Protective role of apigenin nanoparticles in cisplatin induced cardiotoxicity in rats

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Received 31 March 2024
Revised 21 May 2024
24 May 2024
30 May 2024
Accepted 30 May 2024

Abstract

Purpose – This study aims to assess the effect of both apigenin-loaded zinc oxide nanoparticles (ZnONPs) and apigenin only against cisplatin (CP)-induced experimental cardiotoxicity.

Design/methodology/approach – A total of 32Wister rats (male) were randomly divided ($n = 8$) into four groups. Normal control group, CP group received CP (20 mg/kg); treated group I received CP and then received apigenin (0.78 mg/kg/day) orally; treated group II received CP and then received apigenin loaded ZnONPs. At the end of the experiment (10 days), samples were extracted from each rat for the assessment of complete blood picture, lipid profile, atherogenic indices, oxidative status, inflammatory and cardiotoxicity markers as well as histological examination.

Findings – The results indicated that CP produced significant alterations in the complete blood picture, lipidemic profile, atherogenic indices, antioxidation capacity and cardiac inflammatory markers as well as function enzymes as compared with the control group. Administration of apigenin only showed a non-significant change in the atherogenic indices, oxidative status and cardiotoxicity parameters, indicating incomplete cardio-protection against CP upon. Additionally, all the observed alterations in CP group were reversed when apigenin nanoparticle at lower dose was used with ZnONPs which was also confirmed by histopathological investigation.

Originality/value – The apigenin loaded ZnONPs exert protective effects against CP-induced experimental cardiotoxicity and improved cardiac function, suggesting a potential adjuvant role of apigenin nanoparticles against cardiotoxicity.

Keywords Atherogenic indices, Cisplatin, Apigenin, Nanoparticles, Cardiotoxicity

Paper type Research paper

Introduction

A potent chemotherapeutic medication called cisplatin is used to treat a wide range of malignancies. Few researches have been conducted to mitigate the cardiotoxicity of cisplatin. One important factor in cisplatin-induced damage is oxidative stress (Başak Türkmen *et al.*, 2022).

Availability of supporting data: Data is available on request from the authors.
Funding: Don't apply.

Cardiotoxicity following cisplatin treatment is a well-known side effect of cancer chemotherapy for long-term cancer survivors. The mechanism of damage entails a considerable elevation in the serum plasma concentration of lactate dehydrogenase, creatine kinase, creatine kinase isoenzyme MB, and plasma cardiac troponin I, succeeded by a marked elevation in the MDA level. Furthermore, myocytes showed notable reductions in their total protein content, GSH content and SOD activity (El-Awady *et al.*, 2011). According to Kucharz *et al.* (Kucharz *et al.*, 2016), myocardial ischemia (bradycardia), diastolic abnormalities, hypertension and microalbuminuria are among the clinical signs of heart damage brought on by cisplatin treatment. Certain nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase inhibitors appear to mitigate the cardiotoxicity caused by cisplatin (El-Sawalhi and Ahmed, 2014).

Treatment using nanoparticals (NPs) has been demonstrated to be a potentially effective treatment for toxicity caused by cisplatin. Studies have been carried out to clarify the protective function of NPs in non-target organs against cisplatin-induced damage. NPs facilitate the chemo-sensitization of cisplatin-resistant cells by modulating the expression of certain signaling pathways that cause apoptosis (Dasari *et al.*, 2022).

Nowadays, there has been a lot of interest in how nanotechnology is being used in medicine. Because of its unique combination of exceptional chemical, physical, electrical, biological, optical capabilities, long-term environmental stability, low cost and non-toxic features, zinc oxide nanoparticles (ZnO-NPs) are considered as a key component of these nanomedicines that allow the effective exploitation in a therapeutic setting (Wiesmann *et al.*, 2020).

Flavonoids are the largest group of phytonutrients, and flavonoid consumption lengthens life expectancy, aids in weight control, cures diabetes and cardiovascular conditions, protects cancer, and treatments some neurological illnesses. These organic substances derived from plants have a strong sensitizing effect on phenotypes resistant to cisplatin, which enhances the effects of cisplatin treatment (Liu *et al.*, 2020).

Kaempferol a flavonoid compound, is one of the most popular diet flavonoids Cardioprotective, antioxidant, antihyperglycemic, anti-inflammatory and antiapoptotic effects of KPF have been reported in various studies. However, their biological activity is limited due to the low absorption of these substances in the body.

Hence, it was demonstrated that treatment with KPF and KPF-NPs significantly improved cardiotoxicity induced by 5-FU in rats (Safarpour *et al.*, 2022).

Food derivatives have a high possibility in prevention and treatment of numerous types of oxidative stress related health disorders (Alaqeel and Al-Hariri, 2023; Alaqeel *et al.*, 2022). Apigenin (4, 5,7-trihydroxyflavone) is one of the flavonoid groups that is present in different plants such as, wheat sprouts celery oranges and apples (Salehi *et al.*, 2019). Apigenin has an extensive attention because of its massive biological properties and benefits including anti-inflammatory, antioxidant, anticarcinogenic and antiapoptotic (Salehi *et al.*, 2019).

