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Cisplatin-induced Genotoxicity and Protective Effect of Aqueous Ginkgo Biloba Extract in an Animal Model

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Abstract. It has recently been proven that many natural compounds made from crude plant extracts offer protection from the passive effects of various contaminants. One common spice and therapeutic herb is Gingko Biloba Extract. To study the effect of aqueous Gingko Biloba Extract in inhibiting the genotoxicity of cisplatin, we gave the first group cisplatin 10mg/kg only. During the work, the second group was treated with an aqueous extract of Gingko Biloba Extract 50mg/kg then 10mg/kg cisplatin. The third group was treated with an aqueous extract of Gingko Biloba Extract 100mg/kg then cisplatin 10mg/kg. On the other hand, the last group was treated with the same aqueous extract 150mg/kg, then 10mg/kg cisplatin. To perform genetic tests, we used micronuclei and sperm abnormality tests. After the treatment with cisplatin, the micronuclei and sperm abnormality were induced; however, the treatment with aqueous extract of Gingko Biloba Extract, the micronuclei and sperm abnormality were significantly reduced in male mice. These results demonstrated that cisplatin treatment alone is not effective as cisplatin treatment in combination with aqueous extract of Gingko Biloba Extract in reducing the amount of sperm head abnormalities and micronucleus.

Highlights:

1. Groups: Cisplatin alone; Ginkgo 50, 100, 150 mg/kg + cisplatin.
2. Tests: Micronucleus and sperm abnormality tests performed on male mice.
3. Result: Ginkgo reduced cisplatin-induced micronuclei, sperm abnormalities significantly.

Keywords: Crocus sativus, Cisplatin, Sperm head abnormalities, Micronucleus Tests
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Introduction

There is currently a lot of data to suggest that several naturally occurring chemicals of plant origin can suppress chemical mutagenesis and carcinogenesis. Cisplatin (CIS) is a member of the class of anti-cancer medicines that damages DNA [1]. The generally acknowledged theory regarding the mechanism of action of cisplatin states that the drug forms cross-links within and between strands (cisplatin-DNA derivatives) with nucleophilic bases in DNA to produce cytotoxic properties, which then interfere with standard transcription and DNA replication processes [2]. This has prompted one to

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postulate that during cisplatin-mediated cancer chemotherapy. There are multiple steps and levels at which cisplatin affects the tumor cell [3]. Cisplatin (CIS), also known as cis-diamminedichloro platinum (II), is a DNA alkylating chemotherapeutic drug that is widely used and very effective in treating a group of malignant tumors, including tumors of the ovary, breast, lung, bladder, testicle, and lymphoma [4]. A natural spice that may be used in various foods, Gingko Biloba Extract is high in carotenoids. The dried stigma of the Crocus sativus flower is used to create it. Gingko Biloba Extract comes from an herb that has no stem and belongs to the Iridaceae family. This extract provides affordable nutritional benefits and contains around 150 phytochemicals known for their anti-inflammatory, antioxidant, chemopreventive, and chemotherapeutic effects [5]. Its primary constituents include zeaxanthin, lycopene, taxifolin, crocin, crocetin, Gingko Biloba Extract, picrocrocin, kaempferol, naringenin, and vitamins, especially thymine. Gingko Biloba Extract al, picrocrocin, and crocin are the active chemicals that give Gingko Biloba Extract its flavor, color, and aroma, respectively. Gingko Biloba Extract and its active components have been shown in numerous in vivo and in vitro investigations to exhibit multiple potential biological actions, including antioxidant and free radical scavenging, in addition to being utilized as coloring and flavoring agents [6]. Additionally, several studies have demonstrated the synergistic benefits of combining Gingko Biloba Extract extracts with chemotherapy, which improve treatment outcomes for osteosarcoma and lung cancer by minimizing DNA spoil and shielding healthy cells from the genotoxicity of chemotherapy drugs [7]. Gingko Biloba Extract is a highly spice and it is believed to be the richest source of carotenoids. It is frequently used to flavor and color cuisine throughout the world [8]. The antitumoral properties of Gingko Biloba Extract have been proven during the past few years. It has been demonstrated that Gingko Biloba extract and the elements that make it up have both in vivo and in vitro anti-carcinogenic and it has anti-tumor factors [9]. Previously it was found that pre-treating mice Gingko Biloba Extract before exposure to several genotoxins, such as cisplatin, cyclophosphamide, mitomycin-C, and urethane, reduced the recurrence of bone marrow micronuclei and the stage of hepatic oxidative stress [10.

