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Effect of Resveratrol Nanoparticles on Some of Oxidative Indicators and Genetic Parameters in White Male Rats Treated with Cisplatin

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ABSTRACT

The current study was designed with the aim of determining some genetic effects and indicators on the antioxidants caused by cisplatin, in addition to identifying the role played by the regular and nano-extract of resveratrol in reducing the toxicity of the chemical drug caused by it. The 9-12 weeks male rats were divided into six groups (ten animals per group). The results of the gene expression level of the drug group and the nano-extract showed a significant increase in the level of malodihydehyde (MDA) and a decrease in the rest of the antigens (SOD, CAT, GSH) for the positive control group. Contrarily, the results indicated a significant increase for the normal and nano-extract group when compared with the positive control (G2) and other groups. Thus, the current study proved that giving the nano extract showed a significant improvement compared to the normal extract, whether in the extract group alone or simultaneously with the drug for its effective role in reducing the damage and toxic effects caused by the drug.

Key words: Cisplatin, normal and nano-resveratrol extract, oxidative stress

INTRODUCTION

Cisplatin is an anticancer and antineoplastic chemotherapy drug classified as an alkylating agent. It is used in the treatment of advanced bladder, ovarian, testicular, bladder, head, neck, esophageal, lung, small and non-small cell, breast, cervix, stomach and prostate cancers, lymphoma, neuroblastoma, sarcoma, multiple myeloma, melanoma and mesothelioma. Cisplatin is given intravenously, a chemical that can cause inflammation in the vein. Common side effects of the drug include bone marrow suppression, hearing problems, kidney damage, and vomiting (Sarafraz *et al.*, 2018). Other serious side effects include numbness, difficulty in walking, allergic reactions, deformity and heart disease. Use during pregnancy can also harm the baby (Johnstone *et al.*, 2016).

Cisplatin belongs to the family of platinum-based antitumor drugs and works in part by binding to DNA and preventing its replication. Cisplatin interferes with DNA replication, killing the fastest spreading cells, which are theoretically considered cancerous. After administration, one chloride ion is slowly displaced by water to give the aqueous compound in a process called aquation. Intracellular chloride dissociation is preferred because the intracellular chloride concentration is only 3-20% of the 100 mM chloride concentration in the extracellular fluid (Hu *et al.*, 2016). Cisplatin binds to DNA in several different ways, interferes with cell division by mitosis and damaged DNA causes DNA repair mechanisms to appear which in turn activate apoptosis when repair proves impossible (Riddell and Lippard, 2018).

The compound resveratrol derived from stilbene, belongs to a group of plant compounds called polyphenols, as this polyphenolic stilbenoid is produced as a natural defense in response to damage to plants, bruises or attack of microbes such as bacteria or fungi in its chemical structure (Salehi *et al.*, 2018). The compound resveratrol responsible for the pharmacological activity which could eventually lead to a longer life expectancy was detected by Pan *et al.* (2018). The resveratrol was detected in a wide range of about 70 plant species, such as the purple grape, *Vitis vinifera*, blue berry, cranberry, peanut, rhubarb, cassia, jackfruit and pine pines (Hafsan *et al.*, 2022). It was first discovered in the vineyards of the blueberry, *Vitis vinifera,* in 1976 and later in wine in 1992 (Huldani *et al.*, 2022). The highest concentration of 50-100 µg/g of resveratrol was found, as was found in the casing and seeds of grapes (Tiras *et al.*, 2022).

Unified to infect many types of pathological processes, it occurs when there is a serious disease that causes an imbalance between the production of ROS and antioxidants in the body, which is one of the defense systems and these reactive oxygen species are among the highly reactive types that are formed enzymatically and non-enzymatically. In mammalian cells, it causes cell damage either directly or indirectly by interfering with the mediators of diverse signalling pathways in cellular metabolism (Zadeh *et al.*, 2022).

Because of the instability of resveratrol, it has poor solubility in water, inefficiency in systemic delivery, and its low bioavailability, though the successes it achieved (Ansari *et al.,* 2022). In order to overcome the limitations of drug movement, it was loaded onto nanoparticles to give a more strategic force (Bokov *et al.*, 2022).

