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Protective Role of Curcumin Nanoparticles Against PTU-Induced Liver Injury: Modulation of Oxidative Stress, Inflammation, and Histopathological Changes.

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Abstract: *Background: Hepatotoxicity are damage to the liver which can occur, for example, due to propylthiouracil (PTU) induced oxidative stress. It could be assumed that natural antioxidants such as curcumin and its nano-formulations like Curcumin-Chitosan nanoparticles (Cur-Cs-NPs) might be protective in this condition. Aims: To evaluate the protective role of Cur-Cs-NPs against PTU-induced hypothyroidism and hepatotoxicity in male rats by evaluating Gamma Glutamate, protein carbonyl, Tumor Necrosis Factor alpha TNF and histological parameters. Methods: Fifty-five adult male rats used, with fifteen in the preliminary trial and forty in the main experiment. The rats were divided into four groups (n=10 each). G1 control, G2 PTU 50 mg/kg B.W., G3 Cur-Cs-NPs 100 μg/kg B.W., and G4 PTU + Cur-Cs-NPs. Treatments administered orally for 28 days. Rhizomes of Curcuma longa used for the synthesis of Cur-Cs-NPs characterized by UV-Vis, FTIR, XRD, EDX, and zeta potential analysis. Blood samples were collected for the measurement of Protein Carbonyl (PC) and Gamma Glutamyltransferase (GGT) by ELISA; liver tissues were subjected to an analysis of histopathology by H&E staining. Results: Results indicated that PTU treatment in Group 2 raised protein carbonyl levels to 81.10 ± 4.43 ng/ml and gamma glutamate (GGT) to 4.56 ± 0.48 when compared to the control group (Group 1), which were 29.3 ± 3.29 ng/ml and 2.50 ± 0.19, respectively. Administration of Cur-Cs-NPs alone (G3) brought down protein carbonyls to 45.1 ± 3.31 ng/ml and GGT to 2.77 ±0 .18 . Histological observations detected in G4 showed binucleated and trinucleated hepatocytes with a slight increase in Kupffer cells that correspond to hepatic regeneration; therefore, it confirms the above results that Cur-Cs-NPs have a hepatoprotective effect against PTU-induced oxidative stress.. Conclusion: Histopathological analysis evidenced PTU as a significant inducer of hepatic damage.. the co-administration of Cur-Cs-NPs with PTU showed obvious signs of hepatic regeneration, including multinucleated hepatocytes and increased Kupffer cells. From these findings, it can be concluded that the antioxidant activity of Cur-Cs-NPs contributes largely to their hepatoprotective effect in PTU-induced oxidative stress and injury to the liver.*

Keywords: *Curcumin nanoparticles, propylthiouracil (PTU), hepatotoxicity, GGT, PC, TNF a*

INTRODUCTION

Curcumin is the active principle of turmeric (Curcuma longa) and is known for its properties that go well beyond inflammation- antioxidant- hepatoprotective effects. The main mechanisms of action are well documented against oxidative stress and inflammation (1). However, the practical application of curcumin is greatly hampered by low bioavailability due to poor absorption in the intestines. This may be overcome by using piperine which enhances its absorption (2). Curcumin plays a major role in hepatoprotection mainly under conditions related to oxidative stress it acts by adjusting proinflammatory cytokines and reactive oxygen species (3). Nanotechnological advances have already gone toward developing some nanoparticle-based formulations that deliver curcumin with enhanced solubility and bioavailability hence even better therapeutic potential (4). Possible multiple effects on several signaling pathways at once make nanoparticle-based delivery of curcumin more potent for biologic multitarget activity in clinical applications (5).Curcumin has very potent antioxidant as well anti-inflammatory properties. It is actually antioxidative in nature and therefore, the mechanisms by which it acts against diseases related to oxidative stress could be protective. Evidence suggests that curcumin's bioactivity is

