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Research Article

Hepatoprotective activity of *Eclipta alba* against carbon tetrachloride-induced hepatotoxicity in albino rats

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ABSTRACT

Background: Despite the tremendous scientific advancement in the field of gastroenterology over the recent years, there is not even a single effective allopathic medication available for the treatment of liver disorders. Hence, the study was conducted to elucidate the hepatoprotective activity of aqueous extract of traditional medicinal plant *Eclipta alba* against carbon tetrachloride (CCl_4) induced toxicity in male albino rats.

Methods: The hepatoprotective effect of the aqueous extracts of *E. alba* was evaluated by biochemical parameters such as serum alanine transferases (ALT), serum aspartate transferases (AST), alkaline phosphatase (ALP), total serum bilirubin, and serum protein, and confirmed by histopathology of liver. The hepatotoxic agent CCl_4 was used to induce liver toxicity and silymarin was used as a control drug. The aqueous extracts of *E. alba* were administered at the doses of 250 mg/kg/day and 500 mg/kg/day orally for 4 days. One-way Analysis of Variance was used for the statistical analysis of data. A probability value of $p<0.05$ was considered as significant.

Results: *E. alba* administration at doses 250 mg/kg and 500 mg/kg orally demonstrated significant hepatoprotective activity by preventing the increase of ALT, AST, ALP, and serum bilirubin and also confirmed by histopathology of the liver. The results were comparable to that of silymarin.

Conclusion: The results of the study confirmed the hepatoprotective activity of aqueous extracts of *E. alba* at doses of 250 mg/kg and 500 mg/kg against CCl_4 induced hepatotoxicity in rats. However, the dose adjustments may be necessary to optimize the similar hepatoprotective efficacy in clinical settings.

Keywords: Carbon tetrachloride, Hepatoprotective activity, *Eclipta alba*, Silymarin

INTRODUCTION

The liver is the key organ regulating homeostasis in the body. One of the primary functions of the liver includes processing and protecting against the hazards of harmful drugs and substances from the gastrointestinal tract before distributing to the different parts of the body. The common causes of liver disorders include excessive alcohol consumption, infective hepatitis, and drug toxicity. Modern allopathic medicine has very little to offer for the treatment of liver disorders in spite of consistent effort for new drug discovery. There are several herbal formulations used for their hepatoprotective activity in the traditional system of medicine in India and China.[1] However, only a small proportion of these herbal preparations have been evaluated scientifically in animal and clinical studies. *Eclipta alba* grows commonly in moist places as a weed all over the world. In many parts of India, it is grown commercially as a medicinal crop. Aerial parts of the *E. alba* plant are used in medicine.[2] There are very less scientific data regarding the identification and effectiveness of individual *E. alba* for the treatment of various liver disorders. Both the anecdotal reports and scientific studies have found that the aqueous extracts of *E. alba* exhibited hepatoprotective activity against carbon tetrachloride (CCl_4) induced hepatotoxicity in animal models. The study was undertaken to evaluate the hepatoprotective activity of aqueous extracts of *E. alba* against CCl_4 induced hepatotoxicity in albino rats to validate folkloric claim with scientific data.[3] Silymarin, an ayurvedic formulation which has shown to be hepatoprotective in CCl_4, paracetamol, and ethanol-induced hepatotoxicity in various animal models and also in clinical studies is used as a standard control.[4,5] Silymarin is a mixture of mainly three flavonolignans, *viz*, silybin,

silidianin, and silychristine obtained from the seeds of "milk thistle" (*Silybum marianum*). Silymarin has been used medicinally to treat liver disorders, including acute and chronic viral hepatitis, toxin/drug-induced hepatitis, and cirrhosis and alcoholic liver diseases. In the recent past, there has been a paradigm shift toward evaluation of herbal preparations in liver disease models with the modern concept of randomized clinical trials to support safety and efficacy.[6] Thus, the present study is aimed at evaluation of *E. alba* for its hepatoprotective activity in animal models to compile data for standardization of the dose for its efficacy and safety to move forward toward clinical trials of the same.

