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Hepatoprotective activity of lycopene in experimental paracetamol-induced liver injury in rats

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Summary

Aim: To evaluate the hepatoprotective effects of lycopene pretreatment in paracetamol-induced liver damage (PILD). **Methods**: Wistar rats were administered oral lycopene (4 mg/kg/day) by gastric lavage for 8 days. Subsequently, 3 g/kg paracetamol was administered on day 8. After 24 and 72 h, animals were euthanized, and intracardiac blood samples were collected to measure levels of aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase, and alkaline phosphatase (ALP). In addition, the liver was harvested for histological analyses. **Results**: Negative and positive control groups (treated with saline or paracetamol on day 8, respectively) were compared with lycopene- and lycopene-paracetamol-treated (lycopene+paracetamol on day 8) groups. Notably, we observed that 24 h after PILD, lycopene treatment significantly reduced serum transaminase (ALT/AST) levels when compared with those in the saline-treated group. **Conclusion**: Lycopene improved liver recovery following PILD. Although lycopene exhibits antioxidant action and has been indicated for liver diseases, its use must be cautiously undertaken, especially considering the liver pathology involved, as results may vary for each underlying factor.

Keywords: Lycopene, paracetamol, ALT, AST.

Resumo

Atividade hepatoprotetora do licopeno na lesão hepática experimental induzida por paracetamol em ratos

Objetivo: avaliar os efeitos hepatoprotetores do pré-tratamento com licopeno no dano hepático induzido por paracetamol (PILD). **Metodologia**: ratos Wistar receberam licopeno oral (4 mg/kg/dia) por lavagem gástrica por 8 dias. Posteriormente, 3 g/kg de paracetamol foi administrado no dia 8. Após 24 e 72 h, os animais foram eutanasiados e amostras de sangue intracardíaco foram coletadas para medir os níveis de aspartato aminotransferase (AST), alanina transaminase (ALT), gama-glutamil transferase, e fosfatase alcalina (ALP). Além disso, o fígado foi colhido para análises histológicas. **Resultados**: os grupos de controle negativo e positivo (tratados com solução salina ou paracetamol no dia 8, respectivamente) foram comparados com os grupos tratados com licopeno e licopeno-paracetamol (licopeno+paracetamol no dia 8). Notavelmente, observamos que 24 h após PILD, o tratamento com licopeno reduziu significativamente os níveis séricos de transaminase (ALT/AST) quando comparados com os do grupo tratado com solução salina. **Conclusão**: o licopeno melhorou a recuperação do fígado após PILD. Embora o licopeno exiba ação antioxidante e tenha sido indicado para doenças hepáticas, seu uso deve ser realizado com cautela, principalmente considerando a patologia hepática envolvida, pois os resultados podem variar para cada fator subjacente.

Palavras-chave: Licopeno, paracetamol, ALT, AST.

Resumen

Actividad hepatoprotectora del licopeno en la lesión hepática experimental inducida por paracetamol en ratas

Objetivo: evaluar los efectos hepatoprotectores del pretratamiento con licopeno en el daño hepático inducido por paracetamol (PILD). **Métodos**: a las ratas Wistar se les administró licopeno oral (4 mg/kg/día) mediante lavado gástrico durante 8 días. Posteriormente, se administró paracetamol 3 g/kg el día 8. Después de 24 y 72 h, los animales fueron sacrificados y se recolectaron muestras de sangre intracardíaca para medir los niveles de aspartato aminotransferasa (AST), alanina transaminasa (ALT), gamma-glutamil transferasa, y fosfatasa alcalina (ALP). Además, se cosechó el hígado para análisis histológicos. **Resultados**: los grupos de control negativo y positivo (tratados con solución salina o paracetamol el día 8, respecti-

vamente) se compararon con grupos tratados con licopeno y licopeno-paracetamol (licopeno+paracetamol el día 8). En particular, observamos que 24 h después de PILD, el tratamiento con licopeno redujo significativamente los niveles de transaminasa sérica (ALT/AST) en comparación con los del grupo tratado con solución salina. **Conclusión**: el licopeno mejoró la recuperación del hígado después de PILD. Aunque el licopeno exhibe acción antioxidante y ha sido indicado para enfermedades hepáticas, su uso debe realizarse con cautela, especialmente considerando la patología hepática involucrada, ya que los resultados pueden variar para cada factor subyacente.

Palabras clave: Licopeno, paracetamol, ALT, AST.

