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EFFECT OF DIMETHOATE, DICOFOL AND VOLTAREN ON OXIDANT/ANTIOXIDANT STATUS IN MALE RATS: ROLE OF SELENIUM

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ABSTRACT:

In real life, all people are inevitably exposed to pesticides, through environmental contamination or occupational. In the same time, patients of common drugs-dependant (e.g. diabetic, blood pressure, analgesic and anti-inflammatory agents) are further exposed to chemical multi-stressor. The present study describes effects of Dicofol (Dic), Dimethoate (Dim), Voltaren (Vol), Selenium (Se) and their mixtures on the oxidative damage. This study aimed also to study the ability of Se to modulate damage induced by Dim, Dic, Vol and their mixtures. The insecticidal treatments (Dicofol was administered at a dose of 662.12 mg a.i. k_{g-1} b.wt. (1/100 LD_{50}) and Dimethoate 481.65 mg a.i. kg^{-1} b.wt. (1/100 LD_{50})) Voltaren at 0.83 mg kg-1 and Selenium as sodium selenite at (400 µg/person/day (6.66 mg kg^{-1} b.wt). Rats were divided into 16 groups and each group comprised 8 animals. G1 served as control received water only, G2 given Dim, G3 received Dic, G4 given Vol, G5 given Se, G6 received Dim+Dic, G7 given Dim+Vol, G8 given Dic+Vol, G9 given Dim+Dic+Vol, G10 received Dim+Se, G11 given Dic+Se, G12 received Vol+Se, G13 received Dim+Dic+Se, G14 given Dim+Vol+Se, G15 given Dic+Vol+Se and G16 given Dim+Dic+Vol+Se. Administration of Dim, Dic, Dim+Dic, Dim+Vol, Dic+Vol and Dim+Dic+Vol resulted in a significant increase in serum lipid peroxidation (LPO) level, and increase the activity of plasma catalase, while induced significant decreases in the activities of plasma superoxide dismutase (SOD), glutathione peroxidase (Gpx), glutathione reductase (GR), glutathione-s-transferase (GST) and

cytochrome P450. Supplementations of Se ameliorate the adverse effects of exposure to tested compounds.

Keywords: Dimethoate; dicofol; anti-inflammatory drug "diclofenac"; oxidative damage; cytochrome P450; selenium; rats.

INTRODUCTION

Pesticides are known to disturb the biochemical and physiological functions of cell, thereby affecting membrane integrity **(Agrawal et al., 1991; Mansour and Mossa, 2009; Mansour *et al*., 2009)**, and several pesticides exert their biological effects through electrophilic attack on the cellular constituents of hepatic and brain tissues **(Samanta and Chainy, 1995)** with simultaneous generation of reactive oxygen species **(Lemaire *et al*., 1994)**. Additionally, oxidative stress has been implicated in pesticide-induced neurotoxicity based on its role in the cascade of biochemical changes that lead to dopaminergic neuronal cell death **(Jia and Misra, 2007)**. Available reports indicate that insecticides in both *in vivo and in vitro* tests alter the enzyme activities associated with antioxidant defence mechanisms **(Gultekin *et al*., 2000; Oncu *et al*., 2002; Mansour and Mossa, 2009; Mansour *et al*., 2009)**.

The acute and sub-chronic exposures to dimethoate alters the antioxidant status and the histology of liver and induce hepatic lipid peroxidation in mice **(Sivapiriya *et al*., 2006)** and rats **(Sharma *et al*., 2005a, b; Sayim, 2007; Kamath *et al*., 2008)**.

Also, the chlorinated miticide dicofol caused hepatomegaly and increased altered liver foci development in rats initiated with chemical carcinogen nitrosodiethylamine **(Flodstr̥m *et al*., 1990)**.

