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Original Article

Animal Research Section

Hepatoprotective Effects of *Momordica dioica* Against Acetaminophen-induced Liver Damage in Rats: An Experimental Study

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ABSTRACT

Introduction: Hepatotoxicity from acetaminophen is a major contributor to liver damage. Among the most popular analgesics, acetaminophen has few adverse effects when taken in therapeutic dosages; however, acetaminophen abuse frequently results in hepatotoxicity.

Aim: The aim of this study is to investigate the histopathological changes induced by a therapeutic dose of N-acetyl-para-aminophenol (APAP) and to explore the hepatoprotective role of the oral co-administration of *Momordica dioica* fruit extract in mitigating hepatotoxicity induced by APAP in rats.

Materials and Methods: The present experimental study was conducted in the central animal facility of Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India, between February to April 2024. Thirty-six healthy male albino Wistar rats were utilised in this study, randomised and divided into six groups (G1-G6) of six rats each. The rats were administered APAP (i.p.) and *Momordica dioica* (MD) orally for 42 days as follows: (G1) Control (normal saline), (G2) APAP (250 mg/kg), (G3) APAP (250 mg/kg)+silymarin (250 mg/kg), (G4) APAP (250 mg/kg)+Vitamin C (200 mg/kg), (G5) APAP (250 mg/kg)+Vitamin C (200 mg/kg)+MD (250 mg/kg), and (G6) APAP (250 mg/kg)+Vitamin C (200 mg/kg)+MD (500 mg/kg). All animals in groups G2-G6 received the respective drug or ally according to their treatment group for 42 days, one hour prior to acetaminophen induction. Results were analysed using one-way ANOVA for statistical significance.

Results: The results demonstrated that rats given a therapeutic dose of APAP for 42 days experienced substantial histological alterations alongside elevated blood chemistry indicators. Co-administration of *Momordica dioica* extract resulted in significantly fewer histopathological lesions and restored or decreased levels of the tested blood chemistry parameters. Rats treated with silymarin exhibited no histological alterations, while liver histology in the *Momordica dioica* extract group revealed (100%) normal hepatic architecture with minor alterations. According to histochemical staining, APAP-induced hepatotoxicity was characterised by minimal to mild fibrosis (6/6), hydropic degeneration (6/6), necrosis (6/6), and steatosis (6/6).

Conclusion: The oral co-administration of *Momordica dioica* extract possesses significant hepatoprotective properties and mitigates APAP-induced hepatotoxicity by enhancing its antioxidant role and improving tissue integrity. *Momordica dioica* supplementation could represent an effective treatment against APAP-induced hepatotoxicity.

Keywords: Fibrosis, Hydropic degenerations, Liver steatosis, Methanol extraction

INTRODUCTION

Acetaminophen is an extensively used analgesic and antipyretic drug, and although it is safe when used at therapeutic doses, it is associated with significant hepatotoxicity when taken in overdose [1]. Under normal conditions, acetaminophen is primarily metabolised in the liver by glucuronidation and sulfation. A small proportion of the drug is metabolised by several of the cytochrome P450 enzymes into the reactive intermediate N-Acetyl-P-Benzoquinone Imine (NAPQI), which is normally detoxified by glutathione (GSH) both non-enzymatically and enzymatically. In overdose situations, sulfation and glucuronidation become saturated, and GSH is depleted by NAPQI. The excess of NAPQI causes oxidative stress and binds covalently to liver proteins [2].

Although the precise mechanism by which acetaminophen causes cell injury is still unknown, it is suggested that mitochondria may play an important role in the acetaminophen-induced death of liver cells. The majority of the world's population in developing countries still relies on herbal medicines to meet their health needs in cases where synthetic medicine could not address the underlying causes [3]. *Momordica dioica* (spiny gourd, small bitter gourd) is a perennial, dioecious, cucurbitaceous climbing creeper. The fruit of *Momordica dioica* is considered a folk medicinal and nutrient-rich vegetable. It contains a number of specific components, referred to as phytoconstituents (alkaloids, tannins, fixed oils, flavonoids, sterols, and amino acids), as well as secondary metabolites and other important ingredients that may help combat liver damage, diabetes, cancer, and neurodegenerative diseases [4].