MATERIALS AND METHODS

Resveratrol (98% purity) was obtained from Amazon in powder form, and the dose was prepared according to Turkmen *et al.* (2019) at a concentration of 20 mg/kg body weight based on average weight and each animal was dosed daily orally using stomach. Cisplatin was obtained from drug stores in the form of a liquid bottle with a concentration of 50 mg/100 ml. The dose was prepared at a concentration of 2 mg/kg of body weight by dissolving the required concentration depending on the average body weight of the animal. Each animal was injected weekly under the peritoneum for two months. The nanoparticles were prepared for weekly loading of materials in the Graduate Studies Laboratory/Physiology Branch/College of Veterinary Medicine/Al-Qasim Green University. Chitosan nanoparticles were purchased from CAC Center and the produced solution was loaded from the Iranian Yekta Company according to the method of Ehterami *et al.* (2018).

Tripolyphosphate (TPP) solution (supplied from Daejung Chemicals and Metals Company) was prepared by adding 250 mg of sodium tripolyphosphate powder to 100 ml of distilled deionized water to obtain a ratio of 0.25% W/V. Therapeutic materials were loaded onto chitosan by ion gel method according to the method of Ali *et al.* (2017).

Real-time reverse transcription PCR assay was performed to measure the quantitative levels of mRNA to indicate the amount of gene expression of the LCGR gene, and the GAPDH gene was used as a standard regulator gene for calculating gene expression. The level of lipid peroxide in the serum was determined indirectly by measuring the level of MDA, which represented the final product of lipid oxidation.

The measurement of catalase enzyme activity was tested according to the method used by the researchers (Hadwan and Kadhum, 2018). Serum glutathione activity was evaluated using the method used by researchers (Hadwan and Kadhum, 2018). The activity of serum superoxide dismutase was measured using the modified photochemical method Nitroblue tetrazolium (NBT) using sodium cyanide.

The results were subjected to statistical analysis to find out the differences between the averages for the criteria studied in the different groups. The significant differences were determined at a probability level of 5% using the one-way analysis of variance (ANOVA). The significant differences between the means were also tested using the Least Significant Differences (LSD).

RESULTS AND DISCUSSION

The particle size was measured by laser beams, penetrating the liquid containing the particles of the resveratrol extract and revealing the average size of these particles. The average particle size of the resveratrol extract before loading on chitosan nanoparticles was 581.5 nm and the dispersion rate was 0.005 (Polydispersity; Figs. 1 and 2). The infrared frequency transmittance curves

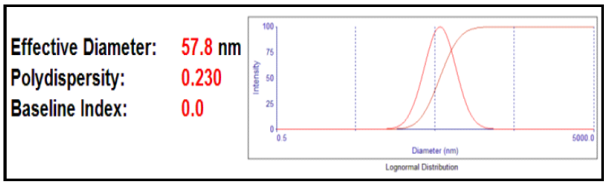

Fig. 1. Size of particles.

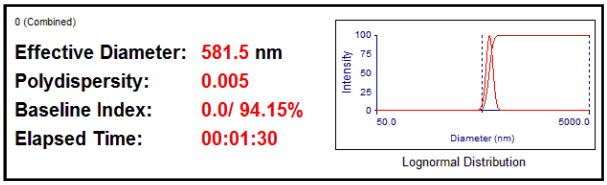

Fig. 2. Chitosan nanoparticles.

for the active substance resveratrol used in this study showed the presence of many different curves through which the functional groups of each substance were inferred according to the absorbance and amplitude of the infrared radiation. The infrared spectrum of the active substance (Fig. 3) indicated that there were many vertices that lie in many waves. The peak at 826.39/cm may be attributed to the bending vibration of the CH aliphatic bond. The peaks at 1697.70, 1651.24 and 1601.45/cm were due to the stretching vibration of the C = C bond. The peak at wavelength 1009.33/cm was due to the stretching vibration of the C-O bond due to the alcohol groups in the polymer. The peaks at 3291.56, 2920.11, 2851.10, 2363.00 and 2332.81/cm may be due to the stretching vibration of the OH group in the carboxylic group of phenol. While 3848.98, 3741.57, 3583.22 and 3549.81/cm were the results of the stretching of the amine bonds NH (Fig. 4).

