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Hepatoprotective effect of *Thymus vulgaris* L. Extract against Paracetamol-induced hepatotoxicity in *Oryctolagus cuniculus* rabbits

Efecto hepatoprotector del extracto de *Thymus vulgaris* L. frente a la hepatotoxicidad inducida por paracetamol en conejos (*Oryctolagus cuniculus*)

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ABSTRACT

This study investigated the hepatoprotective effect of *Thymus vulgaris* L. against paracetamol-induced liver injury in rabbits *(Oryctolagus cuniculus)*. Fifteen male rabbits were randomly divided into three groups: untreated control, paracetamol-intoxicated (250 mg·kg^{-1}), and paracetamol-intoxicated treated with *T. vulgaris* extract (250 mg·kg^{-1}). Clinical parameters remained within normal limits across groups. Biochemical analyses revealed significant increases in aspartate aminotransferase and gamma-glutamyltransferase in the paracetamol-intoxicated group, while treatment with *T. vulgaris* markedly reduced these elevations, restoring values close to controls. Other biochemical markers, renal indices (urea, creatinine), and hematological parameters showed no significant changes, indicating that hepatic function was primarily affected. Histological examination confirmed these findings: livers of the paracetamol-intoxicated group exhibited trabecular disorganization, vacuolization, and necrosis, whereas thyme-treated animals showed largely preserved architecture with attenuated lesions. Renal tissue remained unaltered in all groups. These results demonstrate that *T. vulgaris* exerts a partial protective effect by limiting paracetamol-induced hepatocellular damage, without altering hematological or renal profiles, supporting its potential as a natural adjuvant against drug-induced hepatotoxicity.

Key words: Liver; hepatotoxicity; paracetamol; *Thymus vulgaris;* rabbit

RESUMEN

Este estudio investigó el efecto hepatoprotector de *Thymus vulgaris* L. frente a la lesión hepática inducida por paracetamol en conejos (*Oryctolagus cuniculus*). Quince machos fueron distribuidos aleatoriamente en tres grupos: control no tratado, intoxicado con paracetamol (250 mg·kg^{-1}) y intoxicado con paracetamol tratado con extracto de *T. vulgaris* (250 mg·kg^{-1}). Los parámetros clínicos se mantuvieron dentro de los límites normales en todos los grupos. Los análisis bioquímicos revelaron aumentos significativos de aspartato aminotransferasa y gamma-glutamiltransferasa en el grupo intoxicado con paracetamol, mientras que el tratamiento con *T. vulgaris* redujo notablemente dichas elevaciones, restaurando los valores cercanos a los del control. Otros marcadores bioquímicos, índices renales (urea, creatinina) y parámetros hematológicos no mostraron cambios significativos, lo que indica que la función hepática fue la principal afectada. El examen histológico confirmó estos hallazgos: los hígados del grupo intoxicado con paracetamol presentaron desorganización trabecular, vacuolización y necrosis, mientras que los animales tratados con tomillo mostraron una arquitectura mayormente conservada con lesiones atenuadas. El tejido renal permaneció inalterado en todos los grupos. Estos resultados demuestran que *T. vulgaris* ejerce un efecto protector parcial al limitar el daño hepatocelular inducido por paracetamol, sin alterar los perfiles hematológicos ni renales, lo que respalda su potencial como coadyuvante natural frente a la hepatotoxicidad inducida por fármacos.

Palabras clave: Hígado; hepatotoxicidad; paracetamol; *Thymus vulgaris;* conejo

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INTRODUCTION

Paracetamol (acetaminophen) remains one of the most widely used antipyretic and analgesic drugs worldwide, although its use carries a significant risk of hepatotoxicity in cases of overdose or prolonged treatment [1, 2, 3, 4].

This toxicity is primarily due to the formation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), generated by cytochrome P450, which can lead to oxidative stress, membrane lipid peroxidation, and hepatocellular necrosis, particularly when hepatic glutathione reserves are depleted [5, 6, 7, 8, 9]. Clinical studies have confirmed that paracetamol overdose is a leading cause of acute liver failure in many countries [10, 11, 12].