Very few articles are available on the combination of acetaminophen (APAP) with Momordica charantia (MC) [5], but the combination of *Momordica dioica* (MD) with APAP is being investigated for the first time. Hence, the present study was undertaken to examine the histopathological changes induced by a therapeutic dose of N-APAP and to investigate the hepatoprotective role of the oral co-administration of *Momordica dioica* fruit extract concurrently against hepatotoxicity induced by APAP in rats.

MATERIALS AND METHODS

The present experimental study was conducted in the central animal facility of Sri Ramachandra Institute of Higher Education and Research (SRIHER), Chennai, Tamil Nadu, India with the approval of the Institutional Animal Ethical Committee (Approval No: IAEC/71/SRIHER/858/2023). The study took place between February to April 2024 at the central animal facility of SRIHER, in compliance with the ethical guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSA), Government of India, New Delhi.

Data collection: A total of 36 young, healthy male Albino rats were grouped, housed in polypropylene cages, and maintained on a 12-hour light and dark cycle with a relevant temperature and humidity

of 25±2ºC and 30-70%. The rats were fed a normal pellet diet with free access to water ad libitum.

The study animals were divided into six groups (G1-G6) and were randomly assigned. Acetaminophen (250 mg/kg, intraperitoneally) was administered to induce hepatotoxicity. All animals, except those in Group I, received acetaminophen intraperitoneally every day for 42 days. Group I animals received normal saline only, Group II animals received 250 mg/kg of acetaminophen intraperitoneally, Group III received the standard medication Silymarin (250 mg/kg, b.w.) prepared in water, while Group IV animals received vitamin C (200 mg/kg). Groups V and VI received 250 mg/kg and 500 mg/kg of formulated *Momordica dioica* extract, respectively, orally for 42 days [6]. Silymarin was administered as the standard drug (Group III) for comparison, and Vitamin C (Group IV) was given as a rich antioxidant drug.

Procurement and authentication of herb: The fruits of *Momordica dioica* Roxb. were obtained from the local market in Kadapa District, Andhra Pradesh. They were verified and authorised by a botanist at Yogi Vemana University. To utilise them as experimental material, 3 kg of *Momordica dioica* fruits were harvested, shade-dried, cleaned, and transported in sterile plastic bags to avoid moisture loss during the trip to the laboratory.

Preparation of methanolic extract [7]: The most widely used extraction process is maceration. This method is based on submerging the raw materials in a significant amount of solvent or menstruum fluid. A stoppered container containing the solid medicinal material was filled with approximately 1:5 (MD Powder: Methanol) of menstruum fluid and was then left to stand for at least three days in a warm environment, with frequent shaking. The crude drug and solvent mixture was filtered until the majority of the liquid dripped off. After standing, the mixed liquids were further purified by filtration. Following the extraction, the prepared extract was stored at room temperature (15°C-25°C) while avoiding moisture and sunlight.

Histopathology for the Assessment of Hepatotoxicity in the Liver

Liver samples were preserved in 10% buffered formalin for a minimum of 24 hours prior to processing, and histological specimens from the liver were prepared at the histopathology laboratory. In short, after fixation, the tissues were embedded in paraffin wax, and free or bound water was removed by dehydrating the tissues using ethanol at progressively higher concentrations. A microtome was used to cut the embedded tissues into thin sections of 3-5 µm. Haematoxylin and eosin (H&E) staining, as well as the Masson's trichrome stain procedure, were regularly used to stain the liver sections for histological evaluation, which was carried out on plain glass slides. Sections stained with H&E and Masson's Trichrome (MT) stains were examined under a 100× light microscope to identify any anomalies in the histopathological characteristics. The grading method was employed to determine the degree of hepatocellular alterations.

The severity of each condition progressively shifts into a new inflammatory grading and liver fibrosis staging as inflammation and fibrosis worsen, as shown in [Table/Fig-1]. The swollen or inflamed state is characterised by Grade one pathology, diagnosed as the body's typical response to injury, referred to as minimal effects. In Grade two, fibrosis, or liver scarring, is caused by minimal to mild inflammation; in Grade three, irreversible liver scarring is caused by mild to moderate inflammation; and in Grade four, liver failure, which involves moderate to severe or total cessation of liver function, occurs. These results also demonstrate that different species have varying levels of sensitivity to acetaminophen [8,9].

