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Original Article

Pharmacology Section

Hepatoprotective Effects of Aqueous Extract of *Tagetes patula* Flowers Against Paracetamol-induced Hepatotoxicity in Rats

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ABSTRACT

Introduction: Paracetamol (PCM) overdose is a major contributor to acute liver failure, mainly resulting from oxidative stress and the depletion of Glutathione (GSH) triggered by its toxic byproduct, N-Acetyl-P-Benzoquinone Imine (NAPQI). Conventional hepatoprotective agents have limitations, prompting interest in medicinal plants. *Tagetes patula* (French marigold), traditionally used for hepatic disorders, contains flavonoids and terpenoids with potential antioxidant activity, but its hepatoprotective effects remain underexplored.

Aim: To evaluate the hepatoprotective effect of Aqueous Extract of *Tagetes patula* flowers (AETP) against PCM-induced hepatotoxicity in rats.

Materials and Methods: This an experimental animal study was conducted at the Departments of Pharmacology and Pathology, Regional Institute of Medical Sciences (RIMS), Imphal, India from November 2021 to May 2022. A total of 25 adult male Wistar albino rats were divided into five groups (n=5). Group I received vehicle (control), Group II received PCM (2 g/kg; toxic control), Group III received PCM + silymarin (25 mg/kg; standard), and Groups IV and V received PCM + AETP (200 mg/kg and 400 mg/kg, respectively) for seven days. Serum AST, ALT, and ALP levels were measured, and liver histology was examined. Data were analysed using one-way Analysis of variance (ANOVA) with Bonferroni post-hoc test.

Results: The PCM caused significant elevation of AST, ALT, and ALP ($p<0.001$) and severe histopathological damage. Silymarin markedly reduced enzyme levels and preserved hepatic architecture. AETP treatment produced a dose-dependent hepatoprotective effect: 200 mg/kg partially improved biochemical and histological parameters, while 400 mg/kg significantly reduced enzyme levels ($p<0.05$ vs toxic) and showed improved hepatic architecture.

Conclusion: The AETP flower extract demonstrates dose-dependent protective effects on the liver against PCM-induced liver injury, likely attributed to its antioxidant and anti-inflammatory phytochemicals. Additional research is required to elucidate its underlying mechanisms and validate its therapeutic efficacy.

Keywords: Hepatoprotective, Paracetamol, Silymarin, Wister albino rats

INTRODUCTION

The liver serves as the primary organ responsible for metabolism and is continuously exposed to a variety of xenobiotics, environmental contaminants, and chemotherapeutic agents [1]. Liver disorders represent a significant global health concern, and the conventional pharmacological treatments available are often inadequate or associated with significant adverse effects [2].

The PCM, also known as acetaminophen, is a commonly used analgesic and antipyretic. However, in overdose (not more than 1g every 6 hours), it can cause severe hepatotoxicity due to the formation of a highly reactive metabolite, NAPQI. Normally, NAPQI is detoxified through conjugation with GSH. In cases of excessive dosing, the overproduction of NAPQI depletes hepatic GSH stores, leading to the formation of protein adducts, hepatocellular necrosis, and oxidative stress. These pathological changes are reflected by elevated serum levels of liver enzymes- Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH) and increased bilirubin levels [3-5]. Drug-induced Liver Injury (DILI) accounts for over 50% of acute liver failure cases [6], with acetaminophen overdose alone accounting for approximately 39%.

Medicinal plants have been employed in healing practices since ancient times. Extensive research across the globe has validated the efficacy of many traditional plant-based remedies, leading to the development of modern phytopharmaceuticals [7].

It is estimated that approximately 80% of the active compounds used in contemporary medicine are derived from higher plants, demonstrating a strong correlation between traditional knowledge and modern therapeutic applications [8].

For centuries, medicinal plants have been used traditionally to manage liver disorders. *Tagetes patula* (French marigold), a member of the Asteraceae family, is widespread in India, Europe, and South America. Traditionally, it is used for treating hepatic, gastrointestinal, and rheumatic ailments [9,10].