Recent molecular mechanisms, including the regulation of hepatic metabolic zonation and regeneration pathways, have been described as potential targets to mitigate toxicity [13, 14, 15]. Additionally, novel biomarkers including high mobility group box–1 protein and microRNAs have become promising diagnostic predictors of liver damage in acetaminophen intoxication [16, 17].

In this regard, natural methods have gained more popularity as protective measures. Especially, plant extracts of *Thymus vulgaris* L. (thyme) have been recognized to have antioxidant and anti-inflammatory properties, which are largely due to both phenolic compounds (thymol and carvacrol). A number of experimental models have noted the hepatoprotective properties of medicinal plants against liver damage caused by drugs [18, 19, 20, 21]. Phytochemicals are also noted to be important as a complementary agent in the management of hepatotoxicity [22, 23, 24]

Hepatoprotection has been reported to happen through several extracts, including *Agave americana*, parsley (*Petroselinum crispum*) [25], *Amblygonocarpus andongensis* [26], and *Galium aparina* [27] through experimental research. Additional evidence behind the use of plant–derived antioxidants in research is comparative research with known, classical compounds such as silymarin and N-acetylcysteine [28, 29, 30].

This study thus had the objective of assessing the putative protective effect of *T. vulgaris* L. against the hepatotoxicity of paracetamol in rabbits (*Oryctolagus cuniculus*) using clinical, biochemical, hematological, and histological analysis.

MATERIAL AND METHODS

Animals and Experimental Conditions

In the current study, 15 adult male rabbits, aged 4–5 months and weighing 1.7–2.8 kg, were used. The animals were then acclimated to two weeks under normal conditions (temperature 22 + 2°C, 12 hours (h)/12 h light dark cycle, balanced food, and water *ad libitum*). All the procedures were conducted according to the ethical principles of animal experimentation.

Experimental Groups

The rabbits were randomly separated into three homogeneous groups (n = 5 in each group):

- Control group (CRL): untreated animals.
- Paracetamol group (PARA): rabbits received paracetamol at a dose of 250 $mg \cdot kg^{-1} \cdot day^{-1}$ for 10 days (d) via gavage.
- Paracetamol + *T. vulgaris* group (PARA-TH): rabbits receiving an aqueous extract of *T. vulgaris* (250 $mg \cdot kg^{-1} \cdot day^{-1}$) one h before paracetamol administration (250 $mg \cdot kg^{-1} \cdot day^{-1}$) for 10 d.

The dose of paracetamol (250 $mg \cdot kg^{-1}$) was selected based on previous experimental models showing reliable induction of hepatotoxicity in rabbits and rodents [31, 32]. Similarly, plant extract doses around 200–300 $mg \cdot kg^{-1}$ have been widely used in hepatoprotective studies [33, 34], ensuring both efficacy and safety in short-term experiments.

Preparation of *Thymus vulgaris* extract

Dried *T. vulgaris* was purchased from a local herbalist. The plant material was taxonomically identified by Dr. Sakhraoui, 20 August 1955 University of Skikda, Algeria. The dried thyme was then ground into a fine powder and subjected to aqueous extraction. The resulting solution was freshly prepared daily and administered by gavage at a dose of 250 $mg \cdot kg^{-1}$.

Clinical and physiological surveillance

The body weight was measured on d 0 (at the start of the experiment) and on d 10 using a digital balance (Model FEJ-150, Kern & Sohn, Germany). The measurements of heart rate, rectal temperature and respiratory rate were taken on d 0, 3, 6 and 10 using a stethoscope (Spengler Magister II, France), a digital thermometer (Omron MC-246, Japan) and a respiration monitor (BIOECO, China), respectively.

Biochemical and hematological analyses

On d 10, blood samples were collected from the marginal ear vein after a 12-h fast.

