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The Role of Resveratrol as A Protector Against the Toxicopathological Effects of Zinc Oxide Nanoparticles on Physiological and Histological Parameters In Vivo

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Abstract

Zinc oxide nanoparticles (ZnONPs) have specific properties enabling them to be a drug delivery system and to be incorporated into animal feed. Toxicity has received much attention due to nanoparticles for their natural and therapeutic risks. This experiment investigated the protective effects of resveratrol on liver function and histological damage from ZnONPs. Resveratrol was extracted from grape skins by analytical methods while nano zinc was prepared bioactively from plant extracts. For this investigation, 24 albino rats were utilized and divided into four groups of six rats each. Group 1 (control) did not receive any treatment, group 2 received 50 mg/kg of ZnONPs and 100 µg/kg resveratrol, group 3 received 50 mg/kg of ZnONPs and 150 µg/kg of resveratrol, and group 4 received only 50 mg/kg of ZnONPs. The rats were euthanized and their blood samples collected by cardiac puncture for analysis at the end of the experiment. Results from the ZnONPs group showed a significant increase in liver enzymes (such as ALT and AST) and oxidative stress indicators compared to the control group ($P<0.05$). Histological examination confirmed severe damage, manifested by sinusoidal dilatation and infiltration of inflammatory cells in the liver. In contrast, co-treatment with resveratrol significantly decreased these biomarkers, returning them to near-normal levels ($P<0.05$ in most measurements). The samples also showed a

significant improvement in liver structure and a reduction in inflammatory damage indicators. However, administering resveratrol in combination with ZnONPs significantly reduced the activity levels of these enzymes. These results indicate that treatment with ZnONPs led to certain changes or abnormalities, such as having a protective effect on liver tissues, mitigating the observed changes. Also, protection of hepatocytes was observed from deleterious effects solely due to cellular degeneration and temporal blockage during the zinc nanoparticle treatment. Therefore, it can be concluded that resveratrol can effectively prevent liver dysfunction in mice and protect their cells from symptoms caused by ZnONPs.

Keywords: Toxicpathological, Zinc oxide nanoparticles, Liver function, Histology, Resveratrol, Vivo.

دور ريفستيرول كواقي ضد التأثيرات السمية المرضية لجسيمات أكسيد الزنك النانوية على المعايير الفسيولوجية والنسيجية في الجسم الحي

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الخلاصة

تتميز جسيمات أكسيد الزنك النانوية (ZnONPs) بخصائص مميزة تُمكّنها من أن تكون نظامًا لتوصيل الأدوية، وأن تُدمج في علف الحيوانات. وقد حظيت سمية هذه الجسيمات باهتمام كبير نظرًا لمخاطرها الطبيعية والعلاجية. تهدف هذه التجربة إلى دراسة التأثير الوقائي للريسفيراترول على وظائف الكبد والضرر النسيجي الناتج عن جسيمات أكسيد الزنك النانوية. استُخلص الريفيستيرول من قشور العنب بطرق تحليلية، وحُضّر الزنك النانوي حيويًا من المستخلص النباتي. في هذه الدراسة، استُخدم 24 فأرًا أبيض، وقُسّموا إلى أربع مجموعات، كل مجموعة تضم ستة فئران. تتكون المجموعة الضابطة من الحيوانات التي لم تخضع لأي تدخلات تجريبية، وتتكون من الفئران غير المعالجة، في حين أن مجموعة ZnONPs كانت الفئران التي تلقت 50 ملغ / كغ ZnONP في مجموعة 100 ميكروغرام / كغ ZnONP + ريسفيراترول مشتركة مع الفئران ZnONP بنسبة

50 ملغ / كغ مختلطة مع ريسفيراترول بنسبة 150 ميكروغرام / كغ، تم إعدام جميع الحيوانات، وتم جمع عينات الدم للتحليل التي تم الحصول عليها عن طريق ثقب القلب في نهاية التجربة.