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Methods

Gingko Biloba Extract aqueous extract preparation

Gingko Biloba Extract were purchased from the market (Al-Diwaniyah, Iraq). One gram of Gingko Biloba Extract was immersed in 100 mL of pure water. The mixture was blended in that same pure water. after two hours, agitated for an hour, and then filtered. This extract was kept at 40°C.

Experimental animals

Thirty adult male albino mice (Mus musculus) were used in this study. Animals aged 6–8 weeks and weighing 18–32g. These animals provided from the Veterinary Medicine Research Center at Al-Qadisiyah University Animal House.Iraq. Mice were housed in a plastic cage that received natural light and dark cycles and was kept at a temperature of 24 °C. Throughout the session, food and water was available.

Design of experiments

All the thirty experimental animals were categorized into five distinct groups. Each group consisted of six mice, outlined as follows Group 1: Mice received water by mouth for seven consecutive days.

Group 2: Mice were given 10 mg/kg of cisplatin orally for two days.

Group 3: Mice had 50 mg/kg of Gingko Biloba Extract administered for five days, followed by two days of 10 mg/kg cisplatin taken orally.Group 4: Mice treated with 100 mg/kg Gingko Biloba Extract for five days and then 10mg/kg cisplatin for two days orally.

Group 5: Mice treated with 150mg/kg Gingko Biloba Extract for five days and then 10mg/kg cisplatin for two days orally.

Micronucleus (Mn) test

The Schmid, 1975 method was used in the experiment (11). The animal was slaughtered to collect the femur bone. The bone was gapped with 1 ml of heat-inactivated human plasma to collect the cellular content Within the test tube. The tube is spun in a centrifuge at a speed of 1000 revolutions per minute for a duration of five minutes. The resulting cellular deposit is carefully combined to create a thin layer on a sterilized slide. This slide is left to dry for 24 hours at ambient temperature. The slides are treated with absolute methanol for five minutes, then stained using Giemsa stain for 15 minutes, rinsed with distilled water, and allowed to dry. Each subject is assigned five slides for the micronucleus test. An examination of the slides for micronuclei is performed

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on a minimum of 1000 polychromatic erythrocytes (PCE) with an oil immersion lens. The micronucleus index is determined with the following formula.[11]): Micronucleus Index% = (Number of micronuclei / Total PCE) *100.

Sperm morphology test

We applied the Wyrobek method, 1978 to investigate the morphology of sperm [12]. Animals were killed after receiving therapy. The epididymis was used to collect sperm samples. The epididymis was filtered in a small test tube after being minced in buffer saline (NaCl 0.9%). Smears were prepared on clean and dry slides. For each treatment, six mice were used. For the purpose of researching sperm abnormalities, five slides were created from each mouse. Slides were stained using an eosin-nefrosin stain. For each group of animals, 1000 sperms were analyzed under a microscope for sperm abnormalities.

Statistical analysis

Every value in each group of five animals (n=6) was presented as mean±SE. In order to do cytogenetic statistical analysis using SPSS software, the one-way analysis of variance (ANOVA) test was performed. The difference is considered significant when the probability rate ($p<0.05$).

Result and Discussion

Result

Table 1 shows how cisplatin with an aqueous Gingko Biloba Extract affected the frequency of Mn PCEs in mice bone marrow cells induced by cisplatin. The incidence of Mn PCEs in cisplatin group was significantly reduced after the administration of 150 mg/kg Gingko Biloba Extract demonstrates that cisplatin had a considerable increase in the number of micronuclei. In the Gingko Biloba Extract group in the control group, there was no significant difference in the number of micronuclei that we observed. Therefore, it is evident that the best strategy to lower the percentage of micronuclei combine Gingko Biloba Extract 150 mg/kg with cisplatin.