Biochemistry analysis

The biochemical analyzed parameters are: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), urea, creatinine, blood glucose, total bilirubin, and direct bilirubin, which were determined using an automated biochemical analyzer (Mindray BS–120, Mindray Bio-Medical Electronics Co., Ltd., China) with commercial diagnostic kits (Biolabo, France).

Hematology analysis

Complete blood count, including red blood cell and white blood cell counts, hemoglobin concentration, hematocrit, platelet count, and mean corpuscular volume (MCV), was performed using an automated hematology analyzer (Sysmex KX-21N, Sysmex Corporation, Japan).

All analyses were performed at the Biochemistry Laboratory of CRMT (Sonatrach, Skikda).

Histology study

One animal from each group was euthanized after 10 d. Liver and kidney samples were collected, fixed in 10% formalin, embedded in paraffin, sectioned at 4 µm using a rotary microtome (Leica RM2125RTS, Leica Biosystems, Germany), and stained with hematoxylin and eosin. The slides were examined under a light microscope (Olympus CX23, Olympus Corporation, Japan) at 10×, 40×, and 100× magnifications.

Statistical analysis

Results are expressed as mean ± standard deviation (SD). Comparisons between groups were performed using one-way ANOVA followed by Tukey's test, with statistical significance set at $P \leq 0.05$.

RESULTS AND DISCUSSION

Clinical parameters

The evolution of body weight, rectal temperature, respiratory rate, and heart rate revealed no significant differences among the groups. However, a slight weight loss was observed in paracetamol-intoxicated rabbits (PARA: -3.3%) compared with controls (-1.1%), while the PARA–TH group showed a moderate decrease (-3.0%). Temperature and cardiovascular parameters remained within physiological ranges ($P>0.05$).

These findings indicate that paracetamol intoxication at the tested dose caused only mild physiological disturbances without affecting vital functions. The slight decrease in body weight may reflect transient metabolic stress, while the preservation of temperature and cardiovascular parameters suggests the absence of systemic toxicity.

Biochemical and hematological parameters

Biochemical and hematological analyses revealed distinct changes following paracetamol intoxication (FIGS. 1 and 2). In the PARA group, serum hepatic enzymes showed a significant elevation, particularly AST and GGT, indicating hepatocellular damage. ALT and ALP displayed a moderate but non-significant increase, whereas renal function markers (urea and creatinine), glycemia, and bilirubin fractions remained within physiological limits. Conversely, administration of *T. vulgaris* in the PARA–TH group markedly attenuated the paracetamol-induced enzyme disturbances, with AST and GGT levels approaching those of the control group, highlighting a protective effect on hepatic integrity. Hematological indices (FIG. 2), including red and white blood cell counts, hemoglobin concentration, hematocrit, platelets, and mean corpuscular volume, did not differ significantly among groups, suggesting that short–term paracetamol exposure primarily affected liver function rather than hematopoiesis. These findings emphasize that the main alterations induced by paracetamol were hepatic and that thyme supplementation mitigated the biochemical impact without disturbing hematological homeostasis.

The results of this study confirm that repeated administration of paracetamol at a dose of 250 $mg \cdot kg^{-1}$ in rabbits leads to significant biochemical disturbances, particularly an elevation of hepatic enzymes (AST and GGT), as well as characteristic histological alterations in the liver. These observations are consistent with established data indicating that the liver is the primary target organ of paracetamol toxicity [3, 4, 5, 8]. Similar patterns of enzyme elevation and histological lesions have been documented in rats and mice subjected to comparable doses [9, 11].

At therapeutic doses, paracetamol is mainly metabolized into glucuronide and sulfate conjugates, which are excreted in the urine. However, a minor fraction (5–10%) is metabolized via cytochrome P450 into NAPQI, a highly reactive metabolite responsible for oxidative stress, lipid peroxidation, and hepatocellular necrosis [1, 7, 8]. The current findings replicate this cascade, as evidenced by elevated serum transaminases and hepatic necrosis.

