Original Article

Albosteroid, A Steroidal Glycoside Derived From *Morus Mongolica*, Had A Protective Role In Preventing Nephrotoxicity In Rats Exposed To Paracetamol

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Abstract

Paracetamol (PCM) has an acceptable safety profile when used at the recommended dosage. Nevertheless, an overdose might cause kidney damage, with oxidative stress serving as one of the likely pathways. In this study, the effect of moralbosteroid isolated from Morus Mongolica stem bark [50 mg/kg and 100 mg/kg] on PCM-induced nephrotoxicity was evaluated. There were four sets of six rats containing rats. Other groups were treated with PCM alone (2 g/kg), 50 mg/kg albosteroid + PCM (2 g/kg), and 100 mg/kg albosteroid + PCM (2 g/kg), respectively. The control group received 1 ml vehicle. All of the materials were delivered orally. Albosteroid treatment at dosages of 50 and 100 mg/kg inhibits PCM-induced nephrotoxicity and oxidative damage to the kidney, as demonstrated by a substantially decreased level of blood urea and serum creatinine (P0.01, P0.05, and P0.001). In addition, a substantial rise (P0.05) in glutathione (GSH) concentration and a significant reduction (P0.001) in lipid peroxidation (LPO) were detected. Albosteroid's renoprotective qualities were shown by a decrease in the degree of nephritic cell death, as indicated by histological results. In addition, it was discovered that 100 mg/kg of albosteroid had stronger protective benefits than 50 mg/kg. Albosteroid has a protective effect against PCM-induced nephrotoxicity, the mechanism of which is likely mediated by its antioxidant activity.
Keywords: albosteroid, Antioxidant, Oxidative stress, Nephrotoxicity, Paracetamol

1. Introduction

Presently, there is a rising level of worry over the potential danger presented by natural and manmade substances with detrimental effects on people and animals. Due to the fact that they cause renal impairment, chronic medicines have garnered special attention. This is also the primary objective of eliminating these medications from the market and halting their development [1, 2].

PCM (acetaminophen) is one of the most prevalent and widely used medications for treating pain and fever. PCM is present in several formulations, which are sold as both over-the-counter and prescription drugs. In comparison to ibuprofen and aspirin, the possibility for overdose is much higher due to the drug's widespread availability and relatively higher toxicity. Toxic quantities of PCM may cause renal tubular injury, acute renal failure, and even death in both humans and experimental animals. Those with impaired renal function are susceptible to NSAID toxicity, even at standard doses [3-6].

Currently, a great deal of research is being conducted all over the globe in an effort to identify protective molecules that would give the kidney and other organs with maximum possible protection with little or no side effects during their activity in the body [7, 8]. Albosteroid is a steroidal glycoside identified from Morus Mongolica in our laboratory. Fundamentally, aalbosteroid is connected to -sitosterol, lawsaritol, and stigmasterol [9, 10].

It has been described as a chemical that protects against oxidative stress, gastric ulcer, hepatotoxicity, and anxiety [11, 12]. On the basis of its significant antioxidant activity, we hypothesised that albosteroid extracted from Morus

Mongolica stem bark would protect rats against PCM-induced nephrotoxicity. The nephroprotective impact of albosteroid was investigated in two ways: first, by measuring blood urea nitrogen and serum creatinine; and second, by estimating the GSH and LPO in PCM-induced nephrotoxicity.

2. Materials and methods

All the research conducted were sanctioned by the Institutional Animal Ethical Committee.

2.1. Plant material

Stem bark of Morus Mongolica was collected from the medicinal garden of at the Forest Research Institute in Dehradun and identified it..

2.2. Extraction and isolation of albosteroid

4.5 kilogrammes of powdered Morus Mongolica stem bark was extracted at 50 degrees Celsius for 48 hours with 12 litres of methyl alcohol using reflux abridgement. The resulting extract was exposed to decreased pressure in order to form a slurry (736 g). Methyl alcohol was used as the dissolving solvent for slurry, which was then adsorbed onto silica gel with a mesh size between 60 and 120. Using a gradient system of CHCl3/MeOH and a silica gel column, the white crystals of albosteroid (19.3 g, 0.43 percent yield) were separated from the slurry (9:1; 2.0 L). The structure of the molecule was identified by comparing the spectroscopic information published in the literature. The configuration of albosteroid is shown in Figure 1 [13].