METHODS

Plant material and preparation of extract

E. alba Linn leaves were collected after the plant was identified and authenticated by Dr. B. B. Joshi at the Department of Rashashastra, Ayurvedic Medical College, Heggeri, Hubli, Karnataka, India. The leaves were shade dried and powdered. The powdered materials of *E. alba* were subjected to successive solvent extraction using soxhlet apparatus and refluxed successively with petroleum ether, chloroform, and methanol. The extracts were filtered and concentrated in vacuum using rotary flash evaporator. The crude extract was administered to the animals as aqueous solutions.

Chemicals

CCl_4 was purchased from Qualigens Fine Chemicals, Mumbai. The liver function kits alanine transferases (ALT), aspartate transaminases (AST), alkaline phosphatase (ALP), total serum proteins, and total serum bilirubin were purchased from Bayer Diagnostics India Limited: silymarin was received as a gift from Micro Labs Limited, Goa, India.

Animals

Male albino rats weighing between 150 g and 200 g bred in Central Animal House, Karnataka Institute of Medical Sciences (KIMS), Hubli Karnataka, India were procured and used for the study. Animals were maintained in standard laboratory conditions with 12 hrs of daylight at 25°C±5. The animals were acclimatized to in-house conditions and were fed a commercial pellet diet (Hindustan Lever Limited, Mumbai, India) and water *ad libitum*. Experimental protocol was undertaken in accordance with the ethical guidelines, and the permission of the institutional animal ethics committee was obtained. All the animals received care according to the guidelines of CPCSEA/IAEC code 780. The study was approved by the Institute Animal Ethics Committee (KIMS), Hubli, Karnataka, India.

CCl_4 induced hepatotoxicity model

Hepatoprotective activity was evaluated by the method described by Saraf and Dixit.[7] The rats were divided into five groups of six rats each.

1. Group I served as normal and was administered only vehicle (distilled water) of 1 ml/kg body weight (b.w) for 4 days.
2. Group II served as toxin control and was administered vehicle on the 1st and 4th day and vehicle+CCl_4 at a dose of 2 ml/kg intraperitoneally (i.p) as 1:1 mixture with olive oil on the second and 3rd day, respectively.[8]
3. Group III received silymarin at a dose of 50 mg/kg b.w on the 1st and 4th day and silymarin (50 mg/kg b.w.)+CCl_4 at a dose of 2 ml/kg intraperitoneally (i.p) as 1:1 mixture with olive oil on the 2nd and 3rd day respectively.[9]
4. Groups IV received aqueous extract of *E. alba* at a dose of 250 mg/kg b.w. on the 1st and 4th day and aqueous extract of *E. alba* at 250 mg/kg b.w.+CCl_4 at a dose of 2 ml/kg intraperitoneally (i.p) as 1:1 mixture with olive oil on the 2nd and 3rd day, respectively.[10-13]
5. Groups V received aqueous extract of *E. alba* at a dose of 500 mg/kg b.w. on the 1st and 4th day and aqueous extract of *E. alba* at 500 mg/kg b.w.+CCl_4 at a dose of 2 ml/kg intraperitoneally (i.p) as 1:1 mixture with olive oil on the 2nd and 3rd day, respectively.[10-13]

Assessment of hepatoprotective activity

Biochemical tests

On the 5th day, the animals were anesthetized and blood was collected from the retro-orbital plexus. Serum was separated after coagulating at 37°C for 30 mins and centrifuging at 2000 rpm for 15 mins, and estimated for serum ALT, serum AST, ALP and total serum proteins and total serum bilirubin using kits supplied by Bayer diagnostics India, Limited.[14]

Histopathology of liver

After collection of blood for biochemical estimation, the rats were sacrificed and the liver was carefully dissected, cleaned of extraneous tissue, and fixed in 10% formalin for at least 24 hrs. Then the paraffin sections were prepared (automatic tissue processor, auto-technique) and cut into 5 µm thick sections, using a rotary microtome. The sections were stained with haematoxylin-eosin dye and studied for histopathological changes. The hepatoprotective activity was confirmed through histopathological studies on liver of rats.[15]

Statistical analysis

All the results were expressed as mean ± standard error of mean. One-way Analysis of Variance was used for the statistical analysis of data. Dunnett's multiple comparison

tests was used for determining the significance. A probability value of $p<0.05$ was considered as significant.[16]