Introduction

It is well-established that the liver exhibits endocrine and exocrine functions, and hepatocytes are responsible for bile production (exocrine secretion) and the formation of several endocrine products [1]. In addition, hepatocytes convert harmful substances into non-toxic materials excreted in the bile [2]. Accordingly, the liver is susceptible to the harmful actions of these agents, given the potent metabolism of substances, including therapeutic agents [3, 4].

Toxic hepatitis is characterized by liver damage caused by inhalation, ingestion, or parenteral administration of pharmacological or chemical agents, which remains a critical issue in current clinical practice, accounting for approximately 0.2% of all hospital admissions and 2-3% of hospitalizations attributed to adverse drug effects [5, 6].

Metabolic cell injury can be mediated via various cell injury mechanisms, including covalent binding to cellular structures, lipid peroxidation, oxidative reactions, and glutathione depletion [7-10]. Cell damage may result in mitochondrial alterations, changes in the cytoskeleton structure, or altered ion homeostasis [7-10]. Depending on the extent of mitochondrial involvement and the balance between activating and inhibiting factors associated with intracellular signaling pathways, cells may undergo necrosis or apoptosis; the former mediates inflammatory mechanisms [7-10].

Paracetamol, also known as acetaminophen or N-acetyl-p-aminophenol, is an active metabolite of phenacetin, an analgesic derived from coal tar [11-13]. It remains one of the most widely used analgesic and antipyretic drugs. In the United States (US) and the United Kingdom, paracetamol is the major cause of fulminant liver failure, especially in cases of accidental and intentional overdosage [11-13]. In the 1990s, it was the main drug implicated in deaths reported at toxicity centers in the US [11-13].

Paracetamol undergoes detoxification by phase II drug-metabolizing enzymes in the liver, mediated via glucuronidation and sulfation; a small portion is metabolized by cytochrome P-450, subjected to N-hydroxylation to form a toxic intermediate compound, N-acetyl-p-benzoquinone imine (NAPQI), which is initially conjugated to glutathione and excreted [14]. Toxic doses of paracetamol saturate the glucuronidation and sulfation pathways, and the cytochrome P-450 pathway is critical for drug biotransformation, promoting increased NAPQI formation [14]. Thus, glutathione reserves in the liver are depleted, and the reaction with sulfuric groups of liver proteins is enhanced, interrupting the flow of mitochondrial calcium and resulting in liver cell necrosis [15]. As mitochondrial metabolism is altered, hepatotoxicity also occurs via the formation of reactive oxygen species (ROS), such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-), reactive nitrogen species (RNS), including nitric oxide and peroxynitrite ($ONOO^-$), and products of peroxidation reactions [16, 17]. The reaction is amplified by Kupffer cell activation, cytokine secretion, and free radical production, resulting in apoptosis and centrilobular necrosis in zone 3 [18]. Necrosis is known to occur at this location, given that zone 3 hepatocytes possess the highest concentration of cytochrome P-450, where drug conversion into active metabolites occurs [18].

Lycopene is a potent antioxidant, affording cellular protection by reacting with peroxide radicals and molecular oxygen [19]. *In vitro* and *in vivo* tests suggest that carotenoids are excellent antioxidants that scavenge and inactivate free radicals [20]. The radical scavenging action is reportedly proportional to the number of conjugated double bonds present in carotenoid molecules [20]. The mechanism through which carotenoids protect biological systems from free radicals depends on energy transfer from the excited oxygen to the carotenoid molecule, during which energy is dissipated through rotations and vibrations of the carotenoid in the solvent medium [21]. Lycopene is reported to exhibit the highest capacity to scavenge oxygen free radicals, possibly due to the presence of two unconjugated double bonds, conferring greater reactivity [22]. The consumption of pure tomatoes or products that promote high lycopene concentrations in the blood can be inversely correlated with the risk of heart attack, prostate cancer, and cancers involving other tissue types [23, 24].

Previous studies have shown that the ingestion of tomatoes and derived products enhances the antioxidant system and inhibits lipid peroxidation in humans [25]. In addition, it has been reported that oral lycopene administration for two weeks can inhibit lipid peroxidation in liver tissues of rats [26].

Animal models are valuable for evaluating lycopene as a potential chemopreventive agent, as well as for assessing its protective function against other disorders or the

deleterious actions of toxic agents in different tissues [27]. Accordingly, studies were undertaken to evaluate the action of lycopene in the liver.

In the present study, we aimed to evaluate the effectiveness of lycopene as a hepatoprotective agent against experimental liver damage induced by paracetamol in Wistar rats.

Materials and methods

Animals and experimental design

Herein, we utilized 40 albino Wistar non-isogenic male rats (*Rattus norvegicus*). The animals were provided by the Campus II Animal House of Campinas Catholic University at 50 days of age.

