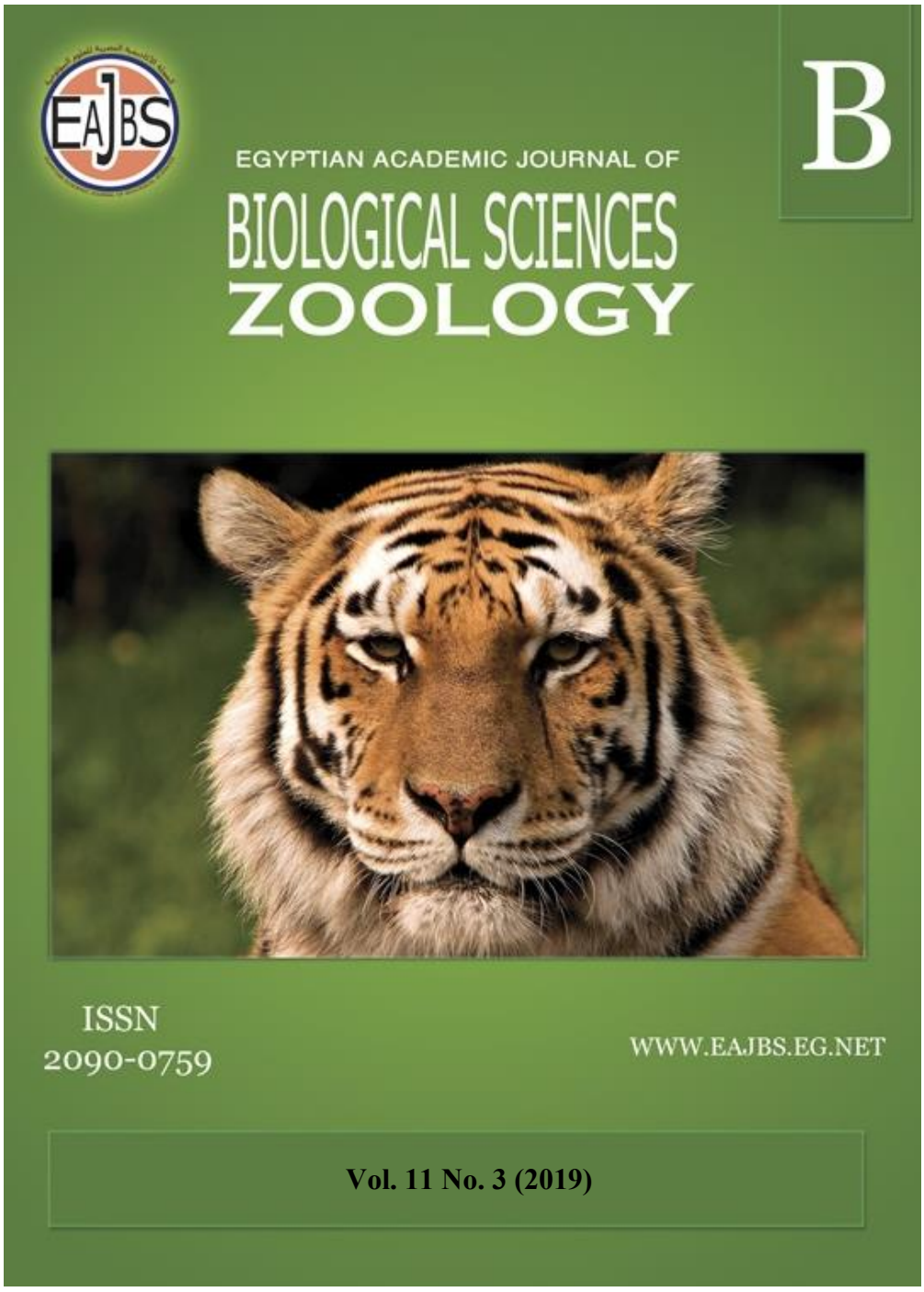

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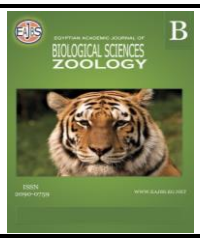

