

Effect of Quinoa seeds against Cisplatin toxicity in female rats

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ABSTRACT

Background and objectives: Cisplatin which is used widely for cancer patients as an effective chemotherapeutic drug was reported to exert many adverse effects on the body. This study aims to investigate the effect of quinoa seeds against cisplatin toxicity in female rats. **Materials and methods:** Thirty six female Wistar rats were used. Thirty of them were divided into five groups each of six rats and injected daily for 8 weeks intraperitoneally with cisplatin dose of 12 mg/kg b. wt./rat, while the remaining group was considered as the negative control and injected intraperitoneally by saline for the same period. The negative control group and the positive control group (injected with cisplatin) were fed on basal diet, the third, fourth, fifth and sixth groups were fed on basal diet + 10% or 20% or 30% or 40% quinoa seed powder, respectively. **Results:** The results revealed that rats consumed quinoa seed powder at different levels showed significant increase in concentration of serum testosterone, estrogen, follicle stimulating hormone (FSH) and luteinizing hormone (LH), compared to the positive control group. Also, administration of quinoa seed powder at different levels improved, lipid profile and antioxidant parameters in female rats. **Conclusion:** The quinoa seed powder is a potent polyphenol, mineral and vitamin rich source with great anti-inflammatory and antioxidant power which can be used to prepare a functional food that can counteract the symptoms of cisplatin toxicity and prevent its complications.

Keywords: Quinoa seeds, cisplatin, FSH, LH, testosterone, estrogen.

Introduction

Quinoa (*Chenopodium Quinoa* Willd) is a grain-like crop which is traditionally used for nutrition and sustenance to Andean indigenous cultures for centuries [1]. Recently, lights were thrown on quinoa and it was described as “one of the 21st century’s grains” as it is of a high nutritional value; it is a gluten free and having therapeutic properties allowing it to be used as a nutraceutical and a functional food [2]. The high nutritional value of quinoa may be attributed to its unique chemical composition as it contains a protein of a high quantity and quality with a balanced essential amino acid pattern. Also, it contains vitamins such as vitamin E, C, B2, B6 and folic acid with relatively high amounts [1]. Moreover, its mineral content is of a great value as it contains calcium, magnesium, copper, iron, zinc and potassium with relatively high amounts compared to other grains and many of these minerals are of a good bioavailability

enough to form a balanced diet [3].

In addition to high nutritional value and being free of gluten, quinoa was also reported to have many health benefits. It can be used for both children and elderly, for lactose intolerance, those who are suffering from either anemia, or obesity, or diabetes or celiac disease or dyslipidemia. It has a high antioxidant and anti-inflammatory potency and can be used as anticancer, neuroprotective and immunomodulatory [1]. These health benefits are due to its content of protein, minerals, vitamins and fiber in addition to its content of phytochemicals and bioactive components [4]. Among the phytochemicals of quinoa are, It has been reported that quinoa is among the richest sources of phytoecdysteroids containing from 138 to 570 µg/g. Phytoecdysteroids are polyhydroxylated steroids involved in plant defense and they have a wide range of health benefits including anti-osteoporotic, anabolic performance enhancing, anti-obesity and anti-diabetic [5].

Cisplatin is considered as one of the most potent chemotherapeutic drugs that is used widely with a high successful rate for the treatment of different types of cancer [6] including testicular cancer, ovarian cancer, soft tissue cancers, sarcoma cancers, cancers of muscles, bones and blood vessels giving a very good prognosis [7, 8]. However, the use of cisplatin has many side effects in the normal tissues. Among these side effects are sexual toxicity, hearing loss (ototoxicity), nephrotoxicity, neurotoxicity, nausea, vomiting, myelosuppression and hepatotoxicity [6, 9, 10].

