Hepatoprotective activity of Albosteroid, a Morus Mongolica triterpenic glycoside ester in experimental animals

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Abstract

Ethnopharmacological relevance: Morus Mongolica has historically been used in China to treat and prevent a wide range of ailments.
Materials and methods: Albosteroid from Morus Mongolica was tested for its hepatoprotective properties. ALT, AST, ALP, total bilirubin, and total protein levels, as well as antioxidant enzymes including SOD, CAT, and GPx, GST, and LPO levels, were all examined in the context of CCL4-induced hepatocellular carcinogenesis.
Results: Albosteroid, in a dose-dependent way, effectively returned towards normality the abnormal levels of serum ALT, AST, ALP, TB, and TP. Histopathological examination of rat liver slices was performed in addition to the biochemical tests that were already conducted. The reversal of the CCl4-diminished activity of antioxidant enzymes such as SOD, Cat, GPx, GST and the lowered CCl4-elevated level of LPO was likewise considerable and dose-dependent. The free radical processes were reduced by scavenging hydroxyl radicals, which albosteroid effectively prevented from increasing in blood levels. A significant rise in the amount of endogenous antioxidant enzymes in CCL4-induced hepatocellular carcinogenesis is also caused by this drug's effect on LPO levels.
Conclusion: The findings of this research reveal that albosteroid may help prevent liver cancer in rats that have been exposed to CCL4-induced carcinogenesis.

Key Words: Morus Mongolica; albosteroid; carbon tetrachloride; silymarin; hepatoprotective; rats

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Introduction

Liver metabolism, excretion of xenobiotics, and detoxification are all carried out by this organ. Toxins from the digestive system may enter the liver, resulting in a wide range of liver diseases that are a major public health issue. It has been more popular in recent years to employ carbon tetrachloride (CCl4) as an in-vivo model for the development of novel anti-hepatoprotective drugs because of the free radical-mediated damage it produces to the liver. A rise in serum levels of glutamate oxidase, pyruvate transaminase, alkaline phosphatase, and total bilirubin was seen after CCl4-induced hepatic damage. Studying medicinal plants, numerous researchers found that plants have active elements capable of scavenging biological systems' (Hepato protective) free radicals [1-4].

In addition to being used as food for silkworms, Morus Mongolica's leaves have also been utilised as a natural food additive in many Asian nations including China, Japan, Korea, and Thailand. Morus Mongolica is a non-toxic natural medicinal substance that belongs to the Moraceae family. It's a powerful antioxidant that's typically included in over-the-counter medications [5, 6]. According to the most recent knowledge, it is an excellent pharmacological meal. Cardiovascular, liver, and spleen problems benefit greatly from the usage of this plant's whole constituent components [7-10].

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The plant has several active phytochemical elements, including alkaloids, flavonoids, glycosides, terpenoids, steroids, volatile oils, tannins, and more [11-14]. Antioxidant, anxiolytic, depressive, neuroprotective, anticancer, and hepatoprotective properties have all been identified in studies on the plant [15-18].

The purpose of this research was to examine the hepatoprotective effects of albosteroid extracted from Morus Mongolica stem bark in experimental mice.

Materials and Methods

Institution's Animal Ethical Committee gave its approval to every study that was done with animals.

2.1. Plant material

Dr. Rahul Kashyap of the Siddhartha Institute of Pharmacy in India gathered Morus Mongolica stem bark from a medicinal garden at the Forest Research Institute in Dehradun and identified it.

2.2 Extraction and isolation of albosteroid

Morus Mongolica stem bark (4.5 kg) dried powder was extracted at 50°C for two days with methanol (12 L). Under lowered pressure, the extract was reduced to a slurry (736 g). Adsorbed onto silica gel was the slurry after it had been mixed with a little quantity of methanol (60-120 mesh). CHCl3/MeOH gradient systems (9:1;2.0L per gradient system) were used to submit the slurry to a silica gel column, and moralbosteroid colourless crystals were eluted (yield 19.3g, 0.43 percent). The spectroscopic data from the published literature was used to identify the structure of the chemical. Figure 1 shows the albosteroid structure [19].

