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Original Research Article

Platinum-Based Anticancer Chemotherapy Tissue Toxicity: The Use of Carrot and Tomato Supplements as a Dietary Intervention in *Rattus norvegicus*

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ABSTRACT

High-dose of cisplatin therapy is limited due to its cumulative toxicity. Recently, diverse natural product and dietary compounds have been exploited as potential protective agents against cisplatin-induced tissue toxicity. This paper aims to examine the effect of a supplementary diet of carrot and tomato against cisplatin-induced dyslipidemia and hepatic transaminase changes and the risk of cardiovascular diseases in male Wistar rats.

Male albino rats weighing (98.4±2.4g) were randomly assigned into five groups (n=6). Group one served as control and was maintained on a control diet for 7days. Rats of groups 2, 3, 4, and 5 were injected a single dose of cisplatin (7.5mg/kg/body weight) and thereafter fed with a control diet, 5% carrot, 5% tomato, and 5% tomato + 5%carrot supplemented diet respectively.

The result revealed that cisplatin caused bodyweight loss, increases the plasma total cholesterol, triglyceride, LDL, AST, ALP, and ALT level significantly. Conversely, it causes a decrease in the plasma HDL cholesterol level. However, supplementation with tomato and carrot causes a decrease in the plasma level of total cholesterol, triglyceride, LDL AST, ALP, and ALT level towards normal (control). Additionally, the atherogenic parameters were observed to be slightly high upon cisplatin injection whereas treatment with tomato and carrot significantly reduced the atherogenic parameters towards normal (control).

These findings suggest the positive effects of tomato and carrot supplementation against cisplatin-induced dyslipidemia, hepatotoxicity, and risk of cardiovascular diseases. Accordingly, carrot and tomato supplementation might serve as unique supplements that can be used in conjunction with cisplatin chemotherapy.

Keywords: Cisplatin, Hepatotoxicity, Dyslipidemia, Supplementation, Lipid profile.

Introduction

Cisplatin, a platinum-containing anticancer drug represents chemotherapy used to treat a variety of cancers.[1] Its structure consists of two chlorine atoms on the same side (cis-) and two ammonia atoms on the other side with platinum coordinated at the center $[Pt(NH_3)_2Cl_2]$. Owing to it cytotoxicity, it is used as a single drug or in combination with other antineoplastic agents against many different cancers of a wide variety of malignancies, comprising of carcinomas of the ovary,[2] breast cancer,[3] brain tumors[4] lung cancer,[5] and leukemia.[6, 7] The use of cisplatin in clinical settings is often limited due to its toxic side effect.[8-11] Animals exposed to cisplatin showed significantly less level of antioxidants with a higher oxidation of both proteins and lipids in addition to causing changes in the enzyme complex of the electron transport system.[12] This platinum-based antineoplastic agent is normally metabolized in the liver and metabolites excreted through the kidneys and as such toxicity occurs on these organs.[13, 14] Studies conducted on amelioration of cisplatin-induced hepatotoxicity by Xanthorrhizol suggested that a combination of both cisplatin and Xanthorrhizol might be a preventive measure to hepatotoxicity than administering cisplatin alone.[15] More investigations have been carried out on organ toxicity due to chemotherapies.[15,16] including biochemical estimation of hepatic enzymes as well as electron microscope examinations.[17, 18]

Dyslipidemia depicts a situation in which there is an abnormal level of lipid in the blood. It could either be above or below the normal level and serves as an important marker for the risk of coronary heart diseases and stroke.[19] High level of triglycerides (hypertriglyceridemia) has been encountered after the treatment of cancer patients with paclitaxel and cisplatin chemotherapy.[20] An earlier study observed that treatment of mice with paclitaxel and cisplatin decreased triglycerides and slightly increased cholesterol and concluded that paclitaxel and cisplatin chemotherapies result in transient dyslipidemia.[20]

Tomato (*Solanum Lycopersicum*) is a nutritious fruit with potent antioxidants, vitamin C, and lycopene, which relief cardiovascular diseases and inflammation.[21-23] The component of this fruit includes bioactive compounds and carotenoids accounting for antioxidants properties,[17, 24] ascorbic acid and phenolic compounds.[25, 26]

