بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

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MONA MAGHRABY

CYTOGENETICAL AND MOLECULAR STUDIES ON THE EFFECTS OF TWO ANTIEPILEPTIC DRUGS ON MALE ALBINO MICE.

A THESIS SUBMITTED FOR

THE AWARD OF THE PH.D. DEGREE OF SCIENCE TEACHER PREPARATION

(ZOOLOGY)

BY

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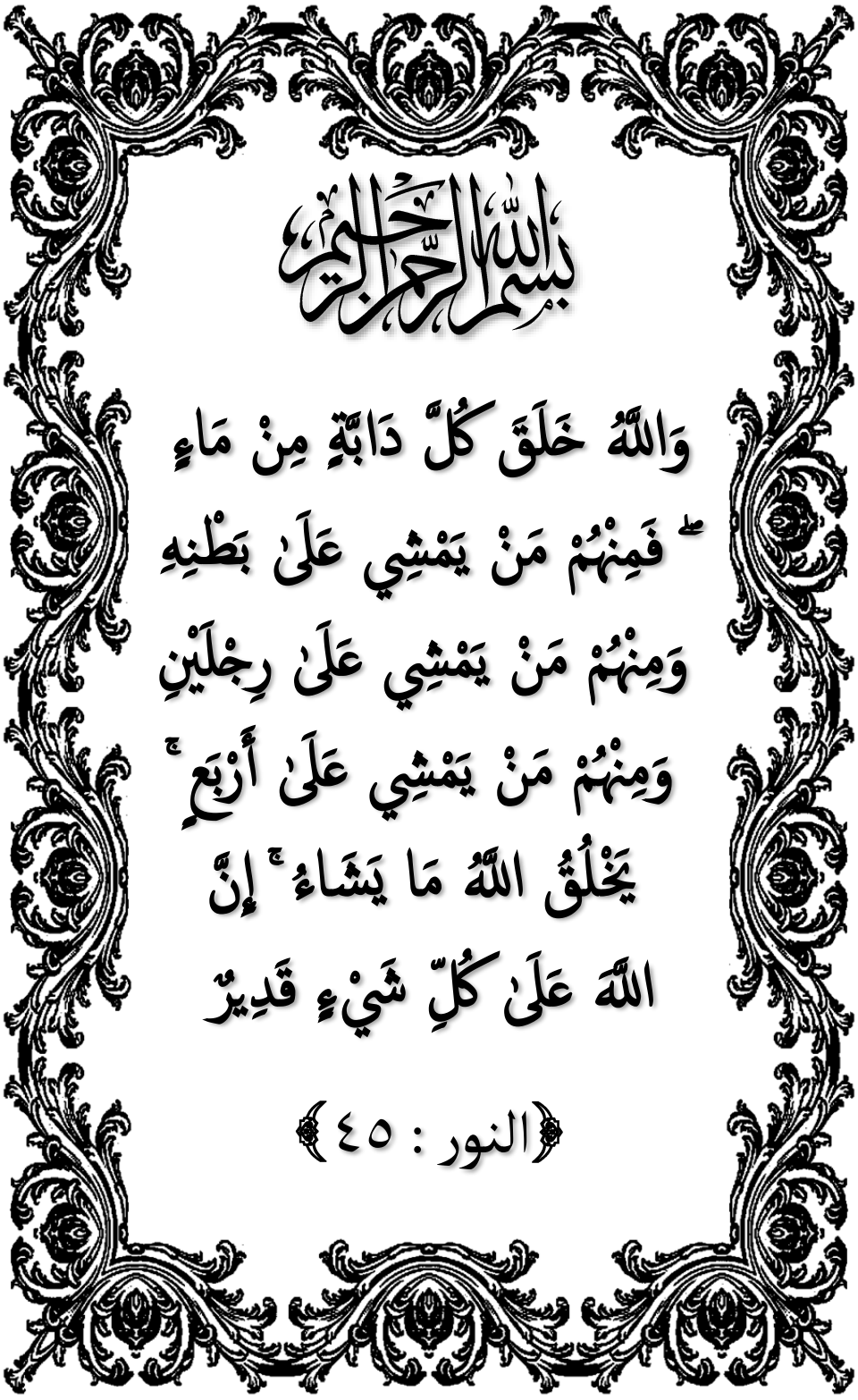
بسم الله الرحمن الرحيم
وَاللَّهُ خَلَقَ كُلَّ دَابَّةٍ مِنْ مَاءٍ
ۖ فَمِنْهُمْ مَنْ يَمْشِي عَلَىٰ بَطْنِهِ
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وَمِنْهُمْ مَنْ يَمْشِي عَلَىٰ أَرْبَعٍ ۚ
يَخْلُقُ اللَّهُ مَا يَشَاءُ ۚ إِنَّ
اللَّهَ عَلَىٰ كُلِّ شَيْءٍ قَدِيرٌ
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Dedication

I am indebted to thank my mother, my father, my wife, my children and my siblings for their continuous encouragement.