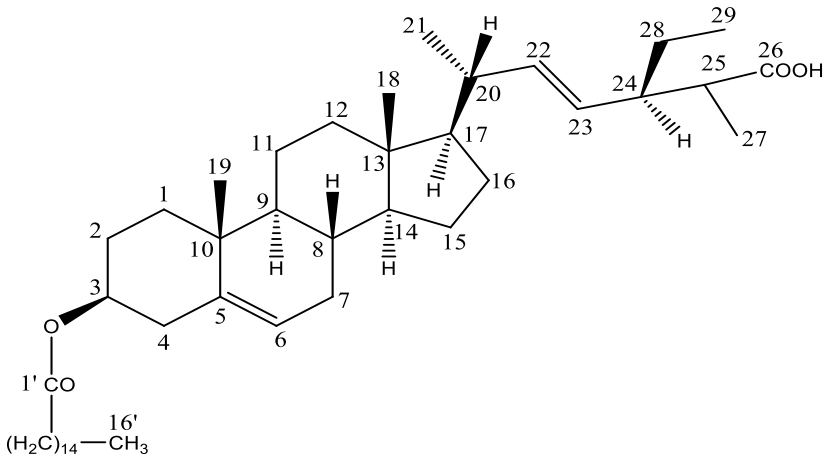

Figure 1: Structure of albosteroid

2.3. Hepatoprotective activity

2.3.1. Animals

Institute of Pharmacy's Central Animal House provided 150-200 g Wistar albino rats, which were housed at 25 ± 1°C, 55 ± 5% humidity, and a 12-hour light/dark cycle. A conventional pellet meal (Lipton rat feed, Ltd., Pune) and free access to water were provided to the animals throughout the study. The 'Institutional Animal Ethics Committee' gave its blessing to the study. We employed albosteroid, which we dispersed in one percent DMSO.

Experimental design

There were six groups of rats, each with six members. A single dosage of 0.5 mL/kg CCl4 intraperitoneally produced hepatic damage in rats. As a point of comparison, we looked at the chemical Silymarin. The following was the set-up for the experiment: CCl4 was administered on day 7 to rats in Group-II who had been treated with distilled water (1.0 ml, p.o.) daily for 7 days as a control. Albosteroid (25, 50, and 100 mg/kg, p.o.) daily for 7 days was administered to rats in Group-III, IV, and V who had been treated with albosteroid (25 mg/kg, p.o.) daily for 7 days as a treatment. Blood was taken from the retro-orbital plexus and centrifuged to separate the serum from the plasma at the conclusion of the experiment. The livers of the animals were removed, rinsed in ice-cold saline, and blotted to dryness before being stored in a freezer. Biochemical experiments were performed on the clear supernatant of a 1 percent homogenate of liver tissue prepared in phosphate buffer (0.1 M; pH 7.4) and centrifuged [20, 21].

Analyses using standard kits were performed on all

three enzymes: ALT, AST, and ALP (Siemens Healthcare Diagnostics Ltd, India). Standard kits were used to estimate TP and TB (Siemens Healthcare Diagnostics Ltd, India).
REMI cooling centrifuge was used to separate the unbroken cells and debris, and the supernatant was utilised for the estimate of LPO, SOD, CAT, GPx, and glutathione transferase by utilising the standard kits (Siemens Healthcare Diagnostics Ltd, India).

2.3.3. Histopathology

For the fixation process, little sections of liver tissue were placed in 10% formalin. Paraffin wax was used to implant the tissues. Hematoxylin and eosin were used to obtain 5- to 6-micron-thick sections. All portions of the tissues were inspected under a microscope to see how the liver tissue was affected by the CCL4 challenge and how it was improved by albosteroid treatment. A histological examination and photos were performed on these specimens. The images show how the liver's structure was enhanced by pretreatment with the test substance and the models used in our investigation (Conducted at Dr. Lal Pathology Lab, [New Delhi]) [22, 23].

2.4. Statistical analysis

The data were presented as the mean standard error of the mean (n=6). Least significant difference (LSD) test after one-way analysis of variance (ANOVA). A statistically significant result was one with a P value lower than 0.05.

Results

Albosteroid (25, 50, and 100mg/kg) has an influence on blood marker enzymes as shown in Table 1. Serum AST, ALT, ALP, and TB levels were considerably (P 0.001) elevated by CCl4 compared to the normal group, but TP levels were dramatically (P 0.001) decreased. It was shown that albosteroid at 50 and 100 mg/kg dosages considerably decreased CCl4-elevated AST, ALT, ALP and TB as well as raised (P0.01, P0.001) the lowered serum levels of TP. Results were comparable when silymarin (25 mg/kg) was used as well (P0.001). In contrast, a 25 mg/kg dosage of albosteroid was ineffective in CCl4-treated rats when it came to altering the levels of blood marker enzymes.

Table 1: Effect of albosteroid on hepatic marker enzymes in CCL4 induced hepatic injury in rats.