It has been confirmed that apigenin helps in the cardiovascular circumstances road to recovery, thought inhibiting platelet aggregation, anti-inflammatory and provoking activity of immune system as well as its antioxidative stress effect that play a vital role against the cardiovascular pathology (Buwa *et al.*, 2016). Unfortunately, apigenin showed both poor solubility and absorption that consequentially affect the bioavailability (Waheed *et al.*, 2023). According to prior studies, apigenin nano formulations have been used to overcome those problems of apigenin free form, to improve cellular uptake (Zhou *et al.*, 2022). Hence, the current experiment was designed to evaluate the effect of apigenin-loaded ZnONPs against CP-induced experimental cardiotoxicity.

Cisplatin caused damage to the testicular tissue and decreased serum testosterone levels, epididymal sperm counts and oxidants. An antioxidant imbalance was detected due to

increasing malondialdehyde (MDA) and reduced glutathione (GSH) levels in testicular tissue (Ismail *et al.*, 2023).

Acute kidney damage is the most common dose-limiting side effect of cisplatin treatment (AKI). Indeed, nephrotoxicity is a common side effect of cisplatin therapy, affecting around a third of patients (Holditch *et al.*, 2019). Furthermore, low doses of Cis which are probably due to cumulative effect in the liver cause massive hepatic toxicity, including dissolution of hepatic cords, focal inflammatory lesions and necrosis (Singh *et al.*, 2015).

Cisplatin monotherapy-induced cardiotoxicity is rare, and the prevalence remains unknown. It is extremely important to stop cisplatin when cardiotoxicity is considered (Hu *et al.*, 2018).

This study's objective was to evaluate any potential protective effects of apigenin, a powerful antioxidant and apigenin ZnONPs, on cardiotoxicity caused by cisplatin through complete blood picture, lipid profile, atherogenic, inflammatory, cardiotoxicity and oxidative stress parameters as well as, histological examination.

Materials and methods

Materials

Wistar albino male rats (32 rats) were used in the current experiment weighing 140 ± 10 g each. They were housed in individual cages and allowed to acclimatize for 7–10 days prior to the experiment. According to Pell *et al.* (1992), the rats kept in separate cages and fed a baseline powdered meal suitable for developing rats at will. The ethical committee gave its approval to the experimental protocol, (IRB-2022-10-192).

Cisplatin (CP), apigenin and grade chemicals were purchased from Sigma-Aldrich, Germany.

Methods

Synthesis of zinc oxide nanoparticles. Triethanolamine (TEA) was added to the solution at a TEA/Zn2+ molar ratio of 1:1 after 6.81 g of zinc chloride salt was dissolved in 100 mL of ethanol to create zinc oxide nanoparticles (ZnONPs). After that, the mixture was left at 60°C for 2 h with 10 ml of sodium hydroxide solution (2 M). Centrifugation of the mixture at room temperature for 10 min was used to separate the white precipitates, which were then washed three times with a 70% ethanol solution to get rid of any unreacted chemicals. The moist precipitates were then air-dried overnight at 80°C (Zak *et al.*, 2011).

Encapsulation of apigenin in zinc oxide nanoparticles. The loading of Apigenin was performed via the post-loading approach. In brief, 10 mg of apigenin powder was dissolved in a 10 mL absolute ethanol solution containing 1% polyethylene glycol (PEG 400), and then 100 mg of ZnONPs was added to the Apigenin ethanol solution and stirred for 24 h in the dark. The apigenin ZnONPs mixture was centrifuged. After the end, the collected apigenin-loaded ZnONPs were dispersed in water and collected again via centrifugation at 6000 rpm (10 min). This process was repeated twice to ensure the removal of free apigenin and subsequently dried at 40°C overnight.

Biological experimental. All the study rats were divided into four equal groups ($n = 8$). Control negative group (8 rats) received only a vehicle saline (1 mL/kg). The second major group of 24 rats was starved for the whole night before being injected Cisplatin (CP) group received 20 mg/kg/body weight intraperitoneal (Coskun *et al.*, 2014) to induce cardiotoxicity in the subgroups. The second main group was split into three subgroups after 48 h of injection (eight rats for each). The initial group of eight rats was kept on a baseline diet and was regarded as a positive control. Eight rats each from the second, and third subgroups

were given a baseline diet received CP then taken separately apigenin and apigenin loaded ZnONPs (20 mg/kg/day) orally for 10 days (Waheed *et al.*, 2023).

Following the 10-day trial period, blood samples extracted and centrifuged at 3000 rpm to give sera. Following that, the serum was stored at −20°C in a deep freezer until it was analyzed. Using a whole blood sample and the methodology outlined by Dacie and Lewis (1984), a comprehensive blood picture, including hemoglobin (Hb), hematocrite (Ht), and platelets, was ascertained. Riley (1960) measured the white blood cells (WBCs) and red blood cells (RBCs).

The serum total lipid, total cholesterol and triglyceride levels were measured in accordance with the recommendations of Knight *et al.* (1972), Burtis and Ashwood (2001) and Fossati and Prencipe (1982). High, low and extremely low levels of low-density lipoprotein cholesterol were measured in serum, as reported by Lopes-Virella *et al.* (1977) and Steinberg (1981).

