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The Prospect Antioxidant Impact Of Date Palm Extract On Certain Biochemical And Hormonal Indices Alterations Induced By Methoxychlor Pesticide In Female Rats

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Abstract:
Background*: The current study was planned to establish the protective role of date palm extract (DPE) versus methoxychlor (MXC) insecticide induced oxidative stress and the resultant dysfunction in female rats' ovary.*
Materials and Methods*: The study was conducted using forty adult female rats. They were determined into four groups: 1st group defined as a control group, 2nd group received DPE (100 mg/kg b. wt. orally) daily for 28 days. 3rd group, received MXC (200 mg/kg body weight, twice / week, orally) for 28 days and 4th group received both DPE & MXC in the same former doses and routes. At the end of the experiment, all animals were sacrificed and serum samples were gathered for some antioxidant and hormonal assessment.*
Results*: The results displayed that administration of MXC for 28 days induced a significant increase in serum levels of lipid peroxidation marker, and nitric oxide (NO) and contrarily a significant reduction in serum levels of glutathione (GSH), glutathione peroxidase (GPx) and superoxide dismutase (SOD). Additionally, MXC treated group exposed a significant reduction in levels of luteinizing (LH) hormone, follicle stimulating (FSH) hormone, estrogen and progesterone while prolactin hormone was significantly elevated. On the other side, administration of date palm extract plus MXC ameliorated significantly the former antioxidant and hormonal parameters comparing to (MXC) treated group.*
Conclusion: *It's concluded that co-treatment with date palm extract could improve the toxicity induced by methoxychlor, which ensure the protective effect of date palm extract (DPE).*
Key Word*: date palm extract (DPE)- methoxychlor (MXC)- Oxidative stress- reproductive hormone.*

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I. Introduction

The awareness of the use of pesticides in agriculture, post -harvest technology and their effect on public health was increased [1]. Pesticides may induce direct damage to structure of cells, reproductive toxicity via numerous mechanisms, and impediment with biochemical processes necessary for normal cell function [2, 3] Methoxychlor was commonly used for pest control to increase crop, vegetables and fruits production as well as livestock productivity in many countries due to it is less toxic than DDT [4]. The drawback of methoxychlor is hindering the role of the endocrine system and has been shown to cause increased levels of oxidative stress [5]. The oxidative stress is the result of imbalance between the antioxidant defense of the body and the generation of free radicals resulting in the output of antioxidants alterations, free radicals, oxygen free radicals, and lipid peroxidation [6]. Nowadays, the trendy use of naturally available botanicals is growing due to their antioxidant merits. Therefore, certain plants possess definite phytochemicals that have been shown to expose antioxidant activity in both in *vitro* and in *vivo* studies versus oxidative stress [7]. Fruits of the date palm (*Phoenix dactylifera* L.) are wide commonly consumed in numerous regions of the world particularly most of the Arabian countries and of between is Egypt. Dates are rich in definite nutrients and give a good source of fast energy due to the presence of easily absorbed carbohydrates in in the form of glucose and fructose [8, 9]. Dates have abundant beneficial values; remedy of different infectious illnesses and cancer, potent antimutagenic and antioxidant activity [10-16]. The antioxidant performance is attributed to the broad range of phenolic compound present in dates [10, 16, 17] and also to the existence of vitamin C [13, 18]. Accordingly, this study was designated to evaluate the role of date extract in protection against the oxidative stress in rats induced by methoxychlor.

II. Material And Methods

Ethical approval

All experimental steps were performed according to the following protocol approved by the Medical Research Ethics Committee, National Research Centre, (1179102021).

Date palm extract preparation

Fresh ripened fruits were collected from ElWahat, Elwady ElGdid Governorate, Egypt. Fruit flesh was extracted via grinding 2 times with distilled water (1/10, w/v), and centrifuged at 4°C for twenty minutes at 4000g then the supernatant was collected. During the experience, the aqueous date fruit extract was daily prepared and administrated to rats.

Animals:

Forty female Sprague - Dawely rats weighing 170 - 180g were obtained from the breeding unit of the National Research Centre, Egypt. The animals were housed beneath standard laboratory circumstances and acclimatized for 7 days prior to the designed experiments. Rats were permitted free access to water and rodent chow.

Chemicals:

Methoxychlor insecticide used in this experiment was obtained from Sigma-Aldrich Com. USA.

Experimental design:

After the acclimatization period, the forty female rats were sectioned into 4 equal groups, each of 10 rats. The duration of the current study was 28 days.

First group (control group), was orally administered normal saline solution by gastric tube once daily.

Second group; was orally received date palm extract (DPE) (100mg/kg bw) dissolved in 3 ml normal saline solution once daily for 28 days [19].

Third group; was orally received 1/25 LD50 of methoxychlor (200mg/kg bw) [20] twice/week for 28 days.

Fourth group was pre orally received grape seeds DPE (100mg/kg bw) for a week then female rats were administered orally dose of 1/25 LD50 of MXC (200 mg/kg bw) twice/ week for 28 days.