Experimental animals were maintained in the Animal House of the Laboratory of Surgical Technique and Experimental Surgery at the Life Sciences Center, Campinas Catholic University, under controlled illumination and ventilation and access to solid Nuvilab ration and water until 60 days of age. The present study was approved by the Animal Ethics Committee of Campinas Catholic University, according to CI CEUA n.° 003/2012 and protocol number 2 012 070 332.

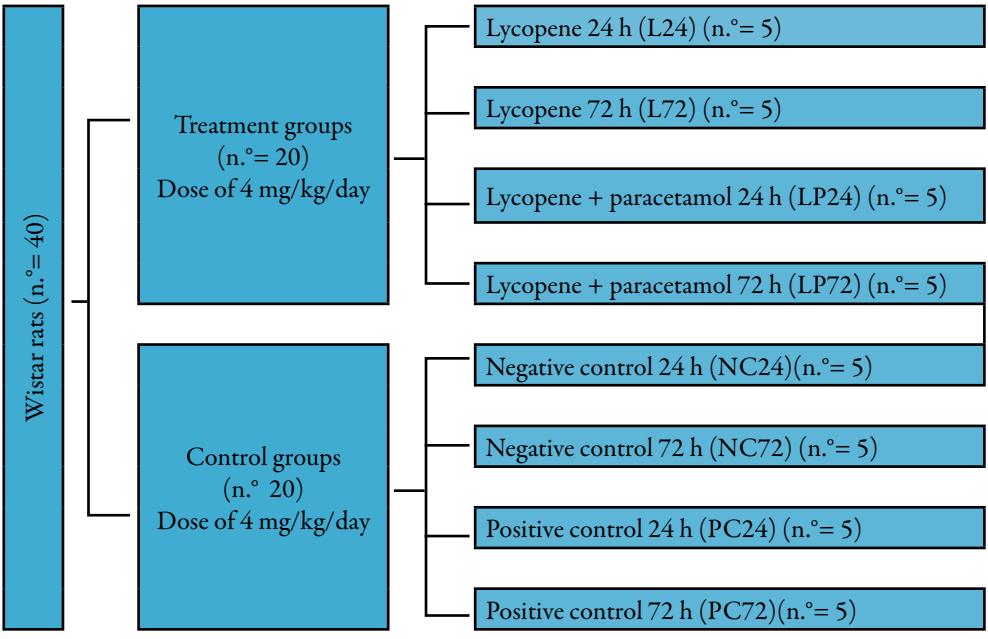

Figure 1. Experimental design.

The animals were divided into two groups (20 animals per group): treatment and control groups. The treatment group was divided into 4 subgroups: lycopene 24 h (L24) and lycopene 72 h (L72) (n=5/group) were orally administered a lycopene suspension for 8 days at a dose of 4 mg/kg/day and sacrificed at 24 and 72 h, respectively, after the last administration; lycopene + paracetamol 24 h (LP24) and lycopene + paracetamol 72 h (LP72) (n=5/group) were orally administered a lycopene suspension for 8 days (4 mg/kg/day), with paracetamol solution (Pharma Nostra lot 09124425G) orally administered on day 8. The rats were sacrificed after 24 and 72 h, respectively.

In addition, the control group was divided into 4 groups: negative control 24 h (NC24) and negative control 72 h (NC72) (n=5/group) received only water for 8 days. These animals were euthanized after the last administration at 24 and 72 h, respectively; positive control 24 h (PC24) and positive control 72 h (PC72), (n=5/group) were orally administered water for 8 days, with a paracetamol solution (3 g/kg) administered on the final day. The rats were sacrificed after 24 and 72 h, respectively. The dose of paracetamol was established as reported by Oyagbemi and Odetola [28]. The lycopene dose was determined according to a study by Bahcecioglu *et al.* [29]. Treatment was administered via the oral route, that is, intragastric gavage. Lycopene was diluted in water prior to oral administration.

Subsequently, animals were anesthetized using a ketamine solution (100 mg/kg intraperitoneal) 24 or 72 h after paracetamol administration. Then, the thoracic region was incised to access the left ventricle of the heart.

Blood was collected to measure hepatic transaminase and alkaline phosphatase (ALP) levels. Subsequently, anesthesia was deepened for euthanizing the animal, and the liver tissue was harvested. For histological analysis, the liver was fragmented and fixed in 10% buffered formalin. In addition to the liver, the kidneys, heart, and lungs were harvested. Fragments weighing approximately 200 mg were frozen for subsequent maceration. Ketamine was selected as the anesthetic agent, as it lacks hepatotoxicity and does not interfere with the experimental findings.