directly proportional to its free radical scavenging ability and the modulation of different signaling pathways (6). That antioxidant activity is therefore considered a central mechanism in its health effects, thus led to better therapeutic results through enhanced bioavailability (7). Curcumin nanoparticles seem to have greatly improved the antioxidant properties of curcumin. Scientific studies demonstrated that nanoparticles improve the physicochemical properties of curcumin and thus solve problems related to solubility issues resulting in increased bioavailability (8). Other researchers revealed that sophorolipid-coated curcumin nanoparticles improve bioaccessibility because it plays a major role in achieving antioxidant activity (9). These findings support the idea that preparation of nanoparticles can very efficiently enhance the therapeutic potential of curcumin, especially in antioxidant applications. Besides, it has been found that attaching curcumin to gold nanoparticles (AuNPs) results in superior antioxidant activity which then establishes the principle that physicochemical interactions between curcumin and nanoparticles are of utmost importance for improved therapeutic efficacy from curcumin. This demonstrates an importance in exploring different kinds of nanoparticles for achieving optimized delivery of curcumin as well as maximum health benefit (10-11).

Liver injury induced by drugs remains leading concern in hepatotoxicity investigations. This was already narrated with the listing of several drugs related to hepatotoxicity by a previous article, stressing how important it is to know the role played by antioxidants like catalase in reducing oxidative stress. (12). Propylthiouracil (PTU) is usually prescribed as a treatment for hyperthyroidism and more specifically in Graves' disease, but it does come with several side effects including liver toxicity. While general hepatotoxicity has been dealt with quite well already, most specific mechanisms regarding PTU-induced hepatotoxicity remain unexplored. Such insights would be valuable as speculation that biochemical pathways perturbed by PTU could have a parallel in those previously described for other hepatotoxic agents-nanoparticles of titanium dioxide would then lead to further speculation about pathophysiological and even emotive alterations resulting from PTU (13).

Protein carbonylation is the most traditionally monitored oxidative protein damage in hepatic injuries. ROS directly attack the amino acid side chains, generating protein carbonyl derivatives as a result of several pathways. It is an irreversible modification, and the carbonyl groups are derivatized and therefore accumulated against oxidative stress, for example in aging and several chronic diseases including neurodegeneration and hepatopathies (14). Thus, increased levels of protein carbonyls in plasma or tissues reflect an oxidative imbalance and are easily used to determine cellular oxidative damage. The gamma-glutamyl transferase (GGT) enzyme participates in glutathione metabolism providing redox homeostasis central control (15). GGT catalyzes glutathione breakdown on the cell surface and it is highly responsive to the changes in oxidative status. Diseases that raise GGT activity include cardiovascular disease plus a liver disease and metabolic syndrome associated with systemic inflammation (16). Another thing to note is that GGT adds to ROS creation via iron pathways, increasing the damage from oxidation even more. For that reason, both protein carbonyl and GGT act as big and matching indicators when looking at diseases related to oxidative stress (17).

The goal of the current study was to evaluate the protective role of Cur-Cs-NPs against the oxidative stress PTU-induced hepatotoxicity in male Wistar rats by evaluating Gamma Glutamate, protein carbonyl, tumor necrosis factor-α (TNF-α) and histological investigations.

METHODS

Experimental Animals

Fifty-five adult male Wistar rats were used in this study. Fifteen of them were assigned to the preliminary study, and the remaining forty were used in the main experimental phase. The animals were kept in well-ventilated rooms in plastic cages under standard environmental conditions (22–25 °C) with free access to water and standard pellet feed. A two-week acclimation period was observed before starting the experiment.Curcuma longa rhizomes were obtained from a local market in Baghdad. The results were thoroughly washed and dried at 40°C before being

ground into a fine powder. Hydroalcoholic Extract: 50 g of the powder was mixed with 500 ml of ethanol heated to 70–80°C for six hours; then, the solvent was evaporated. This extract has also been used in the formulation of Cur-Cs-NPs.

