

Original Article

Role of zinc oxide nanoparticles supplementation on alleviate side effects of cisplatin induced cardiotoxicity in rats

Papel da suplementação com nanopartículas de óxido de zinco no alívio dos efeitos colaterais da cardiotoxicidade induzida pela cisplatina em ratos

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Abstract

Cisplatin is one of the most potent chemotherapeutics for treating a wide range of tumor forms. Its use is severely limited due to cause cardiotoxicity. The goal of this investigate estimated the proactive effect of ZnONPs against cardiotoxicity induced by cisplatin (CP). The rats were classed as control-positive (group two), and different groups from third to seventh were given one milliliter of individually dosed ZnONPs at 10, 20, 30, 40, and 50 mg/kg daily and compared with control negative group (group one). Atherogenic indices (AC, CRR, and AI), lipid peroxidation, heart tissue antioxidant enzymes, cytokines, and specific serum biomarkers lipid profiles (TC, TG, HDL, and LDL), and kidney functions were assessed in serum at the ending of the biological experimental. Findings were in view that these parameters improved gradually when the doses of ZnONPs in the various rat groups were increased to 50 mg/kg/day/bw. Measurements of pro-inflammatory, antioxidant, and oxidant biomarkers in heart tissue also showed that, at a dose of 50 mg/kg/day, the various rat groups progressively recovered to a level equivalent to that of the healthy control group. This clarifies why ZnONPs guard against heart tissue injury. It was determined that ZnONPs, with a more marked improvement, considerably reduced oxidative stress, suppressed inflammation, and inhibited apoptosis, thereby improving cisplatin-induced heart damage.

Keywords: zinc oxide, nanoparticles, cisplatin, cardiotoxicity, rats.

Resumo

A cisplatina é um dos quimioterápicos mais potentes para o tratamento de uma ampla gama de formas tumorais. Seu uso é severamente limitado por causar cardiotoxicidade. O objetivo desta investigação estimou o efeito proativo das ZnONPs contra a cardiotoxicidade induzida pela cisplatina (CP). Os ratos foram classificados como controle positivo (grupo dois), e diferentes grupos do terceiro ao sétimo receberam um mililitro de ZnONPs dosados individualmente em 10, 20, 30, 40 e 50 mg/kg diariamente e comparados com o grupo de controle negativo (grupo um). Índices aterogênicos (AC, CRR e AI), peroxidação lipídica, enzimas antioxidantes do tecido cardíaco, citocinas e biomarcadores séricos específicos, perfis lipídicos (CT, TG, HDL e LDL) e funções renais foram avaliados no soro no final do experimental biológico. Os resultados apontaram que esses parâmetros melhoraram gradualmente quando as doses de ZnONPs nos vários grupos de ratos foram aumentadas para 50 mg/kg/dia/pc. As medições de biomarcadores pró-inflamatórios, antioxidantes e oxidantes no tecido cardíaco também mostraram que, com uma dose de 50 mg/kg/dia, os vários grupos de ratos recuperaram progressivamente até um nível equivalente ao do grupo de controle saudável. Isso esclarece por que os ZnONPs protegem contra lesões no tecido cardíaco. Foi determinado que os ZnONPs, com uma melhora mais acentuada, reduziram consideravelmente o estresse oxidativo, suprimiram a inflamação e inibiram a apoptose, melhorando assim os danos cardíacos induzidos pela cisplatina.

Palavras-chave: óxido de zinco, nanopartículas, cisplatina, cardiotoxicidade, ratos.

1. Introduction

One of the most effective and commonly used medications for the treatment of different types of solid malignancies is cisplatin. Although cisplatin has anticancer properties through a variety of mechanisms, the most plausible one is the creation of DNA lesions by interaction with purine bases on DNA, which is followed by the

activation of various signal transduction pathways and ultimately apoptosis. However, the two innate problems with cisplatin that restrict its use and efficacy are side effects and drug resistance. Cisplatin resistance is caused by decreased drug accumulation within cancer cells, drug inactivation through interactions with glutathione

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and metallothioneins, and quicker DNA lesion repair. Combination therapies are used to reduce the side effects and resistance to cisplatin and have been shown to be more effective in treating malignancies (Ghosh, 2019).

