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# Curcumin nanoparticles attenuate propylthiouracil (PTU) mediated hepatotoxicity in male rats via activation of catalase function

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**Abstract:**

**Background**: Hypothyroidism and 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 Wistar rats by assessing biochemical, molecular, and histological parameters. **Methods**: Fifty-five adult male Wistar 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 catalase (CAT) by ELISA; liver tissues were subjected to an analysis of CAT gene expression using RT-PCR and histopathology by H&E staining. **Results**: The catalase activity in the PTU group was 10.04 ± 0.66 ng/mL as compared to control 20.84 ± 1.57 ng/mL (p=0.0003), thus confirming oxidative stress. Cur-Cs-NPs alone (G3) increased CAT levels to 25.12 ±2.13 ng/mL while G4 showed partial recovery 14.29 ±0.91 ng/mL CAT mRNA expression followed suit, G1 (1.01 ±0.06 fold), G2 (0.8278 ±0.19), G3 (0 .7837 ±0 .15), and G4 (0 .3945 ± 0 .02). A synergistic suppressive effect when PTU and Cur-Cs-NPs are combined has been inferred from these values. **Conclusion**: Cur-Cs-NPs proved to be potent antioxidants and hepatoprotective in PTU-induced hypothyroid rats as evidenced by improved catalase activity, modulated gene expression, and regenerative liver histology. Based on these findings, it is recommended that Cur-Cs-NPs could be a possible therapeutic candidate for managing oxidative damage to the liver in hypothyroidism.

**Keywords: Curcumin nanoparticles, propylthiouracil (PTU), hepatotoxicity, Catalase**

## INTRODUCTION

Curcumin is an active principle extracted from turmeric (Curcuma longa) which has come into the spotlight for its varied health-promoting properties and particularly for its anti-inflammatory, antioxidant, and hepatoprotective activities. The health benefits of curcumin have been reported with very good documentation regarding its antioxidant and anti-inflammatory action (1). However, bioavailability is a major obstacle since curcumin gets poorly absorbed within the intestinal tract. For example, it has been suggested that its absorption be augmented by piperine (2).

Curcumin presents very good results in hepatoprotection regarding oxidative stress-related pathologies. In Sharifi-Rad et al., 2020, the modulation exercised by curcumin on pro-inflammatory cytokines and reactive oxidative response is presented. Developing nanoparticle formulations seeks to address these issues by improving solubility and absorption, thus

achieving more effective therapy potential (3). All those mechanisms become much more effective when curcumin is applied in nanoparticle form; probably better bioavailable forms would enhance the protective effects of curcumin in hepatic protection (4). Curcumin presents a multitarget biological effect in pathology. The possibility that nanoparticles of curcumin may on simultaneously affect numerous pathways of signaling brings also the possibility of improved effectiveness in clinical applications (5).

The protective effects of curcumin nanoparticles are essentially their antioxidant and anticancer activities. Yen et al. (2010) proved that curcumin nanoparticles greatly enhance the physicochemical properties of curcumin, with improved therapeutic outcomes (6). Potential applications of cancer therapy using curcumin-modified nanoparticles, magnetic and silver ones included, show high potential in improving drug delivery as well as therapeutic efficacy (7-8). Curcumin nanoparticles are very promising for neuroprotection, mainly for neurodegenerative diseases. Rahmani et al. (2018) discussed the ability of curcumin to influence amyloid metabolism along with its antioxidant properties; therefore, it is suggested that nanoparticle formulations could enhance these effects within the brain, thus opening a new pathway for conditions like Alzheimer's disease. Liver toxicity, or hepatotoxicity, is a general and significant health risk from a wide variety of environmental and pharmaceutical agents (9). It would be more reasonable to understand how the damage of the liver occurs so that protective measures can be taken. Studies have highly correlated oxidative stress with hepatotoxicity. It was also reported that platinum chemotherapy drugs induce hepatotoxicicity through oxidative damage catalase detoxifies hydrogen peroxide therefore playing an important role in this mechanism of chemotherapy-induced hepatotoxicicity. This paper will therefore highlight how understanding the interplay between catalase activity and oxidative stress by these drugs could reveal protective strategies for cancer patients undergoing treatment (10)..