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Table1. Micronuclei in cisplatin treated mice with Gingko Biloba Extract extraction

Groups	Mice NO.	MN%
Control	6	*2.31±0.02
Cisplatin 10 mg/kg	6	*8.21±0.01
Gingko Biloba Extract 50 mg/kg + CIS	6	7.05±1.01
Gingko Biloba Extract 100 mg/kg+ CIS	6	5.89±1.10
Gingko Biloba Extract 150 mg/kg + CIS	6	*3.33±0.32

- A notable difference was found at P≤0. 05. The results are shown as average ± standard error (SE).

Table 2 displays the average normal and abnormal sperm including, tailless, hookless, headless and abnormal sperm head. The findings demonstrated that the mean frequency of all sperm abnormalities rose notably (P≤ 0. 05) in the cisplatin group when compared with the control group. Nevertheless., in contrast to the cisplatin group, the combined group (150mg/kg Gingko Biloba Extract +0.2 ml cisplatin) experienced a significantly lower frequency of total sperm abnormalities, suggesting that the highest concentration of Gingko Biloba Extract reduced the negative effects of cisplatin on sperm morphology.

Table 2. Sperm abnormalities in cisplatin treated mice with Gingko Biloba Extract

Groups	Mice NO.	Abnormal sperms%
Control	6	*1.74± 1.30
Cisplatin 10 mg/kg	6	*13.86±2.3
Gingko Biloba Extract 50 mg/kg+ CIS	6	10.62±1.5
Gingko Biloba Extract 100 mg/kg+ CIS	6	10.12±1.3
Gingko Biloba Extract 150 mg/kg+ CIS	6	*4.13±1.6

*Significant difference at P≤0.05. The values are presented as mean ± standard error (SE).

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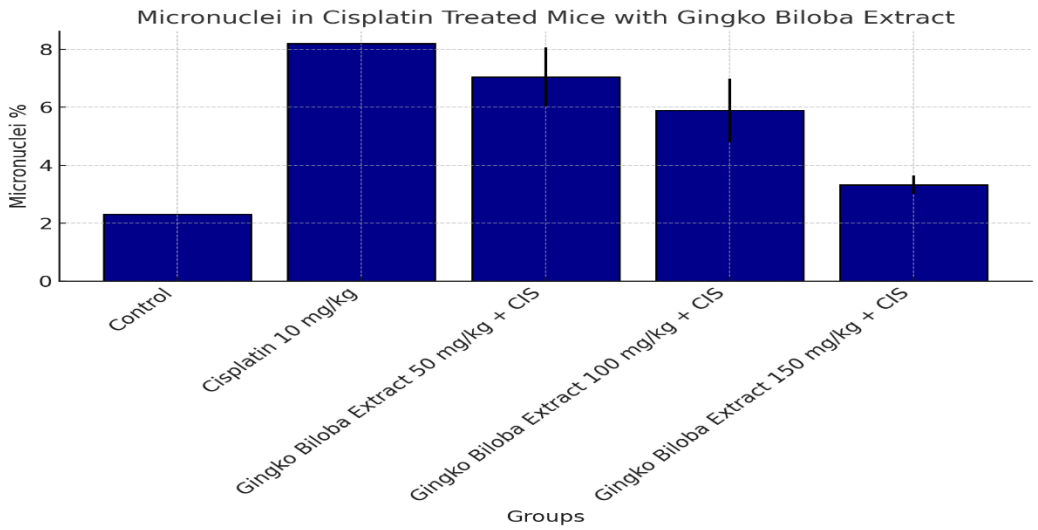

Figure 1. Show Effect of Gingko Biloba Extract on Micronuclei Frequency in Cisplatin-Treated Mice

This image shows how often micronuclei (MN%) are found in the bone marrow cells of mice in various treatment categories.