Access this article online

Website: www.japer.in

E-ISSN: 2249-3379

How to cite this article: Hany Mohamed Ahmed Wahba, Maha Hanafy Mahmoud, Hanaa Farouk El-Mehiry. Effect of Quinoa seeds against Cisplatin toxicity in female rats. *J Adv Pharm Edu Res* 2019;9(3):46-52.

Source of Support: Nil, Conflict of Interest: None declared.

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The aim of the present study is to investigate the effect of quinoa seeds at different levels against cisplatin induced toxicity in female rats.

Material and Methods

Materials

Quinoa seed (*Chenopodium Quinoa* Willd) was obtained from Agriculture Research Center, Giza, Egypt.

Experimental animals

Thirty six female Wistar rats weighing 125 ± 5 g were purchased from the Agricultural Research Centre, Giza, Egypt.

Drugs and chemicals

Cisplatin solution (Platinol AQ) was obtained from Sigma-Aldrich Chemical Co. (St Louis, Mo, USA).

Kits used for determination of testosterone, estrogen, follicle stimulating hormone (FSH) and luteinizing hormone (LH) based on ELISA technique were obtained from Fine Test, Wuhan Fine Biological Technology Co., Ltd., China. Diagnostic Kit used for estimation of plasma triacylglycerols was obtained from Stanbio Laboratory Company, Texas, (USA). Kits used for determination of total cholesterol, HDL-C, LDL-C in plasma were purchased from Chronolab Systems S.L., Barcelona, Spain. Kit used for cholinesterase detection was purchased from Quimica Clinic Aplicada S.A., Barcelona, Spain. Total antioxidant capacity (TAC) and superoxide dismutase (SOD) were measured with kits obtained from Biodiagnostic Co., Egypt.

Methods

Chemical analysis

Quinoa seeds were analyzed for the moisture, protein, fat, ash, fiber and total carbohydrate contents as previously described in AOAC^[11].

Determination of some minerals

Some minerals content including zinc (Zn), calcium (Ca), magnesium (Mg) and iron (Fe) were determined in the diluted solution of ash using the atomic absorption spectrophotometer (3300 Perkin-Elme) as described by AOAC^[11] method.

Preliminary phytochemical screening of quinoa seed

Detection of tannins and resins: Tannins and resins were detected in the plant sample according to the method of **El-Badrawy**^[12].

Detection of saponins: Saponins were detected according to the method of **Trease**^[13].

Detection of terpenes: Terpenes were detected according to the method of **Finar**^[14].

Detection of flavonoids: Flavonoids were detected as described in the method of **Geissman**^[15].

Detection of carbohydrates and glycosides: Carbohydrates and glycosides were detected by Molish test according to the method of **Blabaa, et al.**^[16].

Methods

Experimental design

Adult female Wistar rats were maintained under controlled hygienic conditions. The animal experiment was done in compliance with the Guidelines for animal Care and Ethics Committee of the NRC (Egypt). The weight of rats ranged

between 120 to 140 g. The animals were allocated individually in stainless steel cages. They were fed on the basal diet for 7 days before the beginning of the experiment for adaptation. The basal diet which was prepared according to **Reeves et al.**^[17] comprised of casein, corn starch, sucrose, cellulose, corn oil, mineral mixture, vitamin mixture, DL-methionine and choline bitartrate (220, 539.5, 100, 50, 40, 35, 10, 3 and 2.5 g/kg) respectively, provided that protein content of casein was estimated as 54.6%. Animals were subjected to 12 hours light and 12 hours dark schedule. Then they were divided into six groups (6 rats each) and fed on the experimental diets for 8 weeks. The first group was kept as negative control group and fed on the basal diet only, while the other five groups were daily injected intraperitoneally with cisplatin in a dose of 12 mg/kg body weight according to **Ateşşahin et al.**^[18] to induce toxicity. One of these groups was fed on basal diet only and served as positive control which was group 2. The third, fourth, fifth and sixth groups were fed on basal diet + either 10% or 20% or 30% or 40 quinoa seed powder, respectively. During the experimental period, the feed intake and the body weight were followed carefully and at the end of the experimental period, feed intake, body weight gain and feed efficiency ratio (FER) were calculated.