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 Pandit et al., 2012, stressing how important it is to know the role played by antioxidants like catalase in reducing oxidative stress. 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 (12). It has also been assumed that the hepatotoxic action of PTU comes from its interference with thyroid hormone production-related metabolic disturbances. The role of antioxidants in mitigating PTU-induced oxidative stress remains a critical area of investigation. While some studies have explored the protective effects of various natural products, the specific impact of PTU on liver enzyme levels, lipid peroxidation, and antioxidant status in male rats requires further exploration. Even though the results are previous data about catalase, several missing pieces of information. For example, although the increase of catalase is an important way, the exact paths by which curcumin nanoparticles improve catalase action in the situation of PTU-caused liver poisoning are not completely explained (13).

The goal of the current study was to evaluate the protective role of Cur-Cs-NPs against PTU-induced hypothyroidism and hepatotoxicity in male Wistar rats by assessing biochemical, molecular, and histological parameters.

## METHODS

### Experimental Animals

Fifty-five adult male Wistar rats were utilized in this study. Preliminary experiment comprised fifteen rats, while forty rats were used in the main experiment. All the animals were kept in ventilated rooms in plastic cages under controlled conditions (22–25 °C) with ad libitum access to water and pellet feed. Two weeks of acclimatization to the new environment was observed before the commencement of the experiments.

Curcuma longa rhizomes were procured from a local market in Baghdad; washing followed, then drying at 40°C and grinding. A hydroalcoholic extract was prepared by stirring 50 g of the powder into 500 ml ethanol at 70–80°C for 6 hours, after which the solvent was allowed to evaporate also used in the synthesis of curcumin-chitosan nanoparticles. The characterization methods included:

- UV-Vis Spectroscopy nanoparticle formation.
- FTIR for functional groups and molecular interactions.
- XRD crystalline structure analysis phase.
- Use EDX to find out what elements make up a material.
- Check the stability of nanoparticles by measuring their Zeta Potential.

The primary experiment was conducted to evaluate the protective effects of Curcumin-Chitosan nanoparticles toward hypothyroidism and hepatotoxicity induced by propylthiouracil in rats. A total of forty rats were selected and divided into four different groups comprising ten rats each and treated for 28 consecutive days as follows:

G1 (Control): Oral administration of distilled water.
G2: Treatment with PTU at a dose of 50 mg/kg body weight through oral gavage.
G3: Received Cur-Cs-NPs at a dose of 100 μg/kg body weight orally.
G4: Received PTU (50 mg/kg) alongside Cur-Cs-NPs (100 μg) orally.

At the termination of the experiment, rats were anesthetized using intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg). Blood was obtained through cardiac puncture followed by euthanasia of the animals. Liver tissues were collected. Serum was separated by centrifugation from whole blood that had been allowed to clot at room temperature; the serum aliquots were kept frozen at -18 °C until needed for catalase (CAT) analysis via ELISA using a kit from Humacount. Tissue samples suitable for gene expression analysis of CAT using RT-PCR were stored in liquid nitrogen. The isolation of RNA from liver tissues was performed following the Genaid Korea protocol to determine the expression levels of CAT in the liver tissues. Liver tissue specimens were prepared for histopathological examination according to the method of (15).

### 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 finding of the current study reported that Group G1 (control) had a high catalase level (20.84 ± 1.57 ng/mL), which significantly decreased in G2 (PTU-treated group) to 10.04 ± 0.66 ng/mL (p value=0.0003); this indicates that PTU induces oxidative stress by reducing the levels of antioxidant enzymes. However, the highest catalase activity was recorded in G3 (Cur-Cs-NPs only) and measured to be 25.12±2.13 ng/mL, comparable to that of the control and even above it, thus suggesting very strong antioxidant potential of these nanoparticles. In G4 (Cur-Cs-NPs + PTU), catalase levels were elevated to 14.29+0.91 ng/mL compared with G2 but still significantly lower than in the control and G3; this indicates that there is partial restoration of antioxidant defense by Cur-Cs-NPs when PTU is present .

Superscript letters(a,b) denote statistically significant differences between groups. (as shown in figur 1).