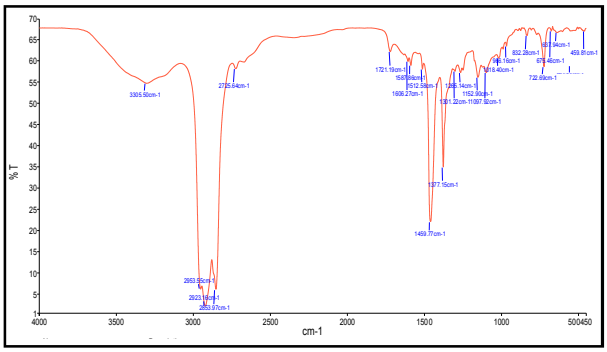

Fig. 3. Infrared spectrum of chitosan.

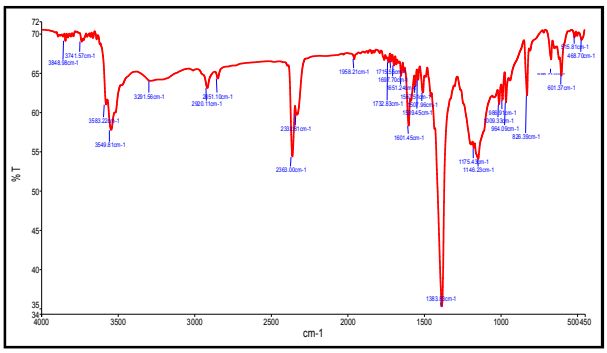

Fig. 4. Infrared spectrum of resveratrol.

The FTIR permeability curve for chitosan particles alone indicated the presence of 722.69 and 675.46/cm which was attributed to the bending vibration at the CH bond. As well as the presence of peaks with the numbers 1587.86 and 1512.58/cm, which was attributed to the C = C expansion of the periodic structure. The wave numbers 1721.19 and 1606.27/cm were attributed to the occurrence of double-stretching of carbon bonds with oxygen C = O of the aromatic group and 3305.50, 2953.55 and 2923.16 to the strong bond in the O-H extended carboxylic acid (Fig. 3).

In the FTIR permeability curve of chitosan particles loaded with resveratrol, the presence of 3910.31, 3788.33, 3696.29 and 3661.67/cm was attributed to the bending vibration at the OH bond. As well as the presence of peaks with numbers 2953.08, 2922.97, 2853.82 and 2724.93/cm was attributed to C-H expansion in the periodic structure. The wave numbers 11893.39, 1723.79 and 1632.89/cm were attributed to the occurrence of double-stretching of carbon-carbon bonds with oxygen C = O of the aromatic group (Fig. 5).

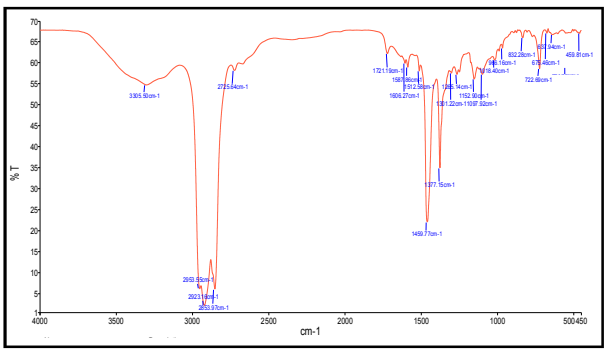

Fig. 5. Infrared spectrum of chitosan-loaded resveratrol particles.

The image of resveratrol loaded with chitosan taken by electron microscopy confirmed the shape and distribution after loading between the polymer nanoparticles and the extract particles. By the measurement of nanoparticles, the large dispersion and appropriate size of nanoparticles were observed in the colloidal solution, which confirmed the homogeneity of the solution and the successful loading process, and this was previously observed during the drop from the polydispersity in the particle size analysis (Figs. 6 and 7).