2.3. PCM induced nephrotoxicity

In the dose response experimentation, albino rats were arbitrarily allotted into 4 groups of 6 individuals each. All the test drugs were administered orally.

Group-I - Negative control (received vehicle 1 ml/kg p.o.)
Group-II - Positive control (PCM 2 g/kg p.o.)
Group-III - albosteroid (50.0 mg/kg p.o.)
Group-IV - albosteroid (100.0 mg/kg p.o.)

Group II received 1 ml/kg of vehicle, while groups III and IV received 50 and 100 mg/kg of albosteroid, respectively, for seven days. On the seventh day, 30 minutes after the administration of vehicle, albosteroid (50.0 and 100.0 mg/kg), and PCM (2g/kg) to groups II, III, and IV, respectively, PCM is administered orally at a dose of 2g/kg. After 48 hours, rats were sacrificed under a light ether anaesthetic. The collection of blood samples for serum biochemical parameter estimation. To assess the tissue GSH and LPO, the kidney is removed, blotted dry, and rinsed with saline. The tissue is then preserved in 10% formalin and set aside for histopathology in order to assess the finer points of renal architecture in each individual group. The obtained blood is immediately centrifuged to isolate the serum for multiple biochemical analyses [14, 15].

2.3.1. Parameter assessed for the renal functions

Blood urea

The estimation of Urea in serum includes the subsequent enzyme catalyzed reactions:

$$\text{Urea} + \text{water} \xrightarrow{\text{Urease}} 2NH_3 + CO_2$$

$$NH_3 + \alpha\text{-KG} + NADH \xrightarrow{\text{GLDH}} \text{Glutamate} + NAD$$

α - KG: α - Ketoglutarate
GLDH: Glutamate dehydrogenase

The measure of reduction in absorbance is observed at 340 NM and is directly linked to the urea concentration in the specimen.

Serum creatinine

Creatinine in alkaline solution reacts with picrate to form a colored compound which absorbs at 500-520 NM. The amount of compound made is directly related to the creatinine concentration [16].

2.3.2. GSH estimation in PCM induced nephrotoxicity

Using an ultra turrax tissue homogenizer, kidney tissue samples were homogenised in ice-cold Trichloroacetic acid (0.5 g tissue + 5 ml, 10 percent TCA). Using a modification of the Ellamn method, GSH levels were

determined. After 10 minutes of centrifugation at 3000 RPM, 0.5 ml of the supernatant is combined with 2 ml of 0.3 M disodium hydrogen phosphate solution. After mixing, 0.2 ml of a dithiobisnitrobenzoate solution (0.4 mg/ml in 1% sodium citrate) is added, and the absorbance at 412 nanometers is measured immediately. The percentage rise in OD is related to the increase in Glutathione levels. Consequently, the % increase in OD is computed [17].

2.3.3. In vivo lipid peroxidation in PCM induced nephrotoxicity

Analyzing the quantity of lipid peroxide generation by detecting the creation of thiobarbituric reactive material.[18]

Reagent stock solution TCA-TBA-HCl: 15 percent by weight of trichloroacetic acid, 0.375 percent by weight of thiobarbituric acid, and 0.25N of hydrochloric acid. This solution may be heated slightly to aid in the breakdown of thiobarbituric acid.

Carefully combine 0.1-2.0 mg of membrane protein or 0.1-0.2 mol of lipid phosphate in 1.0 ml of biological material with 2.0 ml of TCA-TBA-HCl. The solution is cooked in a boiling water bath for one hour. After cooling, the flocculent precipitate is extracted by two minutes of centrifugation at 1,000 RPM. At 535 NM, the absorbance of the sample is measured against a blank containing all the reagents except the fat. The sample's malondialdehyde concentration may be determined using an extinction coefficient of 1.56 105 M–1 cm–1 [18].