The main symptoms of cisplatin cardiotoxicity are variations in electric heart activity, which most frequently manifest as atria fibrillation, ventricular arrhythmias, supra-ventricular tachycardia, and sporadic sinus bradycardia (Raja et al., 2013). Acute myocardial infarction, myocarditis, and pericarditis have all been documented by certain researcher as signs of cisplatin toxicity. They came to the conclusion that the drug's impact on sodium ion channels may be the mechanism by which cisplatin causes cardiac arrhythmias (Altena et al., 2011).

Nanotechnology-based treatments have demonstrated definite advantages over unmodified medicines in addressing these constraints of the medication. These advantages include improved half-life, survival, performance targeting, and fewer adverse effects for patients (El-Sheikh et al., 2020). Due to its growing output and the need for industrial and biological applications, In addition to possessing advantageous qualities, nanoparticles (NPs) are employed in biosensors, food additives, and cosmetics (Bostan et al., 2016) nanotechnology has attracted the interest of scientific researchers worldwide (Asif et al., 2023).

Recently, there has been a tremendous advancement in various scientific fields with nanotechnology and its connected products (Fathi et al., 2016). Because of their higher catalytic effectiveness, solid adsorption capacity, and bigger surface area, nano-minerals interact with organic and inorganic components in the animal body more effectively (Zaboli et al., 2013). According to Hillyer and Albrecht (2001), nanominerals have the ability to pass through the small intestine and enter the bloodstream and interior organs. As an alternative to traditional sources, these nanoscale minerals are therefore intended to be effective in small amounts, offer improved bioavailability, and continually interact with other elements when fed (Hassan et al., 2017).

Nanotechnology has become a highly promising method for a wide range of biomedical applications. One of the most popular nanomaterials for usage in domestic and commercial applications, as well as other consumer goods, is zinc oxide nanoparticles, or ZnO NPs (Liu et al., 2016). Examples of these applications include pigments, cosmetics, and electronic devices (MuthuKathija et al., 2023; Almansorri et al., 2023). Because ZnO NPs are transparent and easily absorb UV A and B radiation, they are perfect for application in topical products, sunscreens, foot care products, ointments, and other cosmetics (Li et al., 2020). Zinc oxide (ZnO) nanoparticles (NPs) exhibit a multitude of advantageous characteristics, including antibacterial and anticancer activities, transparency for visible light absorption, and UV absorption capabilities. These NPs render them outstanding as drug carrier systems and sunscreen agents. In recent years, the annual output of ZnO NPs has expanded quickly worldwide, reaching almost one million tons (Jacobsen et al., 2015). Prasad and Bao (2019) reported that with increasing levels of supplementation compared to control, the thiobarbituric acid-reactive substances (TBARS) of rabbits supplemented with ZnONPs at 0, 20, 40,

60, and 80 mg/kg considerably improved. The findings can be explained by zinc's antioxidant activity, which inhibits the oxidation of macromolecules like proteins and DNA as well as the inflammatory response, both of which eventually result in the down regulation of ROS generation.

Because of zinc oxide's strong efficacy and increased bioavailability, using it as nanoparticles (ZnONPs) has several advantages. Because cisplatin-induced cardiotoxicity was observed in various rat groups, this investigate sought estimated influence dietary inclusion varying concentrates ZnONPs on serum lipid profile, atherogenic, and kidney function, as well as antioxidant enzymes and pro-inflammatory activity in heart tissue.

2. Materials and Methods

2.1. Materials

Male Albino rats (42 rats), weighing 140 ± 10 g apiece, was purchased from King Faisal University's animal facility and used in this work. Before the trial, they were kept in separate cages and given seven to ten days to get acquainted to their surroundings. The rats were housed in individual cages and given a basal diet, according to Pell et al. (1992).

The medication, cisplatin, was bought in a vial that contained 50 milligrams of powder that had been dissolved in 50 milliliters of solution made by the French company Merck. Kits were provided from German-made Bicon Diagnosemittel GmbH and Co. KG Hecke.

2.2. Methods

2.2.1. Synthesis of zinc oxide nanoparticles (ZnONPs)

To make zinc oxide nanoparticles (ZnONPs), 6.81 g of zinc chloride salt was dissolved in 100 mL of ethanol. Tri-ethanolamine (TEA) was then added to the solution at a TEA/Zn²⁺ molar ratio of 1:1. The mixture was then added to 10 mL of sodium hydroxide solution (2 M) at 60 °C for two hours. The solution's hue changed and yellow slurry formed, indicating that ZnONPs were formed. The white precipitates were centrifuged at room temperature. To remove any remaining compounds, the precipitates were then washed three times with a 70% ethanol solution and it air dry for overnight at 80 °C in an electric oven according to Khorsand Zak et al. (2011).