- Use of UV-Vis spectrophotometry for confirmation of nanoparticle synthesis.
- Functional groups and molecular interactions by FTIR spectroscopy.
- Determination of crystalline structure by XRD analysis.
- Elemental composition by EDX analysis.
- Zeta potential measurements for nanoparticle stability.

The main study was conducted to explore the ability of Cur-Cs-NPs to protect against hypothyroidism and liver damage caused by propylthiouracil in rats. A total of 40 rats were randomly assigned into four groups (10 rats in each group) and treated for 28 days as follows:
Control; Received distilled water orally.
G2; Given PTU at a dose of 50 mg/kg body weight by mouth.
G3: Rats were given Cur-Cs-NPs at 100 µg/kg body weight orally.
G4: Rats were treated with both PTU at 50 mg/kg and Cur-Cs-NPs at 100 µg orally.
At the end of the treatment period, the rats were anesthetized using an intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg). Blood was then collected through cardiac puncture, after which the animals were humanely euthanized. The liver tissues were carefully excised for further analysis. The blood samples were allowed to clot at room temperature; serum was then isolated by centrifugation and stored at −18 °C until analysis for Protein Carbonyl (PC), TNF-α and Gamma Glutamyl transferase (GGT) levels using ELISA kits from Humacount. In addition, some portions of the liver samples were processed histopathologically evaluated using standard methods (18).

Statistical analysis:

Data were analyzed statistically by Graph prism 26 (Graph Pad Software, CA, USA) and SPSS version 23.0. On this research, the data was subjected to statistical analysis using the LSD test and Duncan Multiple Range comparing significant different ($P<0.05$) between the means. The presentation of data was done as mean standard error (SE).

RESULTS

The bar chart visibly demonstrates the protein carbonyl content (ng/ml) for the experimental groups presented in tabulated data. PTU treated Group G2 alone showed a significantly elevated level of protein carbonyl 81.10 ± 4.43 ng/ml indicating marked oxidative stress as compared to control G1, which was normal 29.3 ± 3.29 ng/ml $p<0.0001$). Groups G3 and G4, receiving Cur-Cs-NPs alone and combined with PTU, respectively showed statistically significant reductions in protein carbonyl levels to 45.1 ± 3.31 ng/ml and 52.9 ± 2.87 ng/ml respectively against G2 though still higher than the control Cur-Cs-NPs appear to exert a protective antioxidant effect against PTU-induced oxidative damage as reflected by reduced accumulation of protein carbonyls. The two groups, G3 and G4, are sharing the same statistical grouping b; this indicates that Cur-Cs-NPs can be effective in reducing oxidative stress.

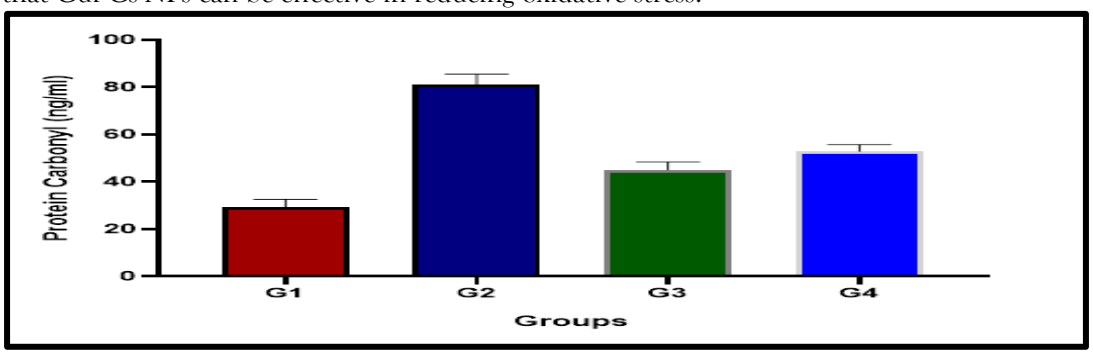

Figure 1. Effects of curcumin nanoparticle nanoparticles on Protein Carbonyl levels in different study groups