Carrot (*Daucus Carota*), a more commonly utilized vegetable consumed for human sustenance is rich in antioxidants, ascorbic acid, tocopherol, and beta carotene.[27] Its use in human nutrition prevents not only vitamin A deficiency but other diseases such as cancer, secure against hypertension, stroke, osteoporosis, cataracts, joint inflammation, coronary illness, urinary tract diseases, and bronchial asthma.[28-30]

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The liver is a key organ in the body concerned with several states of metabolic and physiologic homeostasis of human beings. This paper aims to examine the effect of a supplementary diet of carrot and tomato against cisplatin-induced dyslipidemia and hepatic transaminase changes and the risk of cardiovascular diseases in male Wistar rats.

Materials and Methods

Collection of plant samples
The carrot and tomato used for the experiment were purchased from the Wednesday market, Dutsinma, Katsina State, Nigeria. They were identified in the Biological Sciences Department, Federal University Dutsinma, Katsina State, Nigeria with voucher numbers 0335 and 0336, respectively. Cisplatin injection was purchased from a registered pharmacy in Katsina state.
The collected fresh tomato and carrot were carefully sliced and dried at room temperature after which they were separately pulverized.

Experimental animals
Thirty (30) male Wistar rats weighing 98.4 ± 2.4 g were used for the present study. They were purchased from the animal house of the National Research Institute (NVRI), Vom, Plateau state Nigeria. They were kept in wooden cages and treated following the international standard for caring and the use of laboratory animals. The animals were allowed to acclimatize to housing conditions for 7 days before the experiment.

Ethical clearance
Ethical clearance was obtained from Federal University, Dutsin-Ma Institutional Ethical Committee on the use of animals and human subjects in research with approval number FUDMA/IEC/2018/0078. This permission was obtained in the 2018/2019 sessions, prior to the start of Experimental protocols.

Formulation of the Experimental Diets
The plant materials (carrot and tomato) were measured as follows; 200 g of the starters' mash (control diet) was measured for groups 1 and 2. For group 3, 190 g of the control diet was supplemented with 10 g of carrot in the ratio 19:1. In group 4, 190 g of the control diet was supplemented with 10 g of tomato in the ratio 19:1. Finally, in group 5, 10 g of carrot, 10 g of tomato were supplemented with 180 g of the control diet in the ratio 18:1:1.

Experimental design and procedure
The animals were arbitrarily distributed into five groups of 6 rats each, housed individually in wooden cages. Cisplatin was injected intraperitoneally as a single dose of 7.5 mg/kg body weight. The rats were maintained on the diet based on the starters' mash and based on a supplementary diet (carrot and tomato) thrice in a day for a week (Figure 1). The rats also received distilled water daily.

Animal Sacrifice and Collection of Samples
The animals were weighed and sacrificed by anesthetizing them in a plastic rubber containing cloth soaked in chloroform after 7 days of feeding trial. Blood was obtained through the jugular veins in lithium heparin bottles. The whole blood was spun in a bench top centrifuge at 1500 rpm for 15 minutes to obtain plasma.

Determination of Transaminases Activity
Serum ALT assay is based on the principle of Reitman and Frankel (1957),[31] in which the enzyme catalyzes the transfer of an amino group between alanine and α- ketoglutarate to yielding pyruvate as a product. Serum AST assay is based on the principle of Reiman and Frankel (1957),[31] in which the enzyme catalyzes the transfer of an amino group between aspartate and α-ketoglutarate to yielding oxaloacetate as a product. Serum ALP assay is based on Kind & King's method (1954),[32] in which the enzyme at an alkaline pH hydrolyses di-sodium phenylphosphate to form phenol. The phenol formed reacts with 4-Aminoantipyrine in the presence of potassium Ferricyanide, as an oxidizing agent, to form a red-coloured complex. The intensity of the colour formed is directly proportional to the activity of ALP present in the sample.