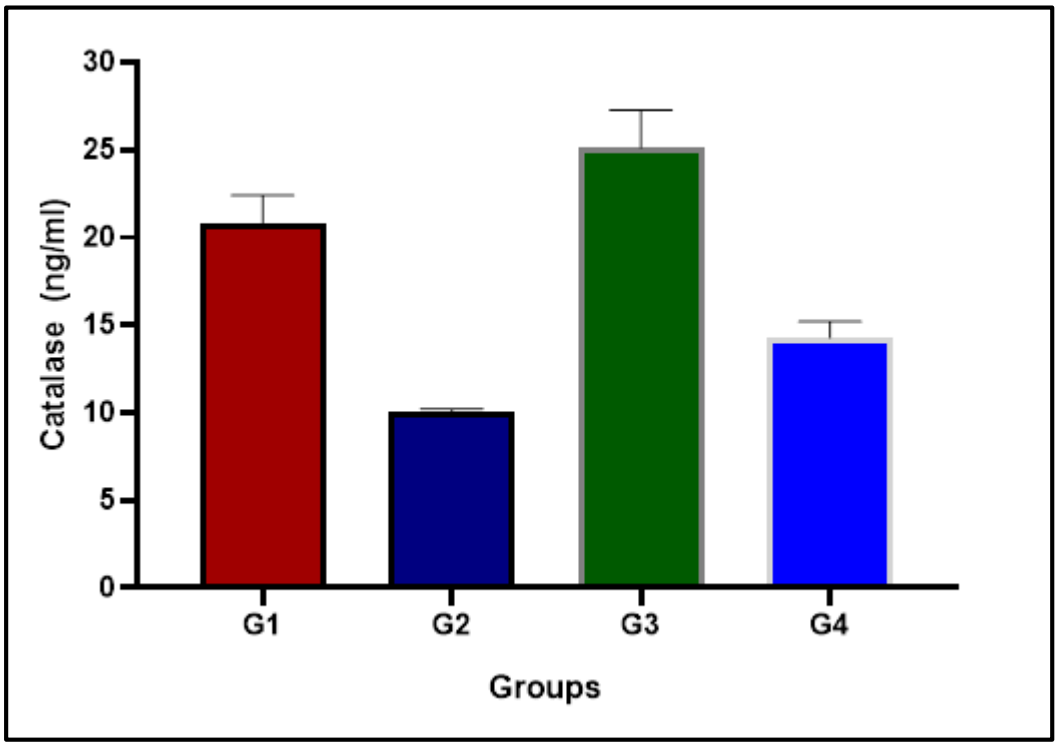



**FIGURE 1.** Effects of curcumin nanoparticle nanoparticles on catalase activity in different study groups

Figure 2 shows the amplification curves for CAT gene expression in liver tissue samples, derived from real-time PCR data. The different amplification profiles confirm successful mRNA detection for CAT across all groups tested. Lower Ct values indicate higher initial expression levels and it is seen that the curves start rising earlier along the x-axis, for example, before cycle 25 which indicates strong catalase gene expression in some groups. On the other hand, delayed amplification curves near or beyond cycle 30 indicate low levels of CAT and may be due to effects of oxidative stress or treatment. These patterns will be used to assess regulation of hepatic antioxidant genes by Cur-Cs-NPs via CAT expression.