The bar graph presents data on gamma glutamate (GGT) for the four experimental groups; it correlates well with the data already tabulated. The PTU-treated group G2 showed the maximum concentration of GGT at 4.56 ± 0.48 ng/ml, which is significantly higher than that in the control group G1 (2.50±0.19 ng/ml). The p-value was 0.0066, indicating increased hepatic stress or damage. In return, Group G3 (Cur-Cs-NPs alone) showed a little increase at 2.77 ± 0.18 ng/ml, not significantly different from control; this means that nanoparticles do not induce toxicity to the liver by themselves and thus can be safely used as carriers of other drugs or active ingredients leading to more solubility and better bioavailability after administration into an organism's body.

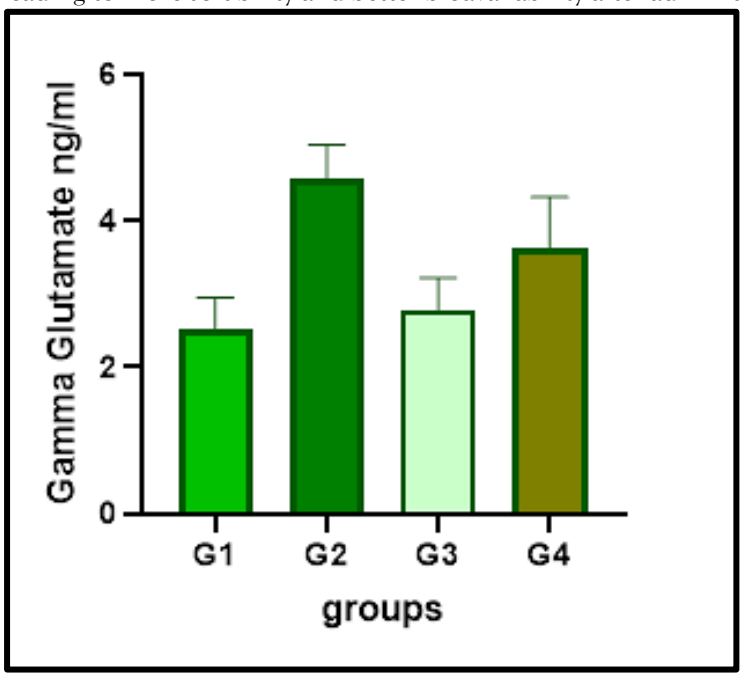

Figure 2. Effects of curcumin nanoparticle nanoparticles on Gamma Glutamate levels in different study groups

The bar chart demonstrates the effect of the treatment with curcumin nanoparticles on TNF-α among four experimental groups. Notably, group G2 showed the highest concentration of TNF-α, meaning either an inflammatory state was induced or not suppressed; groups G1, G3, and G4 expressed reduced levels of this parameter, possibly indicating some modulatory or therapeutic effect relating to curcumin nanoparticles. This therefore indicates differential responses among these groups that could be attributed to variations in dosage, formulation, and treatment duration. Hence, further statistical analyses are required to ascertain whether differences are significant before making any conclusive efficacy statements (See Figure 3.)