The following lipid profile data were used to compute the atherogenic coefficient (AC), cardiac risk ratio and (CRR) atherogenic index (AI) according to Aly *et al.* (2019):

$$\mathrm{AC} = \mathrm{LDL{-}c}/\mathrm{HDL{-}c}$$

$$\mathrm{CRR} = \mathrm{TC}/\mathrm{HDL{-}c}$$

$$\mathrm{AI} = \log\left(\mathrm{TG}/\mathrm{HDL{-}c}\right)$$

Separation and preparation of heart homogenate. Each rat's heart was swiftly removed and cleaned in ice-cold saline under anesthesia (80 mg/kgketamine and 100 mg/kgXylocaine, intraperitoneal). The heart was split into two sections: histopathological investigation and biochemical analysis (Al-Hariri *et al.*, 2019).

Finely chopped heart tissues were then homogenized in phosphate buffer with a pH of 7.4, and then centrifuged using a cooling centrifuge at 4°C for 10 min. Following separation, the supernatant was used to estimate various biochemical parameters (Schulz *et al.*, 2015).

Oxidant/antioxidant parameters: cardiac reduced glutathione (GSH), glutathione peroxidase (GPx) and malondialdehyde (MDA) were estimated. Also, total antioxidant capacity (TAC) in cardiac tissue was determined.

Proinflammatory biomarkers [interleukin 1β (IL-1β) and tumor necrosis factor α (TNF-α)] in cardiac tissue were assessed according to the specifications of the instructions manual by ELISA kits. Biochemical markers of cardiotoxicity [lactate dehydrogenase (LDH) and creatine kinase-MB (CK-MB)] in cardiac tissue were measured by ELISA.

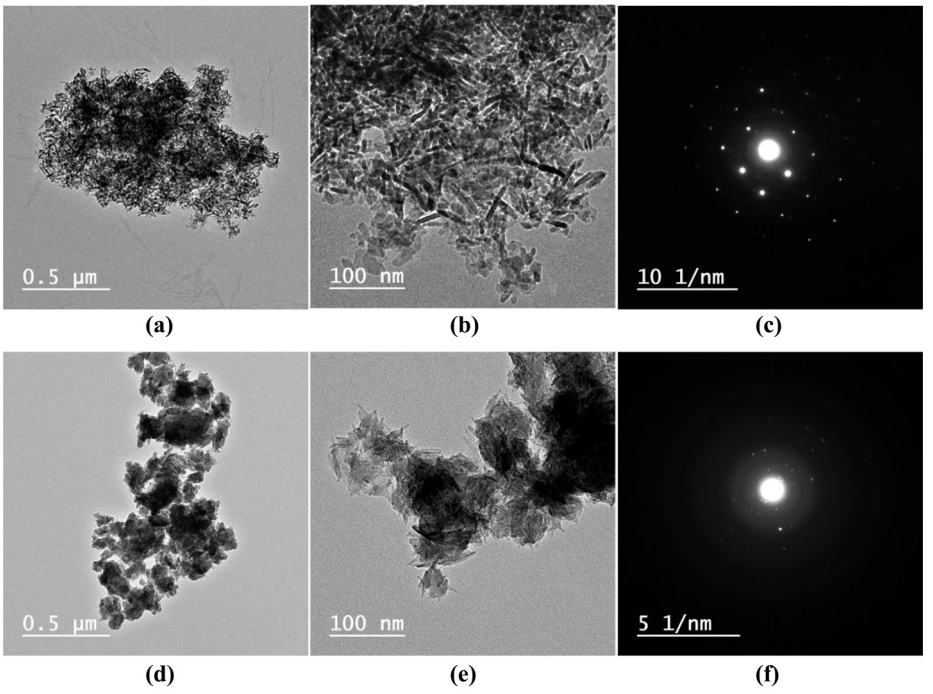
Histopathological examination. Each rat in the various groups had autopsy samples removed from the heart and fixed in 10% saline for 24 h. After being rinsed with tap water, samples were dehydrated. Specimens preparations and examinations were conducted according to the method described in the previously, using hematoxylin and eosin (H and E) stain (El Agawany *et al.*, 2012).

Statistical analysis. The acquired information was put through an analysis of variance. The means were compared using Duncan's multiple range tests at the ($p \leq 0.05$) level. The Statistical Analysis System's ANOVA technique was used to conduct the analysis (SAS System for Windows (Statistical Analysis System), 2008).

Results and discussion

Micrographs of prepared ZnONPs and apigenin-loaded ZnONPs

Using transmission electron microscopy (TEM) examination, the size and form of the samples unloaded and loaded with apigenin ZnONPs were compared in this study. Images from the TEM and selected area electron diffraction (SAED) are presented in Figure 1. Most of the particles have rod-like shapes and range in size from 18 ± 2 nm in width to 100 ± 12 nm in length on average. Overall, TEM results observed a homogeneous shape and size for the prepared ZnONPs. Whereas TEM (Figure 1 (d, e and f) micrographs show that the sample of apigenin loaded ZnONPs sample exhibited tightly bound globular clusters with irregular nanosized that could be attributed to the adsorption of apigenin on the surface of ZnONPs. SAED patterns indicate crystalline nature of the prepared ZnONPs. The lack of diffraction rings corresponding can be due to the poorly ordered state of the nano size crystalline structure of the obtained materials. Because of their intriguing physicochemical characteristics and possible medical applications, nanoparticles have garnered the interest of scientists working in a wide range of fields in recent years. Therefore, because of the special physical, chemical and biological characteristics of the resulting connections, or hybrid materials, interest in mixing flavonoids with metal nanoparticles (NPs) has developed. One of the most widely used techniques for producing noble metal nanoparticles is chemical reduction of the noble metal precursor. It is possible to create metal nanoparticles with active ingredients derived from plants by physical, chemical or biological