Analysis of serum parameters: Following the course of treatment, blood samples were taken from all thirty-six animals and examined. All 36 surviving animals were administered isoflurane anaesthesia,

Group	Hydropic degeneration	Mononuclear cell infiltration	Steatosis	Necrosis	Dilated central vein
G1	+	-	-	-	-
G2	++	++	+++	++	++
G3	+	+	-	-	-
G4	+	+	+	+	-
G5	+	-	+	-	-
G6	+	-	-	-	+

[Table/Fig-1]: Summary of Incidence and/or the Severity of Histopathology findings. The severity of various features of hepatic injury was evaluated based on those following scoring schemes: Grad I - Minimal effect (+); Grad II - Mild effect (++), Grad III - Moderate effect (+++), and Grad IV - Severe effect (++++)

and approximately 4-5 millilitres of blood from each group (6 rats) were collected through retro-orbital puncture. The surviving animals were fasted overnight with unrestricted access to water before blood was collected at the conclusion of the treatment session. A complete blood count analysis in haematology was performed using whole blood. The reference ranges for all parameters were obtained according to the manufacturer's kit.

Alanine Transaminase (ALT) and Aspartate Transaminase (AST) assay: AST and ALT were determined by the method of King. Consequently, the upper reference limit for ALT is higher than normal values (80.48-279.78 U/L), as compared to that for AST (19.16-111.05 U/L).

Alkaline phosphatase (ALP): Serum alkaline phosphatase (ALP) was estimated by the Kind and King method. In hepatocyte injury, ALP is often normal or marginally elevated (51-216.51 IU/L).

Total bilirubin: Serum bilirubin was estimated by the method of Malloy and Evelyn. These values are expressed as 0.09-0.53 mg/dL.

Total proteins: The protein content was estimated by the method of Lowry. The values are expressed as 4.68-8.58 g/dL in serum.

STATISTICAL ANALYSIS

The data obtained were expressed as mean±SD (standard deviation) and subjected to one-way analysis of variance (ANOVA) for comparing more than two means, as well as repeated measures ANOVA for comparing more than two means across different follow-up periods. The Statistical Package for the Social Sciences (SPSS) program for Windows (Standard version 24) was used for this analysis. A significance threshold (p-value) of less than 0.05 was considered significant.

RESULTS

The activities of serum AST, ALT, and ALP (marker enzymes for liver damage) were markedly elevated (approximately two fold) in acetaminophen-treated animals compared to normal control rats (G1), indicating liver damage. In G3, ALT levels were lower than in G1, but both were within the normal range, while ALP levels in G6 were slightly lower, which may be due to a higher concentration of MD. The co-treatment of rats with methanol extract of *Momordica dioica* fruit caused an increase in the serum levels of total protein (TP) and albumin, along with a significant decrease in the serum levels of ALP, AST, and ALT in the livers of extract-treated rats (G5 and G6). The enzyme levels and histological examinations confirmed that *Momordica dioica* methanolic extract (MEMD) was a hepatoprotective drug.

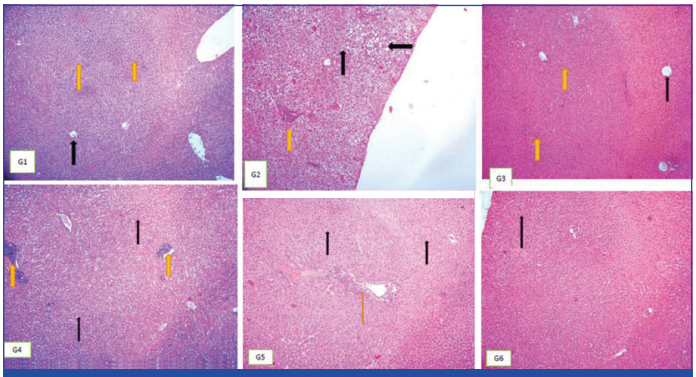
The methanol extract of *Momordica dioica* fruit (G5 and G6), at doses of 250 mg/kg and 500 mg/kg, respectively administered via oral gavage, demonstrated significant hepatoprotective ability against acetaminophen-induced hepatic damage in rats [Table/Fig-2].