تم تقييم مستويات المعايير الكيميائية الحيوية، وتحديدًا إنزيمات الكبد مثل ألانين أمينوترانسفيراز (ALT) وأسبارتات أمينوترانسفيراز (AST) والفوسفاتيز القلوي (ALP)، للكشف عن أي خلل في وظائف الكبد. أشارت النتائج إلى ارتفاع ملحوظ في نشاط إنزيم البلازما في المجموعة المعالجة بجسيمات أكسيد الزنك النانوية (ZnONPs) مقارنةً بالمجموعة الضابطة ($p\leq0.05$). ومع ذلك، عند إعطاء ريفستيرول مع ZnONPs، انخفض نشاط هذه الإنزيمات بشكل ملحوظ. تشير هذه النتائج إلى أن العلاج بجسيمات أكسيد الزنك النانوية (ZnONPs) أدى إلى بعض التغييرات أو الشذوذ. ومع ذلك، عند إعطاء ريفستيرول مع ZnONPs، بدا أن له تأثيرًا وقائيًا على أنسجة الكبد، مما خفف من التغييرات الملحوظة. لوحظت حماية لخلايا الكبد من الآثار الضارة الناتجة فقط عن التنكس الخلوي والانسداد الزمني أثناء العلاج بجسيمات الزنك النانوية. لذلك، يمكن القول أن الريفيستيرول يمكن أن يمنع بشكل فعال خلل وظائف الكبد في الفئران ويحمي خلاياها من الأعراض التي يسببها ZnONPs.

كلمات مفتاحية: السمية المرضية، جسيمات أكسيد الزنك النانوية، وظائف الكبد، علم الأنسجة، ريفستيرول، الجسم الحي.

Introduction

Resveratrol, also known as 3,5,4'-trihydroxy-trans-stilbene, is a biologically active compound present in various foods. Besides offering several health benefits, it is associated with positive effects on overall health (11). Over 300 edible plants contain resveratrol, a phytoalexin that protects them from microbial injury, fungal infection, or environmental stress (31). It has antioxidant properties that protect the body from free radical cellular damage (47). Resveratrol exhibits anti-inflammatory effects, making it a valuable remedy for conditions such as arthritis and skin inflammation (2). Additionally, it can assist in reducing inflammation in the brain and heart by creating a protective barrier for blood vessels, thus preventing damage or injury. Furthermore, its antibacterial and antifungal properties make it useful in treating urinary and digestive tract infections. It can also prevent common conditions such as cancer, diabetes, and Alzheimer's disease (4 and 45).

Resveratrol influences the body in many ways, such as by providing immunomodulatory, glucose and lipid regulatory, neuroprotective, and cardio protective effects (23 and 53). Also, it may aid the body in avoiding insulin resistance, a state where the body is less responsive to the insulin hormone that treats sugar diabetes (48). Research has shown that resveratrol has the potential in treating different disorders related to liver. After liver transplantation, resveratrol has been noted to significantly increase the chances of a person surviving. It is also noted to help reduce fat deposits, tissue necrosis, and ischemia within the liver, all stemming from poor blood flow to the liver.

The above findings advance the potential of resveratrol in the treatment of liver related conditions (25). It is noted to possibly heal the damaging effects of substance use, enhance bile secretion, and mitigate the deleterious impact of alcohol on the liver (50). This underlines resveratrol's role in the health of the liver under different conditions, ameliorating glucose as well as lipid metabolism, and in diminish liver fibrosis and steatosis (57). It also has the ability to shift the profile of fatty acids present in liver cells (13).