Source: Created by author

Figure 1. TEM and SEAD micrographs of prepared ZnONPs (A, B, C) and apigenin-loaded ZnONPs (D, E, F)

means. Microscopic and spectroscopic analyses can be used to characterize the materials. NPs also have the advantage of being inexpensive, easily synthesized and having control over both their sizes and forms. Interestingly, flavonoids themselves can be used to prepare metal nanoparticles (Dikshit *et al.*, 2021; Bordiwala, 2023). They do this by acting as reducing and electrostatic agents during the "green" production of NPs from their metal salt precursors. Metal characteristics like optical polarizability, electrical conductivity, chemical stability and biocompatibility are used in metal nanoparticles (Wijesinghe *et al.*, 2020).

Biological experimental

Effect of apigenin and apigenin-loaded ZnONPs on complete blood picture in cardiotoxicity rats. The current findings in Table 1 demonstrated RBC and WBSc count, Hb content, platelets, and Hct value decreased in cardiotoxicity rats (control positive group) were 4.39 m/cm, 4.35 cm, 7.76 g/dl, 520.62 cm and 35.34%, respectively. These rats experienced anemia, which could have been brought on by the harmful effects of the cisplatin that was used to cause the rats' cardiotoxicity. The degeneration of red blood cells and the slowed-down release of these cells into the bloodstream from the bone marrow may be the cause of this anemia. According to several studies, the erythrocyte cell membrane's increased lipid peroxidation is the cause of this anemia (Helal, 2000). The cardiotoxicity group's total RBC and WBC counts increased significantly which taken orally separately apigenin and apigenin loaded ZnONPs. The enhanced hemopoitic activity brought on by the hemolysis of RBCs in cardiotoxicity rats may be the cause of this rise in total RBCs and WBC count. The number of lymphocytes dropped in the diabetes group. Since lymphocytes are in charge of carrying out the body's defensive mechanism, this might be a reaction to a stressful situation following antigen cisplatein injection, or it could be the result of the development of specific or non-specific antibodies against various antigens (El-Feki *et al.*, 1997). The current study's findings demonstrated a statistically significant rise which taken orally separately apigenin and apigenin loaded ZnONPs-treated group's RBC, WBC, Hb, platelets, and Hct levels. The elevated complete blood count could potentially be attributed to the potent natural antioxidants found in apgenin. Flavonoids have been shown to have antioxidant, chemopreventive, and anticarcinogenic qualities. They can also regulate the immune system's reaction and prevent inflammation, angiogenesis and metastasis. Additionally, polyphenols are thought to trigger apoptosis, activate cell death signals in tumor cells by modifying cell signaling pathways and reverse multidrug resistance through a variety of mechanisms. The primary impediment to the wider application of flavonoids is their quick metabolism, limited solubility and poor absorption. Combining flavonoids with nanocarriers may help address this by increasing their bioavailability and resulting in systems with a larger range of functions. The unusual physicochemical and biological features of hybrid materials, which combine

Table 1.
Effect of apigenin loaded with ZnONPson complete blood picture in cardiotoxicity rats

Groups	Hemoglobin (g/dl)	Hematocrit (%)	Red blood cells (m/cm)	White blood cells (cm)	Platelets (cm)
Control group	12.15 ± 0.83^{a}	42.29 ± 2.53^{a}	8.26 ± 0.76^{a}	6.87 ± 0.52^{a}	800.83 ± 15.35^{a}
Cisplatin group	7.76 ± 0.31^{c}	35.34 ± 1.64^{c}	4.39 ± 0.31^{c}	4.35 ± 0.26^{c}	520.62 ± 10.18^{c}
Treated group I	9.56 ± 0.71^{b}	38.37 ± 1.784^{b}	5.98 ± 0.41^{b}	5.28 ± 0.32^{b}	680.34 ± 11.54^{b}
Treated group II	11.83 ± 0.94^{a}	41.86 ± 2.29^{a}	8.00 ± 0.62^{a}	6.15 ± 0.35^{a}	795.86 ± 14.36^{a}

Notes: The mean ± SD is represented by each value. There is a significant difference ($p \leq 0.05$) in each column's mean, indicated by distinct superscript letters
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metal nanoparticles with flavonoids, have sparked significant interest recently. One such property is better selectivity toward target areas. Furthermore, flavonoids have other uses, even during the first stage of metal nanomaterial synthesis (Sysak *et al.*, 2023).