Diclofenac, (2-[(2, 6-dichlorophenyl) amino] phenylacetate), is a non-steroidal anti-inflammatory drugs (NSAIDs) that is commonly used as anti-inflammatory, analgesic, and antipyretic drugs. It is used in inflammatory and painful diseases of rheumatic and non-rheumatic origin **(Moser *et al*., 1990)**. Also, diclofenac treatment may have some adverse effects, such as gastrointestinal damage, platelet dysfunction, and convulsion. These effects are likely to be associated with the ability of this phenylacetic acid derivative to compete with

arachidonic acid for binding to cyclo-oxygenase (COX), resulting in decreased prostaglandin formation **(Small, 1989 and Vane, 1996)**.

Selenium (Se) is an essential trace element, plays important role in mammalian biology and improves the activity of the seleno-enzyme. It is present in the active center of glutathione peroxidase (GPx), an antioxidant enzyme that protects membrane lipids and macromolecules from oxidative damage produced by peroxides **(Rotruck *et al*. 1973; Harman, 1993)**.

The aim of this study was to evaluate the adverse effects of long-term exposure to pesticides "dimethoate and dicofol" and anti-inflammatory drug "diclofenac" on oxidant/antioxidant status and cytochrome P450 in healthy mal rats and the ameliorative effect of selenium.

MATERIALS AND METHODS

1. Chemicals and reagents

Dimethoate (Dragothoate®, 40% EC, *O*, *O*-dimethyl *S*-*N*-methyl carbomyl methyl phosphorodithioate) was obtained from El-Masryia for agriculture and development company, Egypt; Dicofol (Kelthane®, 18.5% EC, 2, 2, 2-trichloro-1, 1-bis (4-chlorophenyl) ethanol) from El-Nasr Mediate Chemical Company, Egypt; Selenium (Sodium selenite, Na_2O_3Se) from Mallinckrodt. Inc. (Paris, France). Diclofenac sodium (Voltaren®, tablets 50 mg) was supplied from Novartis pharma, Egypt. Kits of super oxide dismotase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRx), glutathione-S-transferase (GST), lipid peroxidase (LPO) and total protein were obtained from Biodiagnostic, Egypt. ***Kits of Cytochrome P 450*** were obtained from Sigma chemical, USA. All other chemicals were of reagent grades and were obtained from the local scientific distributors in Egypt

2. Animals and experimental design

Healthy male albino rats weighing 110±10 g were obtained from Animal Breeding House of The National Research Centre, Dokki, Cairo, Egypt. Animals were kept in clean plastic cages with free access to food (standard pellet diet) and tap water *ad-libitum*, under standardized housing conditions (12h light/dark cycle, temperature was 22 ± 1 ^{o}C and a minimum relative humidity of 40%) in the

laboratory animal room. After adaptation (1 week), the animals were randomly assigned to groups (eight rats/group). The first group of rats served as the control while, the second to sixteen groups was used for single and mixture-treatments with or without selenium (fifteen groups). All treatments were diluted with distilled water and given via oral route for 6 consecutive weeks. Dosages to rats were freshly prepared and adjusted weekly for body weight changes and given at approximately the same time each morning. Dimethoate was administered at a dose of 481.65 mg a.i. kg^{-1} b.wt. (1/100 LD_{50}) and dicofol at a dose of 662.12 mg a.i. kg^{-1} b.wt. (1/100 LD_{50}) based on estimated LD_{50} in our laboratory (unpublished data). The selective doses of diclofenac sodium (0.83 mg/kg/day) was based on pharmaceutical data and daily giving, while selenium was administered at a dose relative to Upper Intake Levels (ULs, 400 µg/person/day (6.66 mg kg^{-1} b.wt)) for human (IOM, 2000) and given daily for 8 weeks. The control group received an equivalent volume of distilled water (0.5 ml /rat).

At the end of treatment periods, rats of each group were kept without treatment for 2 weeks beyond 6 weeks to test toxicant withdrawal effect.

2.3. Blood samples

Blood samples were drawn from all rats at the end of treatments and withdrawal periods under ether anesthesia by puncturing the reteroorbital venous plexus of the animals with a fine sterilized glass capillary and collected in heparinized and non-heparinized glass tubes to separate plasma and sera, respectively. Within 20 min of blood collection, the sera and plasma samples were drawn from blood after centrifugation at 3500 rpm (600g) for 10 min at 4°C using Universal 32 R centrifuge (Hettich-Zentrifugen GmbH, Tuttlingen, Germany). The sera and plasma were kept in a deep freezer (–20°C) until analyzed.