Histologic processing

Liver tissue specimens underwent standard histological processing using histological paraffin (Synth®), obtaining 5-μm thick sections using a Leica RM2245 Rotatory Microtome. The slides were stained with hematoxylin-eosin (HE), Picrosirius red, or periodic acid Schiff (PAS), and images were captured digitally to obtain results using a photomicroscope (Nikon Eclipse E200) coupled to a camera (Nikon Coolpix 4500). For each group, the type and intensity of hepatic lesions were evaluated by observing the presence of steatosis, inflammatory infiltrate, fibrosis, and necrosis.

Measurement of liver transaminases and alkaline phosphatase

After collection, blood samples were centrifuged at 3000 rpm for 5 min to separate serum from other components. Serum samples were then used to estimate levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), indicators of hepatocellular damage. Analyses were performed using LaborLab® enzyme test kits (kinetic-colorimetric method) and measured using a UV Varian spectrophotometer, according to the manufacturer's specifications. For analysis of biochemical parameters, n=4 was used.

Data analysis

Histological analyses of the liver were performed using a specific methodology for each parameter. For evaluating necrosis, the number of centrilobular veins (clv) affected by the lesion was determined (vcl) in HE-stained slides (a section of 2 liver fragments from different lobules), and the results are expressed in vcl/cm^2. For counting, the TPS Dig® 1.30 software was used. For assessing fibrosis, 5 micrographs of the centrilobular area and 5 micrographs of the portal area were randomly obtained from Picrosirius red-stained slides (a total of 50 micrographs/group) at 480× magnification and analyzed using AreaMed® software, measuring the area compromised by fibrosis (collagen fibers). To evaluate the distribution of glycogen and other 1,2-glycols, qualitative assessment of slides stained using PAS was performed, comparing treated animals to NC and PC groups. Micrographs were obtained to present the results.

Statistical analyses of morphometry and levels of AST, ALT, and ALP were performed using Graph Pad Prism® 3.0. Differences between groups were compared using ANOVA, followed by the Bonferroni test. Statistical significance was set at $P < 0.05$.

Results

As shown in Figure 2, animals in the NC and lycopene groups showed normal liver tissue; however, numerous inflammatory infiltrates, with or without necrosis, were detected in the PC and LP groups. In the PC24 and PC72 groups, a greater predominance of this type of injury was observed, especially in the latter group, as confirmed by the number of centrilobular regions affected (figures 2 and 3).

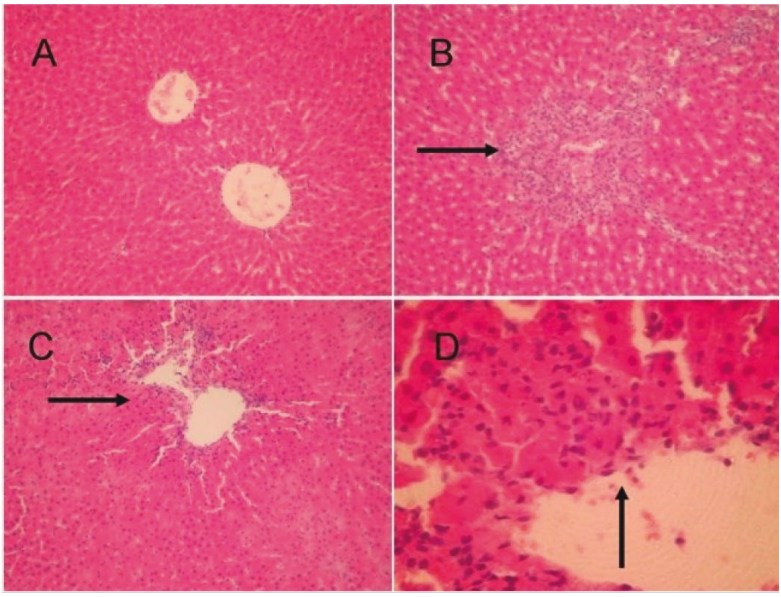

Figure 2. Micrographs showing histopathological changes, especially necrosis and inflammatory infiltration. A: negative control 72 h (150×). B: positive control 72 h (150×). C: lycopene+paracetamol (150×). D: lycopene+paracetamol (600×). Arrows indicate regions with inflammatory infiltrate and necrosis. Hematoxylin-eosin staining.