Effect of apigenin and apigenin-loaded ZnONPs on lipid profile in cardiotoxicity rats. When cisplatin is administered to rats, serum levels of TC, TG and LDL-C are dramatically increased, whereas serum levels of HDL-C are significantly decreased when compared to control negative (Table 2). The results indicated that the highest lipid profile in control positive was 126.4, 103.38 and 82.21 mg/dl and the lowest in HDL-c was 23.51 mg/dl, respectively. These results that significant dyslipidemia has been demonstrated to correlate with the occurrence of atherosclerosis and CVD (Bharadwaj *et al.*, 2014). Dependently, CP can induce cardiotoxicity via the inhibition of fatty acid oxidation (FAO) which is linked with the elevation of TC, LDL-c and TGs. Thus, any impairment in FAO may result in cardiac dysfunction due to the decrease in energy supply (Ferreira *et al.*, 2008). In the same line, the recorded hyperlipidemia induced by CP, could be attributed to the increasing activity of cholesteryl esters synthetase, decreasing lipoprotein lipase activities and cholesteryl esters hydrolase, as well as inhibition of fatty acid oxidation (carnitine palmitoyl-transferase system) (Hong *et al.*, 2002). Meanwhile, the control negative healthy rats give the best results from lipid profile was 87.3, 74.13 and 34.26 mg/dl as well as HDL-C was 38.21 mg/dl, respectively. The primary clinical signs of hypertensive disease are caused by inflammation, endothelial dysfunction and platelet activation, all of which are induced by hyperlipidemia (Onat *et al.*, 2010).

When the two groups' rats were given apigenin and apigenin ZnONPs orally, it decreased the concentrations of TC, TG and LDL-C while raising the levels of HDL-C in the rats with high cholesterol. Furthermore, therapy with apigenin and apigenin ZnONPs ameliorated the lipid profile alterations in rats who were cardiotoxically exposed to cisplatin. In comparison to the positive control group, (Hamed *et al.*, 2021) showed that apigenin at 50 mg/kg dramatically reduced hyperlipidemia as seen by lowered TC, LDL-C and triglyceride and elevation of HDL-C. The outcomes of apigenin were consistent with those of rosuvastatin, the benchmark medication for TC and LDL-C. It was determined that apigenin reduced the levels of triglycerides and plasma cholesterol in mice. Moreover, recent study showed that Apigenin-coated gold nanoparticles decreases doxorubicin-induced cardiotoxicity (Sharifiaghdam *et al.*, 2023). Treatment with apigenin alone attenuates hyperlipidemia in CP group. Additionally, our finding demonstrated that, the treated group with apigenin nanoparticle has a significant difference in lipid profile and Atherogenic

Treatment	Control group	Cisplatin group	Treated group I	Treated group II
TC mg/dl	87.3 ± 1.22^{c}	126.4 ± 1.36^{a}	111.21 ± 1.15^{b}	90.48 ± 1.21^{c}
TGs mg/dl	74.13 ± 1.12^{c}	103.38 ± 1.32^{a}	90.72 ± 1.11^{b}	77.62 ± 1.32^{c}
LDL-c mg/dl	34.26 ± 0.82^{c}	82.21 ± 0.53^{a}	56.006 ± 0.44^{b}	36.32 ± 0.37^{c}
HDL-c mg/dl	38.21 ± 0.76^{a}	23.51 ± 0.34^{c}	26.26 ± 0.22^{b}	36.83 ± 0.24^{a}
AC	0.82 ± 0.62^{d}	3.22 ± 0.45^{a}	2.77 ± 0.64^{b}	1.01 ± 0.25^{c}
CRR	2.11 ± 0.52^{c}	4.62 ± 0.63^{a}	3.82 ± 0.61^{b}	2.63 ± 0.64^{c}
AI	0.28 ± 0.32^{c}	0.73 ± 0.34^{a}	0.67 ± 0.54^{b}	0.32 ± 0.33^{c}

Notes: The mean ± SD is represented by each value. There is a significant difference ($p \leq 0.05$) in each column's mean, indicated by distinct superscript letters; TC = Total cholesterol; TGs = Triglycerides; LDL-c = Low density lipoprotein-cholesterol; HDL-c = high density lipoprotein-cholesterol; AC = Atherogenic coefficient; CRR = Cardiac risk ratio; AI = Atherogenic index
Source: Created by author

Table 2. Mean level of lipid profile and atherogenic indices in the study groups

indices compared with CP and apigenin alone groups, and showed the best effectiveness and the best result, equivalent to the control group. Prior studies have suggested that apigenin is a potent antihyperlipidemic and antiatherogenic agent, through the inhibition of the activity of certain molecule pathways (NLRP3/NF-κB) (Lu *et al.*, 2023), and up-regulating ABCA1-mediated cholesterol efflux (Ren *et al.*, 2018). It has also been shown that apigenin administration improves hyperlipidemia and lowers plasma TC, TG, LDL-C and LOX-1, whereas HDL-C levels were higher in hyperlipidemic rats. Furthermore, it inhibited the oxidation of low-density lipoprotein and increased Bcl-2 levels, which prevented atherosclerosis (Xu *et al.*, 2021).

Apigenin treatment has been demonstrated in animal models of hyperlipidemia to reduce LDL-C, total cholesterol and triglyceride levels in rats. It has also been shown to mitigate the accumulation of total cholesterol and triglycerides in the liver, suggesting that apigenin may have protective effects against fatty liver disease and atherosclerosis. Alongside this, there is a notable decrease in extra body weight. It has been noted that apigenin protects vascular endothelial cells and plays a positive impact in cholesterol metabolism (Zhang *et al.*, 2017).