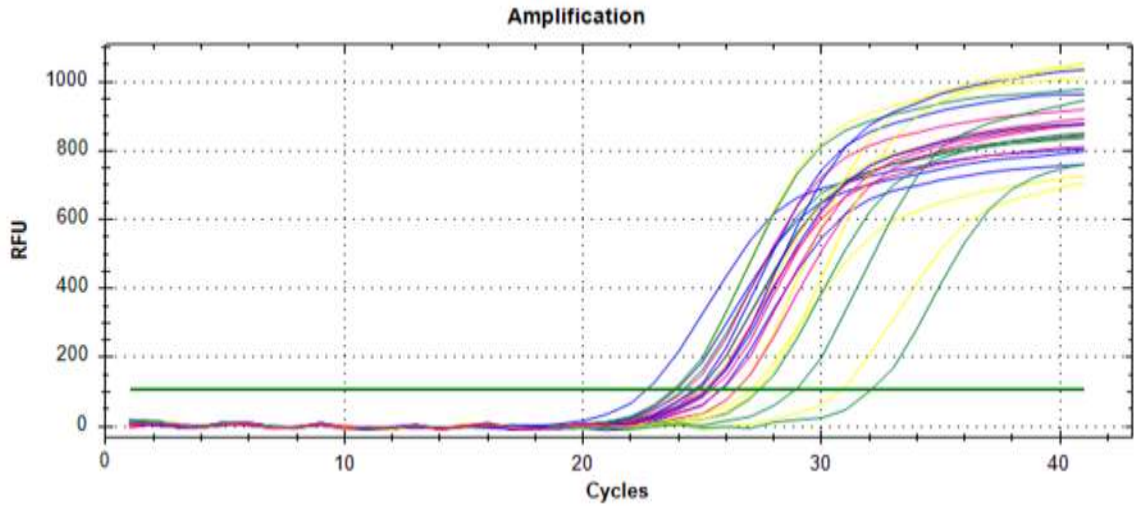


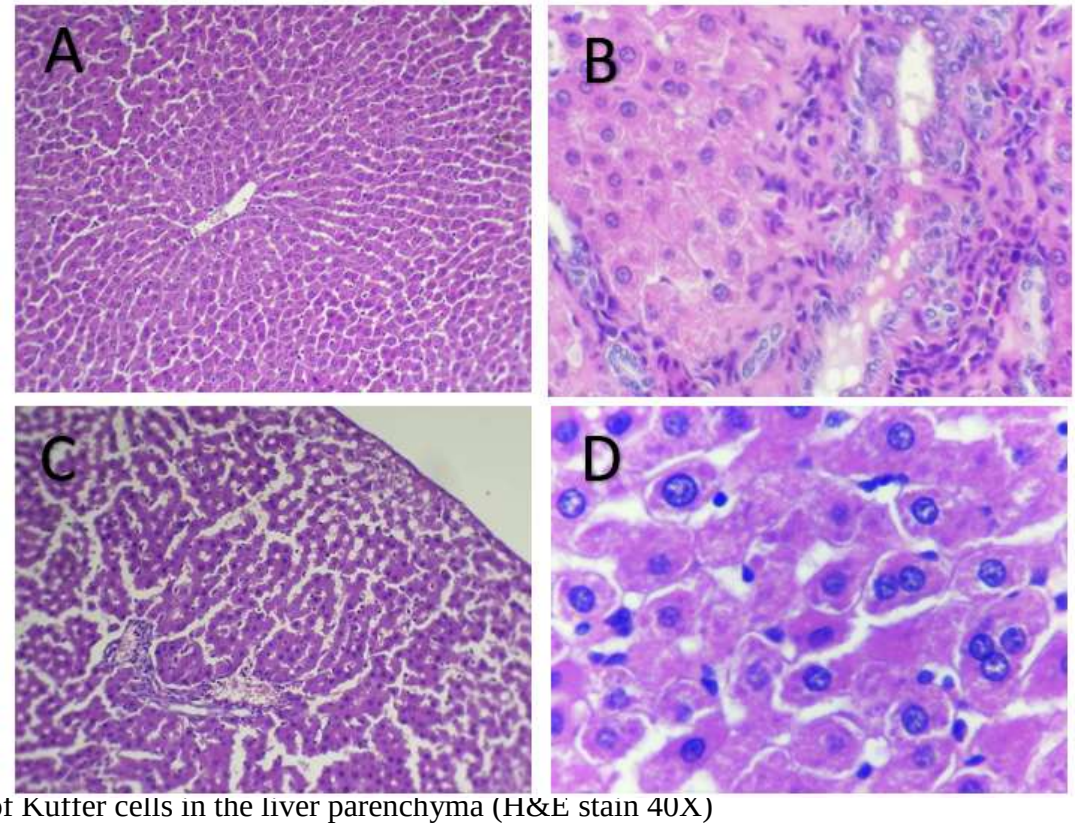

**Figure 2. Amplification curve of the tested samples for expression of gene of interest (CAT).**

CAT mRNA expression fold change varied significantly among the groups under study. In the control group (G1) received only distilled water orally, and gene expression was considered baseline (1.01 ± 0.06 fold). PTU treatment (50 mg/kg B.W.) expressed in Group G2 resulted to suppression of the gene (0.8278 ± 0.19 fold), indicating that PTU has a suppressive effect: CurCsNPs at 100 µg/kg B.W. in Group G3 caused further downregulation of the gene (0.7837 ± 0.15 fold), suggesting a mild downregulating effect: The lowest expression was observed in Group G4 (0.3945 ± 0.02 fold) which received both PTU (50 mg/kg B.W.) and CurCsNPs (100 µg/kg B.W.) orally on a daily basis; it indicates synergistic or additive suppressive effects on CAT mRNA expression when these two agents are combined. (table 1).