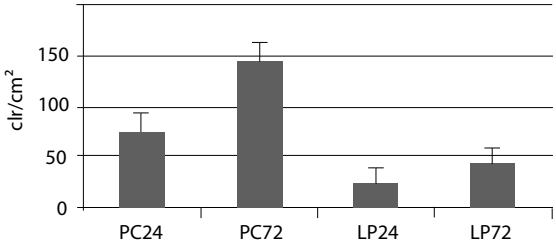

Figure 3. The qualitative analysis of inflammatory/necrotic foci in the centrilobular region of treated and negative control groups. The lycopene (LP) groups show a decreased incidence of injury. Differences between groups were analyzed using ANOVA, followed by the Bonferroni test, with $P<0.05$ deemed significant. PC24, positive control 24 h; PC72, positive control 72 h; LP24, lycopene+paracetamol 24 h; LP72, lycopene+paracetamol 72 h.

On examining Picrosirius red-stained slides, we observed increased collagen in acinar zones 1 and 3; thus, quantification was performed in these regions. All groups exhibited modest collagen deposition, approaching that observed in the NC group (figures 4, 5 and 6).

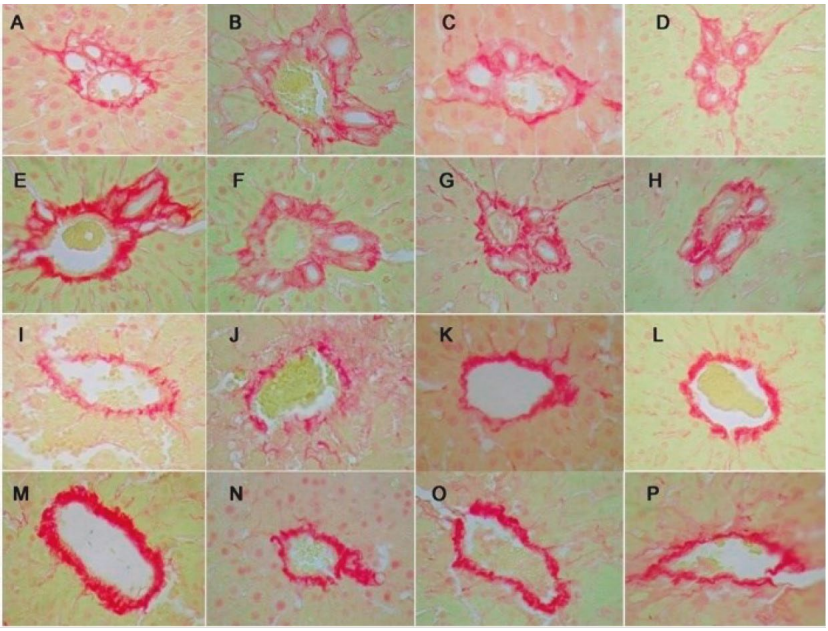

Figure 4. Acinar zone 1. A: 24 h positive control; B: 72 h positive control; C: 24 h negative control; D: 72 h negative control; E: lycopene 24 h; F: lycopene 72 h; G: lycopene+paracetamol 24 h; H: lycopene+paracetamol 72 h; Acinar Zone 3 – I: 24 h positive control; J: positive control 72 h; K: 24 h negative control; L: 72 h negative control; M: lycopene 24 h; N: lycopene 72 h. O: lycopene+paracetamol 24 h; P: lycopene+paracetamol 72 h. Sirius Red Zone, 600×.

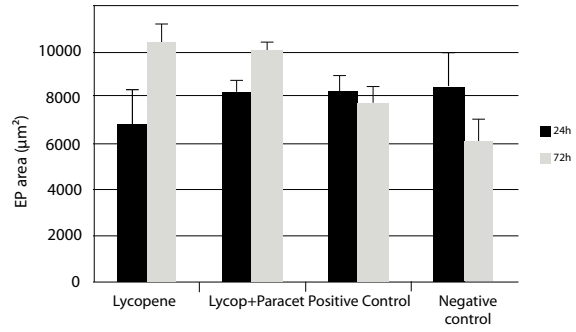

Figure 5. Results of the quantification of collagen fibers in the portal region (acinar zone 1). Small variation in values can be observed, with no significant difference between groups. ANOVA followed by Bonferroni test; P values <0.05 were considered significant. EP

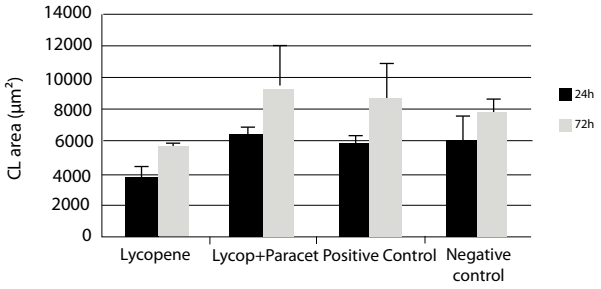

Figure 6. Acinar zone 3. Small variations in values can be observed, with no significant difference between groups. ANOVA followed by Bonferroni test; P values <0.05 were considered significant. CL, centrilobular

On analyzing PAS-stained sections, we observed slight or intense deposition in PAS-positive inclusions in the acinar zone 1 region (portal space), as shown in Fig. 7.