2.2.2. Biological experimental

Seven equal groups (n = 6) were created from the 42 rats as follows:

G1; Negative control (NC) group fed a basal diet.

The six groups of thirty-six rats were given a sedentary diet for the entire night prior to receiving a single intraperitoneal injection of cisplatin (CP) 20 mg/kg/body weight (Jahan et al., 2018). This was done to induce cardiotoxicity, and then divided to (Waheed et al., 2023):

G2; Positive control (PC) group fed a basal diet;

G3; given 1 mL of ZnONPs (dispersed in 0.9% saline) orally at 10mg/kg/daily for 15 days;

G4; given 1 mL of ZnONPs (dispersed in 0.9% saline) orally at 20mg/kg/daily for 15 days;

G5; given 1 mL of ZnONPs (dispersed in 0.9% saline) orally at 30mg/kg/daily for 15 days;

G6: given 1 mL of ZnONPs (dispersed in 0.9% saline) orally at 40mg/kg/daily for 15 days;

G7: given 1 mL of ZnONPs (dispersed in 0.9% saline) orally at 50mg/kg/daily for 15 days.

Blood samples were taken after the 15-day experiment period and centrifuged to produce serum, and also, it was kept at -20 °C until it was examined.

2.2.3. Biochemical markers of cardiotoxicity

The measurements of serum total cholesterol and triglyceride were conducted according to Fossati and Prencipe (1982) and Burtis and Ashwood (2001). High, and low density lipoprotein was tested according to Lopes-Virella et al. (1977) and Steinberg (1981).

The atherogenic index (AI), cardiac risk ratio (CRR), and atherogenic coefficient (AC) were calculated (Aly et al., 2019) using the following lipid profile data (Equations 1 to 3):

$$AC = LDL - c / HDL - c \quad (1)$$

$$CRR = TC / HDL - c \quad (2)$$

$$AI = \log (TG / HDL - c) \quad (3)$$

2.2.4. Determination of kidney functions

The estimation of kidney function was conducted using the techniques outlined by Barham and Trider (1972), George (2009), Schirmeister (1964), Patton and Crouch (1977), and Bjorston et al. (2007), for uric acid, albumin, creatinine, urea, and total protein, respectively. Total bilirubin was determined by Vinchi et al. (2008).

2.2.5. Separation and preparation of heart homogenate

Under intraperitoneal anesthesia (80 mg/kg ketamine and 100 mg/kg Xylocaine), the hearts of each rat were promptly retrieved and cleansed in ice-cold saline (Al-Hariri et al., 2019). After finely chopped heart tissues were homogenized in phosphate buffer (pH 7.4), and it was centrifuged under cooling. The supernatant was used to quantify several biochemical parameters after separation (Schulz et al., 2015).

2.2.6. Measurement of oxidant and antioxidant biomarkers in heart tissue

Yoshioka et al. (1979) estimated the serum lipid peroxidation as malondialdehyde (MDA). Aebi (1995) determined to quantify the activity of the antioxidant enzyme catalase (CAT). Janknegt et al. (2007) tested superoxide dismutase (SOD). Paglia and Valentine (1967) evaluated glutathione peroxidase (GPX). Glutathione (GSH) measured by Habig et al. (1974) using kits from Bio-Merieux, France.

2.2.7. Quantification of pro-inflammatory biomarkers in heart tissue

Favorable to inflammation the biomarkers in cardiac tissue, namely interleukin 1 β (IL-1 β) and tumor necrosis factor α (TNF- α) were estimated using ELISA kits in accordance with the guidelines provided in the instruction manual. ELISA was used to test two biochemical indicators of cardiotoxicity found in cardiac tissue: creatine kinase-myocardial band (CK-MB) and lactate dehydrogenase (LDH).

2.2.8. Analytical statistics

The data that was gathered were subjected to an analysis of variance. At the $P \leq 0.05$ level, the means were compared using Duncan's multiple range tests. The Statistical Analysis System's ANOVA method was used to conduct the analysis (SAS, 2008).