The results of the statistical analysis showed a significant (P>0.05) decrease in the level of LCGR gene expression in the group treated with cisplatin at a concentration of 2 mg/kg body weight (G2) when compared with the control group (G1) and with the rest of the experiment groups. The results showed a significant increase (P>0.05) for the extract group (G3) when compared with the positive control (G2) and the groups represented (G1,

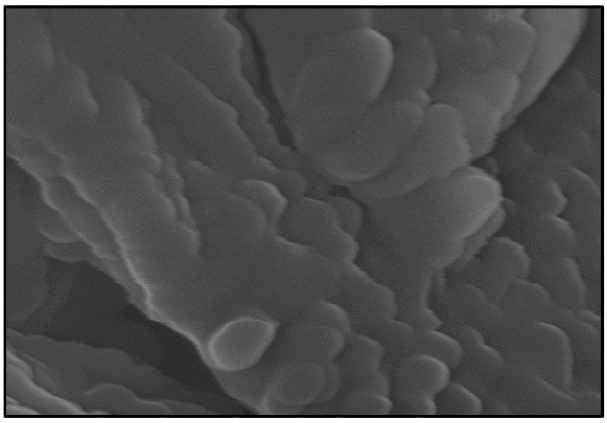

Fig. 6. Resveratrol taken by an electron microscope showing the irregular or oval shape.

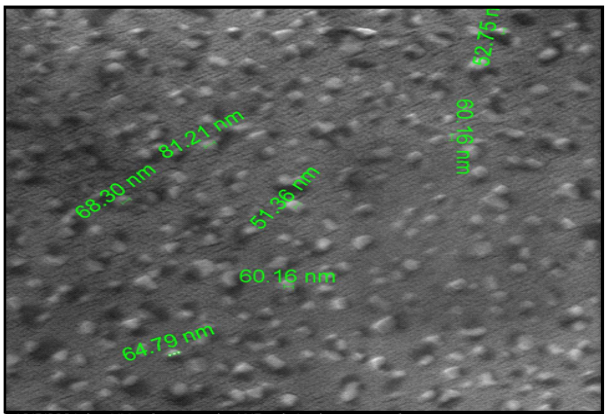

Fig. 7. Resveratrol loaded with chitosan taken by electron microscope showing the regular circular or oval shape and an appropriate size when compared with the extract.

G5, G6) showed a significant decrease (P>0.05) with the nano-extract group (G4). The group that dosed the nano-extract (G4) showed a significant increase (P<0.05) compared with all the experimental groups. The group that dosed the drug and the normal extract simultaneously showed a significant increase when compared with the positive control (G2) and a significant decrease for the rest of the other groups (Table 1). Finally, the results of the level of the gene expression of the drug group and the nano-extract that was dosed simultaneously showed a significant and clear increase when compared with the positive control group (G2) and group (G5), while it recorded a significant decrease when compared with groups (G1, G3 and G4).

Treatment with cisplatin at a concentration of 2 mg/kg of body weight showed a significant decrease in the expression of the gene (LHCGR). The results of the study agreed with the findings of Razavi *et al.* (2019) in male rats

Table 1. Effect of cisplatin, resveratrol and nanoextract on LCGR gene expression rate extracted from testicular tissues of white male rats

Group	Gene expression
G1	1.80±0.05D
G2	0.355±0.04B
G3	3.22±0.30C
G4	3.87±0.15A
G5	1.04±0.10F
G6	1.51±0.02E
The value of the least significant difference	0.193

Values are mean±standard error. Similar letters between any two groups indicate no significant differences, while different letters indicate significant differences at the level (P<0.05).

dosed with chemotherapy that included (Etoposide, Cisplatin, Belomycin), and the decrease in gene expression may be due to the effect of reactive oxygen species formed as a result of treatment with the drug accompanied by a decrease in cellular antioxidants, as these classes affect the process of regulating metabolic pathways in cells. In turn, they affect the expression of genes in general, and free radicals affect the metabolism of cells, and it is known that the increased oxidation of DNA, fats and proteins is stimulated as a result of the accumulation of free radicals in cells, which in turn, leads to cellular damage that causes gene instability. The various pathways of pathological changes in the testicles were involved in the formation of reactive oxygen species, leading to a decrease in the production of steroids in the testis by the oxidative stress that it causes, as the LHCGR gene is a known target of H_2O_2, which affects the functioning of Lydec cells, leading to the inhibition of steroid synthesis in them.

