GmbH, Mumbai, (India); total hyaluronic acid (HA), were purchased from Erba Diagonostics Mannheim GmbH, Mumbai, (India); total lipoprotein (TP), serum albumin (SA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), hepatic malondialdehyde (MDA), and superoxide dismutase (SOD) commercial assay kits were purchased from Erba Diagonostics Mannheim GmbH, Mumbai, (India); total hyaluronic acid (HA), were purchased from Erba Diagonostics Mannheim GmbH, Mumbai, (India); total hyaluronic acid (HA), were purchased from Erba Diagonostics Mannheim GmbH, Mumbai, (India); total hyaluronic acid (HA), were purchased from Erba Diagonostics Mannheim GmbH, Mumbai, (India); 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embedded liver tissues were sliced into 4 µm pieces and stained with Hematoxylin–Eosin (H-E) and Masson–Trichrome (M-T), respectively, for photomicroscopic assessment. A numerical scoring system for histologically assessing the extent of fibrosis was adapted from the formula of Scheuer\textsuperscript{15}, with minor modification\textsuperscript{16}.

Briefly, fibrosis was staged as:

Stage 0: no fibrosis; Stage 1: enlarged, fibrous portal tracts; Stage 2: perportal or portal-portal septa, but intact architecture; Stage 3: fibrosis with architectural distortion; stage 4: probable or definite cirrhosis.

Additionally, hepatocyte necrosis or degeneration severity was also graded as:

Grade 0: no hepatocyte necrosis or degeneration; Grade 1: focal necrosis or degeneration of hepatocytes (mild, lesion <3); Grade 2: multifocal necrosis or degeneration of hepatocytes (moderate, lesion >3); Grade 3, locally extensive or diffuse necrosis or degeneration of hepatocytes (severe). The liver scoring examination was performed by a pathologist who was blinded to rats’ treatment assignment. Fibrosis and hepatocyte scores were given after the pathologist had examined throughout three different areas in the tissue slide for each rat.

**STATISTICAL ANALYSIS**

All values were expressed as the means ±S.E.M. (standard error of means). Significant differences between the groups were statistically analyzed using an one-way analysis of variance (ANOVA), followed by Tukey's Multiple Comparison Test, while liver histopathologic examination data was evaluated using SPSS 17.0 package, P < 0.01 and < 0.001 considered statistically significant.

**RESULTS**

**Acute toxicity study of AI-E:**

In the acute toxicity study, the behavioural signs of toxicity observed in the rats at 2000 mg extract/kg body weight were rubbing of nose and mouth on the floor of the cage and restlessness. Gross pathological study showed no abnormality in all the organs examined. Absence of death in test dose group showed that the LD\textsubscript{50} of the AI-roots extract is greater than 2000 mg extract/kg body weight.

**Protective effects of AI-E on serum index of CCl\textsubscript{4}-injured liver fibrotic rats:**

The activities of AST, ALT and ALP in serum were significantly reduced by AI-E, the contents of MDA and HA in serum were significantly reduced by AI-E, and meanwhile the levels of TP and ALB in serum were also increased by AI-E. The activities of ALT, the contents of HA and TC in serum were significantly reduced by Silymarin, and meanwhile the levels of TP and SOD in serum were also increased by Silymarin (Table 1).

**Table 1:** Effects of AI-E on serum index in CCl\textsubscript{4} injured liver fibrotic rats.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>CCl\textsubscript{4}</th>
<th>Silymarin</th>
<th>AI-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>144.73 ± 7.86</td>
<td>394.92 ± 16.40***</td>
<td>186.87 ± 9.27***</td>
<td>197.43± 11.52***</td>
</tr>
<tr>
<td>ALT</td>
<td>56.33 ± 2.09</td>
<td>282.85 ± 6.04***</td>
<td>67.26 ± 7.96***</td>
<td>59.64 ± 5.19***</td>
</tr>
<tr>
<td>ALP</td>
<td>147.66±9.57</td>
<td>268±17.25***</td>
<td>164±13.75***</td>
<td>159±14.86***</td>
</tr>
<tr>
<td>TP</td>
<td>6.59 ± 0.19</td>
<td>3.27 ± 0.21***</td>
<td>5.49 ± 0.14***</td>
<td>5.26 ± 0.22***</td>
</tr>
<tr>
<td>TC</td>
<td>85.73 ± 1.71</td>
<td>159.36 ± 3.91***</td>
<td>90.66 ± 2.80***</td>
<td>105.28 ± 2.80***</td>
</tr>
<tr>
<td>ALB</td>
<td>3.58 ± 0.10</td>
<td>2.65 ± 0.11***</td>
<td>3.41 ± 0.08***</td>
<td>3.33 ± 0.09***</td>
</tr>
<tr>
<td>MDA</td>
<td>1.69 ± 0.03</td>
<td>2.97 ± 0.13***</td>
<td>2.18 ± 0.09***</td>
<td>1.57 ± 0.07***</td>
</tr>
<tr>
<td>SOD</td>
<td>93.60 ± 0.45</td>
<td>92.70 ± 0.37</td>
<td>93.1 ± 1.39</td>
<td>95.30 ± 1.54***</td>
</tr>
<tr>
<td>HA</td>
<td>54.30 ± 2.51</td>
<td>87.20 ± 1.83***</td>
<td>63.30 ± 2.51***</td>
<td>51.40 ± 2.79***</td>
</tr>
<tr>
<td>LI</td>
<td>3.35 ± 0.08</td>
<td>3.88 ± 0.05***</td>
<td>3.52 ± 0.06***</td>
<td>3.39 ± 0.05***</td>
</tr>
<tr>
<td>LV</td>
<td>3.56 ± 0.08</td>
<td>4.02 ± 0.08***</td>
<td>3.74 ± 0.04***</td>
<td>3.43 ± 0.05***</td>
</tr>
</tbody>
</table>