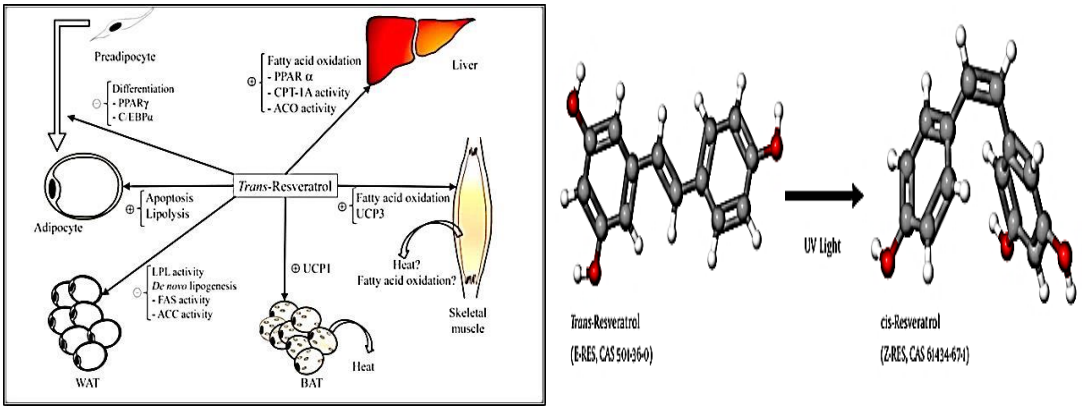

Figure 1: Above: resveratrol - a substance of growing scientific interest; Left: major mechanisms involved in the anti-obesogenic effect of resveratrol (3 and 35).

Nano zinc is a type of zinc oxide which has applications as a supplement feed (34). This compound is known for its high reactivity due to its high surface area-to-volume ratio, which makes it more reactive than conventional zinc. It has high bioavailability, meaning that it is easily absorbed by the body (27). Resveratrol is known to have a high tendency to accumulate in liver tissues and can potentially result in toxicity. As such it is important to examine the potential toxicological impacts of resveratrol and nano zinc on the liver (56). In addition, exposure to nano zinc can cause histopathological changes in liver and lung tissues. These changes may be reversible and include hypertrophy (increase in cell size). There is evidence to suggest that including nano zinc as part of a supplement in animal diets reduces serum TAG. The retention of zinc in liver tissue is higher than that in brain tissue (36). Zinc levels in the liver and other tissues are significantly increased by the dietary inclusion of nano-zinc oxide in broiler chickens (37).

Research indicates that zinc nanoparticles have adverse effects on liver enzymes. Oral administration has been associated with liver damage and dysfunction. In addition, its particles accumulate in liver tissue, which may lead to toxicity. These findings highlight the importance of zinc intake and the potential risks associated with the accumulation of zinc nanoparticles in the liver (37). Long-term exposure to zinc nanoparticles can lead to oxidative stress, DNA damage, and apoptosis in nanoparticles in the liver (24).

The phenol resveratrol can prevent oxidative stress and prevent mitochondrial damage induced by zinc oxide nanoparticles in zebrafish, providing new insights into the protective mechanism of antioxidants against nanomaterial toxicity (16 and 18). However, further studies are needed to determine the effectiveness of resveratrol in

protecting the liver from the toxic effects of nano zinc. Studies show that excessive oral intake of zinc salt and zinc powder can lead to liver damage and dysfunction, with several reports of liver enzyme toxicity (39 and 43). ZnO nanoparticles tend to accumulate in many body tissues including the kidney and liver, causing toxicity (1 and 21).

Materials and Methods

Isolation and purification of resveratrol from grape peels: Resveratrol was obtained from Sigma-Aldrich (Merck) at purities ≥98%. Trans-resveratrol is water-soluble. It was prepared at concentrations of 100 and 150 mg/ml. (6 and 9).

Chemical compounds: The zinc oxide nanoparticles were purchased from Research Nanomaterials, Inc. The average particle size ranged from 10 to 60 nanometers. Diagnostic spectroscopic examinations (UV, scanning electron microscopy, X-ray diffraction) were performed to confirm their nanoscale size. Zinc oxide nanoparticle powder was prepared using physiological saline.

Experimental design: A total of 24 adult male albino mice, aged 16–24 weeks and weighing 177–223 g, were carefully selected and housed in plastic cages under controlled laboratory conditions at 24 ± 1 °C, with 12-h light/dark cycles, and adequate ventilation. To allow adaptation to the laboratory environment, one week of acclimatization was provided before starting the experiments (40). They were then divided into four groups of six mice each, and the duration of the experiment was set at 15 days. The experimental design was as follows:

Group 1: Control - comprising healthy rats that did not receive any treatment.

Group 2: Received 50 mg/kg of zinc oxide nanoparticles and 100 µg/kg resveratrol.