ABSTRACT

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Epilepsy is a neurological disease attack a considerable number of human population around the world without discrimination of age, gender or race. It occurrs as a result of disorder in some cerebral neurons known as focal epilepsy treated with depakine, or extends to all cerebral neurons known as general epilepsy treated with epanutin.

The present investigation deals with the genotoxic effects of depakine drug and/or epanutin drug on bone marrow chromosomes, DNA content and histological structure of liver of male albino mice *Mus musculus*. A total number of sixty-five CD-1 male mice (16-17 weeks) were used and were divided into thirteen groups, each consisted of 5 mice. The **first group** served as control. while **2nd** and **8th groups** were injected daily with depakine 25 mg/kg b.wt. for one and two weeks respectively. The **3rd** and **9th groups** were injected daily with depakine 50 mg/kg b.wt. for one and two weeks respectively. The **4th** and **10th** groups were injected daily with epanutin 3 mg/kg b.wt. for one and two weeks respectively. The **5th** and **11th groups** were injected daily with epanutin 6 mg/kg b.wt. for one and two weeks respectively. The **6th** and **12th** groups were injected daily with depakine 25 +

epanutin 3 mg/kg b.wt. for one and two weeks respectively. The **7th** and **13th** groups were injected daily with depakine 50 + epanutin 6 mg/kg b.wt. for one and two weeks respectively.

It was observed that treatment with depakine and/or epanutin induced structural and numerical chromosomal aberrations on bone marrow of male albino mice. Structural aberrations in groups that were treated with depakine 25 or 50 mg/kg b.wt. and groups that were treated with depakine 25 + epanutin 3 or depakine 50 + epanutin 6 mg/kg b.wt. were centromeric attenuation, ring, centric fusion, fragment, deletion, chromatid gap respectively from most prominent. Structural aberrations in epanutin treated groups were fragment, deletion, chromatid gap, ring, chromosomal gap, centric fusion, centromeric attenuation, end to end associations respectively from most prominent. While numerical aberrations were polyploidy in all treated groups. Total means of chromosomal aberrations were increased by dose and time in all treated groups and statistical analysis showed that total means of chromosomal aberrations displayed significant level ($P < 0.005$) of increase in depakine treated groups. While it showed high significant level of increase ($P < 0.001$) in groups treated with epanutin only and

groups treated with depakine together with epanutin compared to control group.

Results of micronucleus assay in the present study showed that treatment with depakine and/or epanutin resulted in increase the means of micronucleated polychromatic erythrocytes in bone marrow cells of male albino mice by dose and time in all treated groups. Also, results showed that treatment with depakine and/or epanutin induced cytotoxicity in bone marrow cells. Total means of micronucleated polychromatic erythrocytes and cytotoxicity were increased by dose and time in all treated groups and statistical analysis showed that total means of micronucleated polychromatic erythrocytes and cytotoxicity displayed significant level ($P < 0.005$) of increase in depakine treated groups. While it showed high significant level of increase ($P < 0.001$) in groups treated with epanutin only and groups treated with depakine together epanutin compared to control group.

Results of comet assay in the present study showed that treatment with depakine and/or epanutin resulted in increase the means of total comet score in hepatocytes of male albino mice by dose and time in main groups. Statistical analysis showed that means of total comet score displayed significant level ($P < 0.005$) of increase in depakine treated groups. While it showed high

significant level of increase ($P < 0.001$) in groups treated with epanutin only and groups treated with depakine together with epanutin compared to control group.

Results of (RT-PCR) showed that treatment with depakine and/or epanutin resulted in a decrease in the level of hepatic genes expression depending on dose and time in main groups. Statistical analysis showed that means of hepatic genes expression levels displayed significant level ($P < 0.005$) of decrease in depakine treated groups. It showed high significant level of decrease ($P < 0.001$) in groups treated with epanutin only and groups treated with depakine together with epanutin as compared to control group.

Histological analysis revealed that treatment with depakine induced hepatic histopathological changes in male albino mice represented by focal inflammation, cloudy swelling of hepatocytes cytoplasm and hepatic vascular congestion. Groups that were treated with epanutin only and groups treated with depakine together with epanutin showed approximately the same histopathological features in the liver of male albino mice in the form of multi-focal inflammatory areas, hydropic degenerative changes in hepatocytes cytoplasm with nuclear pyknosis in

addition to congestion accompanied with dilatation in hepatic vascular system and blood sinusoids.

Also, it was found that treatment with depakine and/or epanutin resulted in an increase in the level of hepatic aminotransferases in serum, depending on the dose and time in main groups. Statistical analysis showed that means of level of hepatic aminotransferases in serum displayed significant level ($P < 0.005$) of increase in depakine treated groups. It showed high significant level of increase ($P < 0.001$) in groups treated with epanutin only and groups treated with depakine together with epanutin compared to control group.

In conclusion the present study indicated that treatment with depakine and/or epanutin induced genotoxic effect on bone marrow chromosomes, DNA content and histological structure of liver of male albino mice depending on the dose and time duration. Therefore, the using of both drugs should be applied under restricted medical supervision.

Key words: Depakine, Epanutin, Chromosomes, RT-PCR, Micronucleus, Comet assay, ALT, AST, Histopathology, liver.

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