Table 1. Gene expression values between the compared groups (compared fold change for CAT):

| Studied group | Gene expression values |
|---|---|
| Control (G1) | 1.01± 0.06 a |
| PTU (G2) | 0.8278± 0.19 ab |
| Cur-Cs-NPs (G3) | 0.7837± 0.15 ab |
| PTU and Cur-Cs-NPs (G4) | 0.3945±0.02 b |

Histopathological pictures of the liver tissues showed a marked difference among the experimental sets. Normal hepatic architecture was observed in the control group (A), with well-preserved hepatocytes and central veins. The rats in Group G2 (B), PTU-treated, showed moderate inflammatory cell infiltration mainly periportal, congestion of the blood vessels, and bile duct hyperplasia; this is damage to the liver. In Group G3 (C), Cur-Cs-NPs alone administration resulted in liver tissue appearing normal; hence it may suggest a protective or non-toxic effect of the nanoparticles. More interestingly, in Group G4 (D), PTU + Cur-Cs-NPs administration exhibited features of hepatic regeneration such as binucleated and trinucleated hepatocytes besides an increased number of Kupffer cells; this indicates partial recovery and immune activation. From these results, it can be inferred that Cur-Cs-NPs have a hepatoprotective effect against PTU-induced damage (figure 3).

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of Kuffer cells in the liver parenchyma (H&E stain 40X)

## DISCUSSION

The research work carried out established the ability of PTU to cause liver toxicity in most animal models. The basic mechanisms are oxidative stress, inflammation, and apoptosis. For example, carbon tetrachloride (CCl4) hepatotoxicity provides evidence that oxidative stress is a major factor in liver damage (16-17). Free radicals generated can easily be contained by antioxidant defense mechanisms; however, when this balance is tilted in favor of free radicals, mitochondrial dysfunction may ensue and result in cell death-PTU exposure may exacerbate this situation. Elswefy and his colleagues also indicated that inflammation leads to liver fibrosis; it can then be inferred that PTU triggers inflammatory cascades that enhance its hepatotoxicity Several studies have protective agents against hepatotoxicity (18- 19).

The current study has indicated the role of curcumin nanoparticles in the antioxidant protection against hepatotoxicity. Recent research has spotlighted curcumin, particularly as nanoparticles, in protecting against liver injury. Curcumin is a polyphenolic antioxidant derived from turmeric (20). It is known to reduce stress caused by oxidation, majorly contributing to damage in the liver under all other circumstances and PTU-induced conditions. This aligns well with Farzaei et al. (2018), who indicated that curcumin could modulate cellular mechanisms for the enhanced expression of protective enzymes like CAT which detoxifies hydrogen peroxide (H2O2) – a reactive oxygen species involved in injury to the liver (21). Therefore, since activation of CAT is important for protection against oxidative damage in liver cells, it may be asserted that curcumin nanoparticles would provide a therapy for PTU-induced hepatotoxicity (22).

Curcumin formulated as nanoparticles offers a great way to improve the bioavailability and overall therapeutic efficacy of this compound. According to Liu et al.'s research (23), encapsulation in nanoparticles improves the delivery of curcumin and its potential ability to activate cellular protective mechanisms such as catalase. Based on this, it could be assumed that curcumin nanoparticles free not only through direct antioxidant action in the liver but also their better therapeutic potential due to more efficient uptake by cells. In this, catalase acts as an essential detoxifying agent for H2O2 (24). According to Farzaei et al., 2018, curcumin increases the function of catalase thereby reducing oxidative stress leading to the protection of hepatic cells from damage. This feature is highly significant in PTU., which has been reported as an inducer of oxidative stress within liver tissues. Therefore, if curcumin nanoparticles can activate CAT, then they might have a crucial mechanism through that hepatoprotective effect could be mediated (21).