Biochemical analysis

After the end of the experimental period, overnight fasting blood samples were collected from suborbital vein. Serum was separated and kept at $-70\text{ }^{\circ}\text{C}$ until analysis. Different biochemical parameters were analyzed as follows:

Determination of lipid profile

Serum total cholesterol (TC), triacylglycerols (TG) and high density lipoprotein-cholesterol (HDL-C) were determined as described by **Meiattini et al.**^[19], **Scheletter and Nussel**^[20] and **Grove**^[21], respectively. However, low density lipoprotein-cholesterol (LDL-C) was calculated according to **Warnick et al.**^[22] as shown in the following equation:

$$\text{LDL-C} = \text{Total cholesterol} - (\text{HDL-C} + \text{VLDL-C})$$

Where, VLDL-C (very low density lipoprotein-cholesterol) = Triacylglycerols / 5

Determination of serum cholinesterase and antioxidant parameters

Cholinesterase (ChE) activity, superoxide dismutase (SOD) activity and total antioxidant capacity (TAC) were determined according to **Knedel and Boottger**^[23], **Nishikimi, et al.**^[24] and **Koracevic, et al.**^[25], respectively.

Determination of serum sexual hormones

The concentration of serum testosterone, estrogen, follicle stimulating hormone (FSH) and Luteinizing hormone (LH) were determined by an enzyme-linked immunosorbent assay (ELISA) technique according to manufacturer's instructions using ELISA Reader (ELISA Reader Model Start F, Awareness Technology, Inc., Palm City, FL, USA).

Statistical analysis

Data were analyzed statistically using the computerized program SPSS software, version "20" for Windows. The one-way ANOVA test was done followed by Duncan test. Data were represented as mean \pm SD. $P < 0.05$ was considered significant, otherwise was non-significant.

Results and Discussion

Proximate composition on dry weight basis of quinoa seed

As shown in table (1) protein content (15.05 %) and total carbohydrates (60.42 %) were relatively high. The recorded values for fat, ash and fiber were; 4.93 %, 3.78 % and 8.92 %, respectively. Also, table (1) showed that quinoa seeds contain minerals as Mg, Ca, Fe and Zn (126.23, 90.09, 17.46 and 4.86 mg/100g, respectively). These results agreed more or less with those found by Vilcacundo & Hernandez-Ledesma [1]. They also, concluded from their study that protein and carbohydrate content of quinoa were relatively high compared with other cereals like rice and wheat. They added that quinoa seeds of high protein quality since it provides with many essential amino acids which meet the requirements for adults as stated by WHO [26]. Regarding the mineral content of quinoa, it was said to be of great importance since it contains not only relatively high amounts of calcium, magnesium, iron and zinc but also, they are of good bioavailability [3].

Table 1: Proximate composition% on dry weight basis of quinoa seed

Constituents	%
Moisture (g/100g)	6.90
Protein (g/100g)	15.05
Fat (g/100g)	4.93
Ash(g/100g)	3.78
Crude fiber(g/100g)	8.92
Total carbohydrates	60.42
Zn (mg/100g)	4.86
Ca (mg/100g)	90.09
Fe (mg/100g)	17.46
Mg (mg/100g)	126.23

Values are expressed as mean of three triplicates.

The phytochemical screening of quinoa seed

Data tabulated in Table (2) showed that quinoa seeds contained tannins, saponins, resins, terpenes and flavonoids. It was reported previously that quinoa seeds contain many bioactive components, among which are; saponins, terpenes, and flavonoids which seems to be in accordance with our findings [1,4]. Among the phytochemical compounds in quinoa seeds, it was said to contain phytosterols and phytoestrogens [5, 27]. The latter is found with the highest concentration in quinoa among all plants.