3. Results and Discussion

3.1. Lipid profile cardiotoxicity in different rat groups

Given the strong association between hypercholesterolemia and hypertriglyceridemia and cardiovascular risk, lipid profile evaluation specifically, the assessment for hyperlipidemia is frequently utilized to evaluate cardiovascular risks. Plasma level measurement is a common step in a routine lipid cardiovascular risk assessment (Okafor et al., 2014).

Table 1 presents evidence of lipid profile alterations resulting from cisplatin treatment. In control positives, it results in substantial increases of 100.43, 210.76, and 151.92 mg/dl in LDL, TC, and TG, respectively. It has

Table 1. Effect of ZnONPs on lipid profile in cardiotoxicity rats.

Treatments	Triglycerides mg/dL	Total cholesterol mg/dL	LDL mg/dL	HDL mg/dL
Negative group	80.23 $\pm$ 2.25 ^f	140.85 $\pm$ 5.18 ^f	37.62 $\pm$ 1.54 ^f	60.41 $\pm$ 1.57 ^a
Positive control	151.92 $\pm$ 4.73 ^a	210.76 $\pm$ 5.62 ^a	100.43 $\pm$ 2.53 ^a	30.97 $\pm$ 1.09 ^e
Group 3 (10 mg/kg/bw)	138.23 $\pm$ 3.28 ^b	197.65 $\pm$ 5.56 ^b	88.38 $\pm$ 2.66 ^b	36.34 $\pm$ 1.14 ^d
Group 4 (20 mg/kg/bw)	124.54 $\pm$ 3.11 ^c	184.54 $\pm$ 5.38 ^c	75.88 $\pm$ 2.84 ^c	41.67 $\pm$ 1.59 ^c
Group 5 (30 mg/kg/bw)	110.85 $\pm$ 2.48 ^d	171.43 $\pm$ 4.49 ^d	63.83 $\pm$ 2.39 ^d	47.00 $\pm$ 2.01 ^{bc}
Group 6 (40 mg/kg/bw)	97.16 $\pm$ 2.15 ^e	158.32 $\pm$ 4.67 ^e	51.78 $\pm$ 1.81 ^e	52.33 $\pm$ 2.27 ^b
Group 7 (50 mg/kg/bw)	83.45 $\pm$ 2.13 ^f	145.20 $\pm$ 3.61 ^f	40.17 $\pm$ 1.78 ^f	57.82 $\pm$ 2.49 ^{ab}

Values $\pm$ SD in the columns are statistically various when $P \leq 0.05$.

been documented that cisplatin induces cardiotoxicity by means of lipid peroxidation which induce oxidative stress on cardiac cells, resulting in myocyte destruction and physical harm. Moreover, it has been observed that cisplatin raises low-density lipoprotein, triglyceride, and cholesterol levels (Madiha et al., 2012). A portion of the cardiotoxic effect of chronic Dox therapy may be induced by blocking mitochondrial long-chain fatty acid oxidation, which is associated with elevated serum levels of LDL-C, triglycerides, and total cholesterol. Since long-chain fatty acids are thought of significant materials to energy production in the adults heart, their oxidation can be inhibited, which can lead to cardiomyopathy due to lack energy (Ferreira et al., 2008).

The TG, TC, and HDL in the rat groups treated with 10, 20, 30, 40, and 50 mg/kg b.w .ZnONPs fell to 9.01, 6.22, and 17.33%, respectively, and was 45.07, 31.11, and 60.31%. HDL went from 17.33 to 86.70% in the interim. According to Abdelsattar et al. (2023), administering harmala nanoparticle (H/ZnONP) therapy to obese rats in an improved in serum levels of LDL, triglycerides, and cholesterol. The data obtained indicate that H/ZnONP supplementation, especially at high dosages, has a strong anti-obesity impact in rats by improving lipid profiles.

3.2. Atherogenic indices in different cardiotoxicity rat groups

Dyslipidemia is linked to a higher risk of developing CVD and is atherosclerosis (Yang et al., 2014). High-density lipoprotein (HDL) is the main lipoprotein that prevents atherosclerosis, while low-density lipoprotein (LDL) is the main lipoprotein that causes atherosclerosis (Nakamura et al., 2006). Furthermore, because cisplatin therapy affects the lipid profile and cardiovascular system, Hanchate et al. (2017) suggested routine cardiovascular monitoring for patients receiving this medication. The CRR was considerably elevated in cisplatin rat positive control group (6.805) than in the healthy normal control rat group (2.331), as shown by the data in Table 2. This suggests that the rats that injected with cisplatin are more likely to acquire cardiovascular disease.