Magnetic Field Improves the Efficiency of Low Dose Cis-Platin by Alteration the Oxidative Stress in Ehrlich Carcinoma-Bearing Mice

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ABSTRACT

50 Hz and 50 mT magnetic field (MF) with an exposure period of 30 min./day for 15 days was used to enhance the efficiency of a low dose of cisplatin on BALB/C mice. Tumor tissues were evaluated by oxidative stress parameters such as superoxide dismutase (SOD) enzyme activity, malondialdehyde (MDA) and glutathione (GSH) levels. The result shows that treatment with MF and cisplatin decreases the activity of SOD and GSH level and increases the MDA level compared to the treatment with MF or cisplatin alone. In conclusion, these results reveal that MF improves the therapeutic efficiency of cisplatin.

INTRODUCTION

Oxidative stress has occurred when the balance between ROS and the antioxidant defense system has been altered. ROS are known as free radicals, such as superoxide or hydroxyl radicals and non-radical, i.e. hydrogen peroxide and singlet oxygen. Under normal conditions, cells have low ROS levels that are important to critical processes such as cell proliferation, gene expression, and signal transduction. Nevertheless, the widespread ROS degradation of cell lipids, proteins, and nucleic acids through oxidative stress. Elimination of ROS regulated by non-enzymatic antioxidants such as glutathione (GSH) and antioxidant enzymes such as superoxide dismutase (SOD). Oxidative stress has biomarkers in the cells shown as the activity of SOD, levels of GSH and lipid peroxidation products as malondialdehyde (MDA) (Nita and Grzybowski 2016; Ozben 2007).

Cancer is a huge health problem worldwide. In the beginning, it was difficult to treat, but today its diagnosis in early-stage facilitates patient survival. It is a grouping of many diseases that can impact any part of the body. Standard cancer treatment methods include tumor surgery, chemotherapy, immunotherapy, and radiotherapy. While chemotherapy has been a successful strategy for the treatment of different types of cancers, it has been hindered by certain factors such as drug resistance and drug toxicity (Urruticoechea *et al.*, 2010).

Electromagnetic fields (EMFs) capable of penetrating the human body more deeply than the static one. In addition to EMFs can induce an electric charge in tissues and caused physiological effects (Wang and Zhang 2017). Several studies reported that under low frequency and intensity of EMFs exposure, inhibition of cancer cell growth occurred. Also, EMF induces biological effects like cell proliferation, apoptosis, and variations in cell membrane potential. ELF-EMF enhance the concentration and life span of free radicals (ROS) which lead to oxidative stress. EMF produces ROS via Fenton reaction (Buckner *et al.*, 2015; Chen *et al.*, 2010; Nie *et al.*, 2013).

The platinum drugs are considered as an effective and special category of antitumor agents. Cisplatin (cis-diamminedichloridoplatinum(II), cis-[$PtCl_2(NH_3)_2$]) belong to this category, applies clinical activity against many solid tumors like lung, head, and germ cell tumors (Prestayko et al. 1979). Cisplatin-induced DNA adducts have many damaging effects on DNA, including DNA replication and transcription suppression, an unwinding of DNA, and cell-cycle capture. If the cells failed to repair DNA or extreme damage, they undergo apoptosis (Shi 2016; Baik et al. 2003). It is triggers free radicals generation causing oxidative stress followed by DNA damage because of antioxidant defense system depletion.

Platinum is paramagnetic and can effectively by magnetic fields. Therefore, the goal of the present work is to combine a low dose of cisplatin with a magnetic field in order to enhance its efficacy.

MATERIALS AND METHODS

Materials:

Cisplatin (1mg/ml) was acquired from Mylan pharmaceuticals (Saint-priest, France), DetectX® glutathione fluorescent detection Kit from arbor assays (Michigan, USA), superoxide dismutase (SOD) kit was obtained from Sigma- Aldrich (Schnelldorf, Germany) and lipid peroxidation (MDA) kit from bio vision (Milpitas, USA).