Group 3: Received 50 mg/kg of zinc oxide nanoparticles and 150 µg/kg of resveratrol.

Group 4: Received only 50 mg/kg of zinc oxide nanoparticles.

Determination of liver enzyme activity: The coagulated blood was centrifuged quickly to separate them. The Beckmann Model T-6 was used in a 3000-gram setting for 10 minutes. After centrifugation, the product was refrigerated and processed to ensure cleanliness using dry tubes for analysis. Serum samples collected from the rats were stored at -20 °C until further analysis. The determination of biochemical parameters, including the measurement of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), was conducted using colorimetry methods, as described in reference R. Additionally, the activity of alkaline phosphatase (ALP) was determined using a specific method outlined in the study (17 and 29).

Histological study: After preserving liver samples in Bowen solution, the samples underwent a process of drying and disinfection. Subsequently, they were embedded in paraffin wax in order to prepare them for histological examination, which involved using hematoxylin and eosin stains (30). For infrastructure assessment, small portions of the liver were promptly fixed in a 4F:1G phosphate buffer (pH 7.2) at 4 °C for 3 hours. Subsequently, the samples were fixed by immersing them in a 2% solution of osmium tetroxide (OsO_4) in the same buffer at 4 °C for 1-2 hours. This fixation

process helps preserve the cellular structure and allows for further analysis or imaging of the samples.

To facilitate drying, the samples were subjected to a series of ethanol solutions with varying concentrations. After fixation, the samples were embedded in a mixture of Epon Araldite, a type of epoxy resin, and polymerized at 60 °C. This embedding process provides structural support to the samples for further processing. Ultra-thin 50 nm sections were obtained from specific regions of interest. These were then treated with uranyl acetate and lead citrate, which are contrasting agents used in electron microscopy to enhance the visibility of cellular structures. Finally, the prepared sections were examined using a JEOL 100CX electron microscope for detailed analysis and visualization (41).

Statistical analysis: The data were expressed as the least significant difference at probability <0.05. For statistical evaluation between the groups, a one-way analysis of variance (ANOVA) was performed allowing for a comparison of means among multiple groups. All statistical analyses were performed using SPSS (version 25.0, IBM) or any other statistical software, and P<0.05 was adopted as the level of statistical significance. Duncan's new multiple range test allows more detailed comparisons and analysis of data by identifying significant differences between specific groups.

Results and Discussion

Qualitative tests for zinc oxide nanoparticles: Qualitative characterization of zinc oxide nanoparticles involves assessing their morphological and chemical properties. The most common characterization techniques include:

UV-visible spectroscopy: The UV–Vis absorption spectra at room temperature, as shown in Figure 2, revealed that the dispersion of ZnO-NPs in ethanol exhibited a distinct absorption peak at a wavelength of 377 nm. This peak can be regarded as the intrinsic absorption peak of ZnO, attributed to electron transitions from the valence band to the conduction band ($O^2p \rightarrow Zn^3d$).

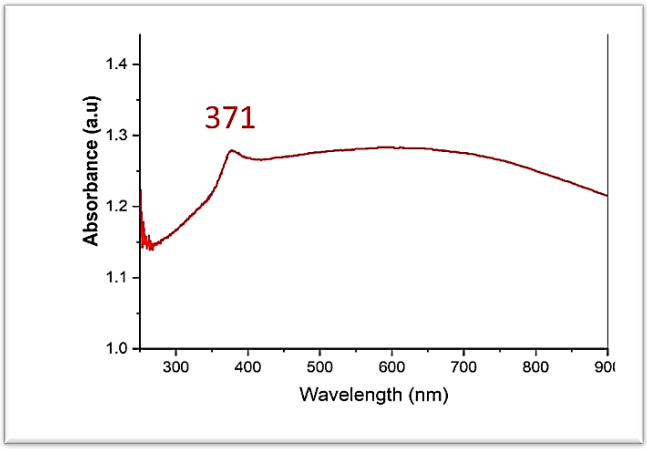

Figure 2: UV–Vis absorption spectrum of zinc oxide nanoparticles in the range of 200 nm to 900 nm.