4. Oxidative damage biomarkers

4.1. Antioxidant enzymes

Superoxide dismutase (SOD), Catalase (CAT), Glutathione reductase (GRx), Glutathione peroxidase (GPx), and Glutathione-s-transferase (GST) were determined in plasma according the methods of **Nishikimi *et al*. (1972), Aebi (1984), Goldberg and Spooner (1983),**

Paglia and Valentine (1967), and Habig *et al*. (1974), respectively. The activities were expressed in terms of µmol/ml for all enzymes.

4.2. Lipid peroxidation

Malondialdehyde (MDA), as a marker for lipid peroxidation (LPO), was determined in serum by the method of **Ohkawa *et al*. (1979)** and expressed in nmol/mL.

5. Cytochrome P 450

Cytochrome P450 determination was carried out according to the method reported by Masters et al. (1967) using Kits and expressed as nmol/ml.

6. Total protein

Total protein determined according to the method described by **Henry (1964)** using Diamond Diagonstics kits.

2.7. Spectrophotometric measurements

The Spectrophotometric measurements were performed by using a Jenway, UK, 6305 UV/Vis spectrophotometer.

8. Statistics

The data were analyzed by using SPSS (version 14.0) for Windows and expressed as means ± S.D. Paired samples *t*-test was used to compare between the data of the control and those of treatments.

RESULTS AND DISCUSSION

Results in Table (1) revealed that rats given each of Dim, Dic, Dim+Dic, Dim+Vol, Dic+Vol and Dim+Dic+Vol for six weeks, treatments caused significant decrease in body weights compared to control. The weekly body weight gains were 6.35%, 6.72%, 8.70%, 6.94%, 6.71% and 6.67%, respectively, as compared with control (15.12 %). The reduction in body weight gains was still significant after the withdrawal period. However, supplementation of Se was improved the body weight gains to the normal range, either in treatments or withdrawal periods. Generally, the increase or decrease in body weight gain is an index of toxic effects **(Lu, 1996)**. Reduction in body weight in experimental animals due to insecticides intoxication (e.g. OPI) is a commonly reported phenomenon **(Chung *et al*., 2002; Kalender *et al*., 2006 and Mansour and Mossa, 2010a, b)**. This occurs probably due to decreased food intake in these animals

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Table (1): Effect of dimethoate, dicofol and voltaren on rat's body weight and the ameliorative role of selenium.

Treatment	Body weight (g)				
	Treatment period (6 week)			Withdrawal period (2week)	
	Initial b.wt.	Final b.wt.	% of weekly b.wt. gain	Final b.wt.	% of weekly b.wt. gain
Control	115.38±4.13	220.67±3.98	15.21	255.33±6.39	15.16
Dimethoate (Dim)	123.38±5.46	170.40±3.68**	6.35	181.67±5.56**	5.91
Dicofol (Dic)	117.88±5.84	165.43±12.47**	6.72	187.33±5.37**	7.36
Voltaren (Vol)	115.13±1.94	214.52±8.98	14.39	251.28±13.73	14.78
Selenium (Se)	119.15±10.01	219.76±5.84	14.07	264.59±5.31	15.26
Dim + Dic	110.50±3.25	168.17±5.81**	8.70	168.33±7.36**	6.54
Dim + Vol	118.50±2.85	167.86±4.32**	6.94	171.67±2.70**	5.61
Dic + Vol	119.38±5.46	167.43±5.53**	6.71	181.45±8.73**	6.50
Dim + Dic + Vol	120.13±4.49	168.17±3.65**	6.67	171.23±4.93**	5.32
Dim + Se	119.25±4.53	219.93±3.41	14.07	248.83±4.62	13.58
Dic + Se	120.25±3.66	210.34±4.50	12.49	251.34±6.88	13.63
Vol + Se	118.88±2.31	219.88±3.59	14.16	259.04±9.10	14.74
Dim + Dic + Se	116.63±3.65	212.51±6.37	13.70	249.23±5.24	14.21
Dim + Vol + Se	114.00±5.31	218.24±5.37	15.24	253.46±5.24	15.29
Dic + Vol + Se	119.75±5.24	213.44±13.78	13.04	258.76±7.32	14.51
Dim + Dic + Vol + Se	117.63±2.94	217.90±3.09	14.21	246.12±6.05	13.65