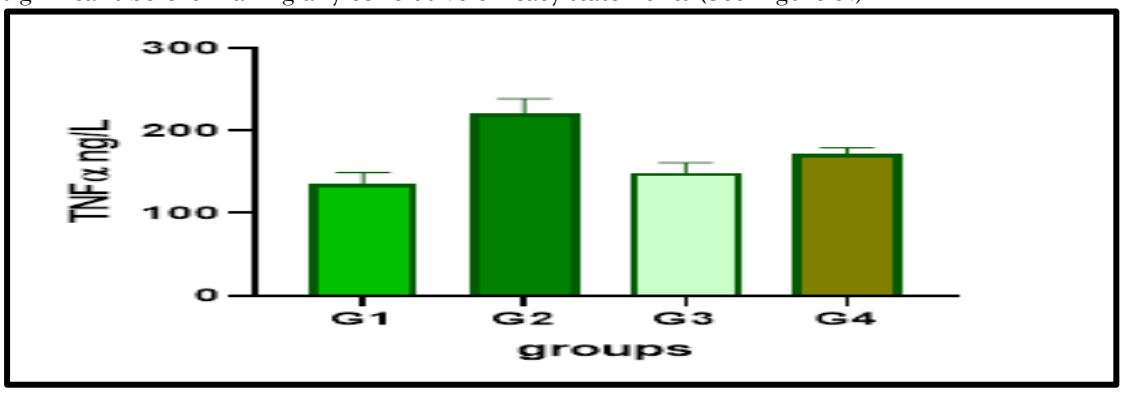

Figure 3. Effects of curcumin nanoparticle nanoparticles on TNF-α levels in different study groups

Hepatic architecture in the control group (Group I) was found to be normal, with neatly arranged hexagonal lobules arranged around a noticeable central vein. Hepatocytes were uniform, polygonal cells with round, central nuclei that were arranged in regular cords (figure 4). Liver sections in Group II (PTU-induced hypothyroidism) revealed clear pathological changes, such as mild to moderate inflammatory cell infiltration around the portal areas, disruption of normal lobular architecture, and vascular congestion (figure 5).

Group III, which received only Curcumin Nanoparticle treatment, showed a slight improvement in hepatocyte morphology along with a slight dilatation of the hepatic sinusoids (figure 6). Only a few inflammatory cells were seen in the portal region, and there was no sign of necrosis. In comparison to Group II, Group IV (PTU + Curcumin Nanoparticles) displayed a notably lower level of hepatocellular damage and almost normal hepatic architecture. The overall tissue structure was better preserved and the sinusoids looked more regular, suggesting that curcumin nanoparticles have a protective effect against PTU-induced hepatic injury (figure 7).

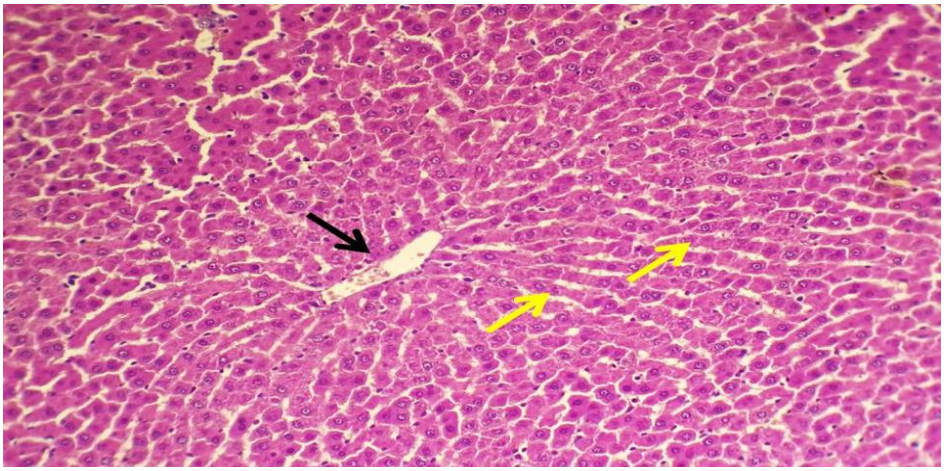

Figure 4: Histological section of liver (control group) show the hexagonal lobules centered around a central vein (black arrow). Hepatocytes separated as regular chain with uniform, polygonal cells with round, central nuclei (yellow arrows). H&E stain. 400X.