Phytochemical analyses have identified bioactive constituents such as flavonoids, terpenoids, thiophenes and essential oils distributed throughout its roots, leaves, and flowers. Its essential oil comprises nearly 21 active compounds, with notable constituents such as α-terthienyl pentatriacontane, and 2-ethyl-dodecanol. Other prominent compounds include piperitone, piperitenone, (E)-β-ocimene, limonene, α-terpinolene, and β-caryophyllene. The plant is also rich in flavonoids like quercetin, quercetagetin, patulin, quercetin-3-glucoside, quercetin-7-glucoside, quercetin-3,7-diglucoside, and lutein. Its flowers and leaves exhibit sedative, diuretic, digestive, antioxidant, and anti-inflammatory properties [11].

Previous studies on related species such as *Tagetes erecta* have demonstrated significant hepatoprotective activity in animal models of chemically-induced liver injury [12,13].

However, scientific validation of the hepatoprotective potential of *Tagetes patula* flower extracts, particularly in PCM-induced

hepatotoxicity models, remains limited. Therefore, the current study aimed to assess the hepatoprotective efficacy of an AETP flower extract against PCM-induced liver damage in Wistar albino rats. The objectives of the study were to assess some of the liver function biomarkers and histopathological changes to determine the extract's effectiveness in mitigating hepatic injury.

MATERIALS AND METHODS

This was an experimental animal study conducted in the Departments of Pharmacology and Pathology, Regional Institute of Medical Sciences (RIMS), Imphal, India, from November 2021 to May 2022. This study received approval from the Institutional Animal Ethics Committee (IAEC) of the Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, under Approval No. 1596/GO/a/12/CPCSEA dated 02/03/2020.

Sample size: Twenty-five healthy adult male Wistar albino rats, each weighing between 150-200 g, were procured from the Central Animal House at RIMS, Imphal. They were housed in polypropylene cages under controlled room temperature conditions with a 12-hour light/dark cycle, and provided unrestricted access to standard pellet feed and water ad libitum. Sample size was based on previous similar experimental studies (n=5/group).

Inclusion criteria: Healthy non pregnant/non lactating rats with serum AST typically ranging from 50 to 150 IU/L, ALT from 10 to 40 IU/L, and ALP from 30 to 130 IU/L were considered [14]. Healthy adult male Wistar rats weighing 150–200 g were included.

Exclusion criteria: Sick animals, animals showing behavioural abnormalities, animals with evidence of infection or injury and animals dying during acclimatisation were excluded.

Study Procedure

Fresh *Tagetes patula* flowers were collected from the Lamphelpat area of Imphal West during January 2022 and authenticated at the Department of Life Sciences, Manipur University (Voucher No. MUMP-003631). The flowers were dried in the shade and then pulverised into a coarse powder with a mechanical grinder. The powdered material was then extracted with distilled water using a Soxhlet apparatus [Table/Fig-1]. The resulting extract (dried) had a yield of 8% and was stored in airtight containers at 4-8°C under refrigeration.

Acute toxicity study: The acute oral toxicity of AETP was evaluated according to the Organisation for Economic Co-operation and Development (OECD) Guideline 423 (Acute Oral Toxicity - Acute Toxic Class Method) [15]. A limit test was conducted by administering a single oral dose of 2000 mg/kg body weight to female Wistar rats (n=3), followed by observation for clinical signs of toxicity and mortality over 14 days. No evidence of toxic effects or fatalities was detected throughout the study period. Based on these findings, doses of 200 mg/kg ($1/10^{th}$ of LD50) and 400 mg/kg ($1/5^{th}$ of LD50) were selected for subsequent pharmacological evaluations.

[Table/Fig-1]: Preparation of plant extract by Soxhlet apparatus.

Phytochemical screening: The AETP flowers were subjected to standard qualitative phytochemical analysis to detect the presence of various constituents, following established procedures. This preliminary step involves using various solvents (like ethanol, water, and chloroform)to extract compounds and then applying colorimetric or precipitation tests to detect these secondary metabolites [16].