X-ray diffraction (XRD): The X-ray diffraction (XRD) pattern of ZnO nanoparticles indicates that the narrow width of the diffraction peaks confirms the

nanoscale nature of the synthesized material. Analysis of the XRD pattern identified the diffraction peaks at 32.04°, 34.74°, 36.5°, 47.83°, 56.9°, 63.17°, 66.65°, 68.24°, 69.43°, 72.81°, and 77.28° as characteristic of the hexagonal phase of ZnO nanoparticles. The average crystallite size of the synthesized ZnO nanoparticles was estimated using the Debye–Scherrer equation to determine the crystal's structure and phase purity. Diffraction peaks corresponding to the hexagonal wurtzite phase confirm the successful formation of crystalline zinc oxide nanoparticles (Figure 3).

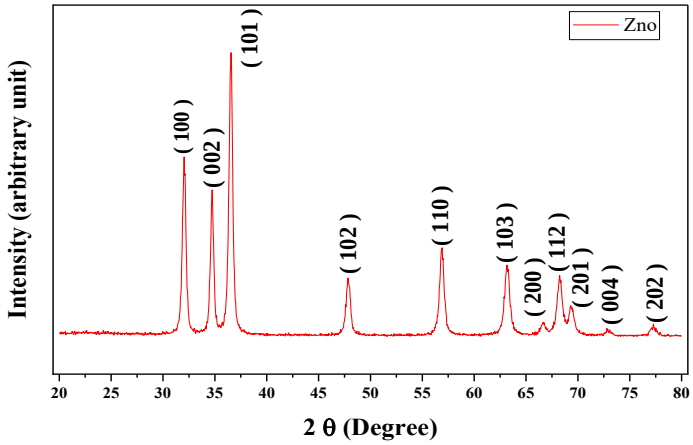

Figure 3: X-ray diffraction patterns of zinc oxide nanoparticles.

Scanning electron microscopy (SEM) and energy-dispersive X-ray spectroscopy (EDX or EDS): A scanning electron microscope (SEM) was employed to examine the surface morphology of the nanoparticles and to estimate their average diameter. Figures 3 show individual ZnO nanoparticles with visible agglomerations, indicating some clustering alongside discrete crystalline particles. The average diameter of the ZnO nanoparticles was calculated to be approximately 120.8 ± 42.8 nm.

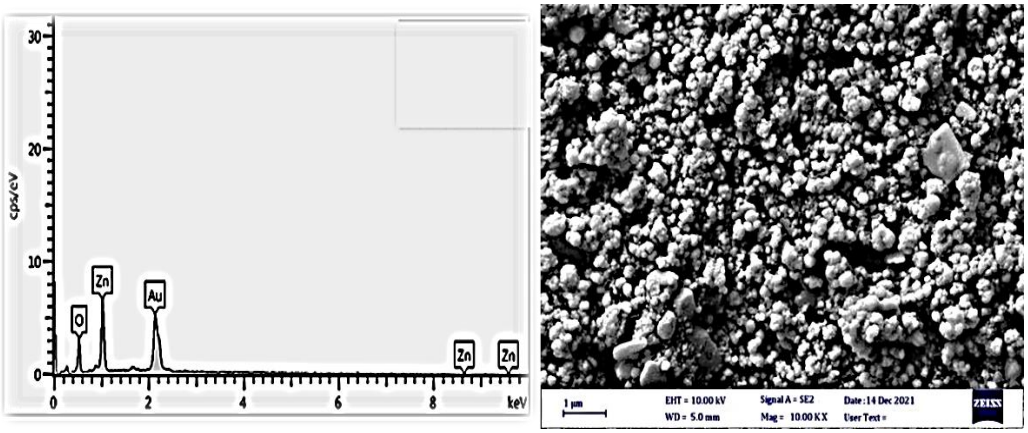

Figure 4: Left: elemental analysis of the ZnO nanoparticle sample performed using EDX; Right: morphology and structure of zinc oxide nanoparticles observed under SEM at 200,000× magnification.