Table 2: Preliminary phytochemical screening of quinoa seed

Quinoa seed	Tannins	Saponins	Resins	Terpenes	Flavonoids
	+	+	+	+	+

Effect of different levels of quinoa seed powder on feed intake, body weight gain and FER

The positive control group, which is injected with cisplatin and not treated with quinoa seeds, showed significant decrease in

body weight gain, feed intake and FER compared to negative control group which may be due to the toxic effect of cisplatin (Table 3). Groups that received quinoa seed powder at different levels (10, 20, 30 and 40%) showed a significant improvement in each of body weight gain, feed intake and feed efficiency ratio (FER) compared to the positive control group. It is worth mentioning that the aforementioned parameters were more or less normalized in the two groups that received quinoa seeds powder at levels of 30% and 40% and they became insignificant with the control negative group. These results were in agreement with those reported by **Mladenovic et al.** [28] & **Al-Shammar and El-Mehiry** [29] who reported that the body weight and feed intake of control positive group that was injected with cisplatin was significantly decreased as compared to the control negative group. They suggested that the differences in the food consumption pattern led to important differences in body weight gain at the end of experimental period. Vega-Galvez [3] mentioned that quinoa is a very nutritious source since it contains a good balance of carbohydrates, lipid, fiber, amino acids, minerals and vitamins. It seems that this may be the reason for restoring the reduction in body weight resulting from cisplatin injection.

Table 3: Body weight gain, feed intake and FER in all treated groups.

Groups	body weight gain g	Feed intake g/day	FER
Negative control	103.01± 8.71 ^a	17.54±1.23 ^a	0.097±.008 ^a
Positive control	51.19 ±5.11 ^c	11.55±1.18 ^b	0.063±0.006 ^c
10%	85.86 ±7.42 ^b	16.54±1.24 ^a	0.085±0.004 ^b
20%	93.72 ±7.31 ^b	16.63±1.27 ^a	0.083±0.002 ^b
30%	97.30 ±8.17 ^{ab}	17.12±1.71 ^a	0.091±0.002 ^{ab}
40%	100.42 ±9.12 ^a	17.45±1.81 ^a	0.092±0.002 ^a

Values are represented by mean ± S.D. Mean values in each column having different superscript (a, b, c, d) are significant while, those that share similar superscripts are non-significant.

FER: Food efficiency ratio

Effect of different levels of quinoa seed powder on lipids profile

Table (4) showed that there was a significant increase of TC, TG, LDL-C and VLDL-C in positive control group when compared to negative control group ($p < 0.05$) while, a significant decrease in HDL-C was noticed for the same group (control positive) compared to the negative control group. However, this alternation in the lipid pattern was restored in the groups that were injected with cisplatin and received the quinoa seed powder at different levels in a dose dependent manner. The four groups that received quinoa seeds showed a significant decline in TC, TG, LDL-C compared to the control positive group and by increasing the amount received of quinoa seeds, the improvement becomes better gradually from the group that received 10% up to the group that received 40% which recorded a value that is near to the value of the control negative group. On the other hand, the HDL-C showed a significant rise in the groups that received quinoa compared to

the control positive group and the increase was gradual from the group of 10% up to the group that received the 40% quinoa seeds which become insignificantly changed compared to the negative control group. This can reflect the cardioprotective effect of quinoa seed powder. Graf et al.,^[30] mentioned that the marked hypocholesterolemic effect of quinoa may be attributed to its content of saponins. Moreover, the fiber content of quinoa may contribute to its hypolipemic effect.

Table 4: Lipid profile of all treated groups.