Histopathological effects of APAP injection on the livers of normal and MD co-treated rats: After 42 days of intraperitoneal APAP injections, notable histopathological lesions developed. Large-scale hydropic degeneration, pyknotic hepatocyte nuclei, and lymphocytic infiltration of the hepatic Porta triad distinguished

Group	AST (U/L)	ALT (U/L)	ALP(U/L)	T.PRO (g/dL)	T.BIL (mg/dL)
G1	153.2±53.74	83.7±25.26	279.7±80.89	6.6±1.13	0.4±0.13
G2	249.83±72.47	158.17±15.33	431.00±227.59	7.82±2.00	0.62±0.20
G3	158.3±26.55**	76.8±6.43**	326.5±66.63**	7.7±0.61**	0.5±0.28**
G4	179.67±45.68**	98.67±14.50**	318.83±73.62**	8.19±0.74**	0.83±0.48**
G5	163.67±51.6**	110.83±31.2**	297.83±63.6**	8.49±0.7**	0.48±0.1**
G6	176.17±29.12**	101.67±14.12**	278.67±62.91**	8.39±0.63**	0.48±0.17**

[Table/Fig-2]: Analysis of serum parameters for all the groups.
Each value is represented as mean±SEM, No. of animals (n) =6, p<0.01 **vs normal control. Data were analysed by ANOVA followed by Students' t-test. Values at p <0.001 were considered significant (difference between groups and within the group). T.BIL: Total bilirubin; T.PRO: Total proteins

this lesion from the hepatocyte architecture of a healthy liver. However, in livers that had previously been treated with MD, hepatocyte deformation was reduced in a dose dependent manner. The liver that received 500 mg/kg MD exhibited the most significant reduction [Table/Fig-3].



[Table/Fig-3]: H&E stain 100X: Group-1: normal histological appearance of hepatocytes (Yellow arrow), central vein (black arrow) and sinusoids.Group-2: Steatosis (black arrow) and mononuclear cell infiltration (Yellow arrow).Group-3: normal histological appearance of hepatocytes (Yellow arrow), central vein (black arrow) and sinusoids. Group-4: showing hydropic degeneration (black arrow) and mild mononuclear cell infiltration.

Control Rats (G1): Microscopic examination of the control rats' livers demonstrated normal architecture, intact histological components of the hepatic lobules, normal portal areas, and central veins bounded by intact endothelium. Parallel hepatic strands radiate from the periphery of the liver lobules towards the central vein, separated by narrow blood sinusoids in control livers.

Acetaminophen (250 mg/kg, i.p) (G2): Animals treated with APAP showed significant necrosis, severe congestion, steatohepatitis, karyopyknosis, and nuclear alterations in their liver sections. Rats given APAP exhibited the following histopathological changes in their livers:

Necrosis: Rats given APAP showed hepatocytes with significant parenchymal necrosis in several regions of the liver.

Steatosis (steatohepatitis): The viable hepatocytes of rats administered APAP exhibited widespread steatosis, or lipid droplet formation.

Dilatation of blood vessels (veins and sinusoids): The blood sinusoids were enlarged and clogged, containing red blood cells and linked to karyopyknosis. Furthermore, the rats given APAP had dilated and clogged central veins.

Hydropic degeneration: In several liver regions of rats given acetaminophen (APAP), sporadic hydropic degenerations linked to severe coagulative necrosis and swelling of hepatocyte cytoplasm were observed.

Disarray of hepatic cords, along with the disappearance of cell margins and hepatic architecture: The livers of APAP-treated rats lost their distinctive architecture; instead of the hepatocytes being separated from one another, they fused together, possibly due to their cell membranes losing the ability to maintain typical hepatic architecture.

Silymarin (250 mg/kg, oral)+Acetaminophen (250 mg/kg, i.p) (G3): Histopathology of the liver revealed a normal histological architecture, consisting of normal hepatocytes, central veins, and sinusoids.