The elemental composition of the ZnO nanoparticles was determined using energy dispersive x-ray spectroscopy (EDS), as shown in Figure 3. The analysis revealed that the sample consisted of 77% zinc and 23% oxygen. Traces of gold detected during the EDS analysis were excluded, as they originated from the gold-coated substrates used in the sample preparation for EDS measurements.

Effect of protective resveratrol on liver enzymes: As depicted in Figure 5, the results indicate a significant increase in the levels of liver enzymes, namely AST, ALT, and ALP, in the ZnONPs group compared to the control group ($P < 0.05$). However, in the groups treated with ZnONPs + resveratrol, the levels of these enzymes significantly decreased and approached or surpassed the levels observed in the control group, indicating a restoration within the normal range. This suggests that the combination treatment of ZnONPs with resveratrol had a beneficial effect in mitigating their adverse impact on liver enzyme levels.

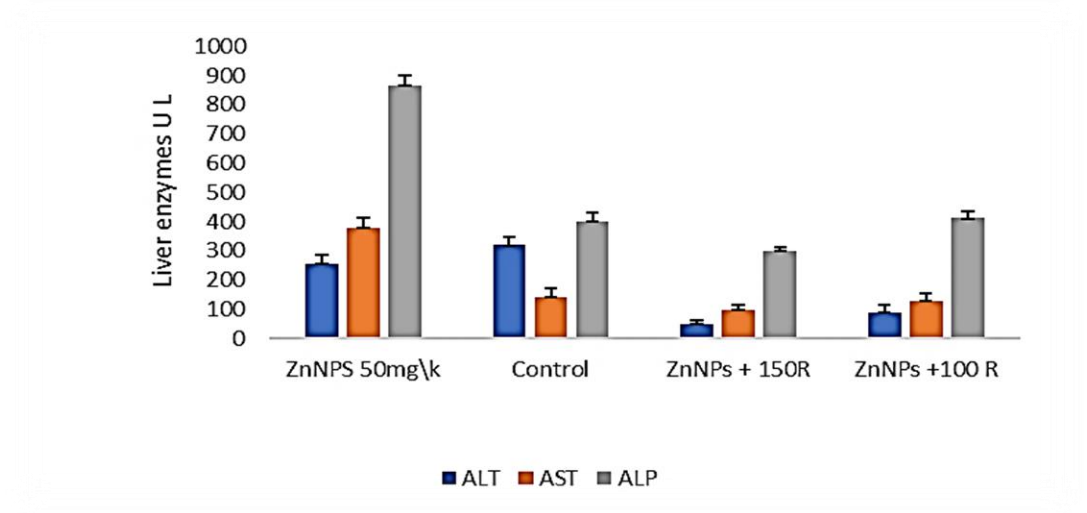

Figure 5: Effect of administration of nanoparticle zinc and/or resveratrol on AST, ALT, and ALP activities in the serum of the differently treated rat groups.
Data expressed as mean LSD = 2.234 (n = 6), the numbers is the mean of three replicates.

Hepatotoxicity is a significant global health concern, emphasizing the urgent need for research focused on liver protection and treatment of liver diseases. The mouse model of liver cirrhosis induced by dimethylnitrosamine (DMN) is widely utilized in studying the mechanisms of liver fibrosis, which closely resembles fibrosis in the human liver (26 and 58). This model is suitable for assessing the effectiveness and potential of both natural and synthetic compounds in providing hepatoprotection (55). The objective of this study was to investigate the protective effects of resveratrol against DMN-induced liver fibrosis, aiming to evaluate its potential as a therapeutic intervention (51).

Exposure to nanoparticles has harmful health effects, including damage to targeted organs such as the liver and kidneys (7, 15 and 46). Since these particles enter the circulatory system through the blood and lymphatic system, they can cause irreversible damage to cells through oxidation, pressure, or severe cellular toxicity (33). The body distributes these nanoparticles to several organs (37), including the liver, which is responsible for most of the metabolism of various substances entering the body, including nanomaterials like ZnONPs (42 and 54). The liver also acts as a detoxifying organ and responds to different types of oxidative stress. Liver cell dysfunction can have a direct impact on the composition of blood serum and the functioning of enzymes (8). In line with previous studies (10), our findings demonstrate that ZnONPs have significant effects on liver function parameters. Alterations in serum biochemical levels serve as direct indicators of the liver's

condition, and elevated levels of serum AST, ALT, and ALP, which are liver-derived enzymes, can disrupt normal liver function and lead to imbalances in overall liver functionality (27).