At the end of the experimental period, blood samples were obtained from each rat in each group by puncturing the inner canthus of the eye. Collected blood samples were stored for15 min at room temperature, then centrifuged at 3000 rpm for twenty minutes to separate serum for achieving some biochemical and hormonal assessment.

Serum Biochemical Analysis:

Determination of glutathione peroxidase activity (GPx), was performed according to method described by Paglia and Valentine [21]. The enzymatic superoxide dismutase (SOD) activity was assessed according to method mentioned by Nishikimi *et al.,* [22]. Determination of malondialdehyde (MDA) concentration as lipid peroxides and reduced glutathion (GSH) activity in serum were carried out using the colorimetric method described by Chanarin [23]. Finally, serum nitrite as NO production indicator was determined using Griess reagent according to the method mentioned by Torre *et al.,* [24].

Serum Hormonal Analysis:

Determination of follicle stimulating hormone (FSH), luteinizing hormone (LH), estrogen, progesterone and prolactin were estimated according to Santner, *et al.* [25], by the coat-A- count technique using the radio immunoassays (RIA).

Statistical analysis:

Statistical analysis was done using In Stat version 16.0 (2019) computer program. The results were expressed as means ± SE. Multiple comparisons were done using one-way ANOVA test according to SPSS 14 [26], followed by Tukey - Kramer as a post- ANOVA test. The level of significance $p > 0.05$ was regarded as non- significantly different, while $p < 0.05$ was considered as significantly different.

III. Result

The data of orally received DPE (100 mg/ Kg Bw) with or without MXC (200 mg/Kg Bw) on serum hormonal parameters of female rats are demonstrated in table (1). A marked decrease in serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels was noticed in methoxychlor group compared to the control group, however their concentrations elevated significantly in the MXC plus DPE treated rats paralleled to the MXC group. Estrogen and progesteron levels were reduced significantly in methoxychlor

treated group, while co-administration of DPE to methoxychlor displayed a marked increase of their levels compared with the MXC group. Moreover, the prolactin hormone level was marked risen in the MXC treated group while its level was fundamentally decreased in the group treated with DPE plus methoxychlor.

Groups	Parameters				
	FSH ng/ml	LH ng/ml	Estrogen ng/L	Progesterone ng/ml	Prolactin ng/ml
Control	4.42 ± 0.082b	2.08 ± 0.011 b	124.78 ± 0.911 b	22.44 ± 0.27 b	3.37 ± 0.15 b
MXC	1.85 ± 0.101a	0.84 ± 0.012a	74.62 ± 0.65a	12.52 ± 0.10a	8.25± 0.12a
DPE	4.30 ± 0.022b	2.05 ± 0.011b	120.47±0.569b	21.23 ± 0.03b	3.45 ± 0.11b
DPE + MXC	3.45 ± 0.080 ab	1.72 ± 0.051ab	102.466 ± 0.782 ab	18.69 ± 0.27 ab	5.52 ± 0.121 ab

Results of orally received (DPE) (100 mg/kg Bw) with or without methoxychlor (200mg/kg Bw) on some serum antioxidant enzymes and nitric oxide of female rats are mentioned on table (2). The analysis of data revealed that, the administration of methoxychlor significantly elevated the levels of malondialdehyde (MDA) and nitric oxide compared with the control group. However, the MDA and nitric oxide levels were marked decreased in the MXC plus DPE group compared with the MXC group. Decreased glutathione (GSH) activity was significantly reduced in the methoxychlor group only parallel to the control, however, GSH activity elevated significantly in the MXC plus DPE treated rats. The superoxide dismutase (SOD) activity in the methoxychlor group displayed a significant minimizing at the end of the 28 days relative to the control group. While (SOD) activity was marked increased in the MXC plus DPE treated rats parallel to the MXC group.

Finally, glutathione peroxidase (Gpx) activity in methoxychlor group demonstrated a significant reduction compared with the control group. While (Gpx) activity was elevated significantly in the MXC plus DPE treated rats in relation to the MXC group.

Groups	Parameters				
	MDA nmol/mg	NO µmol/mg	SOD U/mg	GSH U/g	GPx U/mg
Control	14.89± 0.17 b	6.24 ± 0.05 b	115.46± 0.41b	11.53 ± 0.08b	29.81 ±0.13b
MXC	44.17 ± 0.22a	31.46± 0.37a	51.12 ± 0.03a	5.36 ± 0.05a	13.47 ± 0.11a
DPE	15.83 ± 0.11b	6.33 ± 0.04b	111.61± 0.21b	11.82 ± 0.07b	28.84± 0.17b
DPE + MXC	21.63± 0.21ab	15.88 ± 0.32ab	95.41± 0.17ab	9.56± 0.07ab	22.28± 0.08ab

IV. Discussion

Pesticides are commonly used in agriculture and public health to control weeds, insects, animals' rations, and vectors of diseases. On the other hand, pesticides may be introduced to animals for the control of insects, mites/spider mites or other pests resulting in adverse health impacts on the immune and reproductive system which may end with cancer [27]. Pesticides that may obstruct the hormonal function are often termed endocrine disrupting chemicals (EDCs) [28].

