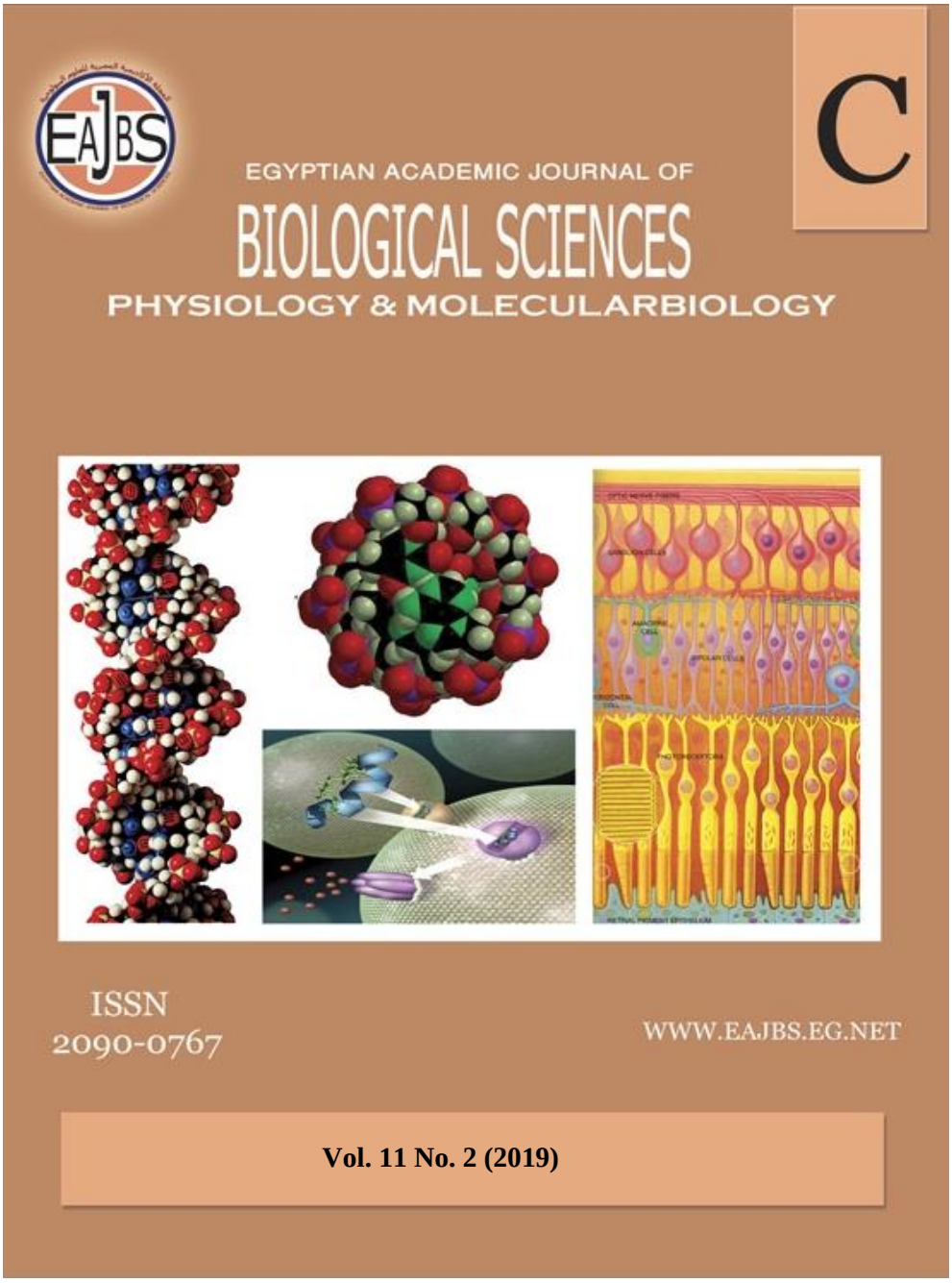

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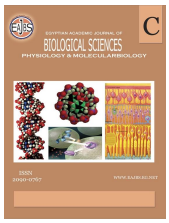

Reduction in the Formation of Micronucleated Polychromatic Erythrocytes Induced by Cisplatin in Bone Marrow Cells of Rats by using Antioxidants.