Groups	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	VLDL-C (mg/dl)
Negative control	107.69±2.66 ^f	89.44±2.85 ^d	61.85±2.23 ^a	39.18±3.23 ^e	17.97±1.08 ^d
Positive control	161.16±8.98 ^a	109.31±6.69 ^a	50.19±±1.87 ^d	88.76±±6.21 ^a	21.96±±1.82 ^a
10%	141.29±4.19 ^b	98.46±4.54 ^b	55.55±1.54 ^c	65.25±6.44 ^b	18.49±1.33 ^b
treated with quinoa seed powder 20%	139.28±3.45 ^c	95.46±2.15 ^b	57.12±2.11 ^b	60.27±2.01 ^b	18.11±1.64 ^c
30%	128.19±3.11 ^d	93.51±±2.31 ^c	59.66±±2.10 ^b	49.15±3.11 ^c	17.50±1.07 ^d
40%	115.68±3.99 ^e	90.52±2.26 ^d	60.61±2.13 ^a	44.97±3.22 ^d	16.30±1.11 ^d

Values are represented by mean ± S.D. Mean values in each column having different superscript (a, b, c, d, f) are significant while, those that share similar superscripts are non-significant. TC: total cholesterol, TG: total triglyceride, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol VLDL-C: very low density lipoprotein cholesterol

Effect of different levels of quinoa seed powder on antioxidant parameters and cholinesterase

Table (5) showed the effect of quinoa seed at different levels on total antioxidant capacity (TAC); activity of superoxide dismutase (SOD) and serum cholinesterase activity on cisplatin intoxicated groups and the control group. Treated group that was fed on 40% quinoa seed powder had the highest TAC level followed by groups that were fed on 30%, 20% and 10% quinoa seed powder, respectively compared to the positive control group. Also, the treated rat groups that were fed on 30% and 40% quinoa seed powder had the highest SOD activity compared to other groups except for the negative control group. However, data showed that cholinesterase activity recorded a higher level in the positive control group compared to the negative control group and there was a significant decrease in cholinesterase activity for all groups that received quinoa seeds compared to the positive control group. Total antioxidant capacity was previously reported to increase due to ingestion of plant sources with high antioxidant content^[31] which is in agreement with our findings in the present study, since TAC was diminished in the group that received cisplatin,

while in all groups that received cisplatin and quinoa with different doses, an increase in TAC was noticed. This improvement was attributed to the antioxidant components in quinoa. Also, it was reported before that increasing the oxidative stress has led to decreasing the activity of SOD in rats^[32] and introducing antioxidant rich sources to the rats was able to restore the decrease in SOD activity. This seems to be in accordance with the obtained data for SOD activity in the present study in which SOD activity was reduced in the group that received cisplatin and then this activity was returned back to near the normal levels of the control negative group by feeding rats on quinoa. This effect of quinoa may be attributed to its antioxidant properties due to the presence of antioxidant polyphenolic compounds as reported by Park et al.,^[33]. Cholinesterase activity was reported to be among the tests that reflect liver function^[34]. Elevated cholinesterase in the group that was treated with cisplatin indicated impaired liver function and this elevation was reduced in the groups that received quinoa with different doses indicating the protective effect of quinoa against liver damage that may be attributed to the high antioxidant content of quinoa^[35].

Table 5: Antioxidant parameters and cholinesterase activity of all groups.

Groups	TAC (U/ml)	SOD (U/ml)	Cholinesterase (U/ml)
Negative control	3.15±0.22 ^a	570.0±0.12 ^a	131.73±13.61 ^d
Positive control	1.27±0.15 ^c	300.61±0.09 ^c	164.70±25.75 ^a
treated with quinoa seed powder 10%	1.98±0.15 ^b	327.99±0.02 ^b	148.00±14.58 ^b
20%	2.74±0.06 ^b	317.1±0.07 ^b	141.83±14.75 ^c
30%	2.88±0.06 ^b	523.51±0.07 ^a	137.83±14.75 ^c
40%	3.11±0.06 ^a	532.49±0.07 ^a	132.83±14.75 ^c

Values are represented by mean ± S.D. Mean values in each column having different superscript (a, b, c, d,) are significant while, those that share similar superscripts are non-significant.

TAC: total antioxidant capacity, SOD: superoxide dismutase.