Group	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	Total protein (mg/dL)	Total bilirubin (mg/dL)
Normal	103.12±7.18	32.17±2.53	117.92±7.92	7.51±0.85	1.31±0.41
CCL4	318.61±21.28a	104.27±7.21a	439.18±12.27a	4.93±0.25a	5.78±0.51a
Albosteroid (25) + CCL4	251.91±19.61	78.51±6.24	351.82±16.01	5.21±0.71	4.51±0.76
Albosteroid (50) + CCL4	178.51±12.14*	61.61±6.17*	173.29±18.21*	6.05±0.82*	2.84±0.83*
Albosteroid (100) + CCL4	139.61±13.28**	42.17±3.61**	149.61±13.37**	6.71±0.73**	2.01±0.51**
Silymarin+ CCL4	128.71±9.38**	38.66±2.16**	123.19±14.02**	7.18±0.31**	1.51±0.28**

Values are expressed as mean±SEM. (n = 6). Statistical significance P < 0.05.
aP<0.001 as compared to normal group
*P<0.01 as compared to CCL4 treated group
**P<0.001 as compared to CCL4 treated group

CCl4-induced lipid peroxidation is shown in Table 2 using albosteroid doses of 25, 50, and 100mg/kg. When mice were armoured with albosteroid (50 and 100mg/kg) and silymarin (25 mg/kg), CCl4 considerably (P0.001) raised the level of LPO, which was significantly suppressed (P0.01, P0.001) in animals. The hepatic cells of mice given CCl4 have a decreased ability to produce antioxidant enzymes. SOD, CAT, GPx, and GST activities were significantly restored (P0.01, P0.001) in albosteroid + CCl4 treated rats, however (50 and 100mg/kg). When rats were given albosteroid (25 mg/kg) it had no effect on the elevated levels of LPO or the lowered levels of several antioxidant enzymes.

Table 2: Effect of albosteroid on antioxidant enzymes in CCL4 induced hepatic injury in rats.

Group	LPO (µM/mg Protein)	CAT (nmol/min/ml)	SOD (U/ml)	GPx (µmol)	GST (U/min/mg Protein)
Normal	6.51±0.71	0.91±0.53	1.57±0.61	7.92±0.87	0.17±0.09
CCL4	13.61±1.59a	0.34±0.62a	0.89±0.83a	3.90±0.91a	0.05 ±0.16 a
Albosteroid (25) + CCL4	10.81±1.05	0.48±0.07	0.97±0.60	4.81±0.27	0.09±0.29
Albosteroid (50) + CCL4	8.07±1.60*	0.71±0.15*	1.26±0.10*	6.69±0.42*	0.11±0.52*
Albosteroid (100) + CCL4	7.31±1.19**	0.89±0.31**	1.46±0.06**	7.58±0.05**	0.14±0.09**
Silymarin+ CCL4	7.43±1.06**	0.91±0.90**	1.52±0.24**	7.75±0.54**	0.16±0.18**

Values are expressed as mean±SEM. (n = 6). Statistical significance P < 0.05.
aP<0.001 as compared to normal group
*P<0.01 as compared to CCL4 treated group
**P<0.001 as compared to CCL4 treated group

The livers of healthy control animals were examined histologically and found to be normal (Fig 2 A). However, a single dosage of 0.5 ml/kg CCl4 intraperitoneally administered to inebriated rats resulted in liver tissue alterations. Animals treated with CCl4 demonstrated centrilobular necrosis, hepatocyte ballooning and infiltration into the portal system and sinusoid of inflammatory cells (such as macrophages and lymphocytes) histopathologically (Fig 2 B). There was a dosage response to pretreatment with albosteroid (25, 50, and 100mg/kg) for CCl4-induced liver lesions (Fig 2 C, D and E). When the maximum dosage examined was administered to rats, there was no evidence of necrosis or inflammatory infiltrates in the liver area. Albosteroid at 100 mg/kg dosage was almost as effective as silymarin (Fig 2 F) and normal control groups.

