RESEARCH ARTICLE

Protective Effects of Aqueous Cranberry Fruit Extract against Genotoxicity Induced by Cisplatin in Mice Bone Marrow Cells

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ABSTRACT

The cranberry (*Vaccinium macrocarpon*) is a North American native fruit and contains a very wide variety of phytochemicals which has several beneficial effects on humans.

Aim: The study was designed to assess the protective effect of cranberry fruit extract on selected genotoxic parameters induced by cisplatin in mice's bone marrow.

Methods: 56 male albino mice were randomLy divided into two equal numbers (28 mice)/for each part of the study [Part one: for the evaluation of chromosomal aberrations and the mitotic index; and Part two**:** for the evaluation of micronucleus index]; and for each part, mice were randomLy divided into 4 groups: Group I [negative Control/orally-administered normal saline]; Group II [Orally-administered cranberry fruit extract alone]; Group III [Single IP injection of cisplatin]; Group IV [Orally-administered cranberry fruits extract followed by a single IP injection of cisplatin].

Results: Treatment with cisplatin significantly-increased total chromosomal aberration (0.159 ± 0.006) and micronucleus appearance (9.740 ± 0.531) but, it has a significant decrease in mitotic index (6.020 ± 0.589) compared to that in negative control bone marrow cells. In addition, results showed that there were significant changes in the total chromosomal aberration, micronucleus appearance, and mitotic index among the Groups (II, III, IV) (0.093 ± 0.015; 0.159 ± 0.006; 0.117 ± 0.002), (5.940 ± 0.568; 9.740 ± 0.531; 8.000 ± 0.479) and (8.720 ± 0.432; 6.020 ± 0.589; 7.480 ± 0.664), respectively in bone marrow cells.

Conclusion: Cisplatin produced a pronounced effect on total chromosomal aberrations, micronucleus appearance, and mitotic index; and the cranberry fruit extract confers a protective effect against cisplatin-induced genotoxicity in mice.

Keywords: Cisplatin, Cranberry fruit extract, Genotoxicity, Protective.

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INTRODUCTION

Cisplatin is one of the most potent chemotherapeutic agents in the platinum-based antineoplastic drugs class.[1] It is used alone or in combination with chemotherapy regimens[2] for the treatment of a wide range of human cancers.[3] Park *et al.* (2018) reported the main target for the genotoxicity of cisplatin is DNA. In addition to lipids, and proteins, and these targets interact with the excess of reactive oxygen species (ROSs) such as superoxide anion radical (O2.-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH.-) that are formed, resulting in the development of oxidative stress (OS) and DNA damage.(4) Other studies (Liu *et al.* (2019); Ghosh *et al.*,(2013)) reported that in addition to DNA damage and inhibition of antioxidant enzyme activity, the excessive production of ROSs induced by cisplatin caused severe impairment in the normal cellular functioning and toxic damage to the organs.[5,6]

Genotoxicity is the damage to the cell's genetic information (chromatin material and DNA) by either exogenous or endogenous sources.[7] The DNA damage/genotoxicity results from harmful factors that are oxidative in nature, including chemically-induced ROSs (as mentioned above), ionizing radiations, environmental factors, chemotherapeutic agents, radiotherapy, and viruses, that have an impact on individual DNA strand breaks; double DNA strand breaks; chromosomal damage; micronucleus (MN) production; sister chromatid exchange, massive deletions, insertions, translocations, transitions, and transversions.[8,9] Furthermore, chromosomal aberrations/abnormalities are alterations in genetic materials

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caused by the loss, gain, or rearrangement of certain segments in chromosomes that can lead to genetic instability/disorders or even cancer, depending on the size, position, and duration of the change.[10] MN testing is a fundamental assay used to evaluate chromosomal DNA damage. An increase in the frequency of micronuclei indicates damage to the genome and instability.[11]

Cranberry (*V. macrocarpon*) is a native North American fruit widely cultivated in the northeastern and north-central United States.[12] It has a very wide variety of phytochemicals such as polyphenolic compounds, including three classes of flavonoids [anthocyanins, proanthocyanidins (PACs), and flavonols]; and it also contains hydroxycinnamic acid, ascorbic acid, triterpenoids, many vitamins, trace elements, and others. These phytochemicals act as antioxidants, which reduce oxidative damage to cells that can lead to cancer.[13]