Effect of different levels of quinoa seed powder on sex hormones

Serum levels of sex hormones in experimental rats were shown in Table (6). A decrease was noticed in testosterone, estrogen, follicle Stimulating hormone (FSH) and luteinizing hormone (LH) in rats of the positive control group compared to their corresponding values in the negative control group. Cisplatin as a chemotherapeutic drug was reported previously to have many side effects among which is the infertility as it affects sex hormones^[8]. On the other hand, the group of rats that were fed on 40% quinoa seed powder showed improving in these estimated hormones which were returned back to more or less the values of the negative control group. This showed the ability of quinoa seed to counteract the toxic effect of cisplatin on the sex hormones. Quinoa was analyzed before for its individual content of polyphenolic compounds by HPLC^[36]. They reported that quinoa contains about 23 phenolic compounds

among which is quercetin. Yiğitaslan et al.,^[37] have reported that quercetin showed estrogen-like activity in female rats. This seems to be in agreement with our findings that quinoa was able to combat the toxic effect of cisplatin on rat estrogen.

Table 6: Sex hormones of all treated groups.

Groups	Testosterone (ng/mL)	Estrogen (ng/dl)	FSH (ng/mL)	LH (ng/mL)	
Negative control	2.52 ± 0.67 ^a	13.84 ± 3.11 ^a	124.38 ± 10.75 ^a	4.18 ± 0.76 ^a	
Positive control	1.10 ± 0.30 ^c	8.79 ± 1.45 ^d	92.17 ± 7.55 ^c	1.35 ± 1.16 ^c	
treated with quinoa seed powder	10%	1.81 ± 0.30 ^b	11.25 ± 2.10 ^c	112.98 ± 9.65 ^b	2.95 ± 0.96 ^b
	20%	2.12 ± 0.96 ^b	11.96 ± 2.15 ^b	119.59 ± 9.80 ^b	3.58 ± 0.96 ^b
	30%	2.31 ± 0.30 ^a	12.49 ± 3.05 ^b	120.78 ± 9.65 ^a	3.96 ± 0.96 ^a
	40%	2.48 ± 0.96 ^a	12.71 ± 3.10 ^b	124.09 ± 9.80 ^a	4.11 ± 0.96 ^a

Values are represented by mean ± S.D. Mean values in each column having different superscript (a, b, c, d,) are significant while, those that share similar superscripts are non-significant.

FSH: Follicle Stimulating hormone and LH: Luteinizing hormone

Conclusion

From the obtained results, it can be concluded that the chemotherapeutic drug; cisplatin exerts a toxic effect on rats as represented by altered pattern of sex hormones, altered lipid profile, increased cholinesterase activity, decreased total antioxidant capacity, and impaired SOD activity. Quinoa seed as a rich source of vitamins, minerals and polyphenols was able to restore all these altered parameters. Thus, quinoa seed can be used for preparing functional food for those cancer patients who are treated with cisplatin to minimize cisplatin toxicity and to prevent its complications.

Significance Statement

This study discovered that feeding rats with quinoa seeds that contain potent antioxidants was able to counteract the deleterious effect of cisplatin by restoring the studied biochemical and nutritional parameters. This will help the researchers to highlight the beneficial effect of quinoa seeds and to use it in preparing a variety of functional foods to combat the concomitant toxicity in cancer patients who are treated with cisplatin.

Author contribution:

Author (1): Put the idea for this work, shared in the animal experiment, shared in phytochemical analysis, shared in the biochemical analysis, shared in carrying out statistical analysis for the data and shared in writing and revising the article.

Author (2): Shared in the biochemical analysis, revised the statistical analysis and shared in writing and revising the article and made the article in the format of the journal.

Author (3): Shared in the animal experiment, shared in phytochemical analysis, shared in the biochemical analysis, shared in carrying out the statistical analysis for the data and shared in writing the article.

Conflict of interest:

There are no conflicts of interestsaponins, polysaccharides, polyphenols and phytoecdysteroids.

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