# Represents statistical significance vs. Normal control.
* Represents statistical significance vs. CCl\textsubscript{4}.
**P < 0.01, ***P < 0.001.
#P<0.05, ##P<0.01, ###P<0.001.

**Effect of AI-E on liver homogenate index:**

Results showed that liver AST activities and MDA production were obviously decreased by AI-E (400 mg/kg) treatment (P < 0.01), liver ALT production and the content of TC (P < 0.001) were markedly decreased by AI-E (400 mg/kg) treatment as compared with model control group. Whereas liver SOD, TG activity and LI were no significant difference when compared with model control group (Table 2).
Table 2: Effects of AI-E on liver indicators in CCl₄ injured liver fibrotic rats.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>CCl₄</th>
<th>Silymarin</th>
<th>AI-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>44.07 ± 5.67</td>
<td>78.01 ± 6.19&lt;sub&gt;###&lt;/sub&gt;</td>
<td>55.11 ± 4.68&lt;sub&gt;####&lt;/sub&gt;</td>
<td>58.38 ± 6.81&lt;sub&gt;**&lt;/sub&gt;</td>
</tr>
<tr>
<td>ALT</td>
<td>32.10 ± 7.34</td>
<td>44.83 ± 5.46&lt;sub&gt;###&lt;/sub&gt;</td>
<td>25.18 ± 5.87&lt;sub&gt;####&lt;/sub&gt;</td>
<td>20.39 ± 5.15&lt;sub&gt;####&lt;/sub&gt;</td>
</tr>
<tr>
<td>TC</td>
<td>85.73 ± 1.71</td>
<td>159.36 ± 3.91&lt;sub&gt;###&lt;/sub&gt;</td>
<td>90.66 ± 2.80&lt;sub&gt;####&lt;/sub&gt;</td>
<td>105.28 ± 2.80&lt;sub&gt;####&lt;/sub&gt;</td>
</tr>
<tr>
<td>TG</td>
<td>0.12± 0.03</td>
<td>0.27±0.07&lt;sub&gt;###&lt;/sub&gt;</td>
<td>0.26±0.07&lt;sub&gt;####&lt;/sub&gt;</td>
<td>0.24±0.07&lt;sub&gt;####&lt;/sub&gt;</td>
</tr>
<tr>
<td>MDA</td>
<td>8.77 ± 1.45</td>
<td>10.28 ± 2.82&lt;sub&gt;###&lt;/sub&gt;</td>
<td>8.88 ± 1.34</td>
<td>6.96 ± 1.13&lt;sub&gt;**&lt;/sub&gt;</td>
</tr>
<tr>
<td>SOD</td>
<td>11.49 ± 0.87</td>
<td>11.16 ± 0.79&lt;sub&gt;###&lt;/sub&gt;</td>
<td>11.19 ± 0.64&lt;sub&gt;####&lt;/sub&gt;</td>
<td>12.16 ± 1.54</td>
</tr>
<tr>
<td>LI</td>
<td>2.14 ± 0.06</td>
<td>3.21 ± 0.07&lt;sub&gt;###&lt;/sub&gt;</td>
<td>2.86 ± 0.06&lt;sub&gt;####&lt;/sub&gt;</td>
<td>3.26 ± 0.06&lt;sub&gt;####&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