The atherogenic coefficient (AC) in the cisplatin positive group was significantly greater (3.242) compared to the normal control rat group was the lowest (0.623). Because of its strong connection with apolipoprotein B levels,

non-HDL cholesterol is considered a suitable surrogate test for total apolipoprotein B. Standardized assays of apolipoprotein B, however, are not usually available in routine clinical procedures (NCEP, 2002).

A newer measure for assessing cardiovascular risk is the atherogenic index (AI), which was found correlation between TG and HDL-C. It has proven to be effective in this regard. It was demonstrated to be a more accurate predictor of atherosclerotic heart disease and myocardial infarction (Onat et al., 2010). This is due to the fact that AI has an opposite relationship with LDL and a positive correlation with the fractional esterification rate of HDL. According to Dobiasova and Frohlich (2001), this ratio is a sensitive indicator of coronary atherosclerosis and cardiovascular risk since it properly represents the existence of atherogenic tiny LDL and HDL particles.

The same table showed that at 10 mg/kg/daily bw rats, AC, CRR, and AI were reduced to 2.432, 5.438, and 0.579, respectively; at 50 mg/kg/daily bw rats, these values were reduced to 0.694, 2.511, and 0.159. These results might be explained by ZnONPs' antioxidant properties. Because zinc oxide nanoparticles (ZnONPs) have a higher bioavailability and are more potent than zinc oxide, using them is very beneficial (El-Bahr et al., 2020).

ZnONPs have the ability to swiftly penetrate the cell membrane and form connections with cellular macromolecules, which can result in beneficial outcomes for specific organs (Barakat et al., 2020). Furthermore, Zn's capacity to reduce inflammation following radiation exposure may be responsible for this (Prasad and Bao, 2019). Because Zn lowers CRR and inflammatory cytokines, it is therefore regarded as an atheroprotective agent (Gammoh and Rink, 2017).

This study reveals changes in serum lipoprotein cholesterol levels, as evidenced by a marked increase in the AI, CRR, and AC. These findings provide further insight into the detrimental effects of cisplatin on the heart. These findings align with the findings of Esmat et al. (2015). In order to measure blood lipid levels, new indices such as the CRR, AI, and VLDL are assessed in addition to the conventional lipid profile. According to Okafor et al. (2014), they are the best markers of dyslipidemia, hyperlipidemia, atherosclerosis, and cardiovascular diseases. Over the years, it has been shown that there is a casual correlation between high serum lipid levels and cardiovascular disorders such

Table 2. Effect of ZnONPs on atherogenic indices in cardiotoxicity rat.

Treatments	Atherogenic coefficient (AC)	Cardiac risk ratio (CRR)	Atherogenic index (AI)
Negative group	0.623 ± 0.07 ^e	2.331 ± 0.06 ^e	0.123 ± 0.02 ^e
Positive control	3.242 ± 0.18 ^a	6.805 ± 0.26 ^a	0.691 ± 0.04 ^a
Group 3 (10 mg/kg/bw)	2.432 ± 0.09 ^b	5.438 ± 0.12 ^b	0.579 ± 0.04 ^b
Group 4 (20 mg/kg/bw)	1.821 ± 0.04 ^c	4.428 ± 0.18 ^c	0.475 ± 0.03 ^c
Group 5 (30 mg/kg/bw)	1.358 ± 0.03 ^{cd}	3.647 ± 0.16 ^{cd}	0.363 ± 0.02 ^{cd}
Group 6 (40 mg/kg/bw)	0.989 ± 0.07 ^d	3.025 ± 0.14 ^d	0.268 ± 0.01 ^d
Group 7 (50 mg/kg/bw)	0.694 ± 0.05 ^e	2.511 ± 0.12 ^e	0.159 ± 0.01 ^e

Values ±SD in the columns are statistically various when $P \leq 0.05$.

as coronary heart disease and atherosclerotic plaques (Radhakrishnan et al., 2001).