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Cisplatin, Vitamin C, Curcumin, Micronucleated polychromatic erythrocytes, Micronucleus test, Antioxidants

ABSTRACT

Cisplatin is extensively used as a main chemotherapeutic drug for the treatment of many types of tumors. Cisplatin exerts excellent anticancer action, but its clinical use is frequently limited due to the development of severe side effects in the treated patients such as nephrotoxicity, anemia and bone marrow damage. Cytotoxicity of cisplatin is closely related to the generation of reactive oxygen species leading to oxidation of vital components of the cell (DNA) and genomic instability. **Results and Conclusion:** The results supported that the combination between curcumin and vitamin C (with more adjusted dose of vitamin C) exerted the best ameliorative effect against the cisplatin induction of micronucleated polychromatic erythrocytes.

INTRODUCTION

Cisplatin (Cis-diaminedichloroplatinum-II) is an inorganic chemotherapeutic drug that is broadly used against several malignancies. Anticancer drugs haven't the ability to target specific cancer cells and unable to distinguish between cancer and healthy cells, especially the highly proliferative ones. So, the anticancer drugs, even the most effective one, can induce dangerous side effects to normal tissues (Choudhury *et al.* 2000; Elsendoorn *et al.*, 2001; Frezza *et al.* 2010 and Florea & Büsselberg, 2011).

To diminish cisplatin cytotoxicity, it's necessary for the cisplatin-treated patients to administrate food supplements and natural dietary antioxidants (AL-Asmari *et al.*, 2015 and Makhija *et al.*, 2017)..

Vitamin C (Ascorbic acid) is an essential dietary supplement act as a co-factor for various enzymes and an essential antioxidant, scavenging reactive nitrogen and oxygen species and protecting tissues against damage mediated by free radicals (Sanchez-Moreno *et al.* 2003).

Curcumin (1,7-bis [4-hydroxy 3-methoxy phenyl]-1,6-heptadiene-3,5-dione, CMN) is the primary active material extracted from *Curcuma longa* rhizome, which used mainly as a spice during the preparation of several kinds of food. It has different medicinal properties including antioxidant, anticancer, antimutagenic effects and immunomodulatory (Atunes *et al.*, 2000; Goel & Aggarwal, 2010 and Goel *et al.*, 2008).

MATERIALS AND METHODS

Forty-five white albino rats (*Rattus norvegicus*) were used in the present work. Their weight ranged from 170-180gm each. They were obtained from the farm of the Faculty of Veterinary Medicine, Zagazig University, Egypt. The animals were kept under hygienic condition, housed in metal cages and bedded with wood shavings; the rats were reared on a standard pellet diet and tap water *ad libitum*. They were accommodated to the laboratory conditions for at least two weeks before being experimented.

Cisplatin was purchased from the local pharmacy in Egypt (EIMC United Pharmaceuticals, Egypt). Each vial (50mg/50ml) was dissolved in physiological saline (0.9 % sodium chloride). The drug was injected intraperitoneally in a dose of 0.4 mg/kg b.wt (Pratibha *et al,*. 2006). Vitamin C was purchased from the local pharmacy in Egypt. Each tablet (1gm L-ascorbic acid) was dissolved in 100 ml distilled water and given orally in a dose of 100mg/kg b. wt.(Ahmad and Al-Jawary 2012).

Curcumin was purchased from National Bio Lab (medical laboratory, Dokki, Giza Egypt). Curcumin was suspended in 0.05% gum acacia solution and given orally at a dose of 20 mg/kg b.wt (Xu *et al.* 2007).

The experimental animals were divided into 9 main groups each group consisted of 5 rats as follows:

I) Water control group: Animals were orally received distilled water daily for 60 successive days using a metallic stomach tube. II) Saline control group: Animals were injected intraperitoneally with physiological saline (0.9 % sodium chloride) daily for 60 successive days. III) Acacia control group: Animals were orally received 0.05% gum acacia solution daily for 60 successive days. IV)Curcumin-treated group: Animals were orally administered curcumin 20mg/kg b.w daily for 60 successive days. V) Vitamin C treated group: Animals have orally administered vitamin C 100mg/Kg b.w daily for 60 successive days .VI) Cisplatin-treated group: Animals were injected intraperitoneally with cisplatin 0.4 mg /kg b.wt. daily for 60 successive days. VII) Cisplatin +curcumin treated group: Animals were orally received curcumin (20 mg/kg b.wt) and after 20min animals were injected intraperitoneally with cisplatin (0.4 mg /kg b.wt) for 60 successive days. VIII) Cisplatin +vitamin C treated group*:* Animals have orally received vitamin C (100 mg/kg b.wt.) and after 20min animals were injected intraperitoneally with cisplatin (0.4 mg /kg b.wt) daily for 60 successive days. XI) Cisplatin +curcumin +vitamin C treated group: Animals have orally received curcumin (20 mg/kg b.wt.) as well as vitamin C (100 mg/kg b.wt.) and after 20min animals were injected intraperitoneally with cisplatin (0.4mg /kg b.wt.) daily for 60 successive days.

Scoring of typical micronucleus was achieved according to the method described by (Schmid,1976 and Heddle *et al.*,1983). The femur bone marrow was taken from each animal and flushed in a graduated test tube containing 6ml of egg yolk serum; the suspension was centrifuged at 1000 r.p.m for 10 minutes. The supernatant was discarded except 1ml, the remaining 1ml and pellet of cells were flushed and then spread on clean glass slides and fixed by absolute methanol for 15 minutes. Then permanent preparations were made and stained with 1.5% Giemsa solution (It was prepared according to the method described by Genest and Auger, 1963) for 10-15 min and 1000 erythrocytes were examined blindly for each rat at X1000 magnification (Oil immersion; 10 eyepiece X 100 objective). Micronucleated polychromatic erythrocytes were recorded and photomicrographs were taken.

All data were expressed as a mean ± standard error of the mean of all the experimental groups. Data were analyzed using SPSS version (15.0). Statistical analysis was performed using one-way analyses of variance ANOVA test (F-test). Duncan's multiple range tests were used (Whose significant level was defined as ($P<0.05$) according to (Snedecor and Cochran 1982) to estimate the effect of different treated groups.

RESULTS AND DISCUSSION

From table (1) and fig. (2), it was clear that the percentage of micronucleated polychromatic erythrocytes in cisplatin-treated group significantly increased ($p<0.05$) and reached 5.58% compared with 3.76% in the saline control group. From the microscopic examination, it was clear that the scored micronuclei appeared in different size and shapes. Most of them had small and dot-like shape others had a significant - round or rod-like appearance (fig 3, 4). At the same time, most of the recognized micronucleated polychromatic erythrocytes contained just single micronucleus (fig. 1, 3), other cells had double micronuclei (fig. 1, 4).

These data confirm the findings concluded by Sharma *et al.*(2017) who supported that cisplatin-induced a significant increase in the frequencies of micronuclei formation and chromosomal aberrations in bone marrow cells of rats when compared to control group (Mazur *et al.*, 2000;Attia, 2010; Rjiba-Touati *et al.*, 2012;George *et al.*, 2017 and Sharma *et al.*, 2017).

Table 1. Comparison between the frequencies of micronucleated polychromatic erythrocytes from bone marrow cells of normal albino rats administered cisplatin, curcumin, vitamin C or their combinations**.**

Groups	No. of rats	No of examined cells 1000/rat	Micronucleated polychromatic erythrocytes									Total (MNPCEs)		
			Single			Double			Multi					
			No	%	Mean±SE	No	%	Mean±SE	No	%	Mean±SE	No	%	Mean±SE
Water control	5	5000	159	3.18	31.80±0.20^{e}	8	0.16	1.60±0.40^{c}	0	0	0.00±0.00^{a}	167	3.34	33.40±0.40^{f}
Saline control	5	5000	178	3.56	35.6±0.40^{d}	10	0.20	2.00±0.00^{c}	0	0	0.00±0.00^{a}	188	3.76	37.60±0.40^{de}
Acacia control	5	5000	161	3.22	32.20±0.66^{e}	17	0.34	3.40±0.24^{b}	3	0	0.60±0.24^{a}	181	3.62	36.20±0.73^{e}
Curcumin	5	5000	180	3.60	36.00±0.44^{d}	8	0.16	1.60±0.24^{c}	0	0	0.00±0.00^{a}	188	3.76	37.60±0.50^{de}
VitaminC	5	5000	180	3.60	36.00±0.31^{d}	20	0.40	4.00±0.31^{ab}	1	0.02	0.20±0.20^{a}	201	4.02	40.20±0.20^{d}
Cisplatin	5	5000	253	5.06	50.60±0.74^{a}	24	0.48	4.80±0.20^{a}	2	0.04	0.40±0.24^{a}	279	5.58	55.80±0.73^{a}
Cisplatin +Curcumin	5	5000	200	4.00	40.00±2.12^{c}	22	0.44	4.40±0.24^{a}	2	0.04	0.40±0.24^{a}	224	4.48	44.80±2.00^{c}
Cisplatin +VitaminC	5	5000	231	4.62	46.20±1.15^{b}	20	0.40	4.00±0.31^{ab}	1	0.02	0.20±0.20^{a}	252	5.04	50.40±0.87^{b}
Cisplatin +Curcumin +VitaminC	5	5000	171	3.42	34.20±0.86^{de}	12	0.24	2.40±0.24^{c}	2	0.04	0.40±0.24^{a}	185	3.70	37.00±0.89^{e}