The absence of significant hematological and renal alterations in intoxicated rabbits is consistent with previous studies [35, 36, 37], which reported that paracetamol-induced nephrotoxicity typically occurs only after prolonged exposure or at higher doses, whereas hepatic injury develops more readily. Clinical studies further indicate that renal damage is less frequent than hepatic failure in cases of acetaminophen poisoning [10, 12].

Histology

In the liver, the micrograph of the CRL group (FIG. 3) showed a normal hepatic architecture, with hepatocyte cords well organized around central veins and separated by regular sinusoids. Hepatocytes displayed a homogeneous, slightly granular cytoplasm, with round centrally located nuclei, without vacuolization or signs of degeneration. The portal tracts contained normal portal triads, with no inflammatory infiltration, congestion, or fibrosis.

In paracetamol–intoxicated animals (FIG. 4), histological examination revealed marked disorganization of the hepatocyte cords, associated with pronounced sinusoidal dilatation. Many hepatocytes exhibited cytoplasmic vacuolar degeneration, particularly in the centrilobular zone, and some cells showed necrotic features with pyknosis and nuclear fragmentation. Small foci of confluent necrosis and ballooned hepatocytes were also observed, indicating significant oxidative stress. In some portal areas, discrete lymphocytic infiltration was noted, suggesting the onset of an inflammatory reaction.

In contrast, in rabbits that received paracetamol together with the aqueous extract of *T. vulgaris* (FIG. 5), lesions were markedly attenuated. The hepatic architecture appeared largely preserved, with better organized trabeculae, less dilated sinusoids, and much fewer necrotic foci. Only a few cells still exhibited moderate cytoplasmic vacuolization, suggesting a protective effect of thyme against paracetamol-induced hepatic injury.

Regarding the kidney, micrographs from the three groups showed no notable differences. In the CRL group, glomeruli were well formed and normocellular, with a regular Bowman's space, while proximal and distal convoluted tubules displayed a well–defined lumen lined by intact cuboidal epithelium. In the PARA group, no lesions were observed: glomeruli and tubules retained their integrity, with no vacuolization or epithelial alteration, and the interstitium was free of inflammatory infiltrates. Similarly, in animals treated with PARA–TH, renal architecture appeared