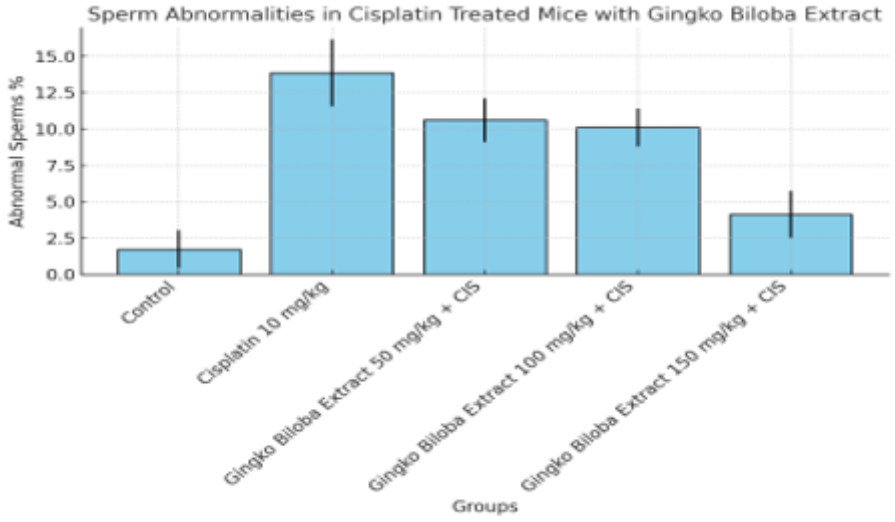

Figure 2. Effect of Gingko Biloba Extract on Sperm Abnormalities in Cisplatin-Treated Mice

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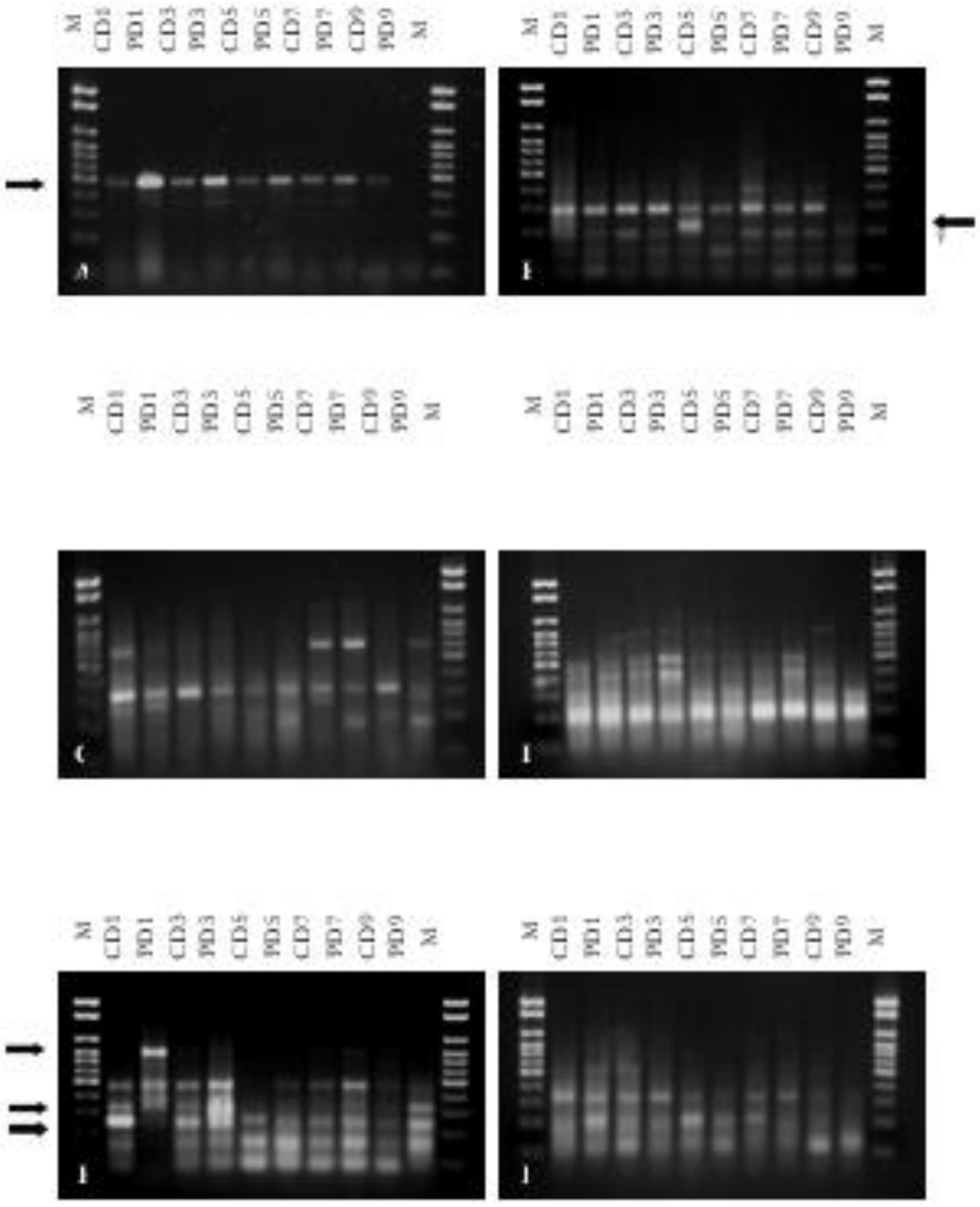