Means within the same column in each category carrying different litters are significant at ($p\leq0.05$) using Duncan's multiple range test, where the highest mean value has a symbol (a) and decreasing in value were assigned alphabetically. Similar letters are nonsignificant on the statistical level.

In our opinion, micronuclei scored in bone marrow cells of albino rats after injection with cisplatin depends mainly on the formation of cisplatin-DNA adducts and induction of reactive oxygen species that cause DNA instability and oxidation of all cell components especially the sensitive DNA molecule and/or protein of spindle fibers. Hence, micronuclei were formed by the breaking of DNA double helix and forming acentric fragments . These acentric fragments could not adhere to the spindle fibers and integrate into the daughter nuclei, therefore left behind during mitosis.

These data were in line with (Mendonca *et al.* 2009) who discussed that cisplatin has various side effects which mainly due to its role in the

formation of reactive oxygen species like superoxide anion and hydroxyl radical, resulting in oxidative damage on the cell components and this may lead to micronucleus formation or DNA fragmentation.

Masuda *et al*.(1994) and Florea & Busselberg (2011) added that the anticancer activity of cisplatin depends mainly on its ability to form cisplatin-DNA adducts with intro and interstrand DNA crosslinks subsequently, inhibit essential cellular processes involving DNA repair mechanisms, translation, replication and transcription(Elsendoorn *et al.* ,2001)

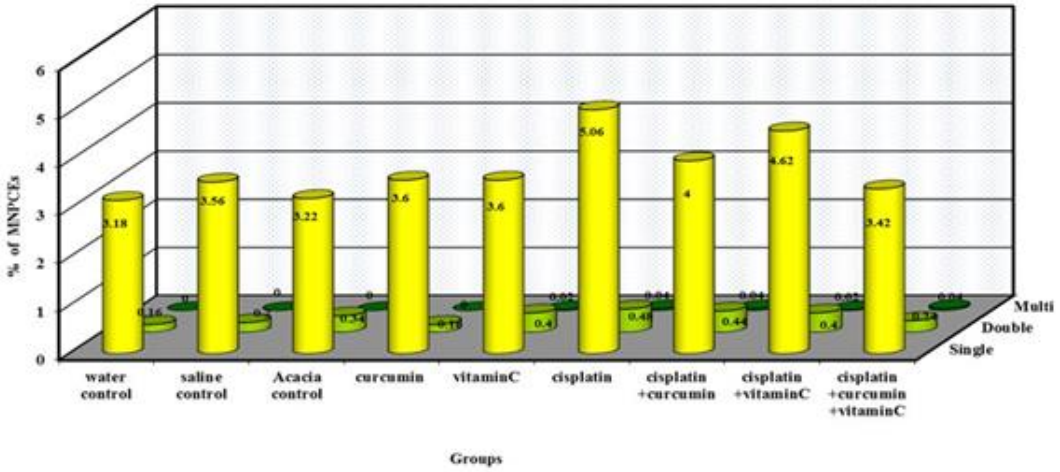

Fig.1.Comparison between the percentages of single,double and multi- micronucleated polychromatic erythrocytes from bone marrow cells of normal albino rats administered Cisplatin, Curcumin,VitaminC or their combinations