2.3.4 Histopathological examination

Two rats were sacrificed from each group on the day of blood withdrawal and kidney isolation. The samples were cleaned with saline and stored in a formaldehyde solution containing 10 percent. The kidney was treated and then encapsulated in paraffin wax. The specimens were stained with Hematoxylin and Eosin, examined with a light microscope, and photographed for future analysis (led at the Dr. Lal Pathology Laboratory, Delhi) [19].

2.3.5 Statistical analysis

The data is presented as mean ± SEM, (n=6). Least significant difference [LSD] test was executed after the analysis of divergence between groups (ANOVA) by using Graph Pad Prism version 5.0. The groups were conceived to be statistically significant if P value was less than 0.05.

3. Results

The PCM-treated group had a higher blood urea concentration of 71.26 mg/deciliter. Although albosteroid supplied at 50 mg/kg and 100 mg/kg restored the increased level to 63.51 mg/dl and 54.91 mg/dl, respectively. In the PCM-treated group, the serum creatinine level rose to 1.46 mg/dL. In contrast, the 50 mg/kg and 100 mg/kg doses of albosteroid lowered the elevated level to 1.14 mg/dl and 0.78 mg/dl, respectively (Table 1).

In those receiving PCM, significant GSH depletion was found. The albosteroid-treated group demonstrated a dose-dependent increase in tissue GSH levels. 50 mg/kg and 100 mg/kg of albosteroid elevated GSH levels in tissue by 38.30 and 56.55 percent, respectively (Table 2). Both dosages of albosteroid effectively reduced the elevated degree of lipid peroxidation induced by PCM. Albosteroid 100 mg/kg exhibited 43.51 percent inhibition, while a dosage of 50 mg/kg exhibited 19.13 percent inhibition (Table 3).

Normal morphology of renal parenchyma, unremarkable glomeruli, normal interstitium, and normal blood vessels were seen by histopathological examination of the kidneys. However, the PCM-treated group had interstitial infiltration with inflammatory cells, tubular necrosis, peritubular necrosis, and glomeruli atrophy. Albosteroid therapy resulted in a dose-dependent decrease of tubular damage and dilatation, absence of vacuolization, and restoration of glomeruli morphology (Figure 2).

4. Discussion

The reduction in kidney function caused by toxic dosages of PCM has been identified as the principal adverse impact and the major dose-limiting factor associated with its clinical usage. Numerous studies testified that PCM-induced changes in kidney function were characterised by indicators of damage, such as a rise in LPO and GSH levels in renal tissue, as well as the levels of creatinine and urea in the blood [20, 21].

Reduced GSH levels make tissues more susceptible to oxidative and chemical harm. The well-established property of GSH is the synthesis of conjugates with electrophilic drug metabolites, which are generated most commonly by cytochrome P-450-linked monooxygenase. According to several studies, the metabolism of xenobiotics typically lowers GSH levels. Reduced GSH levels in the kidneys may significantly exacerbate PCM toxicity. In the PCM-administered group, lipid peroxidation appeared to be facilitated by a significant decrease in GSH levels. In addition, GSH is protected by creating a substrate for the GPx activity that may react directly with various aldehydes produced by membrane lipid peroxidation. The enhanced GPx activity might considerably clarify the biomembrane defence against oxidative damage [22-24].

Numerous studies have shown that PCM nephrotoxicity is associated to LPO in renal tissue, despite the fact that the specific mechanism of PCM-induced kidney injury is not well understood. LPO is attributed to a free radical-mediated chain reaction that destroys cell membranes, and albosteroid's capacity to scavenge free radicals is mostly attributed to a reserve of this process [25, 26].