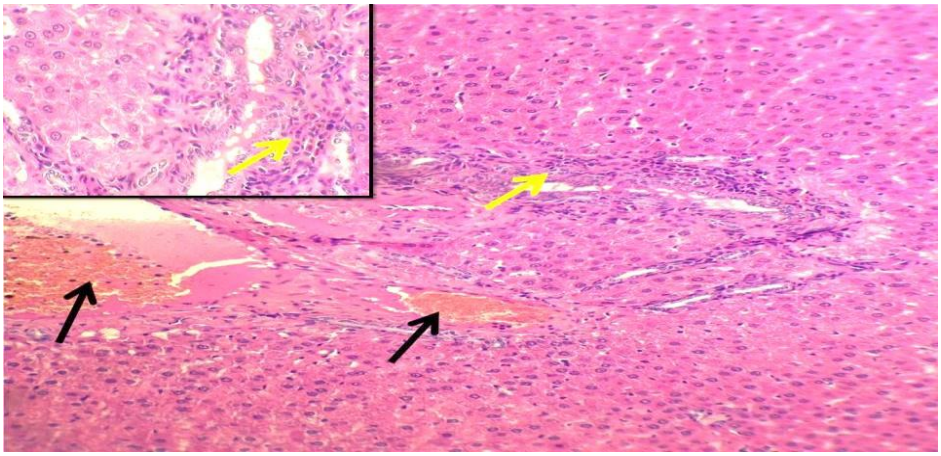

Figure 5: Histological section of liver (G2) show the congestion black arrows) with observed disrupted hepatic architecture with Mild to moderate inflammatory cell infiltration around portal area (yellow arrows). H&E stain. 400X.

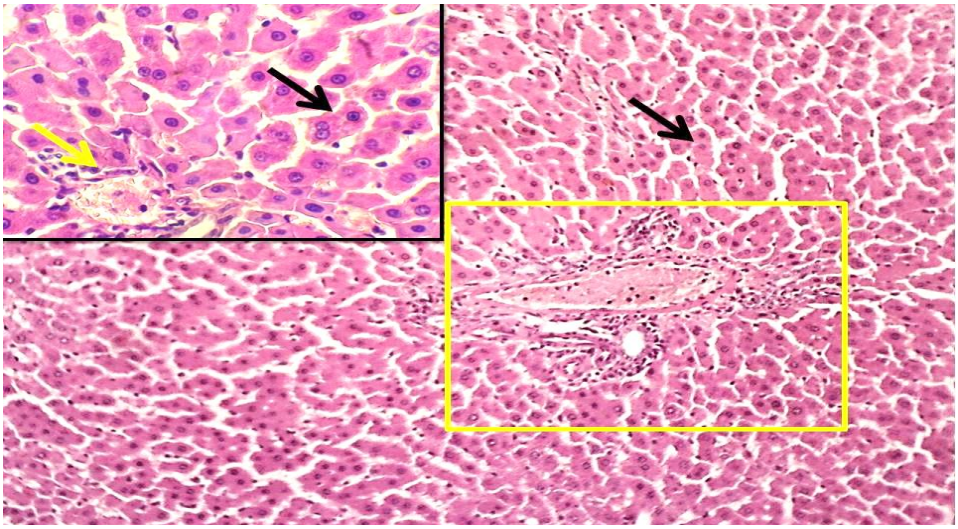

Figure 6: Histological section of liver (G3) show the mild enhancement of hepatocyte morphology (black arrow) with mild dilation of sinusoids, but no necrosis with less numbers of inflammatory cells in portal area. H&E stain. 400X.