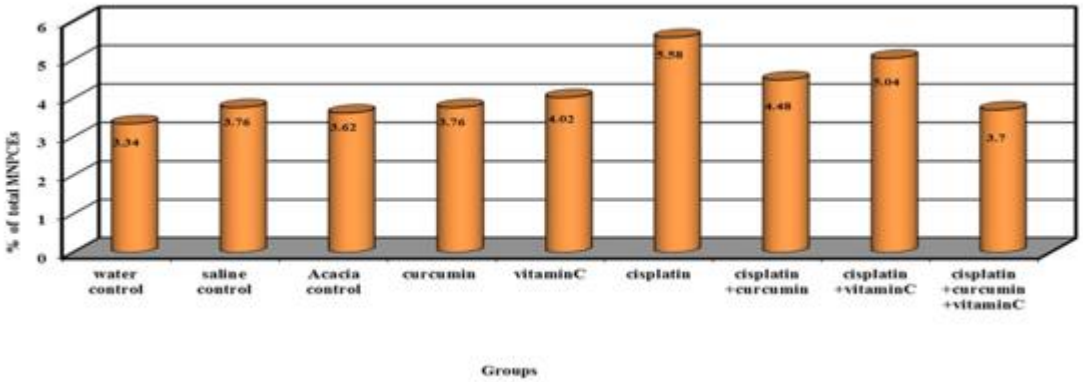

Fig.2. Comparison between the percentages of total- micronucleated polychromatic erythrocytes from bone marrow cells of normal albino rats administered Cisplatin ,Curcumin, VitaminC or their combinations.

In the present work, although there was a significant increase in the percentage of total micronucleated polychromatic erythrocytes in vitamin C treated group (4.02%) compared with water control group (3.34%), the treatment of rats with vitamin C (100mg/kg.b.wt.) prior to cisplatin injection alleviated the percentage of micronucleated polychromatic erythrocytes induced by cisplatin from 5.58% to 5.04% and the value was significant at the statistical level.

Our findings indicated that vitamin C, as an antioxidant, can reduce the frequency of micronucleated polychromatic erythrocytes induced by cisplatin and decrease the oxidative stress through its free radical scavenging activity.

These findings go hand in hand with those of(Longchar &Prasad ,2016) who explained that cisplatin significantly increased the frequency of micronucleated polychromatic erythrocytes while pre-treatment with

vitamin C decreased the rate of cisplatin-induced micronucleated cells in mice bone marrow

Griffiths and Lunec (2001) supported that the protective role of vitamin C on cisplatin mutagenicity depends mainly on direct blocking and scavenging of reactive oxygen species. Vitamin C protects cellular DNA from oxidative stress induced by various agents.

In our view, micronucleated polychromatic erythrocytes scored in bone marrow cells of animal treated with vitamin C alone may be related to the used dose(100mg/kg b.wt) or the duration of administration (60 successive days) that can be adjusted in another future study.

These results were in full agreement with those explained by (Nefic 2008)who concluded that a large dose of vitamin C caused genotoxicity because vitamin C has both pro-oxidant and antioxidant activities.

On the contrast, non-significant changes in the frequency of micronucleated polychromatic erythrocytes were recorded in curcumin-treated group (3.76%) when compared with the acacia control group (3.62%). Treatment of rats with curcumin before cisplatin resulted in a significant decrease in the percentage of micronucleated polychromatic erythrocytes (4.48%) compared with cisplatin-treated group (5.58%).

These data significantly confirmed by(Said *et al.,* 2017) who illustrated that the frequency of micronucleated polychromatic erythrocytes non-significantly changed in mice bone marrow cells after curcumin treatment. The treatment of mice with curcumin before cisplatin injection ameliorated the frequency of DNA damage and micronuclei induced by cisplatin in mice bone marrow cells, this ameliorative role of curcumin could be related to its scavenging activity to reactive oxygen species (Antunes *et al.,* 2000 ;Celik *et al.,* 2013and Mendonca *et al.,* 2015) .

In our view, the ameliorative role of curcumin may be related to its mechanism of action which depends on its free radicals scavenging activity and reduction of oxidative stress induced by cisplatin.