Resveratrol is a natural phenol compound known for its antioxidant, anti-inflammatory, detoxifying, antifibrotic, and anticancer properties (44). This study confirms that it acts as a natural protector against the effects of nanoparticles by improving enzyme concentrations and significantly reducing liver enzyme levels when combined with ZnONPs. On the other hand, it alone caused an increase in liver enzyme levels, leading to impaired liver function. This improvement may be attributed to the biological effects of resveratrol as a naturally active substance. The elevation of liver enzymes in ZnONPs-treated groups indicates hepatotoxicity, and resveratrol may reduce liver cell death. Based on the results of this study, it effectively induces liver injury (19 and 20).

Histological study: The results in Figures 6, 7, and 8 showed significant changes in the groups treated with zinc nanoparticles alone, as characterized by marked changes in liver tissue structure. These changes included liver damage, manifested by the infiltration of inflammatory cells in multiple areas, especially around the central and portal veins, inflammation of the cells, and marked fibrosis around the central and portal veins. Significant hepatocyte necrosis and the presence of multinucleated cells of varying sizes were also observed, along with sinusoidal dilation and intracellular hemorrhage, accompanied by hepatocyte hypertrophy (Figure 6). Exposure to nano-zinc causes histological liver damage (congestion, sinusoidal dilation, and inflammation), typical signs of nanotoxicity dependent on oxidative stress and inflammation.

In contrast, the groups treated with resveratrol plus zinc showed protection from these changes, with liver tissue largely resembling that of the control group (Figure 7). The liver tissue showed normal hepatocytes and normal central venous structure, as well as preserved sinusoidal spaces. The tissue (Figure 8) proves that resveratrol itself is non-toxic to liver tissue at the dosage used.

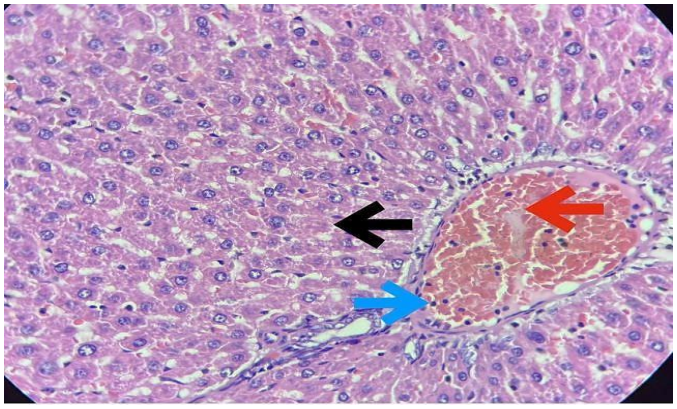

Figure 6: 100 sections of livers of mice treated with 50 mg/ml nano-zinc for 15 days, showing vascular congestion and dilatation (black arrow), portal fibrosis, or inflammatory cell infiltration in the hepatic portal vein (blue arrow), and inflammatory cell infiltration, stained with H&E. (x40).

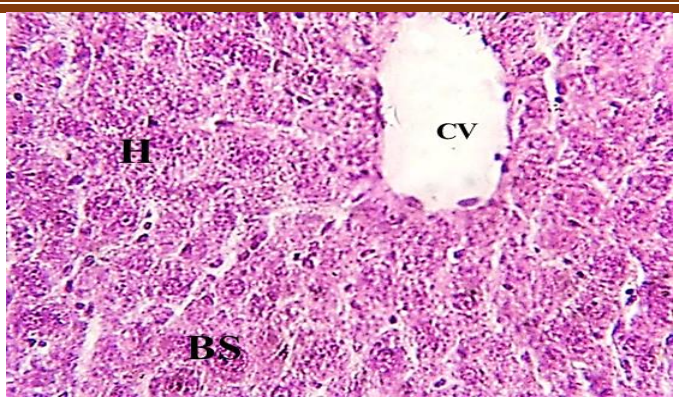

Figure 7: Light micrograph (X100) of a section of the liver from the control group. The image shows normal structure of the liver lobules, hepatocytes (H), central vein, and blood sinusoids (BS) stained with H&E.