Effect of apigenin and apigenin-loaded ZnONPs on atherosclerosis in cardiotoxicity rats. Atherogenic coefficient (AC), cardiac risk ratio and (CRR) and atherogenic index (AI) were determined in different rat group treated with cisplatin to induce cardotoxicityand taken orally apigenin and apigenin loaded ZnONPs and the results are tabulated in Table 2. Due to the fact that atherosclerosis is one of the main underlying causes of cardiovascular and cerebrovascular disorders, the results showed that the group that was cisplatin positive had the greatest level of atherosclerosis. Atherosclerosis is a complicated and multifaceted etiology that includes endothelial dysfunction, oxidative stress, lipid buildup, and chronic inflammation. According to Bahura*n et al.* (Bahoran *et al.*, 2007), oxidative stress in endothelial cells triggers a number of biological processes that increase the production of chemokines, cellular adhesion molecules and pro-inflammatory indicators. Apigenin's antioxidative and anti-inflammatory properties are thought to provide preventive effects against the onset of atherosclerosis.

The two group rats treated orally apigenin and apigenin loaded ZnOnPs atherosclerosis were gradually decreased to (2.77 and 1.01), (3.82 and 2.63) and (0.67 and 0.32), respectively. Apigenin enhanced the functioning characteristics of the heart. When doxorubicin (DOX) with Api 25 was used instead of DOX, there was a significant decrease in the levels of indicators for liver and heart toxicity. When compared to DOX, apigenin treatment resulted in a considerable decrease in the percentage of cardiac fibrosis. Apoptotic proteins (Casp3, Bax) were significantly reduced by apigenin in the DOX plus Api 25 group, whereas anti-apoptotic proteins (Bcl2) were significantly increased. SOD levels significantly raised while MDA levels significantly decreased in the apigenin treatment groups (Zare *et al.*, 2019).

Additionally, Thomas *et al.* (2023) reported that naturally found in food, apigenin is a flavonoid with a broad range of biological activities, including antibacterial, anti-inflammatory, anticancer and antioxidant actions. According to reports, these actions protect against drug-induced cardiotoxicity and are helpful in the treatment of atherosclerosis, stroke, hypertension, ischemia/reperfusion-induced myocardial injury and diabetic cardiomyopathy.

Effect on the cardiac tissues antioxidant enzymes and oxidative stress. Previous research has showed that there is a direct relation between proinflammatory oxidative and cardiac stress markers after CP administration, which is significantly, contribute in the etiopathogenesis of CP-induced cardiotoxicity (Gelen and Şengül, 2020). Moreover, cardiac oxidative stress can also lead to several inflammatory cardiac disorders, such as inflammatory cardiomyopathies, atrial fibrillation and atherosclerosis (Bien *et al.*, 2007).

The results showed that antioxidant enzymes (TAC, GPX and GSH) as well as TAC exhibited a significant decrease, whereas MDA showed a significant increase due to CP administration. In contrast, apigenin-loaded ZnONPs treatment prevented antioxidant and TAC parameter as well as oxidative stress parameters alteration in comparison with CP group and apigenin alone (treated I group) to values comparable to the ones demonstrated in control group (Table 3). Notably, administration of apigenin with ZnONPs significantly prevented the decreased activities of cardiac GSH, GPx as well as TAC and inhibited MDA production and in rats cause by CP, which was in agreement with a prior study used a higher dose (25 mg/kg) (Bahoran *et al.*, 2007).Therefore, blocking of oxidative stress could be one of the effective way by which apigenin works against cardiotoxicity induced by CP (El-Awady *et al.*, 2011).

Oxidative stress in living organisms results from the imbalance between the production of reactive oxygen species (ROS) and the ability to neutralize them. The disparity between excessive reactive molecules and weak endogenous defense leads to damage to cell structures and molecules such as lipids, proteins, and DNA, ultimately contributing to the pathogenesis of a wide range of diseases. ROS, when available in appropriate low amounts, act as signal transduction molecules driving cell activities and also provide cell protection (Vona *et al.*, 2021).

Effect on the cardiac tissues proinflammatory and cardiotoxicity markers. The results of tissue heart function enzyme biomarkers revealed up regulation in the mRNA gene expression levels of proinflammatory (IL-1β and TNF-α) and cardiac function enzymes (CK-MB and LDH) in the CP positive group were the highest than other groups. A few other regulatory mechanisms, including autophagy, the Nrf2 signaling system and the epithelial-mesenchymal transition (EMT) process, have been linked to cisplatin resistance. According to recent research, Nrf2 altered the cytosolic GSH levels, which resulted in medication resistance (Cho *et al.*, 2008). Increased the levels of cardiac enzyme indicate cardiac damage and/or toxicity (Yu *et al.*, 2017). The experimental CP-induced cardiotoxicity considerably elevated the cardiac enzymes (CK-MB and LDH) (Ma *et al.*, 2010).