Hepatoprotective activity

Experimental treatment: The test animals were assigned to five groups, each consisting of five rats. Group I (normal control) was given only the vehicle- 1% Carboxymethyl Cellulose (CMC) in distilled water, administered orally at a dosage of 1 mL/100 g of body weight. Group II (toxic control) was given PCM alone at a dose of 2 g/kg to induce hepatotoxicity, serving as a baseline for liver damage assessment. Group III (standard control) received PCM (2 g/kg) along with silymarin at a dose of 25 mg/kg. Silymarin, derived from milk thistle, is a well-known hepatoprotective agent. It protects the liver from damage by acting as a powerful antioxidant, stabilising cell membranes, reducing inflammation, and promoting liver cell regeneration and repair. Group IV was administered PCM 2 g/kg in combination with the AETP flower at a dose of 200 mg/kg. Group V received PCM 2 g/kg along with AETP at a higher dose of 400 mg/kg.

All test substances, including PCM, silymarin, and AETP, were suspended in 1% CMC and orally administered at a volume of 1 mL/kg, except for group I, which received vehicle only. The treatment was given once daily for 7 consecutive days.

Biochemical analysis: On the eighth day, blood samples (approximately 1.5 mL) were collected into plain tubes from each animal via retro-orbital sinus puncture using a sterile capillary tube under mild ether anaesthesia. The blood samples were left to clot at room temperature for 30 minutes, followed by centrifugation at 3000 rpm for 10 minutes to isolate the serum. The clear supernatant was gently collected and preserved at -20°C for subsequent biochemical evaluation. Levels of AST, ALT, and ALP in the serum were measured using standard diagnostic kits according to the manufacturer's instructions, with readings obtained via a semi-automated clinical analyser.

Histopathological examination of liver tissue: Histopathological tissue sections were prepared using a standard technique [17]. Upon completion of the experimental phase, the animals were euthanized, and liver samples were meticulously excised, rinsed with normal saline, and promptly fixed in 10% neutral buffered formalin for a minimum of 48 hours. Post-fixation, the tissues underwent standard paraffin embedding. Thin sections of 5 µm were sliced using a microtome and placed on glass slides. These were stained with Haematoxylin and Eosin (H&E) after being processed through xylene and alcohol for microscopic examination. Histological sections were examined under a light microscope by a qualified pathologist blinded to the group assignments. The following parameters were graded using a semi-quantitative scoring system (adapted from standard hepatopathology grading references): (–) absent, (+) mild, (++) moderate, (+++) severe. The parameters assessed were: 1) hepatocellular necrosis; 2) cytoplasmic vacuolation; 3) portal inflammation; and 4) sinusoidal/central vein dilatation. Images were captured at both 10X and 40X magnification to ensure adequate representation [17].

STATISTICAL ANALYSIS

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software, version 25.0 (IBM Corp., Armonk,

NY, USA). The quantitative data, including serum levels of AST, ALT, and ALP, were presented as Mean±Standard Deviation (SD) for each group. To evaluate differences among groups, one-way ANOVA was employed, followed by the Bonferroni post-hoc test (When an ANOVA shows an overall significant difference, the Bonferroni test reveals which specific groups differ from each other. It controls the type 1 error of false positives. The original alpha level is divided by the number of pairwise comparisons. A p-value of <0.05 was deemed statistically significant.

RESULTS

Initial qualitative phytochemical screening of the AETP flowers indicated the presence of alkaloids, carbohydrates, flavonoids, saponins, tannins, gums, and proteins.

The serum levels of AST, ALT, and ALP are presented in [Table/Fig-2]. Administration of PCM in the toxic control group (group II) resulted in a marked elevation in serum AST, ALT, and ALP levels (121.65±2.10, 114.81±5.72, and 195.36±2.98 IU/L, respectively) compared to the normal control group (67.04±2.16, 66.35±2.73, and 147.19±4.37 IU/L), indicating significant hepatocellular damage (p<0.001 vs. normal).