Determination of lipid parameters
Plasma cholesterol level was determined following the method of Abell *et al*[33] involve the extraction of cholesterol by organic solvents and subsequent alkaline hydrolysis of the cholesterol esters and oxidation. Triglyceride was determined using the glycerol phosphate oxidase reaction described by Tietz.[34] HDL was determined using the glycerol phosphate oxidase reaction described by Tietz.[34] Low-Density Lipoprotein was calculated by using this formula; Low-Density Lipoprotein = cholesterol triglyceride/2.2 + high-density lipoprotein.[35]

Atherogenic indices
Atherogenic indices are powerful indicators of the risk of heart disease: the higher the value, the higher the risk of developing cardiovascular disease and vice versa. Atherogenic indices are comprised of the atherogenic *index* of plasma (AIP), Cardiac risk ratio (CRR), and Atherogenic coefficient (AC) were calculated by using the values of lipid profile parameters in the following way:

$$\text{Atherogenic index of plasma} = \frac{\text{Log Triglyceride}}{\text{High density lipoprotein} - \text{C}}$$

$$\text{Cardiac Risk Ratio} = \frac{\text{Total Cholesterol}}{\text{High density lipoprotein} - \text{C}}$$

$$\text{Atherogenic Coefficient} = \frac{\text{Total cholesterol} - \text{High} - \text{density lipoprotein} -}{\text{high density lipoprotein} - \text{C}}$$

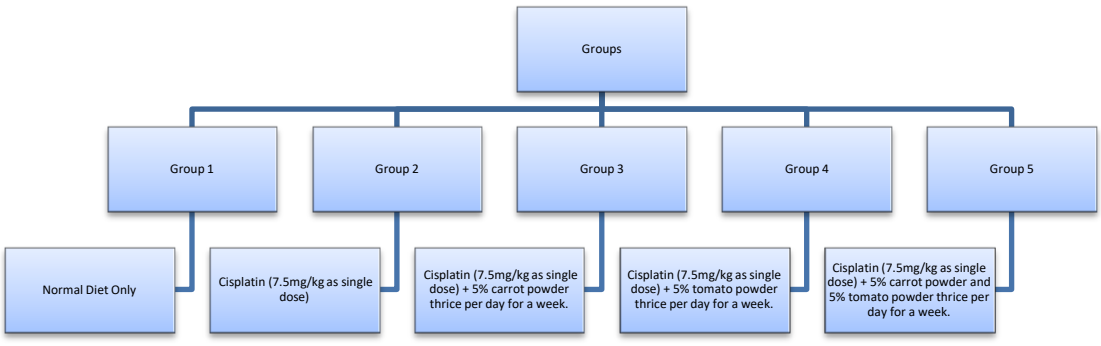

Figure 1: Schematic representation of the Experimental design

Statistical analysis

The experimental results obtained are expressed as mean ± standard deviation (SD). The data were subjected to one-way analysis of variance (ANOVA) and differences between samples were determined by Tukey multiple comparison tests using the SPSS 16 (Statistical Program for Social Sciences) program. The level of significance was set at $p < 0.05$.

Results and Discussion

The results obtained from this study were presented in Tables 1-3 and Figures 2-4. Table 1 shows the result of the change in body weight and liver weight. Values for both the body weight and liver weight showed that rats in groups 3-5 (cisplatin + supplemented diet) did not differ significantly ($P < 0.05$) compared with the control. But, there was a significant difference ($P < 0.05$) between group two (cisplatin only) compared with the other groups. The results of the AST, ALT, and ALP enzyme assayed (See Figures 2-4) in the serum of rats maintained on a supplementary diet and control shows that there was no significant difference ($P < 0.05$) between the concentration of AST, ALT, and ALP in the serum of rats in groups 3-5 (cisplatin + supplemented diet) and the control group. But, there was a significant difference ($P < 0.05$) between rats in group 2 (cisplatin only) compared with the other groups.

The lipid profile parameters obtained for seven days were summarized in Table 2. The result demonstrated that cisplatin-treated rats (Group 2), exhibited a significant increase ($P < 0.05$) in the mean total cholesterol, mean triglyceride, and mean LDL and decrease in HDL level as compared to both the control group and rats placed on carrots and tomato supplements. Supplementation with both carrot and tomato appears to intervene with dyslipidemia as no significant difference was observed between groups 3-5 and the control (See Table 2). The results of the atherogenic parameters were summarized in Table 3. Cisplatin treated group (Group 2) exhibited elevated levels of all three atherogenic indices (See Table 3) as compared to the control group rats ($P < 0.05$). It was also observed that after treatment with carrot and tomato, atherogenic indices in groups 3-5 reverses towards control.