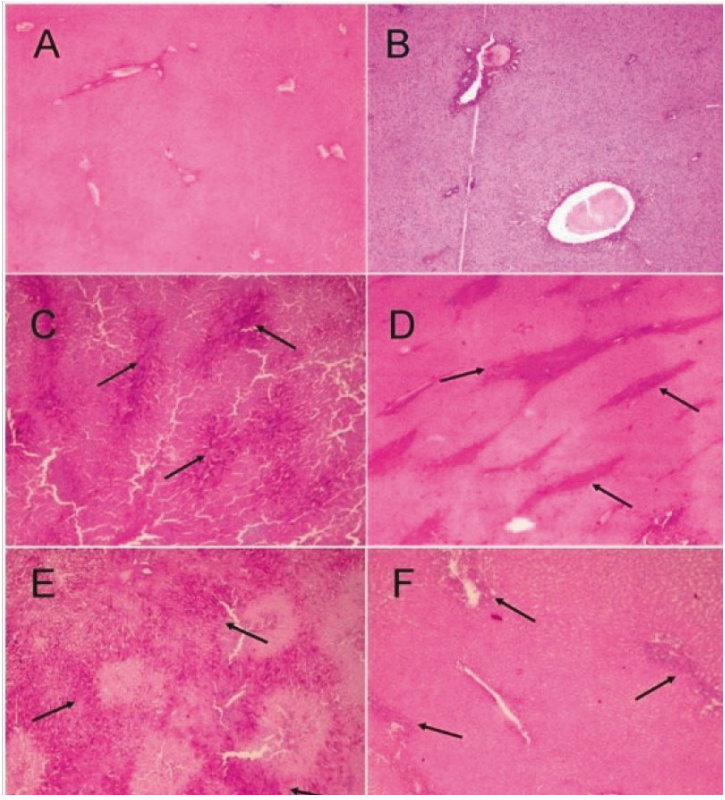

Figure 7. Micrographs of acinar zone 3 showing the distribution of glycogen and other 1,2-glycols. A: 24 h negative control. B: negative control 72 h. C: 24 h positive control. D: positive control 24 h. E: lycopene+paracetamol 24 h. F: lycopene+paracetamol 72 h. Arrows indicate regions with PAS-positive inclusions. Periodic Acid Schiff (PAS), 60×.

In lycopene-treated groups, positive PAS inclusions were preserved, exhibiting 20% lesion reduction in the LP24 group and 60% in the LP72 group, thus indicating the hepatoprotective activity of lycopene (Table 1).

Table 1. Semiquantitative analysis of the deposition of PAS-positive inclusions in acinar zone 1. Note the significant reduction in inclusions in the LP72 group compared to the PC 72 group.

Group	Number of animals			Reduction in relation to PC
	Positive PAS Deposition in Zone 1			
	No deposition (-)	Mild/moderate deposition (+)	Intense deposition (++)	
NC24	5	0	0	-
NC72	5	0	0	-
PC24	0	2	3	-
PC72	1	2	3	-
LP24	1	0	3	20%
LP72	4	1	0	60%

PAS: Periodic Acid Schiff; PC: positive control; NC24: negative control 24 h; NC72: negative control 72; PC24: positive control 24 h; PC72: positive control 72; LP24: lycopene+paracetamol 24 h; LP72: lycopene+paracetamol 72 h.

Pretreatment with lycopene greatly impacted ALT and AST levels. As shown in Figure 8, serum AST and ALT levels were significantly reduced in the LP24 group when compared with those in the PC24 group. No significant changes in ALP and gamma-glutamyltransferase (GGT) levels were detected.