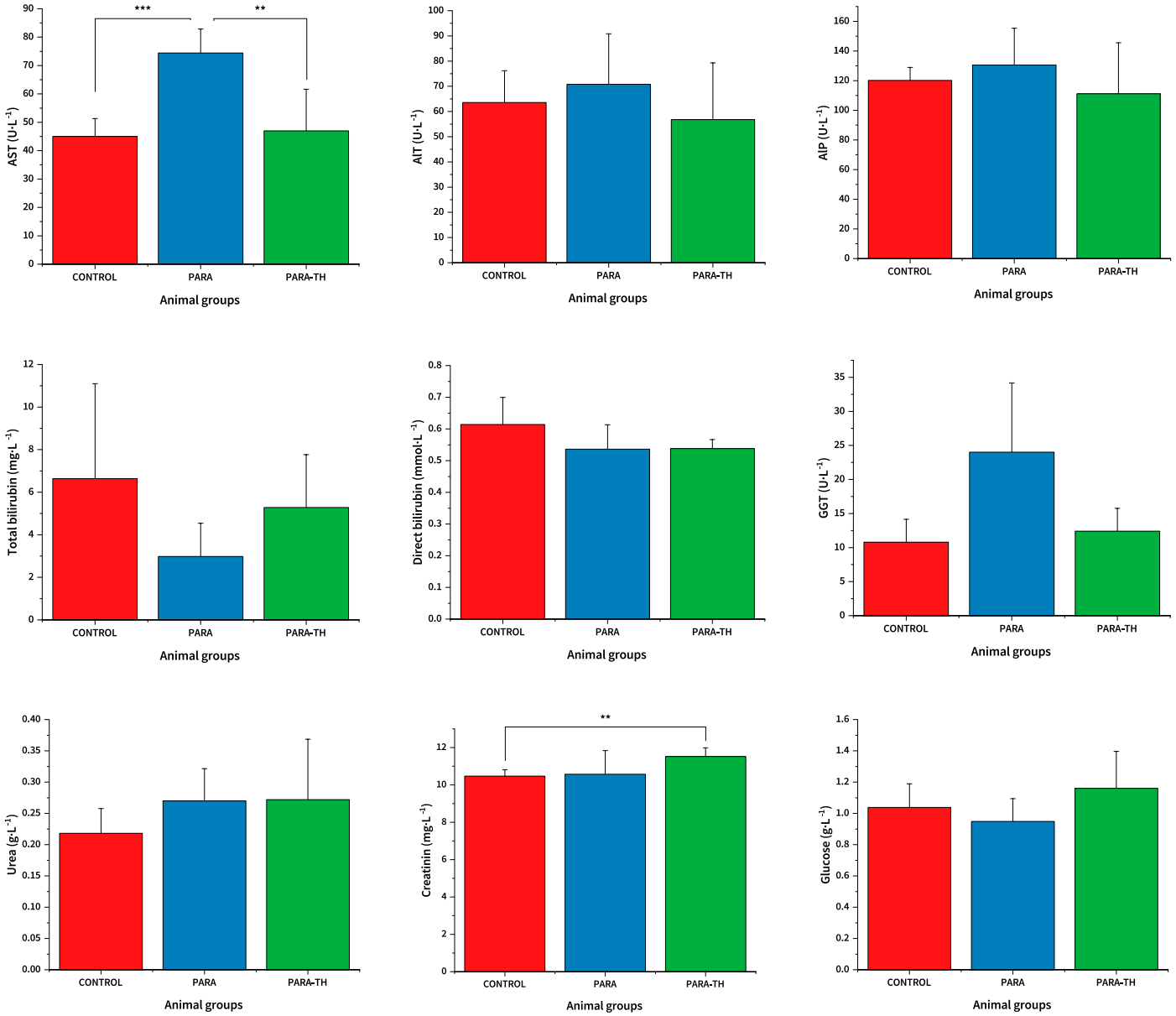

FIGURE 1: Variation of biochemical parameters in different animal groups. AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyltransferase, CONTROL: untreated control, PARA: paracetamol–intoxicated group (250 mg·kg^{-1}), PARA–TH: paracetamol–intoxicated group treated with *Thymus vulgaris* extract (250 mg·kg^{-1}). Results are expressed as mean ± SD (n = 5). Means were compared using one-way ANOVA followed by Tukey's test. **$P \leq 0.01$, ***$P \leq 0.001$, NS: not significant

comparable to that of the control, with intact glomerular and tubular structures and preserved interstitial tissue.

Overall, histological analysis confirmed that the liver is the main target organ of paracetamol toxicity, whereas the kidney did not show significant abnormalities under the experimental conditions of this study. It also suggests that the aqueous extract of *T. vulgaris* exerts a partial protective effect by reducing the severity of hepatic lesions and maintaining better tissue integrity.

Regarding the protective effect of *T. vulgaris*, our findings are noteworthy. We observed a significant reduction in hepatic enzyme levels and histological lesions in the PARA–TH group. These data corroborate reports on the antioxidant activities of thyme extracts [38, 39, 40]. Its main bioactive compounds, thymol and carvacrol, reduce reactive oxygen species, enhance endogenous antioxidant defenses, and stabilize cell membranes [41, 42]. Similar hepatoprotective effects have been observed with *Thymus algeriensis* [34] and other Lamiaceae, as experimental studies have shown that *T. vulgaris* extract can significantly reduce liver