Animals and Treatment Protocol:

Fourteen female BALB / c mice (average body weight and age 23 g, 7 weeks respectively) were (derived from the animal house of " NCI ") and subcutaneously injected with Ehrlich ascites fluids (derived from the National Cancer Institute ' NCI ' of Cairo University) in their right flanks to grow a single and solid form of tumor as a protocol by (Rageh and El-Gebaly 2019). Both animal methods and treatment have been carried out using the standards for the Treatment and Use of Laboratory Animals, Cairo University Institutional Animal Care and Use Committee (CU-IACUC), focused on the investigation of the application number CU / I / F/16/19.

Following 10 days of tumor cell vaccination and tumor volume were about 0.3 to 0.6 cm^3, the mice were randomly classified into four experimental groups.

The control group was treated with saline three times on the test days (1st, 4th and 8th days). A low dose group of cisplatin 3 mg/kg was administered IP three times (1st, 4th and 8th days) on experimental days. MF was subjected to 50 Hz, 50 mT MF, 30 minutes every day for 2 weeks. The low dose + MF group was diagnosed with cisplatin and accompanied by MF as the low dose cisplatin and MF groups. Tumor progression was examined every three days during the treatment protocol (15 days) for all test groups. All mice were killed at the conclusion of therapy, tumor tissues were separated from all animals, cleaned with saline and used to analyze oxidative stress.

Magnetic Field Exposure:

The alternating magnetic field was provided by a vertical coil with an internal diameter of 9.5 cm, attached to the adjustable insulation transformer worked at a frequency of 50/60 Hz, electrical current 2A and main supply (220-230 Volt).

Oxidative Stress Analysis:

Superoxide dismutase (SOD), malondialdehyde (MDA) and reduced glutathione (GSH) levels were assessed using the SOD determination kit (19160), the lipid peroxidation (MDA) assay kit (K739-100) and the DetectX ® glutathione fluorescent detection kit (K009-F1) as instructed by the manufacturer.

Statistical Analysis:

The data were viewed as the mean ± standard deviation (SD) and were examined using SPSS v. 15.0 for Windows.

RESULTS AND DISCUSSION

The effects of treatment with cisplatin and magnetic field on lipid peroxidation were measured as MDA, in tumor tissues and are shown in Fig. 1. Figure 1 shows a significant increase in the level of MDA in tumor tissues in all treatment groups with a low dose of cisplatin, MF and a low dose of cisplatin + MF with approximately 7%, 57%, 136% ,respectively compared to control group. Figure 2 shows a decrease in SOD activity in tumor tissues in all treatment groups with a low dose of cisplatin, MF and a low dose of cisplatin + MF with approximately 10%, 31%, 50%, respectively compared to control group. Figure 3 shows significant depletion of GSH in tumor tissues in all treatment groups with a low dose of cisplatin, MF and a low dose of cisplatin + MF with approximately 26%, 48%, 55%, respectively compared to control group. Such data showed that cisplatin was linked to increased levels of MDA and reduction of GSH and SOD activity in tumor tissues. Such results are consistent with many studies that have documented cisplatin therapy combined with excess production of ROS and disturbance of the antioxidant system. Cellular antioxidant defenses such as GSH and SOD are therefore reduced. In contrast, a rise in lipid peroxidation and its component (MDA) (khan *et al.*, 2010; Sherif *et al.*, 2018). In addition, exposure to MF accompanied by excessive lipid peroxidation and depletion of GSH and SOD. These results confirmed with previous reports suggesting that the magnetic field alters the potential of the cell membrane and the distribution of ions and dipoles by penetrating living organisms. Therefore, the development of free radicals is increased. The oxidative stress caused by MF-exposure was therefore linked to the excessive development of free radicals and reduces the antioxidant defense system of the organism. In addition, the development of free radicals and the behavior of antioxidant enzymes are mainly affected by the intensity and duration of MF exposure. (Coşkun *et al.*, 2008; Kula *et al.*, 2002; Sun *et al.*, 2018).