These data were similar to the data obtained by (Balasubramanyam *et al.* 2003)who discussed that curcumin strongly inhibits the generation of cellular reactive oxygen species. It acts as a scavenger for reactive oxygen species and reduced lipid peroxidation in various animals, preventing DNA oxidative damage .

Supporting the results of our previous researches of cisplatin toxicity on the sperm morphology (Elballat 2016), it is worth to explain that the combination treatment of vitamin C and curcumin before cisplatin injection recorded the best protective or eliciting effect against cisplatin-induced micronucleated polychromatic erythrocytes in bone marrow cells of rats. The percentage of micronucleated polychromatic erythrocytes was decreased from 5.58% to 3.70%, and the result was non-significant compared with the saline control group. This may be due to the synergistic effect between the two antioxidants (vitamin C and curcumin) as both of them have free radical scavenging activities which in turn improving antioxidant defense system and reduce oxidative stress on sensitive DNA molecule and spindle fibers reducing the frequency of micronucleated polychromatic erythrocytes induced by cisplatin drug.

These results were considerably supported by (Tarasub *et al.* 2012) who confirmed that the combined pretreatment with vitamin C plus curcumin could reduce the alterations and give more protection than vitamin C or curcumin alone against cadmium hepatotoxicity. Curcumin might enhance the effect of vitamin C in protecting endothelial cells function through its anti-oxidant activities in diabetic rats (Patumraj *et al.* 2006).

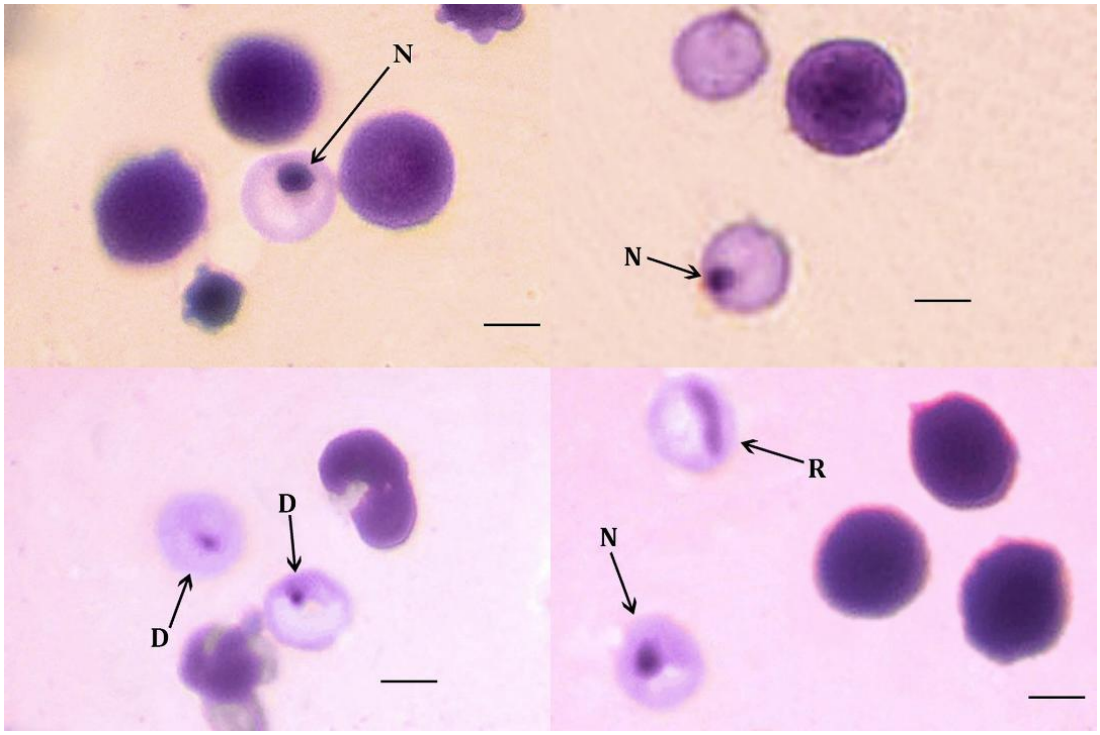

Fig.3. Micronucleated polychromatic erythrocytes from bone marrow cells of normal male albino rats injected intraperitoneally with Cisplatin showing single micronuclei with different shapes and size:
N) Round –shape D) Dot-like structure R) Rod- like shape.