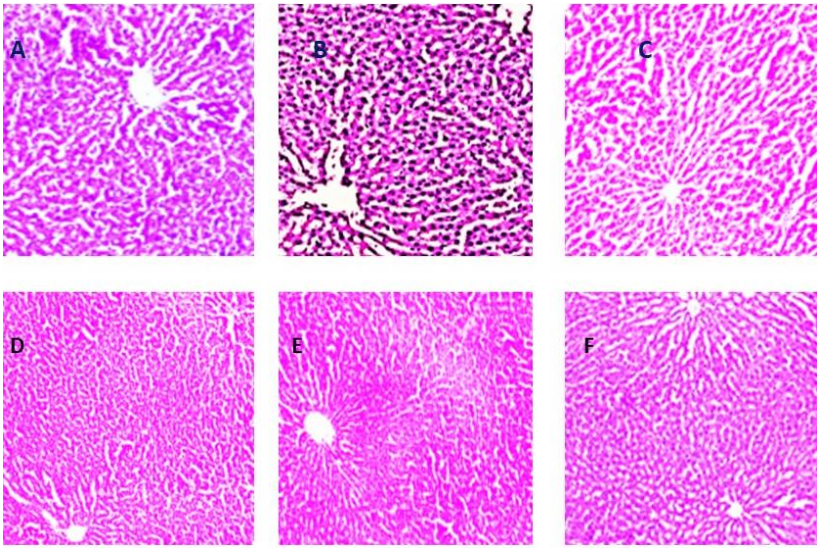

Figure 2: Histopathlogical studies showing Normal (A), CCl4 treated (B), Silymarin (F) and different doses of albosteroid [25 (C), 50 (D) and 100 mg/kg (E)]

Discussion

Hepatoprotective action of albosteroid is shown by reversing CCL4-induced changes in the levels of several liver marker enzymes and antioxidant enzymes. The assessment of serum AST and ALT levels serves as an indirect indicator of the liver's health. The blood AST and ALT values of albosteroid-

treated animals were lower than those of CCL4-treated animals [24, 25]. The concentration of ALT and AST in the cytoplasm of liver cells is greater, and AST is properly preserved in mitochondria. Plasma levels of hepatospecific enzymes rise due to damage to the liver cells, which results in leaking into the bloodstream. Increased levels of blood enzymes like ALT and AST show that the liver cell membrane has been damaged and is no longer functioning properly. It is possible to evaluate a drug's hepatoprotective impact by its capacity to protect the liver's normal functioning mechanism against hepatotoxin damage [26, 27].

ALP, on the other hand, is a marker for pathological abnormalities in biliary flow, whereas elevated serum bilirubin concentrations point to accelerated erythropoiesis. ALP and bilirubin levels in the blood were elevated as a result of CCL4. The albosteroid-treated group showed early changes in the secretory mechanism of heaptocytes by effectively controlling ALP and bilirubin levels [28, 29].

CCL4's toxicity causes a decrease in protein synthesis by destroying and dissociating polyribosomes on the endoplasmic reticulum. The polyribosome was protected by albosteroid, which thereby limited protein production. Histopathological examinations backed up the biochemical results [30-32].

Free radicals harm cells via a variety of processes, one of which is lipid peroxidation (LPO). When CCL4 is administered, lipid peroxidation products such as MDA and 4-hydroxy nonenal are produced. These compounds have the potential to function as catalysts for oxidative stress and the development of carcinogens. LPO, a marker of cancer, is elevated by CCL4 administration [33, 34]. This might lead to an unrestricted creation of free radicals, which could eventually overwhelm the body's own antioxidant defences. LPO levels in the serum of albosteroid-treated mice were significantly lower than those of CCL4-treated animals. Albasteroid's capacity to scavenge free radicals may be responsible for its anti-lipid peroxidation function [35-38].Superoxide anion is said to be converted into H2O2 and O2 by SOD and CAT, respectively, which results in a reduction of free radicals. Reactive peroxides are converted to alcohol and water by GPx. When it comes to detoxifying electrophilic chemicals, GST is a common phase 2 enzyme. Studies have shown , GST plays a vital role in shielding cells from oxidant-induced harm by accelerating the breakdown of lipid hydroperoxides formed by oxidative damage to cellular lipid molecules [39-41].

Cells from patients with hepatocellular carcinoma had decreased levels of SOD, CAT, GPx and GST. Carcinogenic activity in the body may be inhibited by substances that may neutralise excess free radicals. Our findings that albosteroid-pretreated rats' antioxidant enzyme activities rebound to near-normal levels are supported by studies like these, which show that CCL4's ability to initiate carcinogenesis is inhibited by antioxidant enzyme activity [42, 43].

In our investigation, we found that albosteroid effectively prevented the considerable rise in serum indicators and also controlled the free radical processes by scavenging hydroxyl radicals, which is consistent with our findings. A significant rise in the amount of endogenous antioxidant enzymes in CCL4-induced hepatocellular carcinogenesis is also caused by this drug's effect on LPO levels. Using CCL4-induced liver carcinogenesis in rats as a model, we tested the hypothesis that albosteroid could be able to suppress cancer growth.

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