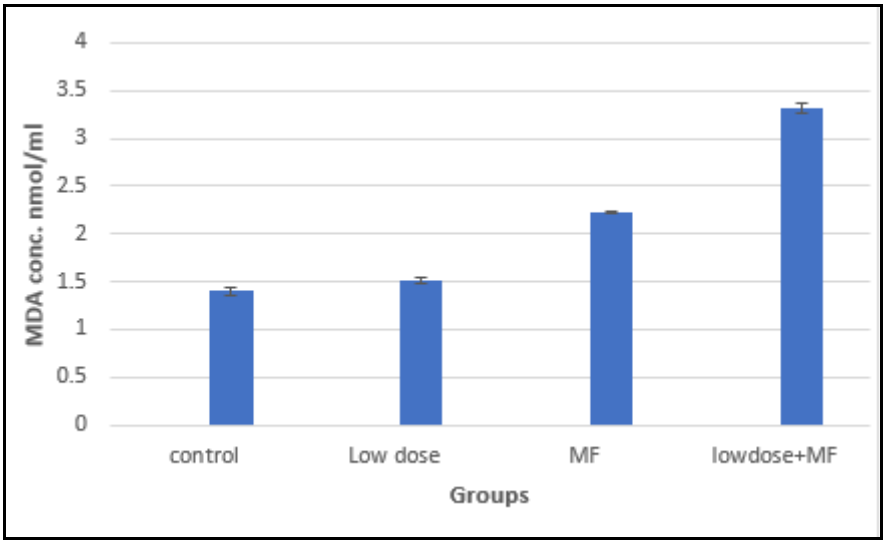

Fig. 1. MDA level in tumor tissues of a control group, a low dose of cisplatin group (3 mg/kg i.p.), MF group (50 Hz, 50 mT, 30 minutes daily for 2 weeks) and low dose + MF group. The data points are represented as mean ± SD (n = 5).

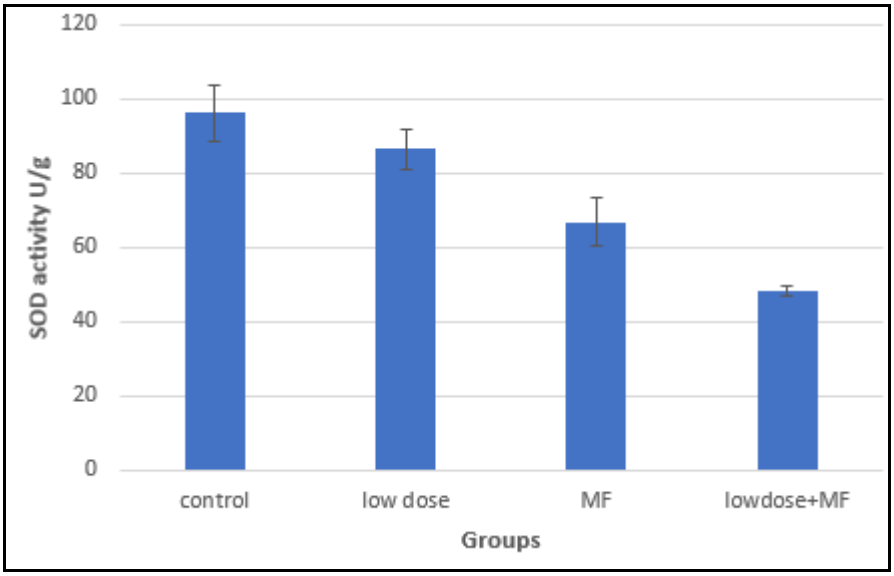

Fig. 2 SOD activity in tumor tissues of a control group, a low dose of cisplatin group (3 mg/kg i.p.), MF group (50 Hz, 50 mT, 30 minutes daily for 2 weeks) and low dose + MF group. The data points are represented as mean ± SD (n = 5).