Values are means ± SD; n=8; Statistical difference from the control: * significant at $P \leq 0.05$ &** highly significant at $P \leq 0.01$.

% of weekly body weight gain = [(Final b.wt. – Initial b.wt.) / (Initial b.wt. x no. of weeks)] x 100

and also, may be a result of the combination of increased degradation of lipids and proteins as a result of the direct effects of organophosphate compound **(Goel *et al*., 2005; Mansour and Mossa, 2011)**.

Superoxide dismutase is a ubiquitous chain breaking antioxidant and is found in all aerobic organisms. It is a metalloprotein widely distributed in all cells and plays a protective role against Reactive Oxygen Species (ROS)-induced oxidative damage. SOD catalyses the superoxide radical dismutation to hydrogen peroxide and molecular oxygen **(Mayer, 1980)**. The present results revealed that the administration of Dim or Dic and their combinations for a period of 6 weeks caused a significant decrease in the activities of SOD (Table 2). The activities of SOD were decrease to 88.37, 89.29, 75.91, 82.00, 85.93 and 69.93 nmol/ml, respectively, as compared to control (93.95 nmol/ml). Supplementations of selenium and withdrawal period were mitigating the adverse effects of exposure to tested compounds (Table 2).

Catalase is one of the cellular defense mechanisms against cytotoxic oxygen species (H_2O_2). However, endogenous H_2O_2 may be converted either by catalase or glutathione peroxidase to H_2O or otherwise it may generate the highly reactive free hydroxyl radical (OH^-) by the Fenton reaction, which is widely believed to be mainly responsible for oxidative damage **(Sharma *et al*., 2005)**. Increase of CAT activity in rats exposed to Dim, Dic, Dim+Dic, Dim+Vol, Dic+Vol and Dim+Dic+Vol was significant ($P \leq 0.01$) either at the end of treatment or after withdrawal period (Table 2). The combined effect of Se significantly ameliorated the increase of SOD and CAT activities. The elevated activity of CAT in rats given Dim and Dic may be result from the adaptive response to the generated free radicals **(Koner *et al*., 1998)**, failure of the total antioxidant defense mechanism to protect the tissues from mechanical damage caused by free radicals **(Samsheshekariaiah *et al*., 1992)**.

Glutathion peroxidase (GPx) constitutes a major defence system against oxidative damage to essential intracellular low molecular weight compounds, proteins and poly-unsaturated fatty acids, particularly as an effective reduction of hydroperoxide to water **(Landry *et al*. 1994)**. Results in (Table 3, 4) revealed that the

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Table (2): Effect of dimethoate, dicofol and voltaren on the activities of superoxide dismutase (SOD) and catalase in the plasma of male rats and the ameliorative role of selenium.