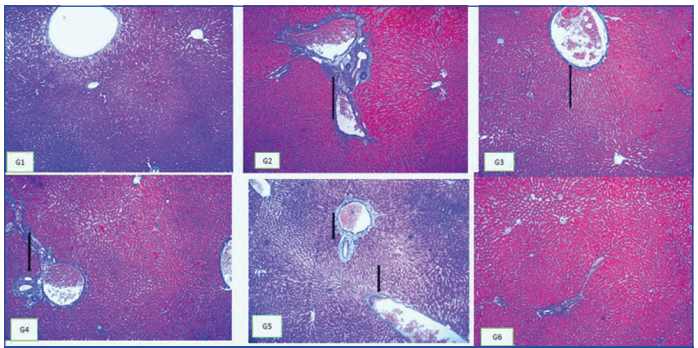
Vitamin C (200 mg/kg)+Acetaminophen (250 mg/kg, i.p) (G4): The liver sections from the APAP+Vitamin C rats (G4) showed an improvement in liver architecture and an absence of significant histological alterations, although mild necrosis and cytoplasmic hydropic degeneration remained visible.

***Momordica dioica* (250 mg/kg, oral)+Vitamin C (200 mg/kg)+ Acetaminophen (250 mg/kg, i.p) (low dose) (G5)**: The liver segments of rats (G5) treated with APAP and 250 mg/kg MD extract demonstrated improved hepatic architecture and a lack of major histological changes, while minor cytoplasmic hydropic degeneration was still discernible.

***Momordica dioica* (500 mg/kg, oral)+Vitamin C (200 mg/kg)+ Acetaminophen (250 mg/kg, i.p) (high dose) (G6):** The histological sections of APAP + 500 mg/kg MD extract-treated rats (G6) showed normal hepatic lobules, an improvement in liver architecture, and an absence of severe alterations, with some cytoplasmic regeneration in the hepatocytes.

Masson's Trichrome stain Image analysis

An analysis of the Masson's Trichrome positive regions in each group showed that the acetaminophen (APAP), as well as the *Momordica dioica* (MD) with Vitamin C (200 mg/kg) groups, produced significantly fewer collagen fibres than the other groups. In the livers of the rats in the control group, the collagen fibres around the central vein and portal tract were somewhat regularly dispersed. Although there was no collagen deposition in the voids between the hepatocytes, the livers of the G2 group of rats appeared to have a greater amount of collagen fibres surrounding the portal tract and dilated, clogged central vein. Rats in the recovery group exhibited livers with less collagen fibre deposition around the portal tract and central vein compared to the hepatocytes [Table/Fig-4].



[Table/Fig-4]: MT stain 100X: Group-1: absence of fibrosis, Group-2: showing mild fibrosis around portal vein. Group-3: showing minimal fibrosis around central vein, Group-4: showing mild fibrosis around portal vein, Group-5: showing mild fibrosis around portal and central vein, Group-6: minimal fibrosis with normal histoarchitecture of liver.

- Control (vehicle) (G1): Histopathology of the liver revealed no fibrosis, with minimal dilation around the central vein and portal vein.

- Acetaminophen (250 mg/kg, i.p) (G2): Histopathology of the liver revealed minimal to mild severity of fibrosis around the central vein, periportal, and perisinusoidal spaces.
- Silymarin (250 mg/kg, oral)+Acetaminophen (250 mg/kg, i.p) (G3): Histopathology of the liver revealed minimal severity of fibrosis around the central vein, periportal, and perisinusoidal spaces.
- Vitamin C (200 mg/kg)+Acetaminophen (250 mg/kg, i.p) (G4): Histopathology of the liver revealed minimal to mild severity of fibrosis around the central vein, periportal, and perisinusoidal spaces.
- *Momordica dioica* (250 mg/kg, oral) + Vitamin C (200 mg/kg) + Acetaminophen (250 mg/kg, i.p) (G5): Histopathology of the liver revealed minimal to mild severity of fibrosis around the central vein, periportal, and perisinusoidal spaces.
- *Momordica dioica* (500 mg/kg, oral)+Vitamin C (200 mg/kg)+ Acetaminophen (250 mg/kg, i.p) (G6): Histopathology of the liver revealed minimal fibrosis with normal histoarchitecture.