There is great interest in determining the potential health benefits of cranberry extracts to humans.[14] Cranberry has several beneficial effects on humans as an antioxidant, prevention of cardiovascular (CV), kidney, periodontal diseases, obesity, cancer, and others.[15]

There is a great interest in using medicinal plants as adjuvants with chemotherapeutic drugs and attenuating their adverse events and toxicity. This study was designed to evaluate the possible protective effect of cranberry fruit extract against cisplatin-induced genotoxicity in BM cells of mice.

MATERIALS AND METHODS

Chemicals

Chemicals utilized in this study include Cranberry pure powder of the fruit extract from Hangzhou Hyper Chemicals Limited (China), from which prepared the solution of the experiment design dose by dissolving it in distilled water then this solution is mixed for use. Cisplatin (50 mg/50 mL) injectable solution from Accord Healthcare (Ireland); Colchicine pure powder obtained from Shaanxi Yuantai Biological Technology Co., Ltd (China); Diethyl ether liquid 98% from May and Baker (England); Fetal bovine serum from Capricorn Scientific Gmbh (Germany); Giemsa stain powder from Fluka (Switzerland); phosphate-buffered saline (FBS) from EuroClone Milan (Italy).

Laboratory Animals and the Experimental Protocol

A total of 56 male albino mice were used in this research and were provided from the Animal House, located inside the College of Pharmacy at the University of Baghdad. Their average weight was (25–30 gms) and was kept at standard conditions of temperature (23–25°C), day/night cycle, and had unrestricted access to industry-standard food (pellets) and water (ad libitum). Both the Ethical Committee of the Department of Pharmacology and Toxicology and the Scientific Committee of the College of Pharmacy, University of Baghdad accepted the study. Mice were arbitrarily divided into 2 parts (28 mice/each). Part one was utilized for the assessment of chromosomal aberrations and mitotic index (MI), and part two was utilized for micronucleus index (MN) assay; and in each part, mice were divided to 4 groups (7 mice/group) as follows:

Group I [Negative Control]. Male mice were orally administered 0.25 mL NaCl daily by gavage tube for 7 days.[16]

Group II [Cranberry (CB)]. Male mice were orally administered cranberry (CB) fruits extract solution (200 mg/kg/day) by gavage tube for 7 days.[17]

Group III [Cisplatin]. Male mice were orally administered 0.25mL NS daily for 7 days by gavage tube, and a single IP dose of cisplatin (12 mg/kg B.W) was injected on day 7.[18]

Group IV [Cranberry (CB)-Cisplatin]. Male mice were given cranberry fruits extract solution (200 mg/kg B.W/day) orally through a gavage tube for 7 days, followed by a single IP injected dose of cisplatin (12 mg/kg B.W) on day 7.

Evaluation of Genotoxicity Markers in Bone Marrow (BM) Cells

Chromosomal Aberrations and Mitotic Index (MI)

After 24 hours of treatment duration ended (*i.e.,* on day 8th), each mouse was IP injected with 1-mg/kg colchicine. After 2 hours, mice were euthanized by cervical dislocation, and bone marrow samples were extracted from the femurs of the mice. Then BM cells were taken and genotoxic analyses were carried out using an aseptic technique for the evaluation of mitotic index (MI).[19,20]

Micronucleus (MN) Test

Mice were sacrificed by cervical dislocation at the end of the experiment (on day 8th). Smears of BM were prepared according to the method of Agarwal and Chauhan, stained with Giemsa, and the calculating incidence of MN appearance.[21]

Statistical Analysis

Data were analyzed by utilizing the Microsoft office excel (2010) program and the unpaired student t-test was utilized throughout all of the statistical analyses that were done for each group pairing. The data were expressed as mean ± standard deviation (Mean ± SD) and the p values < 0.05 were considered to be statistically significant. Further, a one-way analysis of variance (ANOVA) has been performed for comparisons among different groups based on the post hoc Tukey's test. SPSS 20 was utilized for each statistical analysis that was carried out. *p values* < 0.05 were regarded as being statistically significant.