3.3. Influence ZnONPs of kidney functions for cardiotoxicity groups

Prevention of CP-induced nephrotoxicity is made more appealing by the developing field of ZnO NPs (Ashraf et al., 2018).

The effects of various doses on kidney functions were displayed by data in Table 3. The results found cisplatin (CP)-induced cardiotoxicity in positive control, the highest values of urea, creatinine, uric acid, and bilirubin were 65.68, 1.15, 6.92, and 0.98 mg/dl, respectively. Increases values of markers indicate a renal function problem. According to Anders et al. (2018) elevated blood urea and creatinine in rats is an ideal sign of renal failure. Many applications claim that CP has a variety of harmful effects, and impairment of kidney functions (Barakat et al., 2020). It is well established the CPs nephrotoxicity connected with increased ROS generation, even though the exact mechanism of action is still unknown (Zhang et al., 2019). Additionally, albumen and total protein dropped to 2.12 and 4.94 mg/dl, respectively, in cardiotoxicity control positives.

The results from the cisplatin of fifth groups were taken orally 10, 20, 30, 40, and 50 mg/kg rat/day of ZnONPs gradually lowering to equal nearly with to the negative group from above parameters of kidney functions lowered from 60.29, 1.03, 6.31, and 0.91 mg/dl to 29.56, 0.65, 3.05, and 0.54 mg/dl, respectively. These lowering may be due to the high effect of ZnONPs, which lead to improved kidney functions. Whereas, in the cardiotoxicity fifth group, when taken orally at different concentrations of ZnONPs, albumin and total protein elevated gradually from 2.84 and 5.23 mg/dl, respectively, to 6.11 and 10.04 mg/dl, respectively. The results showed improvement in kidney functions was cause the effect of ZnONPs. Prevention of CP-induced nephrotoxicity is made more effect by using of ZnONPs (Ashraf et al., 2018). As a result, the ZnONPs have rapid cellular membrane penetration and attach to cellular macromolecules to produce therapeutic effects in some organs (Barakat et al., 2020). According to earlier research, ZnONPs as a therapy may cause it was entered to the target cells, separate, and release Zn²⁺ ions gradually but steadily. These ions are easily detected in treated cells (Bashandy et al., 2018).

3.4. Measurement of oxidant and antioxidant biomarkers in heart tissue

In various cardiotoxicity-induced cisplatin were treated with ZnONPs at different concentrations, the activity of the antioxidant enzymes Catalase, Superoxide Dismutase, Glutathione Peroxidase, and Glutathione as well as the lipid peroxidation as malondialdehyde were determined and compared with the rat negative group were tabulated in Table 3. Exception of lipid peroxidation whereas malondialdehyde was highest in positive group and lowest in negative group and the finding indicated that the rats in positive group had the lowest levels of antioxidant enzymes, while the rats in negative group had the highest levels of antioxidant enzymes. El-Bahr et al. (2020) showed that ZnONP therapy effectively restored GPx, SOD, and CAT activity in rats exhibiting cardiotoxicity caused by cisplatin by either enhancing GSH production or decreasing oxidative stress. Dietary ZnONPs is lowering levels of MDA and elevated the activity of SOD, and CAT in chickens (Ibrahim et al., 2017). Given that MDA is a widely recognized marker of lipid peroxidation (El-Bahr et al., 2020), the present results validate ZnONPs' antioxidant activity in rat group tissues across all dose ranges examined.

Due to its antioxidant properties, zinc plays a critical defense against oxidative stress (Rabeea et al., 2016). ZnONPs are employed because to their several beneficial qualities, including bond strength, abundance, semi-conductivity, and non-toxic effect. The most well-known ZnONPs are those that are produced at a low cost, may be used to preserve food, and effectively boost immunity (Hamza et al., 2019). In addition Tian et al. (2009), ZnONPs may enhance mitochondrial activity to lessen the production of cytochrome c and apoptosis-inducing factor, which act as internal signals and trigger cell apoptosis. This could ultimately prevent cell death (Table 4).

3.5. Quantification pro-inflammatory biomarkers in heart tissue

Cardiotoxicity is defined as an impairment of the heart's ability to pump enough blood throughout the body due to disruptions in the heart's electrophysiology and normal function of the heart's muscles and tissues (Cross et al., 2015). The World Health Organization (WHO) defined

Table 3. Kidney function different experimental cardiotoxicityrats group.