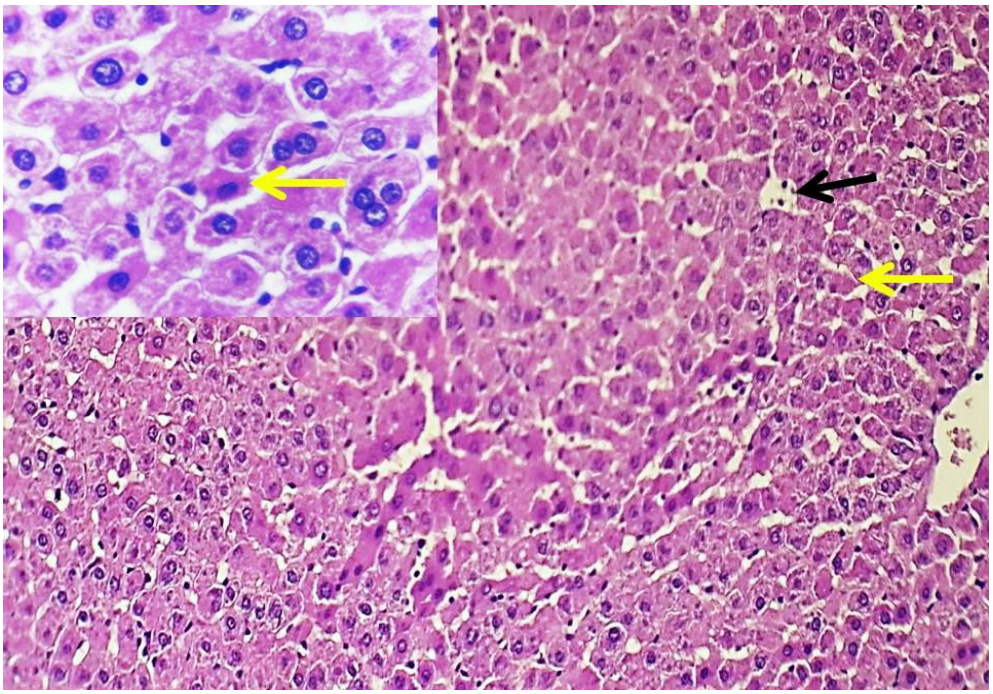

Figure 7: Histological section of liver (G4) show the normal hepatic architecture reduction in hepatocellular damage compared to Group II (yellow arrow). The sinusoids appear more regular. H&E stain. 400X.

DISCUSSION

The study demonstrated the susceptibility of PTU to induce hepatotoxicity in majority animal models. The major mechanisms primarily are oxidative stress, inflammation, and apoptosis. For instance, in hepatotoxicity, oxidative stress is primarily accountable for the damage to the liver; protein carbonyl levels furnish evidence on that (17-18).

The current experiment has been undertaken to elucidate the effects of Cur-Cs-NPs on the serum levels of TNF-α in rats that have been made hypothyroid by PTU. From the results obtained, it was clear that normal group PTU-treated animals had significantly increased amounts of TNF-α in their sera, denoting that a systemic inflammatory response does take place under such

pathological conditions of hypothyroidism. This finding goes with earlier observations in which it was reported that pathologic condition increases more pro-inflammatory cytokines and particular TNF-ά (19).The group that was administered Cur-Cs-NPs alone (G3) expressed a noticeable decrease in the levels of TNF-α as compared to G2. This may probably be due to the fact that curcumin is well known for its NF-kB inhibitory action on downstream cytokine expression (20). A very interesting observation was made in a group treated with both PTU and Cur-Cs-NPs (G4)-this group also showed a marked reduction in the level of TNF-α relative to the group treated with only PTU-thereby indicating that it partially reversed the inflammation induced by PTU. That further attests to the therapeutic potential of curcumin-loaded nanoparticles, once again, toward inflammatory response regulation under hypothyroid state conditions. Earlier studies were conducted to prove that curcumin and its nano-formulations can attenuate TNF-α expression in various models of inflammatory and metabolic diseases (21). The nano-formulation possibly increases the bioavailability as well as the stability of curcumin, thus making it more effective systemically. Also, the lack of increased TNF-α in the control group (G1) reestablishes normal conditions' baseline inflammatory status and intervention efficacy assessment reference. Generally, these present results emphasize the anti-inflammatory potential of Cur-Cs-NPs and their ability to ameliorate systemic inflammation induced by PTU. It, therefore, supports the further study of curcumin-based nanomedicine as adjunctive therapy in thyroid and inflammatory disorders. Normally generated free radicals will be neutralized by antioxidant defense systems; however, when the balance shifts to the side of free radicals, destruction may result in mitochondrial cell death—PTU exposure will aggravate this condition. It is also proven that inflammation leads to hepatic fibrosis, hence PTU may activate inflammatory cascades thereby amplifying its hepatotoxic effects. Several studies have been done on antioxidants against hepatic oxidative stress (22-23).