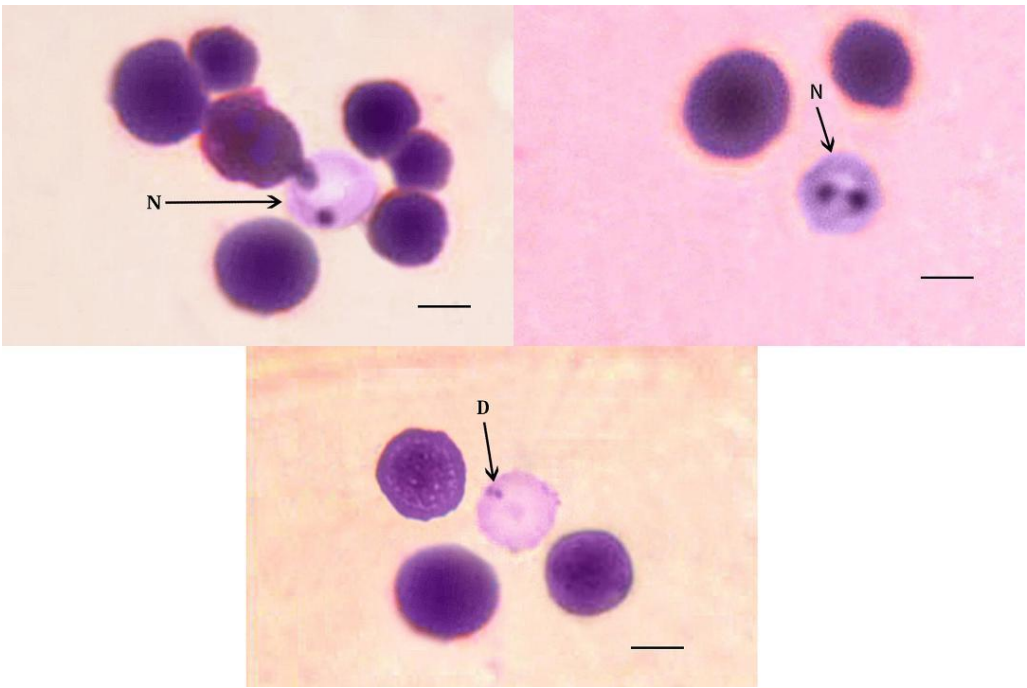

Fig.4. Micronucleated polychromatic erythrocytes from bone marrow cells of normal male albino rats injected intraperitoneally with Cisplatin showing double micronuclei.
D) Dot-like structure N) Round –shape

Conclusions

From the results of the present investigation, it was concluded that the combination treatment of curcumin and vitamin C (with more adjusted dose of vitamin C) before the cisplatin injection recorded the best ameliorative effect against cisplatin induction of micronucleated polychromatic erythrocytes in bone marrow cells of albino rats .

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ARABIC SUMMARY

انخفاض نسبة كريات الدم الحمراء ذات الأنوية الدقيقة التى يسببها السيسبلاتين فى خلايا نخاع عظم الجرذان باستخدام مضادات الأكسده

فوزيه عبد الهادى زايد و صابحه السيد البلاط

قسم علم الحيوان- كلية العلوم-جامعة الزقازيق- الزقازيق-جمهورية مصر العربيه.

يستخدم عقارالسيسبلاتين على نطاق واسع كدواء رئيسي لعلاج أنواع كثيرة من الأورام ويعتبرعلاجا ممتازًا كمضادً لسرطان . لكن الاستخدام السريري له كثيرًا ما يكون محدودًا نظرًا لظهور الآثار الجانبية الخطيره لدى المرضى المعالجين به مثل فقر الدم وتلف النخاع العظمي.وترجع السمية الخلوية لسيسبلاتين الى قدرته على توليد شوارد الأكسجين الحره والتى بدورها تؤدي إلى أكسدة المكونات الحيوية للخلايا (الدنا) وعدم الاستقرار الجينى.من خلال هذه الدراسه تبين ان :الجمع بين الكركمين وفيتامين سى كمضادات اكسده قويه سجل أفضل تأثير محسّن ضد تحفيز سيسبلاتين للكريات الحمراء متعددة النواه فى خلايا النخاع العظمى للجرذان البيضاء