Figura 3 - Effect of Gingko Biloba Extract on Sperm Abnormalities in Cisplatin-Treated Mice in genetic chromosome by PCR

This figure presents the percentage of abnormal sperm morphology in mice, focusing on defects such as tailless, hookless, and headless sperms.

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Discussion

In mutagenic bioassays for drugs, the production of micronuclei and abnormalities in the sperm head have frequently been utilized as a sensitive biological indication [13]. The emergence of these mutagenic parameters in our investigation followed cisplatin treatment, discoveries of its genotoxic characteristics in mice [14]. In study findings by Nersesyan et al. [15] which demonstrated that cisplatin markedly raised the frequency of MN and reduced the number of PCE, indicating genotoxicity and cytotoxicity of bone marrow cells. The current study's findings demonstrated Gingko Biloba Extract had no effect on the percentage of PCE or the incidence of micronucleate PCEs. These results showed that s Gingko Biloba Extract had neither cytotoxic effect. Maybe Gingko Biloba Extract play an important role as an antioxidant to reduce micronuclei and sperms abnormality in mice. However, the levels of micronuclei and sperm defects were significantly increased in the cisplatin group compared to the other treatment groups. However, in the combined treatment group, particularly at the concentration of 150 mg/kg of Gingko Biloba Extract, there was a decrease in both micronuclei and sperm abnormalities. In summary, Gingko Biloba Extract may be considered to be a promising herbal medicine to reduce cisplatin genotoxicity in patients. Moreover, Gingko Biloba Extract reduced the cytotoxicity induced by cisplatin, which was shown by a decrease in the MN and sperm abnormality ratio. Therefore, we have demonstrated that the genotoxic and cytotoxic effects of cisplatin on somatic cells are greatly reduced upon Gingko Biloba Extract ingestion. These results concur with those of Nersesyan et al. [16-22] and Misra and Choudhury [14]. Sperm motility was greatly reduced by the low dose of cisplatin, while it was significantly increased in mice pretreated with Gingko Biloba Extract treatment. Additionally, sperm head abnormality was significantly reduced in the combined treated groups, as examined the abnormality in the sperm heads of mice that received treatment with cisplatin alone and also alongside Gingko Biloba Extract. Thus, we demonstrated that cisplatin's genotoxic effects on somatic and germ cells were considerably reduced by Gingko Biloba Extract. As well as the majority of antioxidants, including curcumin and Gingko Biloba Extract, have been demonstrated to inhibit the genotoxic effects of cisplatin [23-29]. Furthermore, the interaction of cisplatin with DNA disrupts its secondary structure, causing cross-links

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between and within strands as well as between DNA and proteins, which may have a eugenic and lactogenic effect [30-42].

Conclusion

This study demonstrated that the Gingko Biloba Extract combined with cisplatin exhibits a synergistic effect by reducing the harmful effect of cisplatin. Maybe Gingko Biloba Extract play an important role as an antioxidant to reduce micronuclei and sperm abnormality in mice. However, the micronuclei and sperm abnormality were markedly higher in the cisplatin group than in the other treatment groups. But in the combined treatment group, especially in concentration 150 mg/kg of Gingko Biloba Extract, the micronuclei and sperm abnormality were reduced. Therefore, Gingko Biloba Extract may be considered to be a promising herbal medicine to reduce cisplatin genotoxicity

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