Groups	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
I (Normal)	67.04±2.16	66.35±2.73	147.19±4.37
II (Toxic control)	121.65±2.10*	114.81±5.72*	195.36±2.98*
III (Standard)	72.60±1.20	70.83±1.45	160.99±1.85
IV (AETP 200 mg/kg)	101.41±2.18	95.53±1.90	181.40±1.33
V (AETP 400 mg/kg))	92.00±2.51	78.91±2.65	169.53±1.76
ANOVA			
F	51.66	24.14	28.34
df	4	4	4
p	<0.001	<0.001	<0.001

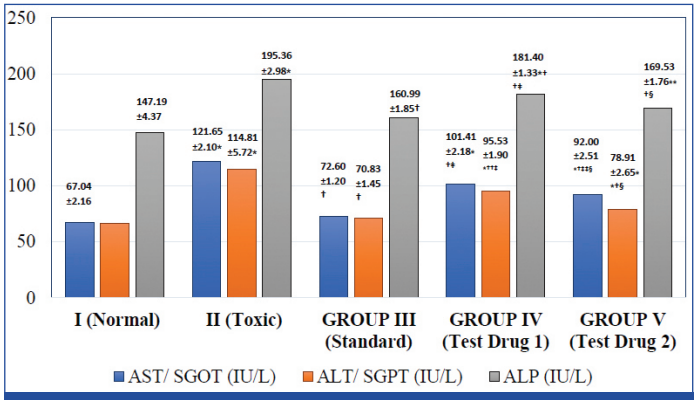
[Table/Fig-2]: Effect of aqueous extract of *Tagetes patula* (AETP) on liver enzymes in Paracetamol (PCM) induced hepatotoxicity.

Treatment with silymarin in the standard drug (group III) significantly reduced AST, ALT, and ALP levels (72.60±1.20, 70.83±1.45, and 160.99±1.85 IU/L, respectively) compared to the toxic control group (p<0.001).

AST, ALT, and ALP levels in group IV receiving AETP 200 mg/kg were 101.41±2.18, 95.53±1.90, and 181.40±1.33 IU/L, respectively. These levels showed a significant decrease in values compared to the toxic control (p<0.001 for AST, p<0.01 for ALT and ALP), but remained significantly increased compared to the normal control group (p<0.001). These enzymes were still significantly higher than those of the standard group (p<0.001).

A higher dose of AETP (400 mg/kg; group V) led to a further decline in AST (92.00±2.51 IU/L), ALT (78.91±2.65 IU/L), and ALP (169.53±1.76 IU/L) compared to the toxic control (p<0.05 vs. normal; p<0.05 vs. toxic control). These levels were significantly lower than those observed in the 200 mg/kg group (p<0.05 vs. AETP 200 mg/kg) and approached those of the standard drug group (p<0.05 vs. standard), indicating a dose-dependent hepatoprotective effect [Table/Fig-3].

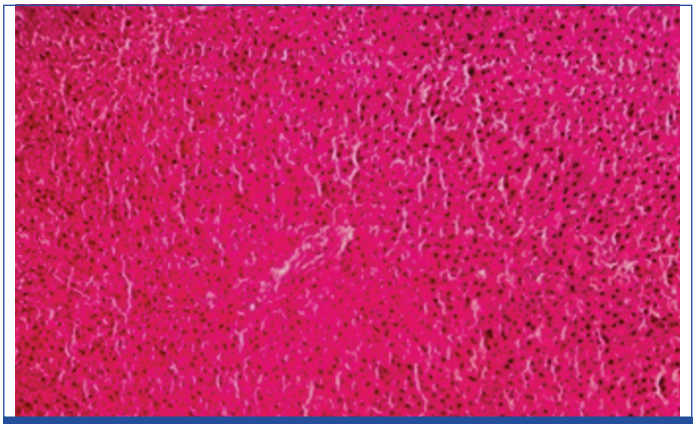
Histopathological examination revealed distinct differences among the experimental groups [Table/Fig-4]. Grading criteria adapted from Suvarna K et al., [17] . Group I (normal control): Liver sections showed normal architecture with no signs of degeneration or inflammation [Table/Fig-5]. In contrast, group II (toxic control) showed severe hepatocellular damage with moderate cytoplasmic vacuolation and necrosis, severe portal inflammation and central vein dilatation [Table/Fig-6]. Group III (standard): Liver tissue appeared largely normal with only mild portal triad inflammation [Table/Fig-7]. Group IV (AETP 200 mg/kg): Moderate portal inflammation and mild necrosis, vacuolation, and sinusoidal/central vein changes were noted, indicating partial hepatic recovery [Table/Fig-8]. Group V (AETP 400 mg/kg): Picture showed minimal inflammation and nearly normal liver architecture [Table/Fig-9].