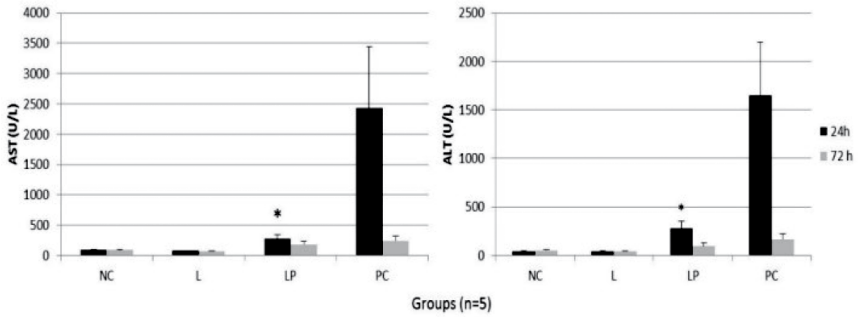

Figure 8. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. NC: negative control group; L: lycopene; LP: lycopene+paracetamol; PC: positive control group. ANOVA followed by Bonferroni test. *P <0.05 compared to the PC24 group. Reference values for rats: ALT, 51 U/L; AST, 81 U/L [30].

Discussion

Free radicals (ROS) are naturally and continuously generated during energy production, and most organisms possess protective mechanisms against these oxidants [31]. Maintaining a balance between oxidant and antioxidant species within intracellular and extracellular environments is critical for optimal metabolism. It is well-known that energy is obtained from the metabolic breakdown of dietary macronutrients; however, this degradation can generate ROS and RNS, also called free radicals, potentially damaging lipids, proteins, and DNA.

Under normal conditions, there exist mechanisms to neutralize excess ROS or RNS, thus protecting against an imbalance of excessive oxidants, often referred to as "oxidative stress" [31]. Oxidative stress contributes to various disorders and chronic diseases, such as cancer, cardiovascular disease, osteoporosis, diabetes, and cataracts. Thus, antioxidants can eliminate free radicals and prevent damage [31]. However, these mechanisms become ineffective under conditions inducing exacerbated production and activity, resulting in cell and, consequently, tissue damage. Therefore, the search for new molecules or substances with antioxidant properties, such as lycopene, remains crucial to combat diseases and injuries triggered by ROS, and in the present study, paracetamol intoxication.

Histological analysis was performed with three main objectives: (1) observation and quantification of necrosis and inflammatory infiltration using HE staining, (2) quantification of collagen fibers to determine fibrosis using Picrosirius red staining, and (3) qualitative analysis of glycogen and other 1,2-glycols using PAS staining.

On assessing the first parameter, we observed that paracetamol, at the dose employed, caused necrosis and hepatic inflammatory infiltration in all animals in the 24 and 72 h groups, with the latter group exhibiting severe lesions. Lycopene reduced inflammatory infiltrate and necrotic foci; however, these findings were not significant when compared with the PC group (figures 2 and 3). A previous report has reported that lycopene protected hepatocytes in lesions caused by D-galactosamine/lipopolysaccharide-induced lesions, as determined by morphological analysis [32]. Thus, histopathological studies can serve as direct evidence indicating the efficacy of lycopene as a potential hepatoprotectant.

Picrosirius red-stained sections enable the quantification of collagen fibers to identify fibrosis. Following computational analysis of obtained images (figures 3, 4, and 5), we detected no significant difference between groups in terms of acinar zone 1 or 3 when compared with the lycopene-treated group. This result can be explained by the low

intensity of collagen fibers observed and measured in the PC group, corroborating the findings of several previous reports, which did not detect the presence of fibrosis in paracetamol-induced toxic hepatitis [18].

On assessing the third listed histological parameter, we observed that animals treated with high-dose paracetamol exhibited an increase in PAS-positive inclusions in the portal region and a decrease in these inclusions in the centrilobular region when compared with the NC group. A paracetamol-induced decrease in hepatic glycogen was noted, possibly via an irreversible association with a reactive metabolite or the inhibition of mitochondrial energy metabolism, deemed an indicator of drug-mediated hepatotoxicity [33]. Although a quantitative analysis was not performed, it was clearly observed that lycopene pretreatment promoted the homogeneous distribution of glycogen. The decrease in glycogen in acinar zone 1 was expected, as the P450 complex enzymes are found in greater quantity in this region, and consequently, where paracetamol-induced histopathological lesions occur. Notably, we documented a 60 % reduction in glycogen depletion in the LP72 group when compared with the PC group (Figure 7 and Table 1), thus indicating the efficacy of this phytopharmaceutical in preserving cytoplasmic glycogen in hepatocytes.