Shirani *et al.* (2020) indicated that treatment with chemotherapy (bleomycin, etoposide, cisplatin) inhibited the gene expression of the luteinizing hormone receptor (LHR), as well as reduced the expression of the enzymes cytochrome P-450scc (CYP11A1), hydroxy-delta-5-steroid dehydrogenase-3 beta (HSD3B), which was one of the main enzymes in the manufacture of the hormone testosterone. It was responsible for transporting cholesterol to the steroid-producing Leydig cells. Further they indicated that the imbalance between oxidants and antioxidants in the body caused damage to the pituitary cells, which led to a decrease

in the production of the hormone LH, which was due to the disruption of the pituitary-testicular axis caused by oxidative stress resulting from chemotherapy.

The groups treated with the normal and nano-extract (G3, G4) showed a significant increase when compared with the negative and positive control group. This showed the role and strength of resveratrol in improving the functioning of the testicular and pituitary functions and preserving the cell components represented by DNA, RNA, nucleic acids and lipids in cell membranes by reducing the peroxidation of fats and the increase of antioxidants in the tissues. It was positively reflected in the improvement of tissue composition and performance, and this is what appeared in the treatment of the overlapping groups between the extract and the drug, which showed a significant increase in gene expression from the level of positive control. The reason for this was due to the action of the therapeutic extract of tissues and reproductive organs by increasing the antioxidants (CAT, GSH, SOD), while inhibiting lipid peroxidation and maintaining the integrity of cell components and membranes, leading to an improvement in the performance of vital tissue functions (Shirani *et al.*, 2020).

The results of the current study showed a significant increase (P<0.05) in the MDA level of male rats treated with cisplatin (G2) at a concentration of 2 mg/kg compared to the negative control group and the rest of the other groups. The results also showed a significant increase (P<0.05) in the MDA level of male rats treated with the normal extract at concentration 20 mg/kg body weight (G3) compared with the negative control (G1), while showing a significant decrease when compared with the rest of the study groups. G5 did not indicate significant differences compared to the nano-extract group G6, while the treatment with nano-extract (G6) showed a significant increase (P< 0.05) in the level of MDA compared with the negative control group, while it showed a significant decrease when compared with the groups (G2, G5 and G6). When the comparison was made between the group of the normal extract and the simultaneously dosed drug, it indicated a significant increase (P<0.05) compared with the groups (G1, G3, G4 and G6) in which it led to a significant decrease when compared with the control (Table 2). The present results indicated that there was a significant decrease in the MDA level of the nano-extract group with the drug concurrently compared with the positive control and group (G5), but when compared with the groups (G1 and G3), it showed a significant increase with the nano-extract group J (G4).

The study showed a significant decrease in the level of catalase and in the level of SOD and in the level of glutathione for male rats treated with cisplatin (G2) compared to the negative control group and the rest of the other groups. The results also showed a significant increase (P< 0.05) in the groups treated with the normal extract (G3) at a concentration of 20 mg/kg of body weight compared with the positive control and the groups represented by G1, G5 and G6. It did not indicate significant differences when compared with the nano-extract group (G4). As for the comparison between groups of the extract with the drug dosed simultaneously (G5) with the other groups, the results indicated a significant increase (P<0.05) compared to the positive control group and a significant decrease for the rest of the other groups. There was a significant increase (P<0.05) in the level of the above criteria for male rats treated with the