RESULTS

Biochemical tests

The activity levels of serum ALT, AST, ALP, total serum bilirubin, and total serum protein were taken as biochemical indices for hepatotoxicity induced by CCl_4 in Group II. In the CCl_4 administered Group II, ALT, AST, ALP, total serum bilirubin were increased significantly ($p<0.001$) to 61.76±4.95 U/L/min/mg protein, 106.23±8.02 U/L/min/mg protein, 31.16±2.31 KA units, 1.98±0.21 mg/dL, respectively, whereas these values in control Group I showed 23.36±1.75 U/L/min/mg protein, 68.50±4.08 U/L/min/mg protein, 11.76±0.84 KA units, 0.26±0.11 mg/dL, respectively. The total serum proteins in CCl_4 administered Group II decreased significantly ($p<0.001$) to 4.26±0.20 g/dL from 6.83±0.26 g/dL in control Group I. Administration of aqueous extract of *E. alba* at a dose of 250 mg/kg b.w in Group IV showed statistically significant improvement ($p<0.05$) in the serum ALT, AST, ALP, total serum bilirubin levels to 38.36±3.04 U/L/min/mg protein, 85.46±5.80 U/L/min/mg protein, 23.13±0.56 KA units, 1.49.±0.11 mg/dL, respectively, which were comparable to control Group I and also standard control silymarin at 50 mg/kg in Group III. The total serum proteins in Group IV increased significantly ($p<0.05$) to 6.28±0.26 g/dL from 4.26±0.20 g/dL in CCl_4 administered Group II and comparable to 6.83±0.26 g/dL in normal control Group I and 6.81±0.24 g/dL in silymarin at 50 mg/kg of Group III. Treatment with aqueous extract of *E. alba* at a dose of 500 mg/kg in Group V also showed statistically significant ($p<0.05$) improvement in the serum ALT levels to 37.46±1.04 U/L/min/mg protein, AST to 83.36±3.64 U/L/min/mg protein, ALP to 22.10±0.66 KA units, total serum bilirubin levels to 1.52±0.12 mg/dL which are comparable to control Group I and silymarin Group III. The total serum protein in Group V increased significantly ($p<0.05$) to 5.83±0.33 g/dL from 4.26±0.20 g/dL in CCl_4 administered Group II and comparable to 6.83±0.26 g/dL in Group I, 6.81±0.24 g/dL in silymarin treated Group III and 6.28±0.26 g/dL in *E. alba* at 250 mg/kg treated Group IV. Silymarin used as standard positive control in Group III showed a statistically significant ($p<0.05$) improvement compared to CCl_4 administered Group II of ALT 36.26±2.04, AST 81.16±4.91, ALP 24.21±1.07, total serum bilirubin 0.63±0.07, and total serum protein of 6.28±0.24 demonstrated that it is an effective hepatoprotective agent (Table 1).

Histopathological studies of rat liver

The typical architecture of liver tissue was observed with a central vein (CV) and radiating chords of hepatocytes. The portal triad was seen consisting of hepatic artery, portal vein (PV), and bile duct. The zone 1 constituted surrounding areas of the hepatic artery, while zone 2 and zone 3 were situated to further periphery. The area around the CV is called centrizonal or centrilobular area (Figure 1).

The comparison of the liver section of rats administered with CCl_4 in Group II showed a high degree of damage characterized by cell vacuolation and pyknotic degeneration of the nucleus. The normal architecture of the liver was lost. The intralobular vein was severely damaged with wide spaces at sinusoids. CCl_4 administration produced extensive hemorrhagic necrosis of the liver, which was more pronounced in the centrizonal also known as zone three regions with infiltration of inflammatory cells. Apart from fatty changes, hepatocytes showed hydropic changes and the sinusoids were congested (Figure 2).

Silymarin used as a standard control in Group III at the doses of 50 mg/kg along with CCl_4 showed only mild to moderate necrosis, with multiple tiny foci of liver cell injury (Figure 3).

The aqueous extract of *E. alba* at 250 mg/kg b.w and CCl_4 in Group IV showed radially arranged hepatocytes along with vacuolation similar to that of normal. The intralobular vein was normal in structure, but the wall was damaged and no pyknosis in the nucleus. The recovery was comparable to that with silymarin in Group III, a standard hepatoprotective agent (Figure 4).