Treatments	Urea (mg/dl)	Creatinine (mg/dl)	Uric acid (mg/dl)	Bilirubin mg/dl	Albumin (mg/dl)	Total protein (mg/dl)
Negative group	28.35 ± 1.14 ^e	0.68 ± 0.01 ^e	3.11 ± 0.14 ^e	0.56 ± 0.01 ^e	6.24 ± 0.22 ^a	10.22 ± 0.83 ^a
Positive control	65.68 ± 5.32 ^a	1.15 ± 0.02 ^a	6.92 ± 0.15 ^a	0.98 ± 0.02 ^a	2.12 ± 0.12 ^c	4.94 ± 0.17 ^c
Group 3 (10 mg/kg/bw)	60.29 ± 4.38 ^a	1.03 ± 0.02 ^a	6.31 ± 0.12 ^a	0.91 ± 0.02 ^a	2.84 ± 0.11 ^a	5.23 ± 0.15 ^c
Group 4 (20 mg/kg/bw)	55.17 ± 4.36 ^b	0.92 ± 0.04 ^b	5.92 ± 0.43 ^b	0.81 ± 0.03 ^b	3.45 ± 0.14 ^b	6.11 ± 0.23 ^d
Group 5 (30 mg/kg/bw)	44.68 ± 3.28 ^c	0.83 ± 0.04 ^c	5.33 ± 0.24 ^c	0.73 ± 0.03 ^c	4.67 ± 0.16 ^a	7.35 ± 0.31 ^c
Group 6 (40 mg/kg/bw)	36.4 ± 2.66 ^d	0.71 ± 0.03 ^d	4.43 ± 0.25 ^d	0.61 ± 0.02 ^d	5.65 ± 0.23 ^a	8.92 ± 0.57 ^b
Group 7 (50 mg/kg/bw)	29.56 ± 1.32 ^e	0.65 ± 0.01 ^e	3.05 ± 0.13 ^c	0.54 ± 0.02 ^e	6.11 ± 0.23 ^a	10.04 ± 0.79 ^a

Values ±SD in the columns are statistically various when $P \leq 0.05$.

Table 4. Influence of ZnONPs on CAT, SOD, GSH, and GPX, in cardiotoxicity rat groups.

Treatments	CAT (U/L)	SOD (U/L)	GPX (U/L)	GSH (U/L)	MDA (nmol/mL)
Negative group	7.23 ± 0.27 ^a	13.75 ± 0.77 ^a	50.23 ± 4.31 ^a	24.25 ± 1.67 ^a	180.34 ± 3.44 ^a
Positive control	4.12 ± 0.19 ^d	6.48 ± 0.47 ^c	22.36 ± 1.0 ^d	13.89 ± 0.55 ^d	384.39 ± 3.59 ^d
Group 3 (10 mg/kg/bw)	4.74 ± 0.34 ^d	7.92 ± 0.62 ^d	27.91 ± 1.73 ^d	15.82 ± 0.75 ^{cd}	344.47 ± 4.36 ^c
Group 4 (20 mg/kg/bw)	5.36 ± 0.63 ^c	9.36 ± 0.86 ^c	33.46 ± 2.35 ^c	17.75 ± 0.94 ^c	304.55 ± 4.29 ^c
Group 5 (30 mg/kg/bw)	5.98 ± 0.67 ^c	10.80 ± 0.84 ^{bc}	39.01 ± 2.47 ^c	19.69 ± 1.21 ^b	264.62 ± 5.17 ^b
Group 6 (40 mg/kg/bw)	6.60 ± 0.71 ^b	12.24 ± 0.91 ^b	44.56 ± 3.86 ^b	21.61 ± 1.08 ^{ab}	224.71 ± 4.56 ^{ab}
Group 7 (50 mg/kg/bw)	7.00 ± 0.31 ^a	13.51 ± 0.84 ^a	49.98 ± 2.39 ^a	23.54 ± 1.78 ^a	184.10 ± 3.48 ^a

Values ± SD in the columns are statistically various when $P \leq 0.05$.

Table 5. Effect of ZnONPs on pro-inflammatory biomarkers and biochemical markers of cardiotoxicity in rat groups.