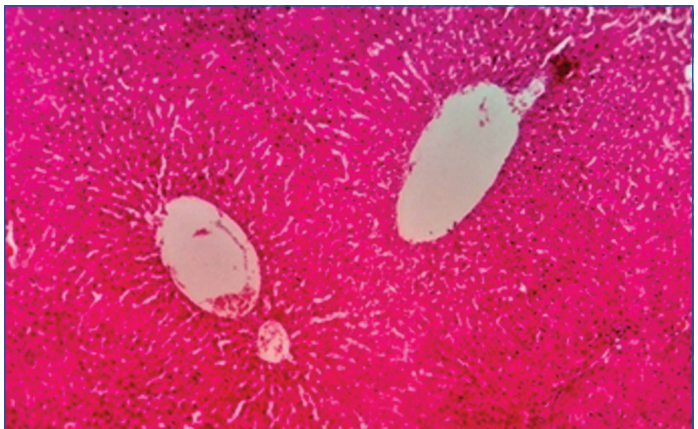
[Table/Fig-3]: Effect of Aqueous Extract of *Tagetes Patula* (AETP) on liver enzymes in Paracetamol (PCM) induced hepatotoxicity.

Group	Necrosis	Vacuolation	Inflammation	Sinusoidal/Central vein Dilatation
I (Normal control)	–	–	–	–
II (Toxic control)	+++	++	+++	++
III (Standard)	–	–	+	–
IV (AETP 200 mg/kg)	+	+	++	+
V (AETP 400 mg/kg)	–	–	+	–

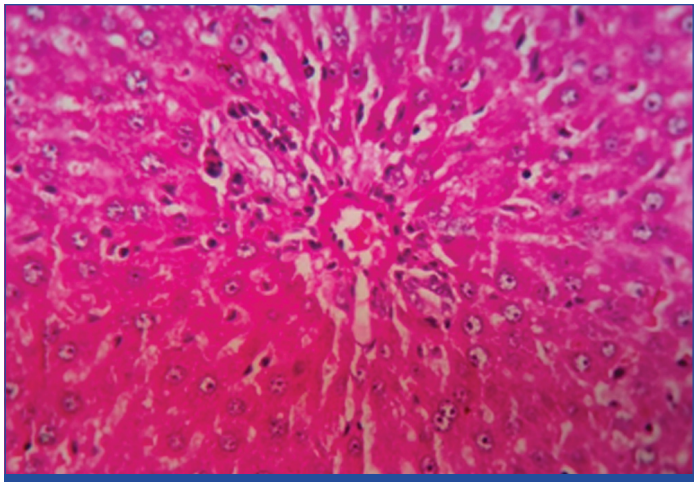
[Table/Fig-4]: Histopathological grading of liver sections across experimental groups (H&E Staining; Grading: – absent, + mild, ++ moderate, +++ severe).
Note: Grading criteria adapted from Suvarna K et al., [17]