RESULTS

Table 1 demonstrated that there was no statistically significant difference ($p > 0.05$) in each of the chromatid breaks, chromatid gaps, acentric chromosome, and dicentric chromosome in BM cells of mice with orally-administered CB fruit extract alone (200 mg/kg/day) (Group II) compared to the aforementioned structures in the BM cells of group I/negative control mice. Moreover, in mice injected IP with a single dosage of cisplatin CP (12 mg/kg B.W) Group III, there was a statistically-significant ($p < 0.05$) increase in chromatid breaks, chromatid gaps, acentric chromosome, and dicentric chromosome compared to the aforementioned structures in the BM cells of negative control/Group I mice.

Table 1: The effect of cranberry (CB) fruit extract on cisplatin (CP)-Induced chromosomal aberrations in Mice's bone marrow cells

No. of groups	*Names of groups*	*Chromatid break*	*Chromatid gap*	*Acentric chromosome*	*Dicentric chromosome*
Group I	Normal Saline(Control)	0.06 ± 0.008 b	0.058 ± 0.008 b	0.200 ± 0.057 b	0.180 ± 0.018 b
Group II	Cranberry extract alone (200 mg/kg/day)	0.05 ± 0.007 b	0.050 ± 0.012 b	0.190 ± 0.053 b	0.176 ± 0.015 b
Group III	Cisplatin (12 mg/kg/day)	0.09 ± 0.018 a	0.104 ± 0.043 a	0.308 ± 0.056 a	0.226 ± 0.040 a
Group IV	Cranberry extract (200 mg/kg/day) + cisplatin (12 mg/kg/day)	0.06 ± 0.013 b	0.062 ± 0.031 b	0.254 ± 0.039 ab	0.194 ± 0.011 ab

*Data expressed as Mean ± SD; N=7 animals/group.

*Values with non-identical small letters (a, and b) are significantly different ($p < 0.05$).

*Values with identical small letters (a or b) are non-significantly different ($p > 0.05$).

*Values with both (ab) letters in the acentric- and dicentric-chromosome columns indicate that "a" is a non significantly different ($p<0.05$) compared to Group III mice, and " b" is non-significantly different compared to Group I and II mice.

On the other hand, BM cells of mice with orally-administered CB prior to CP (Group IV) revealed a significant decrease ($p < 0.05$) in the chromatid breaks and chromatid gaps in comparison to such structures in the BM cells of group III mice (IP injected with a single dose of CP); but, there have been no significant differences ($p > 0.05$) in the aforementioned BM structures in Group IV compared to that in the negative control (Group I) mice.

Additionally, Table 1 demonstrated no statistically significant differences ($p > 0.05$) in the acentric-, and dicentric-chromosome in the BM cells of mice CP (Group IV) compared to such structures in the BM cells of -Group III/CP-group, -Group I/negative control and -Group II (CB-treated) mice.

Table 2 showed there were non-significant differences ($p > 0.05$) in the ring chromosomes, deletion chromosomes, chromosome breaks, chromosome gaps, and total chromosomal aberrations in BM cells in group II mice [orally-administered CB fruit extract alone (200 mg/kg/day)] compared to corresponding chromosomal structures in the negative control/group I mice.

Furthermore, there was a statistically significant increase ($p < 0.05$) in the ring chromosomes, chromosome breaks, chromosome gaps, and total chromosomal aberrations in BM cells of group III (IP injected with a single dose of cisplatin) compared to such structures in the BM cells of group I/negative control mice; but there were no statistically significant different ($p > 0.05$) in the chromosomal deletion in the BM cells of Group III compared to such structures in the BM cells of group I/negative control mice.

In addition, Table 2 demonstrated a significant reduction ($p > 0.05$) in the -ring chromosomes,-chromosome breaks, -chromosome gaps, and -total chromosomal aberrations in the BM cells of group IV mice (treated with CB prior to cisplatin) compared to such structures in the BM of group III mice, but, no-significant differences ($p > 0.05$) in such aberrations in the BM cells of group IV compared to that in the BM cells of negative control (Group I) mice.