Liver sections of rats that were administered aqueous extract of *E. alba* at 500 mg/kg b.w along with CCl_4 in Group V

Table 1: Effect of *Eclipta alba* aqueous extracts on the activities of ALT, AST, ALP, total serum bilirubin, and total serum protein (mean±SEM).

Group	ALT (IU/L/min/mg protein)	AST (IU/L/min/mg protein)	ALP (KA units/dL)	Total serum bilirubin (mg/dL)	Total serum protein (g/dL)
Group I	23.36±1.75	68.50±4.08	11.76±0.84	0.26±0.11	6.83±0.26
Group II	61.76±4.95**	106.23±8.02**	31.16±2.31**	1.98±0.21*	4.26±0.20*
Group III	36.26±2.04*	81.16±4.91*	24.21±1.07*	0.63±0.07	6.81±0.24*
Group IV	38.36±3.04*	85.46±5.80*	23.11±0.56*	1.49±0.11*	6.28±0.26*
Group V	37.46±1.04*	83.36±3.64*	22.10±0.66*	1.52±0.12*	5.83±0.33*

Values are mean±SEM, *$p<0.05$ compared with Group II; **$p<0.001$ compared to Group I; ALT: Alanine aminotransferases, AST: Aspartate aminotransferases, ALP: Alkaline phosphatases, SEM: Standard error of mean

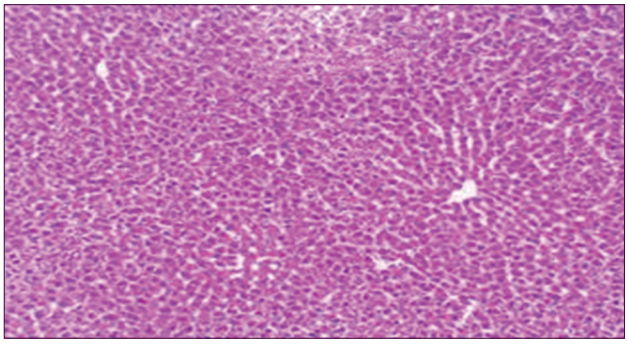

Figure 1: Normal control Group I. Normal histological architecture of rat liver with central vein and radiating chords of hepatocytes.

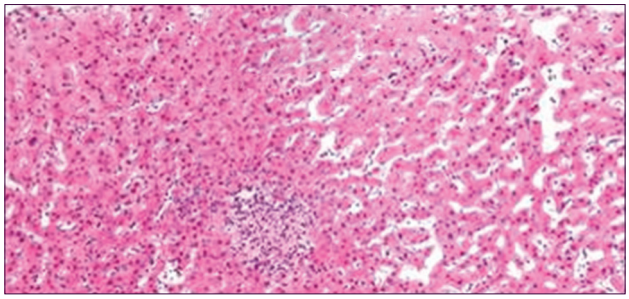

Figure 2: Carbon tetrachloride-induced hepatotoxicity. Carbon tetrachloride-induced hepatotoxicity showing extensive areas of confluent necrosis and also showing fatty changes and hydropic degeneration. H and E stain ×100. portal vein; bile duct.

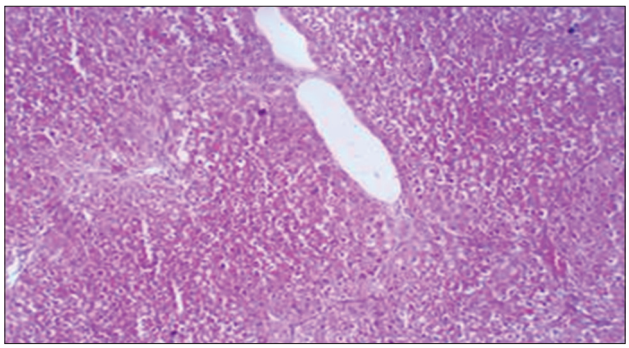

Figure 3: Group III of Silymarin (50 mg/kg) and CCl_4 treated group showing partial centrizonal protection. H and E stain 40 and ×100.

exhibited a high degree of protection to the liver by the absence of necrosis with few fatty vacuoles and normal arrangement of hepatocytes (Figure 5).