Methoxychlor is one of organochlorines which defines that they comprise chemically combined carbon and chlorine, this binding is very potent and resists degradation by normal physical and biochemical processes, so they have a long half- life and they stack in the environment as persistent organic pollutants [29].

However, MXC was emerged to be a replacement for the banned pesticide DDT due to it is less toxic [30], but it was found that MXC may have a potential endocrine disruption that simulate estrogenic activity and niggles the endocrine system [31]. Metabolites of MXC have been assumed to be more toxic than the parent compound and may be responsible for ovarian toxicity [32, 33].

The results of the current study displayed a significant reduction in the level of follicle stimulating hormone (FSH), luteinizing hormone (LH), estrogen and progesterone in the group treated with methoxychlor. These findings are in harmonized with [20, 34] who assumed that organochlorine pesticide and particularly methoxychlor [35] acts as endocrine disrupter and have been reported to possess estrogenicity in *vivo* as the level of LH, FSH have dropped. MXC reduces steroidogenic enzyme levels, elevates metabolic enzyme expression and this in turn result in decreased sex steroid hormone levels [36].

The prolactin hormone level in the group received methoxychlor (200 mg/kg B.W) showed a marked increase as compared with control group. This finding was in agreement with Lafuente *et al.,* [37] as well as Lafuente *et al.,* [38] who reported elevation of prolactin level in male rats post -administered 25 or 50 mg/kg/day of methoxychlor S/C in sesame oil for one month. While, Goldman *et al.,* [39] mentioned that MXC at doses of 25 or 50 mg / kg for 8 weeks decreased pituitary prolactin level.

Our results showed decreased serum progesterone and estrogen levels in female rats group acutely exposed to methoxychlor (50 - 100 mg/kg), the data were coincided with a study reported inhibition of

progesterone and estradiol production in human placental JEG-3 cells administered with MXC. Interestingly, our results revealed that co-administration of date palm fruit extract (DPE) with methoxychlor to female rat caused significant recovery which was observed in the increase of the hormonal levels of stimulating hormone (FSH), luteinizing hormone (LH), estrogen and progesterone and a reduction in prolactin hormone level parallel to methoxychlor group.

On the other side, the current study displayed that MXC administration lead to a significant elevation in serum MDA and nitrite levels. While GSH, SOD and GPx activities decreased significantly in relation to control group. It is suggested that MXC exerted increase in the activity of reactive oxygen species (ROS) which are embraced as substantial pathologic mediators in numerous disorders as stimulated lipid peroxidation [40].

Our findings are in agreement with former study of Suzuki *et al.,* [41] who found alterations in oxidative stress, cytotoxicity and lipid peroxidation followed exposure of the organochlorine compounds in a dose- and time-dependent manner.

Previous studies revealed that methoxychlor is sequentially demethylated by mammalian liver microsomes, during this reaction, reactive metabolites, probably free radicals combine covalently to microsomal components. Fundamentally, antioxidants/free radical scavengers and sulfhydryl-containing compounds prohibit covalent binding of MXC in human liver microsomes, assuming that human cytochrome- P450 enzymes are responsible of the conversion of MXC into its prime metabolites with production of ROS [42-44].

Our findings displayed that co-administration of date palm fruits extract with methoxychlor, has improved significantly the values of MDA,NO,GSH, SOD and GPx in parallel to MXC treated group. Administration of antioxidants effectively prevented the oxidative damage caused by lipid peroxidation [45].

Date polyphenols, do a beneficial effects that comprise antioxidant, anti-carcinogenic, anti-allergic, anti-inflammatory, antibiotic, anti-ageing, anti-ulcer, anti-diarrheal, cardioprotective , antithrombotic, vasorelaxing and neuroprotective properties [46].

Numerous reports assumed that natural antioxidants constitute efficient remedy of toxicity triggered by xenobiotics. Nonenzymatic natural antioxidants such as vitamins C, and polyphenolic compounds could act to overcome the oxidative stress. However, it is potential that polyphenolic compounds (anthocyanins, flavonoids and phenolic acids), as well as trace elements (copper, manganese, selenium and zinc), in addition to vitamin C exist in the date palm fruit are the responsible compounds for this protection [12, 47-51] 2014; 2017; 2019; 2020; 2023).

Actually, Vayalil [52] confirmed the antioxidant activity of the aqueous date palm extract, as observed by the prohibition of lipid peroxidation and protein oxidation and also by the efficiency to sweep superoxide and hydroxyl radicals in vitro. The antioxidant performance of DPE may be attributed to the ability of its active ingredients to detoxify free radicals and to suppress lipid peroxidation [53].

V. Conclusion

Methoxychlor induced reproductive hormonal disruption, oxidative stress represented by reduction in antioxidant parameters and elevation in lipid peroxidation in serum of female rats. Treatment with date palm fruit extract revealed a protective effect versus methoxychlor toxicity; improvement of the induced reproductive hormonal alterations. In addition, the results of our study showed that co-treatment with date palm fruit extract produced a high strong protective effect versus oxidative stress; as demonstrated by the marked decrease of lipid peroxidation, as well as the improvement of enzymes' antioxidant status.