The current study shows that cisplatin caused body weight and liver weight loss within the experimental period (Table 1). In the current study, we examined the possibility of using a supplementary diet containing carrot and tomato both synergistically and individually to protect and lessen the hepatotoxicity and dyslipidemia induced by cisplatin on normal liver tissues of male albino rats.

The significant difference observed in the body weight of rats injected with cisplatin in group 2 compared with the other groups might be due to the highly emetic effect of cisplatin which leads to decreased food intake and body weight retardation. It was reported that cisplatin dose-dependently induced both gastric stasis and stomach distension thereby decreasing the animal motivation to eat or drink.[36]

Reduction in liver weight observed for mice in group 2 is consistent with the result from previous experimental studies which indicated that cisplatin treatment for 15 days in BALB/C mice resulted in liver weight loss.[37]

The result obtained from in the liver function test revealed that the supplements (tomato and carrot) when administered individually or together decrease the licking of hepatic compartmentalized enzymes (aspartate transaminase, alanine-aminotransferase, and alkaline phosphatase) (Fsigure 2-4). When damaged, membranes of the liver cells can become permeable, allowing for the escape of high levels of aspartate transaminase, alanine-aminotransferase, and alkaline phosphatase into the bloodstream.[38] They are therefore used as biomarkers to predict possible toxicity in some organs such as liver cirrhosis.[39]. It was reported that cisplatin at high dose may cause abnormal Tests of liver function such as ALT and AST.[40] Suggestion has been made that chemotherapies alone or in combination may cause hypersensitivity and altered liver function, which could lead to altered drug metabolism thereby causing non-hepatic toxicity.[41]

Our results are in agreement with studies conducted by other authors[42, 43] whose study showed that an increase in ALT, AST, and ALP levels in the experimental group was related to liver cell damage and many other changes in the hepatic function. The hepatocytes are known to accumulate significant amounts of cisplatin, so hepatotoxicity is attributed to cisplatin storage in hepatocytes.

As ALT exists mainly in the liver cell cytoplasm and mitochondria, it is one of the most sensitive parameters for liver cell function tests as recommended by WHO. AST is found more in cardiac muscle than in liver cells. AST has 2 isoenzymes, ASTs, and ASTm, respectively. In the normal serum, AST exists mainly as ASTs, and when necrosis occurs, ASTm is released from liver mitochondria, and its level in the blood serum increases. ALT and AST are the key indices used in measuring the level of liver cell injury.[44]

The increase in the plasma total cholesterol, LDL, and triglyceride and reduced HDL in the cisplatin-treated group as compared to the control group as revealed in the current study confirm with the previous study by Saleh *et al*[45] The elevated plasma total cholesterol, triglyceride and LDL might be due to centrilobular necrosis, which results in translocation and accumulation of fats from peripheral adipose tissue in the liver, increased hepatic synthesis of fatty acids and reduce cholesterol catabolism.[46]

Also, the elevated LDL level in cisplatin-treated rats may be due to hepatic secretion of apoprotein B-100 which is elevated upon cisplatin administration and responsible for the secretion of LDL that eventually causes an increase in its blood level.[47] On the other side, the reduction in HDL may be related to the reduction in Apo-A1, which is a principal protein of HDL synthesis (i.e., impaired synthesis of HDL) that can be induced by cisplatin intoxication as clarified by Mohammadi *et al*.[48] The elevation of triglycerides level in the cisplatin-treated group may be due to the impaired removal and destruction of triglycerides rich in lipoproteins such as, LDL, IDL, VLDL, and remnants or due to the increased hepatic synthesis of fatty acids.[49]

A marked recovery was observed in the carrot, tomato, and carrot + tomato treated group (Table 2). There was a significant increase the body weight as compared to the cisplatin-treated group. It seems that its phytochemical constituent could act as a gastrointestinal tract stimulant that relief lack of appetite and indigestion.[50] Moreover; the supplementary diet used in the present study was effective in reducing the values of the biochemical parameters of lipid profiles (Table 2). There was a significant decrease in plasma total cholesterol, triglycerides, and LDL-cholesterol and an increased plasma HDL-cholesterol, as compared to cisplatin-treated groups (Table 2). These results are in the same line as those of Bushuty and Shanshan.[51] The anti-hyperlipidemic and hypocholesterolemic effects of carrot and tomato could be attributed to the presence of antioxidants and phytochemicals which exert their actions to prevent absorption of cholesterol in the intestine, inhibit lipoprotein production, increases expression of hepatic LDL receptors; which results in the net removal of LDL-cholesterol from the blood and its clearance from the body.[52]