Considering liver transaminases, lycopene exhibits hepatoprotective potential. AST is a well-known enzyme found in high concentrations in the cardiac muscle, liver, and skeletal muscle and, specifically, in the kidneys and pancreas. In liver cells, AST is located in the cytoplasm (40%) and mitochondria (60%). ALT or glutamic-pyruvic transaminase is an enzyme predominantly found in the liver, at moderate concentrations in the kidneys, and in smaller amounts in the cardiac and skeletal muscle. In liver cells, ALT is located in the cytoplasm (90%) and mitochondria (10%). Tissue damage or diseases affecting the liver parenchyma will induce the release of these enzymes into the bloodstream, raising serum levels of AST and ALT, thus indicating hepatocellular disease.

Previous studies have evaluated AST and ALT levels in patients with acute and chronic liver disease. The AST/ALT ratio provides useful clinical information regarding the cause and severity of the underlying liver disease in these patients. Advantages of using these parameters include easy estimation and interpretation at a low cost, allowing widespread application [34]. Elevated serum levels of ALT and AST can be attributed to damage liver structure, given that these enzymes are located in the cytoplasm and are released into the bloodstream after cell damage [35].

Thus, we observed that serum AST and ALT levels were lower in the LP24 and LP72 groups than in the PC group (treated with paracetamol). In line with the findings of the

present study, several previous reports have confirmed the hepatoprotective action associated with decreased serum AST and ALT levels following toxic hepatitis [18, 32, 36].

ALP reflects pathological changes in the bile duct [37]. Thus, elevated serum ALP levels in rats with induced hepatitis can be associated with a disturbance in the secretory activity, metabolite transport, or the synthesis of certain enzymes altered during other hepatotoxic conditions [34]. Based on our findings, we observed no discernible change in the levels of this enzyme, even in the PC group. The absence of elevated ALP levels in the PC group (and in other groups) was in agreement with the histological findings, given that no changes were observed in bile ducts on light microscopy examination, thus indicating that paracetamol-induced hepatotoxicity is cytolytic and not cholestatic [18].

GGT is an enzyme known to be involved in the transport of amino acids and peptides across cell membranes, protein synthesis, and regulation of tissue glutathione levels. This enzyme is primarily found in the liver and kidneys. In the liver, GGT is located in the canaliculi of liver cells and epithelial cells lining bile ducts; thus, along with ALP, changes in serum levels of GGT indicate biliary involvement, demonstrating more sensitivity and persistent effects. We noted no change in GGT levels in any examined groups, thus indicating that paracetamol intoxication does not cause biliary damage.

Lycopene is a fat-soluble, red pigment carotenoid found to occur in certain plants and microorganisms, where it helps protect against ultraviolet B rays. Notably, lycopene is synthesized by plants and microorganisms but not animals [38]. This carotenoid possesses 40 carbon atoms ($C_{40}H_{56}$), containing 11 conjugated and 2 unconjugated double bonds, predisposing lycopene to isomerization and degradation upon exposure to light, excessive heat, and air [38].

The mechanism of lycopene absorption has been well-characterized. Lycopene ingested in natural form is poorly absorbed. Processed tomatoes or tomatoes that induced isomerization of the *trans* to *cis* configuration exhibit increased bioavailability. In addition, given its fat-soluble component, lycopene absorption can be improved by ingesting oils. Reportedly, its concentration in human tissues exceeds that of all other carotenoids. Lycopene is mainly distributed to adipose tissues, as well as organs such as adrenal glands, liver, or testes [39].

Lycopene has been described as the most important antioxidant of the carotenoid group. It also has an important anti-inflammatory effect and acts as a scavenger of free radicals, thus reducing induced cell damage [40]. Numerous studies using *in vivo* models of radiation exposure have demonstrated that lycopene protects against radiation toxicity via its antioxidant mechanism [41]. *In vitro* models have revealed that the use of lycopene prior to radiotherapy can reduce the effects of radiation-induced oxidative

damage in rats [41]. In addition, lycopene has hepatoprotective action against D-galactosamine/lipopolysaccharide-induced damage [32].

Lycopene can afford hepatoprotective benefits by preventing mercury-induced oxidative stress [42]. Literature have reported that tomato pulp, which contains high doses of lycopene, has hepatoprotective activity against carbon tetrachloride-induced intoxication [43]. However, no study has reported the non-hepatoprotective effects of lycopene.

Conclusion

Based on the findings of the present study, we concluded that lycopene could afford hepatoprotective action following paracetamol-induced acute intoxication, as shown by the histological decrease in necrosis and inflammatory foci, preservation of glycogen and other 1,2-glycols in acinar zone 3, and reduced serum levels of ALT and AST.

Disclosure statement

The authors declare that there are no conflicts of interest.

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