DISCUSSION

The methanolic extract of *Momordica dioica* was found to have a hepatoprotective effect in the current investigation, as evidenced by a notable reduction in the concentrations of AST, ALT, and ALP in rats with acetaminophen-induced hepatotoxicity. Furthermore, the methanol extract of *Momordica dioica* decreased the levels of lipid peroxide and increased the activities of antioxidant enzymes (total bilirubin and total protein) in these animals, indicating that the mechanism of its hepatoprotective effects is likely related to the reduction of oxidative stress in this context.

Acetaminophen is a common over-the-counter medication used to treat fever, headaches, and other ailments. It acts as both an antipyretic and an analgesic. However, it is a powerful hepatotoxin that can cause fulminant hepatic and renal tubular necrosis when consumed at hazardous levels. This condition can be fatal for both humans and experimental animals [10,11]. Acetaminophen-induced hepatotoxicity exhibits laboratory characteristics similar to those of other acute inflammatory liver diseases, including a substantial elevation in AST, ALT, and ALP levels [12].

In the current investigation, liver damage in the acetaminophen-induced hepatotoxicity animal model was reflected in the elevated serum levels of the hepatic enzymes AST, ALT, and ALP. However, the methanol extracts of *Momordica dioica* at doses of 250 and 500 mg/kg may reduce the levels of AST, ALT, and ALP in these acetaminophen-intoxicated rats.

According to studies on the metabolic activation and biochemical processes of acetaminophen-induced hepatotoxicity, this drug has been shown to produce centrilobular hepatic necrosis, liver function failure, and mortality in both humans and experimental animals [13]. The primary detoxification and metabolism processes for acetaminophen at therapeutic dosages are glucuronidation and sulphation, followed by renal excretion [14]. However, when consumed in hazardous amounts, acetaminophen is converted into the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). In the cases of acetaminophen overdose, cytochrome P450 oxidises the electrophilic intermediate NAPQI, creating a highly reactive and hazardous metabolite [15,16]. NAPQI can rapidly react with glutathione (GSH), leading to hepatocellular injury and mitochondrial dysfunction, which may result in a 90% depletion of total hepatic GSH in cells and mitochondria [17].

Additionally, previous research provides further evidence that the ultimate result of acetaminophen-induced liver injury (AILI) in rat models is regeneration. It has also been discovered that the liver can self-regenerate following damage caused by an acetaminophen toxic assault. In this study, liver damage observed in acetaminophen-treated rats was mitigated, and liver regeneration occurred at a later period after the toxic insult was cleared due to a rise in hepatic GSH, which reduced the accumulation of NAPQI and oxidative stress.

The impact of methanolic extraction of *Momordica dioica* on liver enzymes was noted. The toxic group in this study exhibited significantly higher levels of ALT, AST, and ALP than the control group (NaCl). The histological analysis of the liver intoxicated by APAP and co-treated with the appropriate test solution showed a correlation with serum biochemical parameters. Interestingly, the levels of these enzymes were significantly reduced following oral administration of 250 mg/kg and 500 mg/kg of *Momordica dioica* methanolic extract (MEMD).

Furthermore, determining the effect of a lower dosage of acetaminophen on the various stages of hepatotoxicity based on dosage and duration may provide valuable insights. Additionally, this could suggest possible hepatoprotective mechanisms involved and aid in isolating and identifying the responsible bioactive compounds derived from MEMD.

Limitation(s)

The present study was limited by the fact that only adult male Wilstar rats were included.

CONCLUSION(S)

The present study showed that all hepatic enzyme markers, which were negatively impacted by acetaminophen-induced hepatotoxicity, were elevated. This revealed that, although co-treatment with MD extract raised protein levels, it may have provided protection. The MD extract offered protection by maintaining the structural integrity of the hepatocellular membrane against APAP, most likely due to its membrane-stabilising activity that prevents intracellular enzyme leakage. The elevated levels of all liver enzymes and other parameters were reduced to nearly normal levels following treatment. The potent antioxidant components, including flavonoids and phenolic compounds, found in the methanolic extract of *Momordica dioca* may be the reason for this, as they may work individually or in combination. These findings demonstrate how the methanolic extract of MD fruit, when taken together, can prevent and treat acute liver damage caused by the drug acetaminophen.

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