Moreover, Table 2 showed that there was no -significantly different ($p > 0.05$) in the chromosomal deletion of Group IV mice in comparison to such structure in the BM cells of group III, and Group I (negative control) mice.

Table 3 shows no-significantly differences ($p > 0.05$) in the MN appearance in BM cells of Group II mice (CB-treated) in comparison to a similar appearance in the BM cells of negative control Group I mice.

Moreover, the MN appearance in BM cells was significantly elevated ($p<0.05$) in Group III/mice IP injected with a single

Table 2: The effect of cranberry (CB) fruit extract on the rest of chromosomal aberrations in Mice's bone marrow cells induced by cisplatin (CP).

No. of groups	*Names of groups*	*Ring chromosome*	*Deletion chromosome*	*Chromosomal breaks*	*Chromosomal gaps*	*Total chromosomal aberrations*
Group I	Normal Saline(Control)	0.178 ± 0.0507 b	0.034 ± 0.018 ab	0.048 ± 0.027 b	0.058 ± 0.008 B	0.101 ± 0.017 bc
Group II	Cranberry extract alone (200 mg/kg/day)	0.170 ± 0.043 b	0.028 ± 0.020 b	0.038 ± 0.026 b	0.048 ± 0.016 B	0.093 ± 0.015 c
Group III	Cisplatin (12 mg/kg/day)	0.276 ± 0.048 a	0.056 ± 0.019 a	0.098 ± 0.014 a	0.110 ± 0.044 A	0.159 ± 0.006 a
Group IV	Cranberry extract (200 mg/kg/day) + cisplatin (12mg/kg/day)	0.214 ± 0.011 b	0.036 ± 0.015 ab	0.056 ± 0.039 b	0.062 ± 0.035 B	0.117 ± 0.002 b

* Data expressed as Mean ± SD; N= 7 animals in each group.

*Values with non-identical letters (a, b, and c) are significantly different ($p < 0.05$).

*Values with identical letters (a or b or c) are non-significantly different ($p > 0.05$).

*Values with both (bc) letters in the total chromosomal aberrations column indicate that "c" is non-significantly different (P<0.05) compared to Group II mice, and "b" is non-significantly-different compared to Groups IV mice.

Table 3: The effect of cranberry (CB) fruit extract on micronucleus appearance (MN) mitotic Index (MI) in mice' bone marrow cells

No. of groups	*Names of groups*	*Micronucleus appearance (MN)*	*Mitotic Index (MI)*
Group I	Normal saline(control)	5.820 ± 0.476 c	9.040 ± 0.492 a
Group II	Cranberry extract alone (200 mg/kg/day)	5.940 ± 0.568 c	8.720 ± 0.432 a
Group III	Cisplatin (12 mg/kg/day)	9.740 ± 0.531 a	6.020 ± 0.589 c
Group IV	Cranberry extract (200 mg/kg/day) + cisplatin (12 mg/kg/day)	8.000 ± 0.479 b	7.480 ± 0.664 b

* Data expressed as Mean ± SD; N=7 animals/group.
* Values with non-identical letters (a, b, and c) indicate a significant difference ($p < 0.05$).
* Values with identical letters (a or c) indicate no significant difference ($p > 0.05$).

dose of cisplatin (1.67folds increase) compared to such appearance in the BM cells of negative control/Group I mice.

Table 3, also showed that in group IV mice (CB-Cisplatin) a significant decline ($p < 0.05$) in the MN appearance in BM cells compared to the similar appearance in the BM cells of group III mice/(IP injected with a single dose of CP); but there was a statistically significant increase ($p < 0.05$) in the MN appearance in the BM cells of group IV mice in comparison to such appearance in the BM cells of Group I/negative control mice.

Also, it demonstrated that there were no significantly different ($p > 0.05$) in the MI in BM cells in mice of group II (CB-treated) compared to the corresponding index in group I/ negative control mice; the levels were [8.720 ± 0.432 and 9.040 ± 0.492], respectively.