Both serum urea and serum creatinine are important nephrotoxicity markers, however serum urea concentration is often a more reliable predictor of renal function than serum creatinine. Blood urea nitrogen is found in liver protein derived from dietary or tissue sources and is mostly eliminated via urine. In contrast, most creatinine is produced from endogenous sources via tissue breakdown. In the present study, rats administered with a nephrotoxic dosage of PCM had significantly higher blood levels of urea and creatinine than the normal control group [27, 28].These findings are consistent with those of Isik B et al., who showed a rise in blood urea and creatinine in rats given PCM. In addition, a rise in blood urea and creatinine was documented in a woman three days before to hospital admission, after therapeutic dosages of PCM. The existence of significant correlations between nephrotoxicity and oxidative stress clarified this rising amount of urea and creatinine. Histological observations of glomerular and tubulo-interstitial necrosis in the untreated model control group confirmed these biochemical alterations. Albosteroid treatment did give nephroprotection in a dose-dependent manner to PCM-injured renal rats, with 100 mg/kg providing the highest level of protection [29-31].

Albosteroid with stomach ulcer and liver protective characteristics has been demonstrated to mediate their protection via antioxidant and/or free radical scavenging effects. Albosteroid is a member of the -sitosterol family of chemicals. -sitosterols have been found to possess nephroprotective properties [32, 33].

By reversing the nephrotoxic effects of PCM, such as glomerular congestion, interstitium with inflammatory cells, peritubular necrosis, tubular necrosis, and intraluminal casts indicating large overall necrosis, the nephroprotective function of the albosteroid was established. It is probable that the protective effect of the albosteroid against PCM-induced nephrotoxicity is mediated by antioxidant and/or free radical scavenging effects, but these mechanisms were not investigated in the present work [34, 35].

5. Conclusion

The results of this investigation demonstrated biochemically and histopathologically the beneficial nephroprotective effect of albosteriod against PCM-induced oxidative damage. Albosteriod restores the structural integrity of the cell membrane in a dose-dependent manner and amplifies histopathological and biochemical abnormalities. All of the aforementioned alterations support our hypothesis that albosteroid have a probable protective effect on PCM-induced kidney damage in experimental mice.

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Table 1: Effect of albosteroid on Paracetamol induced renal damage in rats

GR (n=6)	Treatment regimen	Blood urea (mg/dl)	Serum Creatinine (mg/dl)
I	Negative Control (1ml vehicle)	42.18±1.27	0.64±0.18
II	Positive Control Paracetamol (2 g/kg p.o.)	71.26±1.03	1.46±0.61
III	Paracetamol+ albosteroid (2 g/kg p.o.)+ 50.0 mg/kg p.o.)	63.51±1.38**	1.14±0.13*
IV	Paracetamol + albosteroid (2 g/kg p.o.)+ 100.0 mg/kg p.o.)	54.91±1.07***	0.78±0.04***

Values are the Mean ± S.E.M. of six rats / treatment
Significance *P<0.05, **P<0.01,***P<0.001 (vs. Control)

Table 2: Effect of albosteroid on tissue GSH levels in Paracetamol induced renal damage in rats

Treatment	Absorbance Mean±SEM	% Increase
Negative Control (1ml vehicle)	0.772±0.05	--
Positive Control Paracetamol (2 g/kg p.o.)	0.389±0.16	--
Paracetamol+ albosteroid (2 g/kg p.o.)+ 50.0 mg/kg p.o.)	0.538±0.01*	38.30
Paracetamol + albosteroid (2 g/kg p.o.)+ 100.0 mg/kg p.o.)	0.609±0.05**	56.55

Values are the mean ± S.E.M. of six rats/ treatment
Significance *P<0.05, ***P<0.001, compared to paracetamol treatment

Table 3: Effect of albosteroid on tissue LPO levels in Paracetamol induced renal damage in rats

Treatment	Absorbance Mean±SEM	% Inhibition
Negative Control (1ml vehicle)	0.168±0.16	--
Positive Control Paracetamol (2 g/kg p.o.)	0.324±0.08	--
Paracetamol+ albosteroid (2 g/kg p.o.)+ 50.0 mg/kg p.o.)	0.262±0.53**	19.13
Paracetamol + albosteroid (2 g/kg p.o.)+ 100.0 mg/kg p.o.)	0.183±0.06***	43.51

Values are the mean ± S.E.M. of six rats /treatment.
Significance**P<0.01, ***P<0.001, compared to Paracetamol treatment