In addition, it was observed that this ameliorative role of tomato and carrot was also effective when both foods were used in together and this may be due to the fact that; When ingested as a mixture, phytochemicals in food undergo multifaceted interactions, promoting health benefits and protecting humans against diseases due to the nature of their diverse mechanisms of action that work simultaneously, it is difficult but critical to identify these natural interactions and to elucidate some of the most powerful naturally derived mixtures.[53]

The elevation in atherogenic indices in cisplatin-treated groups as compared to the control group is due to the aforementioned elevation in total cholesterol, LDL, and triglyceride (Table3). This reveals that cisplatin induction might increase the risk of cardiovascular diseases.

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Table 1: Body and liver weight of rats maintained with supplementary diet

GROUPS	Body Weight (g)		Weight of liver (g)
	Initial	Final	
Group 1	97.53 ± 2.30[a]	125.70 ± 2.10[a]	5.60 ± 0.10[a]
Group 2	98.32 ± 2.50[a]	95.00 ± 2.50[b]	3.44 ± 0.32[b]
Group 3	97.62 ± 2.40[a]	122.60 ± 1.40[a]	5.37 ± 0.20[a]
Group 4	98.10 ± 2.20[a]	121.20 ± 1.20[a]	5.25 ± 0.40[a]
Group 5	96.86 ± 2.40[a]	120.20 ± 1.20[a]	5.39 ± 2.90[a]

Values are expressed as mean ± SD. Values along the row with the same superscript are not significantly different (P < 0.05).

Table 2: Lipid profile parameters of control and treated groups (mmol/L)

Parameters	Group I	Group II	Group III	Group IV	Group V
Total Cholesterol	3.32 ± 0.17*	4.50 ± 0.18**	3.61 ± 0.13*	3.62 ± 0.14*	3.28 ± 0.13*
Triglyceride	1.29 ± 0.11*	2.39 ± 0.13**	1.49 ± 0.11*	1.51 ± 0.12*	1.28 ± 0.11*
HDL	0.91 ± 0.15*	0.63 ± 0.07**	0.82 ± 0.09*	0.90 ± 0.06*	0.91 ± 0.06*
LDL	3.65 ± 0.14*	4.21 ± 0.38**	3.75 ± 0.16*	3.74 ± 0.21*	3.60 ± 0.10*

Values are expressed as mean ± standard deviation of six determinations. Mean with the same asterisk within the same row are not significantly different (p < 0.05).

Table 3: Atherogenic indices of control and treated groups

Parameters	Group I	Group II	Group III	Group IV	Group V
Atherogenic Index of Plasma	0.17 ± 0.07*	0.58 ± 0.08**	0.27 ± 0.06*	0.26 ± 0.05*	0.15 ± 0.05*
Cardiac Risk Ratio	3.61 ± 0.52*	7.20 ± 0.82**	4.19 ± 0.45*	4.16 ± 0.38*	3.62 ± 0.35*
Atherogenic Coefficient	2.74 ± 0.75*	6.20 ± 0.82**	3.47 ± 0.45*	3.04 ± 0.64*	2.62 ± 0.36*

Values are expressed as mean ± standard deviation of six determinations. Mean with the same asterisk within the same row are not significantly different (p<0.05).