# Represents statistical significance vs. Normal control.  
* Represents statistical significance vs. CCl₄.

**P < 0.01, ***P < 0.001.  
## P<0.01, ###P<0.001.

**Effects of AI-E on pathological examination**

Liver histopathological examination showed no histological abnormalities in normal control liver, portal areas were clear, the hepatic lobular architecture was normal, did not see connective tissue proliferation (Fig. 1A and B); liver tissue in untreated CCl₄ injured rats had more steatosis, cell necrosis and inflammatory infiltration than those in normal control rats. Histological abnormalities in model rat livers also showed apparent formation of fibrotic septa, encompassing regenerated hepatocytes into pseudolobules, the surface of liver was unsmooth, lobular structure was damaged, and accompanied by higher collagen content in the liver, which fulfilled the diagnostic standard for chronic hepatitis (Fig. 1C and D); AI-E (400 mg/kg) treatment markedly alleviated the degree of liver fibrosis and significantly lowered collagen deposited (Table 3 and Fig. 1E and F).

Figure 1: Histological image of liver tissues. The normal lobular architecture with central veins and radiating hepatic cords in normal control rat (A and B). Fatty degeneration, necrosis, infiltration of inflammatory cells and apparent formation of fibrotic septa in the CCl₄ model rat (C and D). The degree of liver damage and fibrosis were significantly reduced in the AI-E (400 mg/kg) treatment rat (E and F). Magnification of microscope is 200X.
DISCUSSION AND CONCLUSION

In this present study, AI-E was evaluated for the hepatoprotective activity using CCl₄ induced hepatotoxicity in rat. CCl₄ is being used extensively to investigate hepatoprotective activity on various experimental animals[17,18]. The changes associated with CCl₄ induced liver damage are similar to that of acute viral hepatitis, due to preferred as the experimental model[19,20]. The ability of a hepatoprotective drug to reduce the injurious effects or to preserve the normal hepatic physiological mechanisms that have been disturbed by a hepatotoxin is the index of its protective effects[21]. The hepatotoxicity induced by CCl₄ is due to its metabolite CCl₃, a free radical that alkylates cellular proteins and other macromolecules with a simultaneous attack on polyunsaturated fatty acids, in the presence of oxygen, to produce lipid peroxides, leading to liver damage[22]. Hepatocellular necrosis leads to elevation of the serum marker enzymes, which are released from the liver into blood[23]. The increased levels of AST, ALT, ALP and serum bilirubin are conventional indicators of liver injury[24,25].

Many cases it was found that oxidative damage is a substrate for hepatic fibrogenesis. Oxidative stress has been considered as a major molecular mechanism involved in CCl₄ toxicity[26]. Previous reports have shown that oxidative stresses play an important role for the inactivation of Kupffer cells in the initial CCl₄-induced rat liver fibrosis[27,28].

Hepatic fibrosis is usually initiated by hepatocyte damage. Biologic factors (such as hepatitis virus, bile duct obstruction, cholesterol overload, schistosomiasis, etc.) or chemical factors (such as CCl₄ administration, alcohol intake, etc.) were known to contribute to liver fibrosis. The incidence of chronic fibrosis is high, but there have been no satisfactory agents with ascertained effectiveness and few side effects. So, finding effective ways to inhibit liver fibrosis and prevent the development of cirrhosis are of great significance.

In this study, CCl₄-induced liver fibrosis model was established to investigate the anti-fibrotic effects of AI-E in vivo. The results have shown that the rats receiving CCl₄ caused a significant elevation of liver index, serum ALT, AST, and HA, while after treatment with AI-E these indexes were markedly reduced. Moreover, the degrees of pathological changes followed chronic intoxication with CCl₄ which were also ameliorated remarkably by AI-E treatment, indicating AI-E have positive antifibrotic effects.

In this present study, CCl₄-induced increased serum AST and ALT were significantly suppressed by treating with AI-E. In chronic liver diseases such as alcoholic hepatitis, hepatic fibrosis, hepatic cirrhosis, the serum ALB and TP levels were reduced due to protein synthesis disorder in hepatocytes[29]. As Table 1 showed, treatment with AI-E elevated the ALB and TP levels revealed the ability of enhancement of liver cells regeneration.

In conclusions, the hydro-alcoholic extracts of root of Alocasia indica Linn. exhibited protective effect against CCl₄-induced hepatotoxicity and possess antifibrotic activities. The result supports the use of the plant as described in folk medicine, that the root of plant can be used to treat liver and gastric disorders. Further studies are required to isolate the active constituents involved in the antifibrotic and hepatoprotective activity of the plant.

CONFLICT OF INTEREST:

The author declare that there is no conflict of interest

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