Furthermore, there was a significant decrease ($p < 0.05$) in MI in BM cells in mice of groups III (IP injected of a single dose of cisplatin), in comparison to that in mice of group I/ negative control; the levels were [6.020 ± 0.589 and 9.040 ± 0.492], respectively.

In addition, Table 3 showed that in mice of group IV [treated with CB prior to cisplatin], there was a significant increase ($p < 0.05$) in the MI in BM cells (7.480 ± 0.664) (1.242 folds increase) compared to the corresponding index in Group III mice (6.020 ± 0.589). Furthermore, Table 3 showed that there was a significant decrease ($p < 0.05$) in the MI in the BM cells of group IV mice compared to such index in Group I/negative control mice (9.040 ± 0.492).

DISCUSSION

Cisplatin is one of the most platinum-based chemotherapeutic drugs used frequently for a wide range of various types of cancer;[22] since, after entering the cell, it becomes a potent electrophile that has the ability to bind with a number of nucleophiles such as RNA, DNA, and proteins [Ghosh, Sumit (2019)].[23] Numerous studies found that cisplatin's induction of genotoxicity was related to the generation of a significant amount of reactive oxygen species (ROS) (Aksu *et al*., 2016; Sadeghi *et al*., 2018);[24,25] where ROSs can attack DNA destabilize the double helix, and disruption of the DNA repair mechanism through the formation of intra-and inter-strand crosslinks (cisplatin–DNA adducts) leading to DNA strand breakage, and mutations at DNA sites. ROSs can also lead to the creation of micronuclei and chromosomal abnormalities (Huang *et al*., 2019).[26]

Moreover, researchers also observed that platinum could induce DNA damage and MN generation, both of which are indicators of genotoxic occurrences and chromosomal instability and indicate genomic damage that can increase the risk of developmental or degenerative diseases.[27,28] where a single IP dose of cisplatin injected on day seven of the current study produced a significant increase in chromosomal aberrations and MN appearance with a decrease in the cell proliferation (Tables 2 and 3).

Besides, Ganaie *et al*, (2019) stated that natural flavonoids possess antioxidant properties and can exert protective effects against DNA damage,[29] and this was observed in the present study where oral administration of 200 mg/kg of CB fruit extract for seven successive days before cisplatin injection on day seven (Group IV) produced a significant rise in the cell proliferation with a decline in the MN appearance and chromosomal aberrations (Tables 2 and 3).

Wu X, *et al.* (2020) stated that CB extracts mainly contained polyphenol-rich antioxidants, consistent with its higher content of flavonoids and proanthocyanidins, with trace amounts of triterpenes which are well-known radical scavengers that are capable of inhibiting oxidative processes; and these compounds can contribute to the chemopreventive properties of CB.[30] Moreover, a study by Izquierdo-Vega J.A, *et al.* (2017) reported that a variety of fruits involving (cranberries) are frequently consumed by humans and can be considered a potential antigenotoxic effect. Moreover, analysis of phytochemicals extracted from fruits also mentioned the antigenotoxic capacity of such part of the plant in various tests, including the chromosomal aberrations, and MN assay.[31] In addition, Madrigal, et al (2012) reported that the cranberry ethanolic extract (CEE) was not genotoxic nor cytotoxic, in contrast, it reduced the incidence of the MN that the genotoxic compound had produced, which suggests that the anticlastogenic activity of such plant extract is associated to the antioxidant potential of the mixture of phytochemicals that are present in its chemical structure.[17]

Furthermore, it has been reported that the flavonoid "quercetin" that is found in many fruits (including cranberries), vegetables, leaves, seeds, and other plant sources has been demonstrated to promote apoptosis in cancer cells *in-vitro* and enhanced synergistically. The anti-proliferative activity of cisplatin in these cells increases cisplatin's ability to cause apoptosis in cancer cells.[32]

CONCLUSION

According to results obtained from the present study, cisplatin has considerable effects on total chromosomal aberrations, MI, and MN appearance; and the orally-administered CB prior to CP improves the genotoxic effects induced by cisplatin; in other words, it has geno-protective effects against such chemotherapeutic drug in mice' BM cells.

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