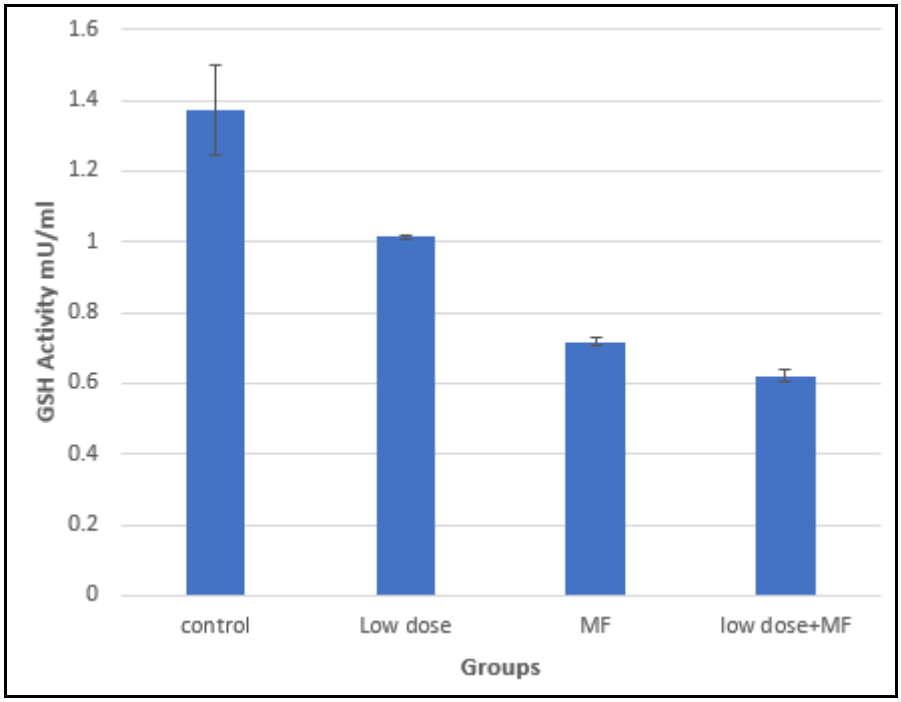

Fig. 3 GSH level in tumor tissues of a control group, a low dose of cisplatin group (3 mg/kg i.p.), MF group (50 Hz, 50 mT, 30 minutes daily for 2 weeks) and low dose + MF group. The data points are represented as mean ± SD (n = 5).

The tumor volumes were suppressed in all treatment groups (low dose of cisplatin, MF, low dose + MF) at the end of treatment protocol (day 15) by about 70, 20, and 90% respectively compared to the control group as shown in table (1). Cisplatin and MF inhibition of solid tumor growth may be due to oxidative stress that has led to apoptosis and/or necrosis of tumor cells (Tofani *et al.*, 2001).

Table 1: Tumor volume (cm^3) in all groups.

Groups	Days				
	Day 0	Day 3	Day 6	Day 9	Day 12
Control	0.33 ± 0.04	0.34 ± 0.01	0.45 ± 0.02	0.51 ± 0.01	0.67 ± 0.06
Low dose	0.29 ± 0.04	0.28 ± 0.05	0.18 ± 0.001	0.16 ± 0.1	0.16 ± 0.1
MF	0.33 ± 0.05	0.34 ± 0.003	0.42 ± 0.01	0.47 ± 0.01	0.54 ± 0.02
Low dose + MF	0.33 ± 0.04	0.16 ± 0.06	0.1 ± 0.07	0.06 ± 0.04	0.04 ± 0.03

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ARABIC SUMMARY

المجال المغناطيسي يحسن كفاءة جرعات منخفضة من السيسبلاتين عن طريق التغيير من الإجهاد التأكسدي في الفئران الحاملة لسرطان إرليش

منيرة راجح ، ابتسام محمد ، مروة الجارحي
قسم الفيزياء الحيوية، كلية العلوم، جامعة القاهرة، الجيزة، مصر

تم استخدام مجال مغناطيسي بقيمة 50 ملي تسلا بقيمة تردد 50 هرتز مع فترة التعرض لمدة 30 دقيقة / يوم لمدة 15 يوما لتعزيز كفاءة جرعة منخفضة من سيسبلاتين على الفئران . تم تقييم أنسجة الورم عن طريق المعلمات الكيميائية الحيوية مثل نشاط إنزيم سوبروكساید ديميتاز، مالون داي الديهايد، ومستويات الجلوتاثيون. تظهر النتيجة أن العلاج باستخدام المجال المغناطيسي والسيسبلاتين يقلل من نشاط مستوى سوبروكساید ديميتاز والجلوتاثيون ويزيد من مستوى مالون داي الديهايد مقارنة بالمعالجة باستخدام المجال المغناطيسي والسيسبلاتين فقط. في الختام، تظهر هذه النتائج أن المجال المغناطيسي يحسن الكفاءة العلاجية للسيسبلاتين