Treatment	Oxidative stress biomarkers			
	Superoxide dismutase (nmol/ml)		Catalase (nmol/ml)	
	Treatment period	Withdrawal period	Treatment period	Withdrawal period
Control	93.95±1.84	94.19±3.20	0.49±0.11	0.49± 0.02
Dimethoate (Dim)	88.37±1.42*	89.57±3.12	0.69± 0.02**	0.68± 0.01**
Dicofol (Dic)	89.29±0.73*	90.37±0.90	0.63±0.04**	0.61±0.02**
Voltaren (Vol)	94.16±4.20	95.75±6.09	0.48±0.07	0.47±0.09
Selenium (Se)	93.26±1.56	93.24± 2.11	0.49±0.08	0.49± 0.03
Dim + Dic	75.91±6.90**	77.78±5.48**	0.85±0.04**	0.85±0.03**
Dim + Vol	82.00±0.39**	84.85±0.47**	0.82±0.05**	0.80±0.02**
Dic + Vol	85.93±4.02**	86.02±2.38*	0.76±0.01**	0.73±0.05**
Dim + Dic + Vol	69.93±1.55**	71.51±1.07**	1.01±0.02**	1.00±0.02**
Dim + Se	94.68±3.83	94.23± 4.16	0.48±0.02	0.47±0.092
Dic + Se	93.35± 1.21	95.17±8.55	0.49±0.05	0.49±0.02
Vol + Se	94.28±5.19	96.75±2.03	0.48±0.01	0.47±0.015
Dim + Dic + Se	93.49±7.50	94.09±3.83	0.52±0.04	0.49±0.10
Dim + Vol + Se	92.07±3.54	95.54±4.72	0.48±0.02	0.47±0.092
Dic + Vol + Se	94.16±3.86	94.85± 2.19	0.48±0.03	0.48±0.03
Dim + Dic + Vol + Se	90.22±5.62	92.99±5.12	0.52±0.07	0.51±0.04

Values are means ± SD; n=8; Statistical difference from the control: * significant at $P \leq 0.05$ & ** highly significant at $P \leq 0.01$.

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Table (3): Effect of dimethoate, dicofol and voltaren on the activities of glutathione peroxidase (GPx) and glutathione reductase (GR) in the plasma of male rats and the ameliorative role of selenium.

Treatment	Oxidative stress biomarkers			
	Glutathione peroxidase (nmol/ml)		Glutathione reductase (nmol/ml)	
	Treatment period	Withdrawal period	Treatment period	Withdrawal period
Control	0.85±0.06	0.84±0.02	85.06±2.41	85.36±1.65
Dimethoate (Dim)	0.70± 0.03**	0.76± 0.01*	61.26±1.67**	63.45±2.01**
Dicofol (Dic)	0.79±0.03	0.79± 0.01	65.97± 2.10**	70.93±1.88*
Voltaren (Vol)	0.84±0.04	0.85± 0.07	85.03±5.75	82.71±2.12
Selenium (Se)	0.84±0.03	0.83±0.02	85.07± 3.39	86.25±2.07
Dim + Dic	0.59±0.04**	0.71±0.02**	47.67±4.77**	49.36±3.76**
Dim + Vol	0.64±0.01**	0.71±0.02**	50.69±7.42**	53.17±5.39**
Dic + Vol	0.66±0.02**	0.72±0.05**	63.65±0.99**	64.49±12.38**
Dim + Dic + Vol	0.47±0.02**	0.51±0.02**	40.63±1.38**	58.88±25.38**
Dim + Se	0.86±0.10	0.84±0.07	84.79±1.71	84.17±3.08
Dic + Se	0.84±0.03	0.83±0.01	84.30±2.29	85.85±1.39
Vol + Se	0.86±0.06	0.85± 0.02	85.99±3.39	84.25±2.16
Dim + Dic + Se	0.85±0.03	0.86±0.02	83.50±1.21	83.50±3.44
Dim + Vol + Se	0.84±0.02	0.86±0.04	86.11±2.43	85.33±5.81
Dic + Vol + Se	0.84±0.07	0.85±0.03	85.17±2.17	84.79±3.99
Dim + Dic + Vol + Se	0.76±0.06*	0.80±0.015	84.98±5.20	85.47±2.06

Values are means ± SD; n=8; Statistical difference from the control: * significant at $P \leq 0.05$ & ** highly significant at $P \leq 0.01$.

Table (4): Effect of dimethoate, dicofol and voltaren on the activities of glutathione-s-transferase (GST) in plasma and lipid peroxidation (LPO) in the sera of male rats and the ameliorative role of selenium.