Table 2. Catalase, malondialdehyde, SOD and GSH level

Groups	Glutathione (µmol/l)	SOD (U/ml)	Catalase (U/ml)	MDA (µmol/l)
G1	3.32±0.06B	1.93±0.07B	0.77±0.05C	1.73±0.06A
G2	1.57±0.07E	1.02±0.1E	0.34±0.05F	2.53±0.1B
G3	3.38±0.05AB	0.08A±1.99	0.91±0.07B	1.83±0.06C
G4	3.44±0.05A	2.10±0.09A	1.02±0.09A	1.89±0.04CE
G5	2.55±0.09D	1.53±0.08D	0.56±0.08E	2.04±0.07D
G6	C3.09±0.07	1.70±0.05C	0.67±0.06D	1.94±0.07E
LSD	0.094	0.110	0.095	0.096

Values are mean±standard error. Similar letters between any two groups indicate no significant differences, while different letters indicate significant differences at the level (P<0.05).

nano-extract and the drug simultaneously compared to the positive control group and the group (G5), while it indicated a significant and clear decrease for the rest of the groups (G1, G3 and G4) as well.

Cisplatin transformed metabolism into a potent toxicity that caused damage to DNA, mitochondrial DNA and cellular respiration, with activation of programmed cell death pathways and initiation of the inflammatory response (Pan *et al.*, 2018). The drug activated the oxidative stress that caused the activation of the transcription factor-nuclear factor kappa (NF-KB) and this in turn enhanced the production of proinflammatory cytokines such as TNf-a. This factor (NF-KB) had key roles in oxidative stress, inflammation, regulation of the genetic code of cytokines and programmed death (Pan *et al.*, 2018). Therefore, oxidative stress usually generated free radicals that had a major role in the damage of body cells, causing chronic or acute diseases. These arose when the biological system and its antioxidants were unable to neutralize free radicals, so reactive oxygen species attacked proteins, fats, nucleic acids and carbohydrates, as the body was unable to produce some of the antioxidants necessary to neutralize free radicals, such as ascorbic acid, vitamin C, vitamin A, and others, so it was taken by eating or drinking. The results of the antioxidant enzymes tests (Shirani *et al.*, 2020) showed that the animals treated with cisplatin had different changes in the activity of these enzymes represented by a significant decrease in the levels of CAT, SOD and GSH indicating a weak efficacy of endogenous antioxidant factors, while a significant increase in the amount of MDA was observed, which oxidizes lipid peroxide. Studies had indicated that the main cause of many diseases was an imbalance in antioxidants due to the increase in MDA production after taking cisplatin, which increased oxidative stress.

Resveratrol was mainly designed to carry an O-diphenoxyl group, which played a role in inhibiting ROS-induced DNA damage, promoting copper-induced DNA damage, and inducing apoptosis. Several studies showed the protective ability of resveratrol due to its anti-cancer properties (Radovanovic *et al.*, 2019). It also had the ability to overcome the resistance caused by chemotherapy in myeloma and had a great challenge in treating this disease.

Airaodion *et al.* (2019) observed that the MDA level was increased and the level of CAT, SOD and glutathione decreased in mice treated with ethanol. When adding 5 g/kg of resveratrol daily during ethanol treatment, MDA synthesis was inhibited and the enzymatic activity of antioxidants improved. In other studies, it increased the mRNA levels of catalase, SOD1 and GST in lymphocytes isolated from Alzheimer's patients (Rapyal, 2016). Resveratrol increased the expression of the mRNA gene of enzymatic antioxidants and decreased the activity of the nuclear factor NF-KB for ROS (ROS-Sensitive transcription factor). It reactivated SOD and thus accelerated the dissolution of O_2 to H_2O_2, which was rapidly removed by catalase to protect liver and kidney tissues in diabetic rats against its high activity and toxicity of hydroxyl radicals, thus preventing lipid peroxidation (Zhang, 2016). This indicated during present study the role of nano-resveratrol compared to the normal extract, which agreed with many studies that showed the role of resveratrol loaded with nanoparticles (Khatun *et al.*, 2016; Giordo *et al.*, 2020).

CONCLUSION

The results indicated a significant increase for the normal and nano-extract group when compared with the positive control (G2) and other groups, and the current study proved that giving the nano extract showed a significant improvement compared to the normal extract, whether in the extract group alone or simultaneously with the drug for its effective role in reducing the damage and toxic effects caused by the drug.

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