Moreover, from the results, it could be showed that the rat group taken cisplatin and apigenin give lower in IL-1β and TNF-α to give 43.57, and 39.65 pg/ml, as well as CK-MB and LDH were 702 and 1251U/I, respectively than control positive group. Whereas, the results from rat group taken cisplatin and apigenin-loaded ZnONPs give the best results nearly and/or equal control negative rat to proinflammatory was 23.42 and 28.16 pg/ml and also cardiac function

Treatment	Control group	Cisplatin group	Treated group I	Treated group II
GSH (mmol/g)	5.1 ± 0.3^{a}	2.36 ± 0.13^{c}	3.2 ± 0.41^{b}	4.7 ± 0.47^{a}
(GPx) (U/g)	4.50 ± 0.23^{a}	2.62 ± 0.23^{c}	3.192 ± 0.38^{b}	4.22 ± 0.25^{a}
MDA (nmol/g)	28.23 ± 2.30^{c}	41.35 ± 2.81^{a}	39.21 ± 1.24^{b}	30.21 ± 2.25^{c}
TAC (Mm/L)	3.11 ± 0.14^{a}	1.01 ± 0.13^{c}	1.64 ± 0.16^{b}	2.98 ± 0.34^{a}
IL-1β (pg/ml)	23.16 ± 1.11^{c}	52.19 ± 1.30^{a}	43.57 ± 1.04^{b}	23.42 ± 1.41^{c}
TNF-α(pg/ml)	29.31 ± 1.42^{c}	45.51 ± 1.22^{a}	39.65 ± 1.40^{b}	23.16 ± 1.31^{d}
CK-MB (U/l)	541 ± 8.21^{d}	742 ± 8.43^{a}	702 ± 7.20^{b}	632 ± 7.13^{c}
LDH (U/l)	889 ± 8.2^{d}	1347 ± 8.1^{a}	1251 ± 9.65^{b}	993 ± 7.75^{c}

Notes: The mean $\pm$ SD is represented by each value. There is a significant difference ($p \leq 0.05$) in each column's mean, indicated by distinct superscript letters; GSH = glutathione reduced; GPx = Glutathione peroxidase; MDA = Malondialdehyde; TAC = Total antioxidant capacity; IL-1β = Interleukin 1β; TNF-α = Tumor necrosis factor α; LDH = Lactate dehydrogenase; CK-MB = Creatine kinase-MB
Source: Created by author

Table 3. Mean level of oxidants and antioxidants parameters as well as inflammatory and cardiotoxicity parameters in the study groups

enzymes was 612, and 993U/I, respectively. Interestingly, the current study is in agreement with a recent work by Sharifiaghdam *et al.* (2023) which showed that administration of apigenin remarkably alleviated the study cardiac enzyme especially when administered with ZnONPs (Sharifiaghdam *et al.*, 2023). However, this work used different setting; apigenin-coated gold nanoparticles against doxorubicin-induced cardiotoxicity, parenteral route (intravenous), for higher dose and longer duration (20 mg/kg/week) for two weeks. This may be explained on the bases that apigenin loaded ZnONPs protects against the damage of cardiac tissues, thereby restricting the leakage of these enzymes (Yu *et al.*, 2017). Proinflammatory biomarkerssuch as IL-1β and TNF-α,generally associated with cardiotoxicity induced by CP (Topal *et al.*, 2018), and are increased in patients with cardiac diseases (Tamariz and Hare, 2010). Administration of apigenin as a good anti-inflammatory agent (Wu *et al.*, 2021) with ZnONPs prevented the increased of cardiac proinflammatory cytokines.

Additionally, it was discovered that apigenin decreased LPS-treated macrophage production of IL-1β, IL-6 and TNF-α. Apigenin's atheroprotective action has been linked to the TLR-4/NF-κB pathway's beneficial suppression. Apigenin's anti-inflammatory actions result from its reduction of IκB-α phosphorylation, which stops NF-κB from translocating into the nucleus. Apigenin (25 μM) treatment resulted in a notable reduction in THP-1 monocyte adherence to oxidized LDL-activated HUVECs. THP-1 monocytes are a human monocytic cell line. The down regulation of adhesion molecules, VCAM 1, and E-selectin is responsible for this impact (Jeong *et al.*, 2007). This suggests even more of apigenin's possible antiatherogenic effects on the oxidized LDL-mediated pathway linked to atherosclerosis. Numerous studies show that co-administration of apigenin reduces the organ damage caused by chemotherapeutic medicines and boosts the effectiveness of these drugs against cancer cells (Shankar *et al.*, 2017).

Histopathological investigations. Histopathological results confirmed the biochemical results and appeared that there were normal histological structures in myocardial bundles in the control group as illustrated in Figure 2(a), whereas in the CP group, focal inflammatory cell infiltrations were detected between myocardial bundles [Figure 2(b1)], in addition to Oedema between the myocardial bundles in cardiac toxicity group [Figure 2(b2)]. In treated group I, the group that received apigenin alone, there was a focal hemorrhage in between the myocardial bundles as observed in Figure 2(c). In comparison with other experimental rats, apigenin-loaded ZnONPs showed notable cardiac histological integrity and architecture improvement as shown in Figure 2(d).