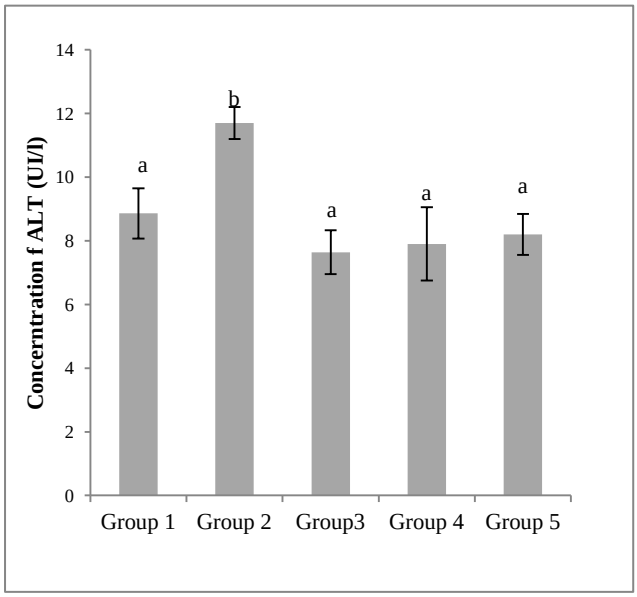

Figure 2: Effect of supplementation on cisplatin-induced alanine amino transferase changes.
Values are expressed as mean ± standard deviation of six determinations. Mean with the same alphabet do not significantly different (p<0.05).

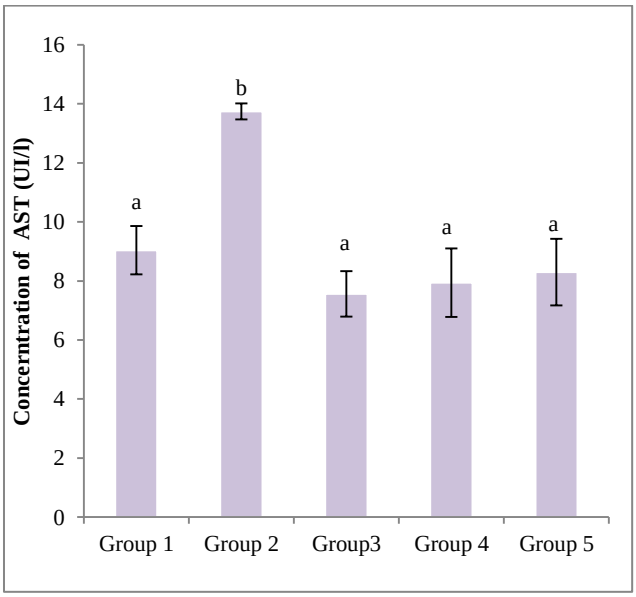

Figure 3: Effect of supplements on cisplatin-induce Aspatate amino Transferase changes.
Values are expressed as mean ± standard deviation of six determinations. Mean with the same alphabet do not significantly different (p<0.05).

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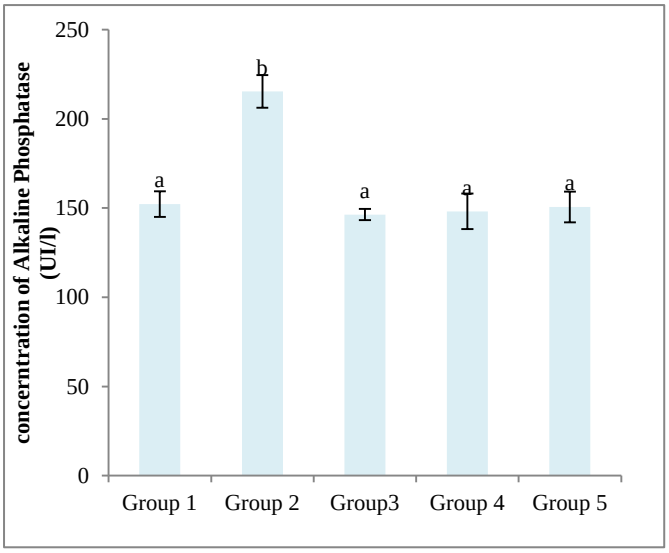

Figure 4: Effect of supplements on cisplatin-induce alkaline phosphatase changes.
Values are expressed as mean ± standard deviation of six determinations. Mean with the same alphabet do not significantly different ($p < 0.05$).

Conclusion

We have concluded that carrot and tomato supplementations ameliorated the changes in lipid profile and hepatic toxicity caused by cisplatin injection. This amelioration effect might be attributed due to their antioxidants activity. The synergistic effect of carrot and tomato has also been observed to ameliorate the cisplatin-induced toxicity. These supplements, therefore, can be used in conjunction with anticancer drugs in cancer patients.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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