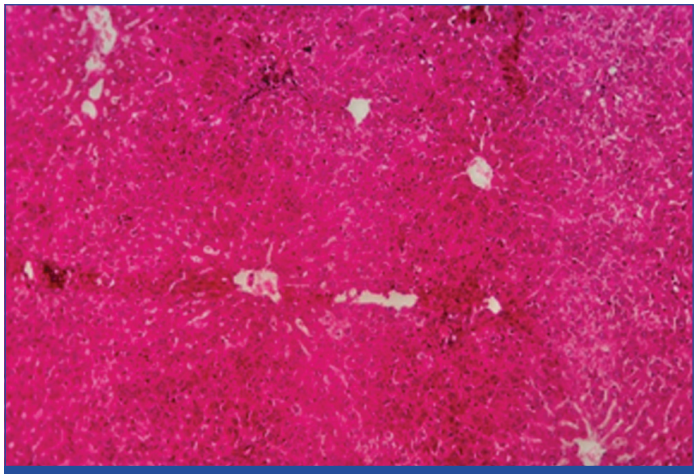
[Table/Fig-5]: Liver sections from group I showed normal hepatic architecture with well-defined hepatic lobules, central vein, and portal tracts. Hepatocytes appeared polygonal with prominent nuclei and no evidence of degeneration, necrosis, or inflammation (H&E stain 10X).



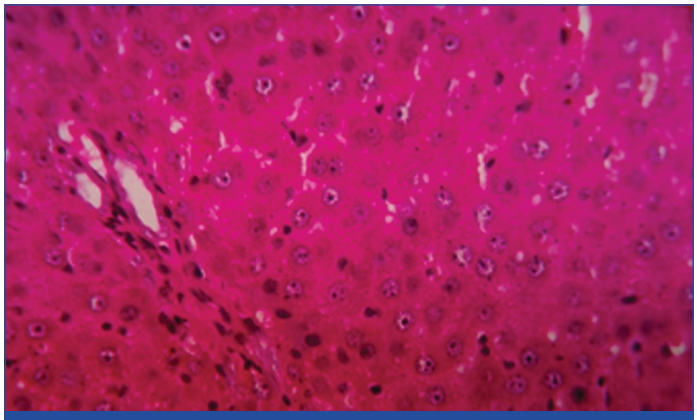
[Table/Fig-6]: Sections from group II revealed severe hepatocellular damage, including extensive necrosis (graded +++), moderate cytoplasmic vacuolation (++), severe portal inflammation (+++), and moderate dilatation of sinusoids and central vein (++). Loss of normal lobular architecture was evident (H&E stain, 10X).



[Table/Fig-7]: Liver sections from group III (Silymarin) showed largely preserved hepatic architecture with well-defined central veins and minimal portal triad inflammation (+). No significant necrosis or vacuolation was observed (H&E stain 40X).



[Table/Fig-8]: Group IV sections showed moderate portal inflammation (++) and mild but observable necrosis (+), vacuolation (+), and sinusoidal/central vein changes (+), indicating partial hepatic recovery (H&E stain 40X).



[Table/Fig-9]: Group V sections showed minimal inflammation (+) and nearly preserved hepatic architecture, with no significant necrosis or vacuolation, indicating substantial recovery from paracetamol (PCM)- induced injury (H&E stain 40X).

DISCUSSION

The PCM-induced hepatotoxicity remains a widely used model for evaluating hepatoprotective agents in experimental pharmacology due to its well-characterised mechanism of liver injury and reproducibility in animal models, particularly rats, which share physiological and biochemical similarities with humans [18]. Hepatotoxicity induced by PCM arises primarily from the metabolic conversion of PCM to NAPQI by cytochrome P450 enzymes, particularly CYP2E1. Under normal circumstances, NAPQI is detoxified through conjugation with GSH. However, toxic doses of PCM deplete hepatic GSH reserves, allowing NAPQI to bind covalently to cellular macromolecules, initiating oxidative stress and lipid peroxidation, ultimately leading to hepatocellular necrosis [19-21].

In the present study, PCM administration produced significant hepatotoxicity as evidenced by marked elevations in serum hepatic marker enzymes (AST, ALT, and ALP) and histopathological alterations. The toxic control group showed a pronounced rise in AST, ALT, and ALP levels compared to the normal control, which is consistent with extensive hepatocellular damage. These enzymes are normally localised within the hepatocytes, and their leakage into circulation reflects membrane damage and loss of functional integrity of the liver [22].