Curcumin has very frequently enhanced the activity of all antioxidant enzymes increases, including catalase. In one study, it was shown that treatment with curcumin significantly increased the activity of catalase in macrophages under conditions of oxidative stress. It indicates the protective role of curcumin against oxidative damage (8). In another study, not only did they find that curcumin elevated catalase activity but also that it activated the Nrf2-Keap1 signaling pathway The transcription of antioxidant genes and among them are also catalase (25). Such a mechanism may imply that curcumin nanoparticles have potential efficacy in such action—to enhance function accompanied by cellular protection.

Previous studies reported that curcumin nanoparticles' physicochemical properties bear great importance in their biological activity. For instance, Meng et al. (2020) explored zein/carboxymethyl dextrin nanoparticles for encapsulating curcumin. They mostly highlighted improvements in stability and controlled release properties (26). These are the conditions most desired by the antioxidant effects of curcumin, including catalase activation. Further, research proved that present curcumin-modified nanoparticles greatly boosted antioxidant activity. For example, Pu et al. (2014) talked about the ability of nanoparticles to react to oxidative stress thus helping release curcumin and improve its therapeutic effectiveness (27). This hint suggests further optimization in designing curcumin nanoparticles for better catalase activation. Curcumin activated catalase. This activation of catalase by curcumin is apparently mediated

through more flexible signaling pathways. Citing Ren et al. (2020) research curcumin relieves oxidative stress through Sirt1-Foxo1 as well as PI3K-Akt signaling pathways, it can also intersect with catalase activity (28). Such multiple ways of improving the function of catalase via different paths present a very attractive way to look more into curcumin nanoparticles. Shah et al., (2016) showed that curcumin wrapped in chitosan-tripolyphosphate very small particles had better ability to be absorbed and antioxidant action, saying that such mixtures could really help increase catalase work inside living things (29-30).

## CONCLUSION

Cur-Cs-NPs proved to be potent antioxidants and hepatoprotective in PTU-induced hypothyroid rats as evidenced by improved catalase activity, modulated gene expression, and regenerative liver histology. Based on these findings, it is recommended that Cur-Cs-NPs could be a possible therapeutic candidate for managing oxidative damage to the liver in hypothyroidism.

## REFERENCES

1. Hewlings, S.., & Kalman, D.. (2017). Curcumin: A Review of Its' Effects on Human Health. Foods , 6 . http://doi.org/10.3390/foods6100092
2. Abd Al-Jaleel, R. A. (2012). Use of turmeric (Curcuma longa) on the performance and some physiological traits on the broiler diets. The Iraqi Journal of Veterinary Medicine, 36(1), 51–57. https://doi.org/10.30539/iraqijvm.v36i1.548
3. Sharifi-Rad, Javad., Rayess, Y.., Rizk, A.., Sadaka, Carmen., Zgheib, R.., Zam, W.., Sestito, S.., Rapposelli, S.., Neffe-Skocińska, Katarzyna., Zielińska, D.., Salehi, B.., Setzer, W.., Dosoky, Noura Sayed., Taheri, Yasaman., Beyrouthy, Marc El., Martorell, M.., Ostrander, Elise Adrian., Suleria, H.., Cho, W.., Maroyi, A.., & Martins, N.. (2020). Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications. Frontiers in Pharmacology , 11 . http://doi.org/10.3389/fphar.2020.01021
4. Farzaei, M.., Zobeiri, Mahdi., Parvizi, F.., El-Senduny, Fardous F.., Marmouzi, I.., Coy-Barrera, E.., Naseri, Rozita., Nabavi, S.., Rahimi, R.., & Abdollahi, M.. (2018). Curcumin in Liver Diseases: A Systematic Review of the Cellular Mechanisms of Oxidative Stress and Clinical Perspective. Nutrients , 10 . http://doi.org/10.3390/nu10070855
5. Stohs, S.., Chen, O.., Ray, S.., Ji, Jin., Bucci, L.., & Preuss, H.. (2020). Highly Bioavailable Forms of Curcumin and Promising Avenues for Curcumin-Based Research and Application: A Review. Molecules , 25 . http://doi.org/10.3390/molecules25061397
6. Yen, F.., Wu, Tzu-hui., Tzeng, Cheng-Wei., Lin, Liang-Tzung., & Lin, Chun-ching. (2010). Curcumin nanoparticles improve the physicochemical properties of curcumin and effectively enhance its antioxidant and antihepatoma activities.. Journal of agricultural and food chemistry , 58 12 , 7376-82 . http://doi.org/10.1021/jf100135h
7. Goozee, Kathryn., Shah, T.., Sohrabi, H.., Rainey-Smith, S.., Brown, B.., Verdile, G.., & Martins, R.. (2015). Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease. British Journal of Nutrition , 115 , 449 - 465 . http://doi.org/10.1017/S0007114515004687
8. Yang, Xiao Xi., Li, Chun Mei., & Huang, C.. (2016). Curcumin modified silver nanoparticles for highly efficient inhibition of respiratory syncytial virus infection.. Nanoscale , 8 5 , 3040-8 . http://doi.org/10.1039/c5nr07918g
9. Rahmani, A.., Alsahli, M.., Aly, S.., Khan, M.., & Aldebasi, Y.. (2018). Role of Curcumin in Disease Prevention and Treatment. Advanced Biomedical Research , 7 . http://doi.org/10.4103/abr.abr_147_16
10. Farhan, L. O., Mustafa, S. A., & Hameed, A. S. (2016). Partial purification and characterization of catalase from banana peels. Baghdad Science Journal, 13(2), Article 65. https://doi.org/10.21123/bsj.2016.13.2.2NCC.0392