DISCUSSION

The liver plays an important role in providing protection from exposure to foreign substances by detoxification and elimination. Excessive exposure of the liver to environmental toxins, alcohol, drug overdose, and other commonly used therapeutic agents such as paracetamol, rifampicin, and bicalutamide can cause hepatotoxicity. The traditional herbal

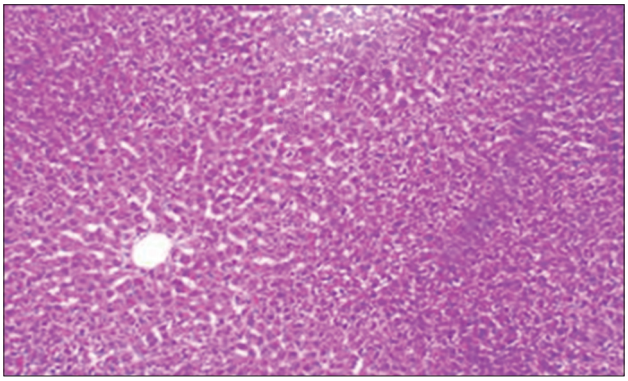

Figure 4: Group IV of *Eclipta alba* at 250 mg/kg and carbon tetrachloride (CCl_4) showing almost complete protection of hepatocytes against carbon tetrachloride induced hepatotoxicity.

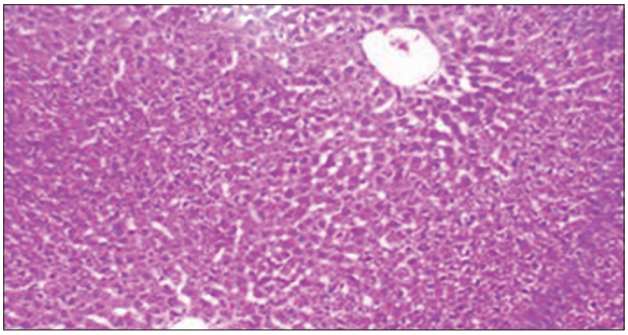

Figure 5: Group V of *Eclipta alba* at 500 mg/kg and carbon tetrachloride (CCl_4) showing almost normal architecture of liver with few fatty vacuoles. H and E stain 40 and ×100.

treatments for liver diseases have reached new dimension with the support of modern evidence-based medicine in clinical studies.[17] CCl_4 is commonly used for induction of experimental liver toxicity in animal models. Its metabolites such as trichloromethyl radical (CCl_3) and trichloromethyl peroxy radical are involved in the pathogenesis of liver toxicity. The activated free radical binds covalently to the macromolecules and induces peroxidative degradation of membrane lipids of endoplasmic reticulum, which are rich in polyunsaturated fatty acids.[18] This leads to the formation of lipid peroxides which in turn gives product such as malondialdehyde (MDA) that cause damage the membranes.[19] The increased liver MDA contents in rats treated with CCl_4 only suggest that the natural anti-oxidant defense mechanism to scavenge excessive free radicals has been compromised. This results in changes in structures of the endoplasmic reticulum and membranes of other organelles, loss of metabolic enzyme activation, reduction of protein synthesis and loss of glucose-6-phosphatase activation, leading to liver injury and elevated levels of serum transaminases, ALP, and bilirubin. Increased serum bilirubin level could also be looked upon as a compensatory/retaliatory phenomenon in response to cellular peroxidative changes. This is because bilirubin functions in vivo as a powerful antioxidant, anti-mutagen, and an endogenous

tissue protector. Serum ALT, serum AST, and ALP were found to be significantly elevated after CCl_4 administration though the rise in bilirubin level was not to the same extent as ALT, AST, and ALP (Table 1). This could be explained by the fact that bilirubin reaches peak serum level in the 2nd hr after CCl_4 administration and probably declines afterward. Blood collection in the present study was 48 hrs after CCl_4 administration and the serum bilirubin levels would have been on the decline. Administration of CCl_4 causes centrizonal necrosis (around the CV in the liver), fatty changes, hydropic degeneration and hepatocytes with pyknotic nucleus and leakage of liver marker enzymes like ALT, AST, ALP, and bilirubin and a decrease in serum total protein (Figure 2).