Silymarin, a standard hepatoprotective agent derived from *Silybum marianum*, has been extensively studied for its antioxidant, anti-inflammatory, and membrane-stabilising properties. It exerts hepatoprotective effects through free radical scavenging, enhancement of cellular GSH levels, modulation of nuclear transcription factors such as Nrf2 and NF-κB, and inhibition of hepatic stellate cell transformation, which are critical for fibrosis development [23,24].

Treatment with the standard hepatoprotective agent restored enzyme levels toward normal, suggesting effective protection against PCM-induced hepatotoxicity. The AETP also demonstrated a dose-dependent hepatoprotective effect. At 200 mg/kg, AETP significantly reduced the elevated enzyme levels, though values remained higher than those of the standard group, indicating partial protection. At 400 mg/kg, AETP produced a more pronounced reduction in AST, ALT, and ALP, approaching near-normal levels and showing superiority over the lower dose. This indicates that higher doses of AETP are more effective in mitigating hepatocellular damage. The present study findings are consistent with those of Khan MA et al., who demonstrated that the polyherbal formulation DRDC/AY/8060 exhibited significant hepatoprotective activity against PCM- and D-galactosamine-induced hepatic toxicity at doses of 120 mg/kg and 240 mg/kg [25].

Histopathological findings corroborated the biochemical results. The toxic control group revealed severe structural alterations, including hepatocellular necrosis, cytoplasmic vacuolation, portal inflammation, and dilatation of the central vein. These changes confirm the hepatotoxic effect of PCM. The standard-treated group exhibited almost normal hepatic architecture with only mild inflammation, in line with the near-normal enzyme profile. AETP at 200 mg/kg showed moderate portal inflammation, mild necrosis, and sinusoidal/central vein changes, supporting partial recovery. In contrast, AETP at 400 mg/kg showed minimal inflammation and nearly preserved hepatic architecture, indicating significant recovery and protection against PCM-induced hepatic injury. The present findings are in agreement with Hamza R and Al-Harbi M, who reported that the combined administration of silymarin and *Nigella sativa* extract exerted a synergistic effect in mitigating PCM-induced hepatotoxicity and enhancing liver function and antioxidant status in mice [26].

Taken together, both biochemical and histological evidence suggest that AETP possesses dose-dependent hepatoprotective activity. The protection could be attributed to the presence of phytoconstituents such as flavonoids, tannins, and phenolic compounds, which are known to possess antioxidant and membrane-stabilising and anti-inflammatory properties [27-30]. These compounds may attenuate oxidative stress, a major contributor to PCM-induced hepatic injury, thereby preserving hepatocyte integrity.

Thus, the findings of the present study strongly support the hepatoprotective potential of *Tagetes patula* aqueous extract, particularly at the higher dose (400 mg/kg), which demonstrated effects comparable to the standard treatment.

Limitation(s)

The present study has certain limitations that need to be acknowledged. The relatively small sample may limit the statistical power and generalisability of the results. The experiment was conducted over a short duration and restricted to a single model of PCM-induced

hepatotoxicity. Moreover, only two doses of the AETP were tested. The lack of phytochemical standardisation makes reproducibility and dose extrapolation difficult. In addition, the study did not include mechanistic evaluations such as oxidative stress biomarkers or inflammatory mediators, which would have provided deeper insights into the hepatoprotective mechanism. Active phytoconstituents were not quantified. Intermediate and higher dose levels were not investigated.

CONCLUSION(S)

The current study demonstrates that AETP flowers exert significant hepatoprotective effects against PCM-induced hepatotoxicity in rats, as evidenced by biochemical and histopathological parameters. The protective effect is likely mediated by the presence of bioactive phytochemicals, including flavonoids, saponins, and tannins, which contribute to antioxidant and anti-inflammatory mechanisms. However, further studies with a broader range of doses, chronic administration, and evaluation in different models of hepatotoxicity to better establish the extract's efficacy and safety. Mechanistic investigations focusing on oxidative stress parameters, antioxidant enzyme levels, and inflammatory mediators will help to elucidate the underlying pathways of hepatoprotection.

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