Treatment	Oxidative stress biomarkers			
	Glutathione-s-transferase (nmol/mg protein)		Lipid peroxidation (nmol/mg protein)	
	Treatment period	Withdrawal period	Treatment period	Withdrawal period
Control	1.08±0.02	1.06±0.03	1.35±0.08	1.36±0.07
Dimethoate (Dim)	0.79±0.02**	0.90±0.03**	1.97±0.03**	1.89±0.03**
Dicofol (Dic)	0.88± 0.02**	0.91±0.03**	1.90±0.03**	1.81±0.04**
Voltaren (Vol)	1.08±0.07	1.06±0.03	1.33±0.14	1.34±0.03
Selenium (Se)	1.07± 0.04	1.05±0.02	1.34±0.06	1.34±0.16
Dim + Dic	0.71±0.02**	0.71±0.04**	2.13±0.12**	2.05±0.18**
Dim + Vol	0.79±0.02**	0.85±0.03**	2.11±0.01**	1.88±0.08**
Dic + Vol	0.64±0.07**	0.69±0.03**	1.98±0.02**	1.89±0.03**
Dim + Dic + Vol	0.84±0.03**	0.88±0.01**	2.47±0.21**	2.13±0.16**
Dim + Se	1.06±0.03	1.04±0.025	1.32±0.18	1.36±0.03
Dic + Se	1.05±0.03	1.04±0.005	1.37±0.24	1.36±0.24
Vol + Se	1.05±0.06	1.06±0.07	1.34±0.16	1.33±0.06
Dim + Dic + Se	1.08±0.02	1.08±0.025	1.39±0.10	1.37±0.04
Dim + Vol + Se	1.07±0.05	1.07±0.02	1.33±0.13	1.36± 0.04
Dic + Vol + Se	1.06±0.08	1.05±0.015	1.38±0.25	1.35±0.02
Dim + Dic + Vol + Se	1.00±0.02*	1.04±0.015	1.43±0.01	1.37± 0.03

Values are means ± SD; n=8; Statistical difference from the control: * significant at $P \leq 0.05$ & ** highly significant at $P \leq 0.01$.

administration of a single dose of each of Dim, Dic and their combination for a period of 6 weeks caused a significant decrease in the activities of GPx, GRx and GST compared to control. The activities of GPx was control, o.85 nmol/ml in control group to 0.70, 0.59, 0.64, 0.66 and 0.47 nmol/ml in Dim, Dim+Dic, Dim+Vol, Dic+Vol and Dim+Dic+Vol-treated groups, respectively.s In contrast, after withdrawal period (2week) the changes in the activities GPx, GRx and GST were still significantly lower than that of control. The more pronounced effect was recorded in Dim+Dic+Vol treatments rats. Supplementations of selenium ameliorated the adverse effects of exposure to tested compounds. Similarly, the current study showed that LPO level was increased after treatment with Dim, Dim+Dic, Dim+Vol, Dic+Vol and Dim+Dic+Vol, while cytochrome P450 activity was reduced either after the single and combination of Dim, Dic for 6 weeks or withdrawal period (Table 4, 5). The cytochrome P_{450} is monooxygenases and catalyzes oxidation by addition of one atom of molecular oxygen into a substrate (organophosphate) by an electron transport pathway **(Jakoby and Ziegler, 1990; White, 1991)**. In this reaction reactive oxygen species are generated. The OP change normal antioxidant homeostasis resulting in antioxidant depletion, if the requirement of continuous antioxidants is not maintained **(Banerjee et al., 1999; Chambers *et al*., 2001; Vidyasagar *et al*., 2004; Possamai *et al*., 2007)**. The Lipid Peroxixation level and cytochrome P450 activity were mitigating after supplementations of selenium. Also, it is known that halogenated hydrocarbons are metabolized to dehalogenated metabolites by reductive dehalogenation and cytochrome P450 was involved in the dehalogenation **(Oka *et al*., 1996)**. The increase in the levels of malondialdehyde MDA indicate enhanced LPO leading to tissue injury and failure of the antioxidant defense mechanisms to prevent the formation of excess free radicals **(Cheesman and Slater, 1993; Al-Omar *et al*., 2004)**. The present study also shows that the increase in LPO is accompanied by the concomitant decrease in the activities of antioxidant enzymes such as SOD, CAT and GPx in pesticides exposed rats.