Treatments	IL-1 β (pg/mL)	TNF- α (pg/mL)	CK-MB (U/L)	LDH (U/L)
Negative group	13.16 ± 1.11 ^e	19.31 ± 1.42 ^d	541 ± 8.21 ^d	889 ± 9.23 ^f
Positive control	52.19 ± 1.30 ^a	45.51 ± 1.22 ^a	742 ± 8.43 ^a	1347 ± 8.15 ^a
Group 3 (10 mg/kg/bw)	44.31 ± 1.51 ^{ab}	40.29 ± 1.24 ^a	701 ± 9.25 ^a	1254 ± 10.76 ^b
Group 4 (20 mg/kg/bw)	36.63 ± 1.36 ^b	35.17 ± 1.35 ^b	660 ± 7.29 ^{ab}	1161 ± 9.54 ^c
Group 5 (30 mg/kg/bw)	28.55 ± 1.24 ^c	30.05 ± 1.51 ^{bc}	619 ± 7.15 ^b	1068 ± 8.27 ^d
Group 6 (40 mg/kg/bw)	21.17 ± 1.14 ^d	24.63 ± 1.27 ^c	578 ± 6.38 ^c	979 ± 6.28 ^e
Group 7 (50 mg/kg/bw)	12.30 ± 0.11 ^e	18.53 ± 1.41 ^d	530 ± 5.11 ^d	872 ± 7.68 ^f

Values ± SD in the columns are statistically various when $P \leq 0.05$.

myocardial infarction as having elevated blood levels of lactate dehydrogenase, creatine kinase-myocardial band, and total creatine kinase (Mythili and Malathi, 2015).

Pro-inflammatory biomarkers (IL-1 β), and TNF- α), and biochemical markers of cardiotoxicity (LDH and CK-MB) were assessed of cardiac tissue, and results are tabulated in Table 5. Moreover, ZnONP's impact on proinflammatory cytokines was examined by measuring the quantities of TNF- α and IL-6 in each group's proteins. The findings indicated that, in comparison to the healthy control rats, the cardiotoxicity rats (control positive) had higher levels of TNF- α and IL-6 protein. Rats had 2.97 fold rises in IL-1 β and 1.37 fold increase in TNF- α . Proinflammatory biomarkers, like IL-1 β and TNF- α , are elevated in individuals with heart conditions and are typically linked to cardiotoxicity brought on by CP (Topal et al., 2018). While among all current treatment options, 10 to 50 mg/kg ZnONPs treatment significantly attenuated the gradually decreased TNF- α and IL-1 β levels in cardiotoxicity rats (from 40.29 to 18.53 pg/mL and from 44.31 to 12.30 pg/mL, respectively). ZnONP had contained from anti-inflammatory properties (Gammoh and Rink, 2017). It does this by preventing the development of inflammatory cytokines, which are known to generate reactive oxygen species (ROS) (Hassan et al., 2021).

Tissue heart function enzyme biomarkers showed that the CP-positive group had greater regulation in the cardiac function enzymes (CK-MB and LDH) (742 and 1347 U/I) than the control-negative healthy rat (541 and 889 U/I) compared to other groups treated with varying ZnONP concentrations. Elevated cardiac enzyme levels suggest

toxicity or injury to the heart (Yu et al., 2017). The cardiac enzymes (CK-MB and LDH) were significantly raised by the experimental CP-induced cardiotoxicity (Ma et al., 2010). Additionally, the rats in each group that received ZnONP treatment saw a steady drop in LDH from 1254 to 872 U/I and CK-MB from 701 U/I at level 10 mg/kg bw to 530 U/I at level 50 mg/kg bw. This could be explained by the fact that ZnONPs prevent cardiac tissue damage, which limits the amount of these enzymes that leak out (Yu et al., 2017).

4. Conclusion

Since cisplatin was found to cause cardiotoxicity in the current investigation, adding ZnONPs (ranging from 10 to 50 mg/kg bw in various rat groups) significantly reduced the serum lipid profile while maintaining renal function. ZnONPs generally decreased MDA and, in a dose-dependent manner, increased levels of antioxidant enzymes and pro-inflammatory cytokines in heart tissues. As a result, the current study suggested adding the investigated dose of ZnONPs 50 mg/kg in particular as an anti-inflammatory, antioxidant, and hypolipidemic drug to protect rats against cisplatin-induced cardiotoxicity and hematological changes.

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