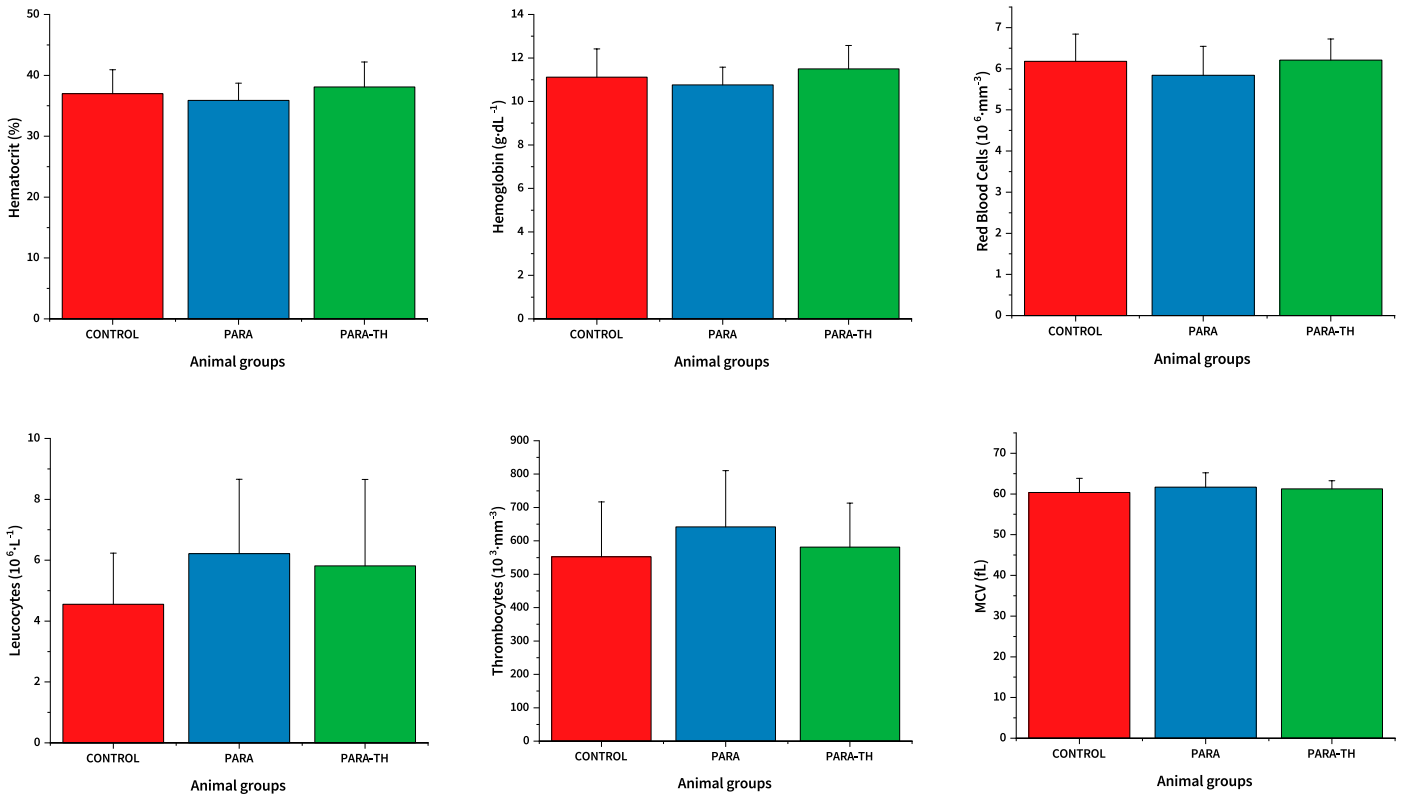

FIGURE 2. Variation of hematological parameters in different animal groups. MCV: mean corpuscular volume; CONTROL: untreated control; PARA: paracetamol-intoxicated group (250 mg·kg⁻¹); PARA-TH: paracetamol-intoxicated group treated with *Thymus vulgaris* extract (250 mg·kg⁻¹). Results are expressed as mean ± SD (n = 5). Means were compared using one-way ANOVA followed by Tukey's test. NS: not significant