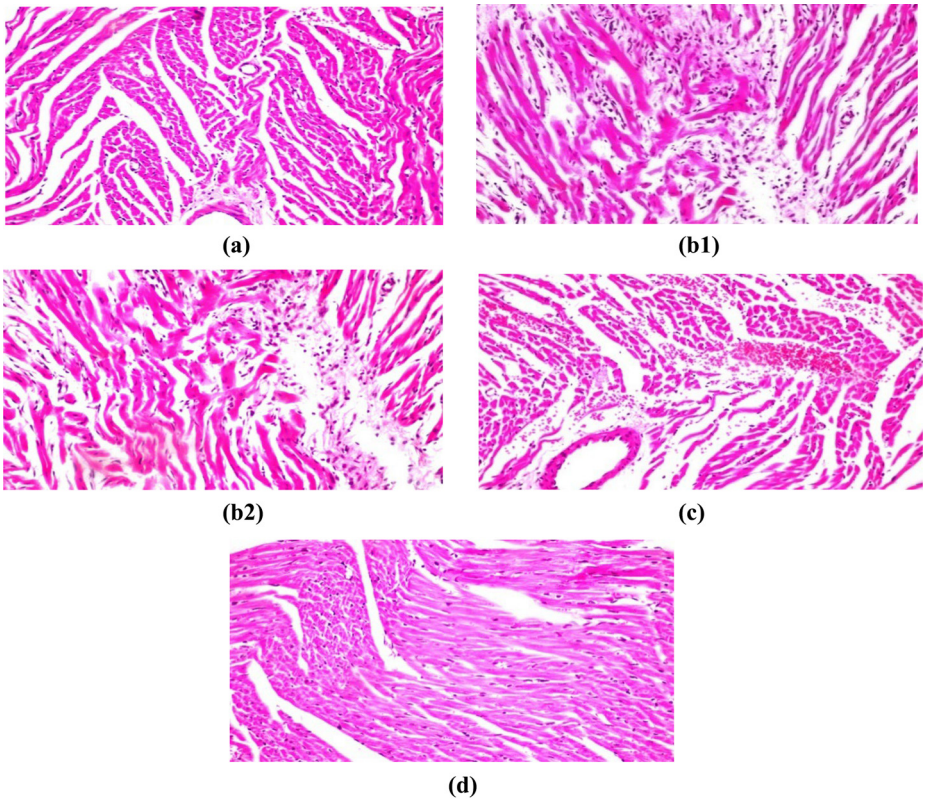
The results are also supported by histopathological investigations. Injection of CP to rats resulted in histopathological changes. A continuous hemorrhage was found in the cardiac tissue of animals treated with apigenin alone. Meanwhile, administration of apigenin with ZnONPs was able to abrogate these alterations induced by CP in the cardiac tissues as much as feasible. Thus, the demonstrated cardiac-protective effects, as indicated by H and E stained of apigenin loaded ZnONPs, may have prevented the elevation of the study cardiotoxicity markers.

A powerful chemotherapeutic medication called cisplatin is used to treat a variety of malignancies in people. Its mode of action is covalent binding to DNA, which forms adducts and, by a cascade of biochemical events including oxidative stress, DNA damage and interference in many signal transduction pathways, causes apoptosis and/or necrosis (Dasari *et al.*, 2022). According to Kachadourian *et al.* (2007), the mechanism by which flavonoids enhance the effects of cisplatin treatment is the depletion of the oxidative machinery within the cell, which facilitates mitochondrial malfunction and ultimately results in apoptosis. Other flavonoids that have been isolated from Artocarpus heterophyllus heartwoods, such as artocarpanone, artocarpin, cycloartocarpin and

cyanomaclurin, work in concert with cisplatin to treat non-small lung and breast cancers (Daud *et al.*, 2019). Recent research has demonstrated that by reducing tubular damage, quercetin and apigenin avoided cisplatin nephrotoxicity (Casanova *et al.*, 2021). Flavonoids from Morus alba called isoquercetin and rutin have been demonstrated to considerably increase the therapeutic efficacy of cisplatin when used in the treatment of stomach cancer, as opposed to cisplatin given as a single dose (Ghavami *et al.*, 2020). Research on the administration of 6-methoxyflavone, a gamma-aminobutyric acid (GABA) modulator, to rats revealed a protective effect against neuropathic allodynia and hypoalgesia produced by cisplatin (Shahid *et al.*, 2017).

Conclusion

The results concluded that the apigenin-loaded ZnONPs give the best results than apigenin only antihyperlipidemic, antioxidant action and anti-inflammatory, besides its effect against cardiotoxicity induced with cisplatin. In addition, it could be noticed that the application of nanoparticles as a carrier to enhance the bioavailability and absorbability of apigenin at a lower dose toward the targeted tissue. Therefore, the current results show a significant change between consumed apigenin-loaded ZnONPs



Source: Created by author

Figure 2.
(a) There was no histopathological change in the control group; (b1) focal inflammatory cells infiltration was detected in between the myocardial bundles in cardiotoxicitygroup; (b2) oedemawas detected in between the myocardial bundles in cardiac toxicity group; (c) there was focal haemorrhage in between the myocardial bundles in treated group I; (d) there was no histopathological alteration in treated group II

and all other treated groups which indicates effectiveness of the using nanoparticles as a vehicle for apigenin.

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