11. Pandit, A.., Sachdeva, T.., & Bafna, P.. (2012). Drug-Induced Hepatotoxicity: A Review. journal of applied pharmaceutical science . http://doi.org/10.7324/JAPS.2012.2541
12. Younes, Naima Rihane Ben., Amara, S.., Mrad, I.., Ben-Slama, Imen., Jeljeli, M.., Omri, K.., Ghoul, J.., Mir, L.., Rhouma, K.., Abdelmelek, H.., & Sakly, M.. (2015). Subacute toxicity of titanium dioxide (TiO2) nanoparticles in male rats: emotional behavior and pathophysiological examination. Environmental Science and Pollution Research , 22 , 8728-8737 . http://doi.org/10.1007/s11356-014-4002-5
13. Amisha F, Rehman A. Propylthiouracil (PTU) [Updated 2023 Jun 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549828
14. Glorieux, C.., & Calderon, P.. (2017). Catalase, a remarkable enzyme: targeting the oldest antioxidant enzyme to find a new cancer treatment approach. Biological Chemistry , 398 , 1095 - 1108 . http://doi.org/10.1515/hsz-2017-0131
15. Bancroft, J. D., & Gamble, M. (2008). Theory and practice of histological techniques (6th ed.). Churchill Livingstone Elsevier.
16. Jasim, A. M., & Hasan, H. F. (2019). Evaluation of Vorapaxar and TPGS-PLGA loading Vorapaxar to reduced apoptosis and liver damage in atherosclerosis male rats. Iraqi National Journal of Chemistry, 19(1), 22–24.
17. Abdel-Daim, Mohamed M.., El-Ela, F. I. Abo., Alshahrani, Fatima K., Bin-Jumah, M.., Al-zharani, Mohammed., Almutairi, Bader O.., Alyousif, M.., Bungău, S.., Aleya, L.., & Alkahtani, S. H.. (2020). Protective effects of thymoquinone against acrylamide-induced liver, kidney and brain oxidative damage in rats. Environmental Science and Pollution Research , 27 , 37709 - 37717 . http://doi.org/10.1007/s11356-020-09516-3
18. Elswefy, S. E.., Abdallah, F. R.., Atteia, H.., Wahba, A.., & Hasan, R.. (2016). Inflammation, oxidative stress and apoptosis cascade implications in bisphenol A-induced liver fibrosis in male rats. *International Journal of Experimental Pathology* , 97 . http://doi.org/10.1111/iep.12207
19. Hameed, H. A., & Hassan, A. F. (2023). The hepatoprotective effect of omega-7 against paracetamol-induced hepatotoxicity in male rats. *Iraqi Journal of Pharmaceutical Sciences*, *32*(3), 85–94. https://doi.org/10.31351/vol32iss3pp85-94
20. **Hashim, F. J.** (2011). *The effect of ethanolic extract of Curcuma longa rhizomes on two types of leukemic cell lines and karyotyping of human lymphocytes treated by nickel* (Master's thesis). University of Baghdad, Iraq. https://search.emarefa.net/detail/BIM-600737
21. Farzaei, M.., Zobeiri, Mahdi., Parvizi, F.., El-Senduny, Fardous F.., Marmouzi, I.., Coy-Barrera, E.., Naseri, Rozita., Nabavi, S.., Rahimi, R.., & Abdollahi, M.. (2018). Curcumin in Liver Diseases: A Systematic Review of the Cellular Mechanisms of Oxidative Stress and Clinical Perspective. Nutrients , 10 . http://doi.org/10.3390/nu10070855
22. Aghetaa, H. F. K., Dawood, R. A., & Aladhami, A. K. (2023). Resveratrol administration ameliorates hepatotoxicity in mercuric chloride-induced liver injury in rats. The Iraqi Journal of Veterinary Medicine, 47(2), 1–8. https://doi.org/10.30539/ijvm.v47i2.1482
23. Liu, Juan., Chen, Zhiqiang., Wang, Jie., Li, Ruihong., Li, Tingting., Chang, Mingyang., Yan, Fang., & Wang, Yunfang. (2018). Encapsulation of Curcumin Nanoparticles with MMP9-Responsive and Thermos-Sensitive Hydrogel Improves Diabetic Wound Healing.. ACS applied materials & interfaces , 10 19 , 16315-16326 . http://doi.org/10.1021/acsami.8b03868
24. Wali, A. T., & Alqayim, M. A. J. (2019). Biosynthesis, characterization and bioactivity of selenium nanoparticles synthesized by propolis. The Iraqi Journal of Veterinary Medicine, 43(1), 197–209. https://doi.org/10.30539/iraqijvm.v43i1.490
25. Lin, C. Y., Tsai, C. H., Hsiao, Y. H., Huang, P. H., & Lee, Y. C. (2019). Curcumin upregulates Nrf2-Keap1 signaling and increases expression of antioxidant enzymes in human hepatoma cells. *Journal of Functional Foods*, *57*, 176–184. https://doi.org/10.1016/j.jff.2019.04.024