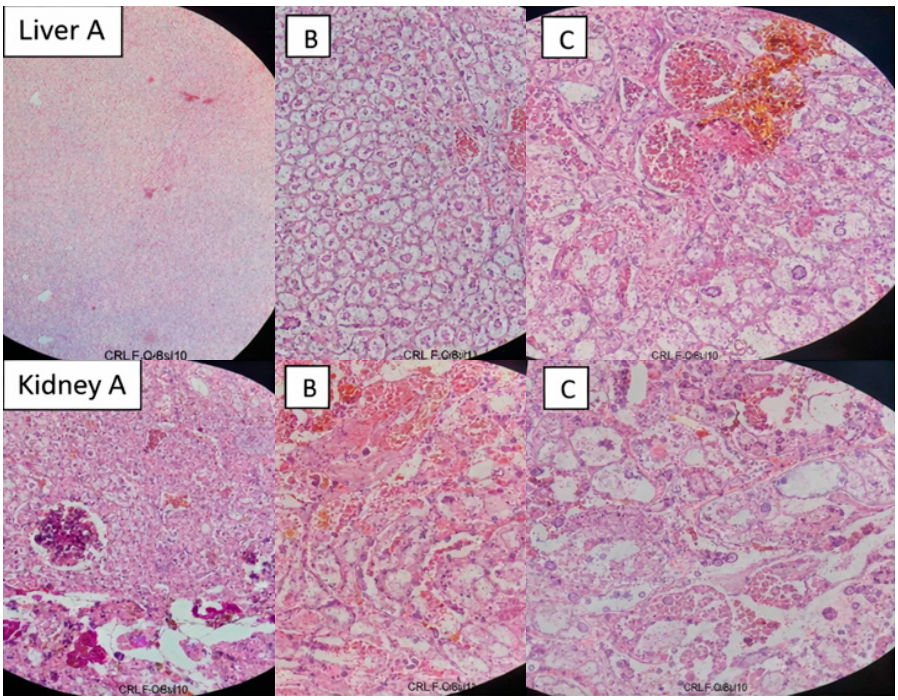

FIGURE 3. Micrographs of the liver and kidney of a rabbit from the untreated control group (CRL). A: 10×, B: 40×, C: 100×. Hepatic tissue shows normal architecture with organized hepatocyte cords, intact central veins, and regular sinusoids. No signs of degeneration, inflammation, or fibrosis are observed. Renal structures appear normal with well-defined glomeruli and tubules

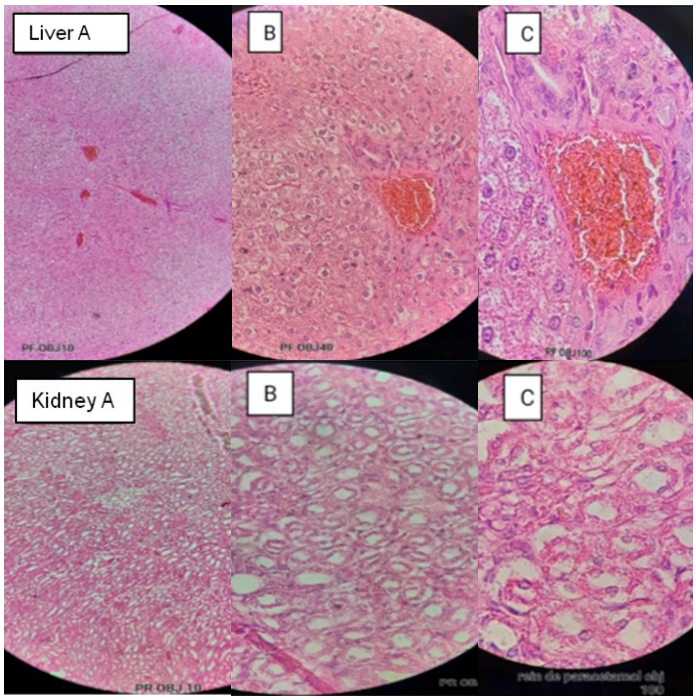

FIGURE 4. Micrographs of the liver and kidney of a rabbit from the paracetamol-intoxicated group (PARA). A: 10×, B: 40×, C: 100×. Liver sections exhibit severe architectural disruption, including sinusoidal dilatation, vacuolar degeneration, necrosis, and inflammatory cell infiltration. In contrast, kidney morphology remains unaffected, with preserved glomerular and tubular integrity