Figure 1: Structure of albosteroid

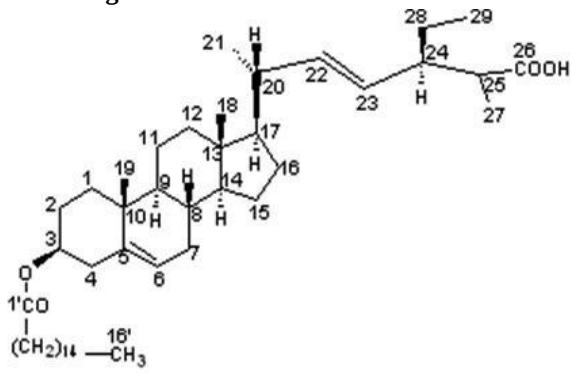
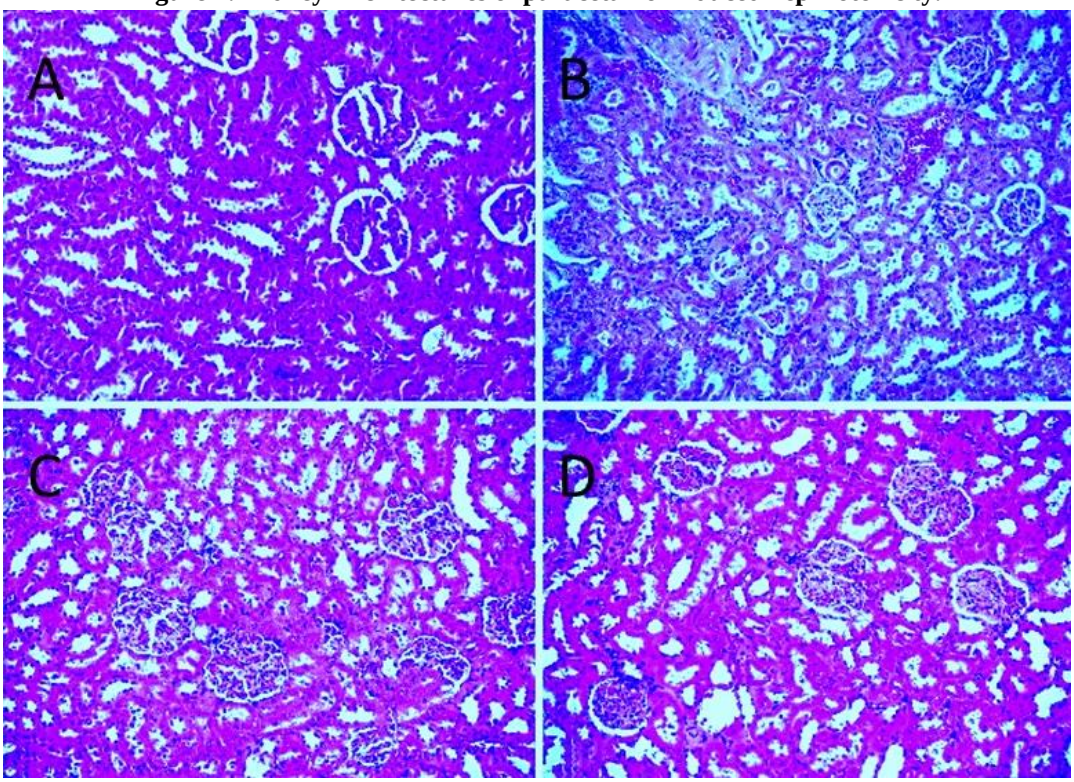


Figure 2: Kidney Architectures of paracetamol induced nephrotoxicity.



Photomicrographs of rat kidney (hematoxylin and eosin, 400 x) from (A) control group showing normal renal architecture; (B) paracetamol-treated group showing infilteration of interstitium with inflammatory cells, tubular necrosis, peritubular necrosis and an atrophy of glomeruli; (C) group showing marked improvement in the histological picture with minimal tubular damage without vacuolization; (D) the normal kidney structure of rats treated with albosteroid 100 mg/kg.