The present study revealed the mechanism by which curcumin, in its nanoparticle form, acts as an antioxidant in protecting against hepatotoxicity. New studies bring to the front curcumin, mostly in the form of nanoparticles, as an agent that shields from liver damage. Curcumin is a polyphenolic antioxidant extracted from turmeric (24). It is known to minimize oxidative stress, which is the main way of damage in the liver both under normal conditions and PTU-induced conditions. The primary detoxification organ is the liver; hence very much prone to oxidative stress and hepatotoxicity. Therefore elevated protein carbonylation will be increased in most pathologies as it is also an oxidative damage marker common elevated in diseases of the liver. Thus well-documented antioxidant capacity of curcumin opens doors for CNPs to be explored as possible reducers of protein carbonyl levels generally associated with liver damages (25). The other study conducted by Liu et al. Another improved Curcumin therapeutic efficacy proved through nanoparticles in diabetic wound healing which is also a hepatic complication (2018). Therefore within these findings it can be inferred that CNPs may enhance antioxidant defenses hence reduce protein oxidation in the liver. They have reviewed different Curcumin nanoformulations with their prospects for better health to the liver through enhanced drug metabolism and detoxification processes. This would mean that an improved delivery of curcumin as nanoparticles would drastically reduce protein carbonyl levels offer protection against hepatotoxicity (26). Another study, that of Zoi et al., on the antioxidant effects of curcumin in quails should support your idea that CNPs can greatly enhance liver function by quenching oxidative stress protein carbonyls it can cause. This opens the use of CNPs much more broadly to keep liver function high under all kinds of stressors (27). The 2014 contributor claimed that bioavailability is the main factor that increases antioxidant capacity. Accordingly, it leads colloidal delivery systems for curcumin nanoparticles because higher solubility and stability may turn into better protection for the liver against damage from oxidative stress as well as protein carbonylation (28-29).

Curcumin, formulated as nanoparticles, would present an excellent drug delivery system to increase the bioavailability and overall therapeutic efficacy of the compound itself (30). When curcumin is encapsulated in nanoparticles, not only does it stabilize the compound but also

facilitates active targeting to the tissues. This is particularly applicable to hepatotoxic conditions, where good concentrations are required for beneficial effects on liver function and gamma glutamate levels (31). The protective action of curcumin against hepatic toxicity has been well documented in several studies; a few reports indicated that curcumin could ameliorate liver damage caused by toxic agents such as cisplatin (32). This kind of protective mechanism probably operates through antioxidant activity and enhancement of normal enzyme functioning in the liver. From these findings, one can imply that curcumin may increase gamma glutamate levels by improving general functioning in addition to hepatotoxicity. Thus, curcumin becomes a compound relevant in the management of inflammatory conditions since an association has been found between these and liver dysfunction plus metabolic disorders (33). Curcumin's capacity to elevate the sensitivity of insulin as well as that of β-cells could indirectly promote good health for the liver and therefore gamma glutamate. Improved function in metabolic disorder-associated conditions is thus another reason for curcumin nanoparticles having a possible way to help in hepatotoxic situations. Such an elevation in gamma glutamate, an essential amino acid for operations within the liver concerning metabolism plus detoxification, can happen when curcumin improves bioavailability through nanoparticle-based delivery systems achieving therapeutic concentrations within the liver (34-37).

CONCLUSION

Histopathological analysis evidenced PTU as a significant inducer of hepatic damage, inflammation, vascular congestion, and bile duct hyperplasia. Treatment with Cur-Cs-NPs alone exhibited no apparent adverse effects on liver tissue; therefore, it can be considered safe. However, the co-administration of Cur-Cs-NPs with PTU showed obvious signs of hepatic regeneration, including multinucleated hepatocytes and increased Kupffer cells. From these findings, it can be concluded that the antioxidant activity of Cur-Cs-NPs contributes largely to their hepatoprotective effect in PTU-induced oxidative stress and injury to the liver.

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