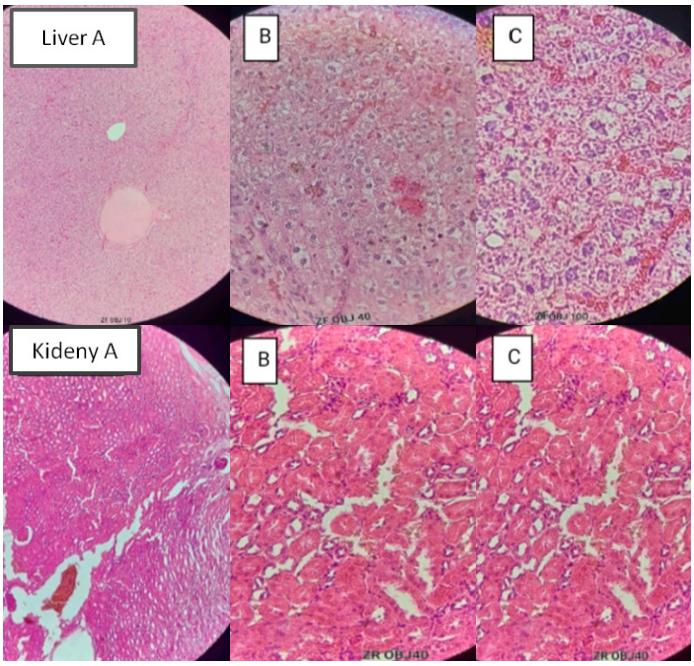

FIGURE 5. Micrographs of the liver and kidney of a rabbit from the paracetamol-intoxicated group treated with the aqueous extract of thyme at a dose of 250 mg·kg^{-1} (PARA–TH). A: 10×, B: 40×, C: 100×. Liver tissue shows notable improvement, with reduced necrotic areas, less vacuolization, and more preserved hepatic architecture, indicating a hepatoprotective effect of thyme. Kidney histology remains comparable to the control, showing no pathological changes

enzyme elevations, oxidative stress, and histopathological liver damage in animal models [22].

The phytochemical variation depends on many factors such as the stage of development of the plant, season, and solvent used in extraction, the part of the plant utilized, the geographical source, storage conditions of the plant materials, and the analytical methods used in the analysis [43, 44, 45].

The current results are consistent with previous experimental studies that have demonstrated that thyme and other medicinal plants reduce liver damage caused by toxins like carbon tetrachloride, ethanol, or drugs [18, 19, 20, 33]. According to recent reviews, polyphenols do not just occupy the role of an antioxidant; they are also anti-inflammatory modulators using both NF-κB and Nrf2 signaling pathways [23, 46]. This process may be the reason why necrotic foci have been attenuated and hepatic trabeculae preserved in this case.

Taken together, these findings reinforce the concept that plant–derived compounds may complement standard treatments such as N–acetylcysteine [28] in mitigating paracetamol–induced hepatotoxicity. However, further mechanistic studies, larger sample sizes, and chronic exposure models are needed to confirm these protective effects and clarify their clinical translation.

CONCLUSION

In the current study, paracetamol induces an elevation of hepatic enzymes and characteristic histological lesions in rabbits. Treatment with *Thymus vulgaris* extract significantly improved biochemical parameters and reduced histological damage, suggesting a protective role against hepatotoxicity. Further studies, including a larger number of animals, different doses, and extended follow-up, are required to confirm these findings and to clarify the underlying molecular mechanisms.

Conflict of interest

The authors declare that they have any conflict of interest.

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