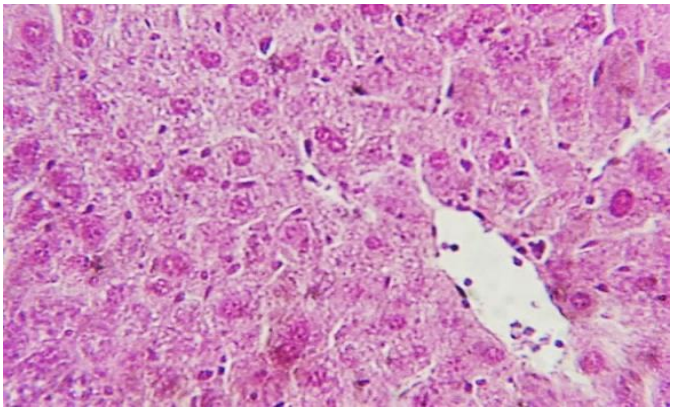

Figure 8: Light micrograph (X40) of liver sections of rats given 150 µg/kg resveratrol for 15 days. Showing normal blood vessels (BV), stained with H&E.

Studies indicate that resveratrol is one of the antioxidants that contribute to defending against toxicity resulting from liver poisoning in mice (14). It works to protect vital organs from the harmful effects of free radicals. It is a polyphenol with antioxidant properties that helps protect liver cells from damage (12). The preventive effects of phenols against oxidative damage are primarily attributed to their genetic effects and the polyphenol-rich water consumed. In experiments where resveratrol was administered, the histological appearance showed a close resemblance to the natural state, with expansion and congestion of the hepatic portal vein, presence of binuclear hepatocytes, and expansion of sinusoids compared to the control group. This indicates that this substance acts as a protector against the toxic effects of zinc nanoparticles on liver tissue (1).

Resveratrol has emerged as a promising compound with potential therapeutic effects in various liver diseases. It exhibits hepatoprotective properties, offering protection against liver damage caused by chemicals, cholestasis, and alcohol consumption. Additionally, resveratrol has been found to improve glucose metabolism, regulate lipid profiles, reduce liver fibrosis and steatosis, and modify the fatty acid composition of liver cells. In the context of non-alcoholic fatty liver disease (NAFLD), resveratrol has shown efficacy in improving liver steatosis and insulin resistance (52). It has demonstrated a significant protective role in liver fibrosis

induced by dimethylnitrosamine in rat models. While the hepatoprotective effects of resveratrol are well established, further clinical studies with robust designs and larger patient cohorts are needed to better understand its true impact in individuals with liver disease (50). Overall, resveratrol holds potential in the prevention and treatment of liver diseases, particularly in reducing liver fibrosis (48). Further research and clinical investigations are warranted to explore its therapeutic benefits and ascertain its efficacy in clinical settings**.**

Conclusions

This study showed that resveratrol has an enhanced effect on hepatotoxicity caused by nanoparticles, including zinc nanoparticles, both physiologically and histologically. This is due to the fact that it is a polyphenol compound which has an antioxidant effect against hepatotoxicity, Resveratrol acts as a free radical scavenger, reducing oxidative stress caused by zinc nanoparticles. In turn, it helps regulate inflammatory pathways (such as inhibiting tumor necrosis factor-α), thereby reducing inflammatory cell infiltration and tissue damage. It helps maintain the integrity of the cell membrane of hepatocytes, thus preventing necrosis or apoptosis.

Supplementary Materials:

No Supplementary Materials.

Author Contributions:

Methodology, writing—original draft preparation, review and editing. The author has read and agreed to the published version of the manuscript.

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The study was conducted following the protocol authorized by the Head of the Ethics Committee, University of Anbar, Iraq Republic.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Data available upon request.

Conflicts of Interest:

The authors declare no conflict of interest.

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