The herbal drugs or polyherbal combinations are traditionally used in the treatment of liver diseases caused by viral hepatitis, alcohol, toxic drugs and plant toxins. Silymarin from *S. marianum*, andrographolide from *Andrographis paniculata*, curcumin from *Curcuma longa*, picroside and kutkoside from *Picrorrhiza kurroa*, phyllanthin and hypophyllanthin from *Phyllanthus niruri*, glycyrrhizin from *Glycyrrhiza glabra* are traditionally studied for their chemical and biological profile and hepatoprotective efficacy in animal models.[20-22] These herbal preparations show hepatoprotection due to antioxidant effect, but other effects like immunomodulatory, antiviral, anti-inflammatory, antifibrotic, membrane stabilizing, and antiprotozoal activities are also documented. The flavonoids and wedelolactone present in *E. alba* may probably prevent the accumulation of excessive free radicals and protect the liver against CCl_4 intoxication.[3,23] We have tried to evaluate the hepatoprotective activity of *E. alba* against CCl_4 induced hepatotoxicity in a rat model in this study by assessing biochemical markers and histopathological study. *S. marianum* or silymarin, a plant secondary metabolite, is a complex mixture of four flavonolignan isomers, namely, silybin (60-70%), silychristin (20%), silidianin (10%), and isosilybin (5%). Silymarin is used as a standard control for hepatoprotective activity in CCl_4 induced hepatotoxicity in our study. Silymarin has been reported to have antioxidative, anti-inflammatory, immunomodulatory, and liver regenerating properties. The elevated levels of liver enzymes such as aspartate and ALT, AST, ALP, and total serum bilirubin found in CCl_4 induced liver injuries are reduced significantly by its use of silymarin both in animal and clinical studies.[24]

Administration of aqueous extracts of *E. alba* showed significant hepatoprotective activity at 250 mg/kg and 500 mg/kg, which were comparable to the standard control silymarin at 50 mg/kg. The hepatoprotective effects were more pronounced with a higher dose of 500 mg/kg of aqueous extract of *E. alba*. The increased serum levels of ALT, AST, ALP, and serum total bilirubin levels in CCl_4 treated animals might be due to the leakage of enzymes into the serum. The significant decrease in the serum levels of the ALT, AST, ALP, and total bilirubin in *E. alba* aqueous extract administered animals might be due to decreased leakage from the liver cells. This suggests that the aqueous extract of *E. alba* was able to repair the probable hepatic injury and/or restore the cellular permeability; thus reducing the toxic effect of CCl_4 on the liver tissue. The qualitative phytochemical investigations on the aqueous extract of *E. alba* also showed positive for wedelolactone and flavonoids, which possess antioxidant properties and were found to be useful in the treatment of liver diseases. Since formation of free radicals by cytochrome P 450 after metabolism of CCl_4 has been implicated in lipid peroxidation mediated hepatocyte injury, the hepatoprotective property of *E. alba* can be ascribed to its inhibitory effect on the microsomal enzymes so that generation of free radicals is bound to be limited. *E. alba* is also claimed to act as a free radical scavenger thereby preventing lipid peroxidation by its anti-oxidant property and a stimulatory effect on hepatic regeneration (23). It is also assumed that the hepatoprotective effect of *E. alba* aqueous extract may be related to glutathione (GSH)-mediated detoxification. *E. alba* is reported to enhance GSH status in cells and thereby afforded protection to hepatic cells from toxic damage. There are still unexplained mechanisms of *E. alba* which may be assumed to be involved in the protection of liver from CCl_4 induced toxicity (1;10).

The present study had a few limitations as the safety profile of *E. alba* was not studied and the hepatoprotective drugs were given as pretreatment. Further, the pharmacokinetic studies of *E. alba* are largely unknown. An elaborate investigation is needed to explore the pharmacokinetic profile of *E. alba* and also for isolation and structure determination of the active hepatoprotective principle(s) ingredients.

It can be concluded from the present study that the aqueous extract of *E. alba* possesses hepatoprotective activity against CCl_4 induced hepatotoxicity in a rat model. Aqueous extract of *E. alba* have demonstrated hepatoprotective activity based on biochemical parameters ALT, AST, ALP, and total bilirubin levels, and also by histopathological studies by preserving the normal architecture of liver tissue to a large extent. Therefore, the study scientifically supports the further investigation for exploration of this aqueous extract of *E. alba* in animal and clinical studies before its introduction into medicine for treatment of liver disorders.

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