26. Meng, Ran., Wu, Zhengzong., Xie, Qiutao., Cheng, Jie-Shun., & Zhang, Bao. (2020). Preparation and characterization of zein/carboxymethyl dextrin nanoparticles to encapsulate curcumin: Physicochemical stability, antioxidant activity and controlled release properties.. *Food chemistry* , 340 , 127893 . http://doi.org/10.1016/j.foodchem.2020.127893
27. Pu, H.-L., Chiang, W.-L., Maiti, B., Liao, Z.-X., Ho, Y.-C., Shim, M. S., Chuang, E.-Y., Xia, Y., & Sung, H.-W. (2014). Nanoparticles with dual responses to oxidative stress and reduced pH for drug release and anti-inflammatory applications. *ACS Nano, 8*(2), 1213–1221. https://doi.org/10.1021/nn4058787
28. Ren, Bincheng., Zhang, Yu-Fei., Liu, Shan-shan., Cheng, Xiao-jing., Yang, Xin., Cui, X.., Zhao, Xinrui., Zhao, Hui., Hao, Minfeng., Li, Mengnan., Tie, Yuanyuan., Qu, Li., & Li, Xueyi. (2020). Curcumin alleviates oxidative stress and inhibits apoptosis in diabetic cardiomyopathy via Sirt1-Foxo1 and PI3K-Akt signalling pathways. *Journal of Cellular and Molecular Medicine* , 24 , 12355 - 12367 . http://doi.org/10.1111/jcmm.15725
29. Shah, Bakht Ramin., Zhang, Chunlan., Li, Yan., & Li, Bin. (2016). Bioaccessibility and antioxidant activity of curcumin after encapsulated by nano and Pickering emulsion based on chitosan-tripolyphosphate nanoparticles.. *Food research international* , 89 Pt 1 , 399-407 . http://doi.org/10.1016/j.foodres.2016.08.022
30. Yahya, S. A., & Al-Shawi, N. N. (2024). Hepatoprotective effect of Nobiletin against 5-fluorouracil induce hepatotoxicity. *Current research in pharmacology and drug discovery*, 7, 100199. https://doi.org/10.1016/j.crphar.2024.100199