Provirus studies concerning oxidative stress induction in intoxication there are several pathways by which pesticide is thought to induce oxidative stress. It inhibits the mitochondrial electron-transfer chain

Table (5): Effect of dimethoate, dicofol and voltaren on the activities of cytochrome P450 in the plasma of male rats and the ameliorative role of selenium.

Treatment	CytochromeP450 (nmol/mg protein)	
	Treatment period	Withdrawal period
Control	0.136± 0.01	0.137± 0.001
Dimethoate (Dim)	0.103±0.014**	0.119±0.0011**
Dicofol (Dic)	0.107±0.001**	0.122±0.0013**
Voltaren (Vol)	0.136±0.012	0.135± 5.014
Selenium (Se)	0.135±0.0014	0.137± 0.0011
Dim + Dic	0.087±0.003**	0.092±0.005**
Dim + Vol	0.096±0.005**	0.100±0.009**
Dic + Vol	0.108± 0.0011**	0.113±0.005**
Dim + Dic + Vol	0.071±0.0012**	0.080±0.0010**
Dim + Se	0.138±0.0013	0.137±0.002
Dic + Se	0.136±0.001	0.138±0.001
Vol + Se	0.138±0.0013	0.139±0.001
Dim + Dic + Se	0.137±0.0013	0.137±0.001
Dim + Vol + Se	0.136±0.0013	0.137±0.002
Dic + Vol + Se	0.136±0.0089	0.136±0.001
Dim + Dic + Vol + Se	0.136±0.0046	0.138±0.003

Values are means ± SD; n=8; Statistical difference from the control: * significant at $P \leq 0.05$ & ** highly significant at $P \leq 0.01$.

reaction, leading to accumulation of semi ubiquitous, which enables it to transfer one electron (e-) to molecular oxygen to form superoxide radicals **(Wang *et al*., 2004)**; it may also interference with cellular interference with cellular antioxidant defense system via alteration in activities of antioxidant enzymes viz. SOD and catalase and status of glutathione **(Panda *et al*., 1997; Sandrini *et al*., 2006)**. In contrast, NSAIDs also produce a broad range of toxic effects, frequently causing gastrointestinal (GI) toxicity that result in ulceration, bleeding and perforation of stomach **(James and Hawkey, 2003)**. The toxicity of NSAIDs is mainly attributed to inhibition of prostaglandin synthase activity that inhibits prostaglandin production in the GI tract resulting in accumulation of intracellular arachidonic acid **(Toborek *et al*., 1999)**; NSAIDs also causes induction of mitochondrial injury in hepatocytes through uncoupling of oxidative phosphorylation **(Somasundaram *et al*., 2000)**; and production of reactive metabolites that covalently bind to critical cellular proteins **(Boelsterli, 2002)**. The protective role of selenium against oxidative damage could be explained by stimulation of free radical scavenger by change the activities of antioxidant enzymes which protect levels of antioxidants such as N-acetyl cysteine **(Suramana *et al*., 2001)** and to stimulate several antioxidative enzymes of prevent damage from free radicals insult **(El-Khawaga, 2005)**. Selenium increased antioxidant capacity in cells by increasing the activity of glutathione reductase which enhances the availability of glutathione "one of the most intrinsic antioxidants that prevents cell damage" **(El-Khawaga, 2005)**.

In conclusion, these results suggest that long-term exposure to insecticide "dimethoate and dicofol" and anti-inflammatory drug "diclofenac" induces oxidative damage and altering cytochrome P450 in male rats. In addition, selenium treatment could protect the tissues against the toxicity of insecticides it reduced LOP level and enhancement the activities of antioxidant enzymes and cytochrome P450.

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الملخص العربي

يتم دراسة تأثير كلا من الدايمثوايت والديكفول والفولتارين على الاكسدة/مضادات الاكسدة على جرذان التجارب : دور السلينيوم

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إن التأثيرات الضارة للمبيدات على الانسان لايمكن انكارها فلذلك تهدف هذه الدراسة الى تقيم الاثار التى تحدثها المبيدات ومخاليطها وايضا عند تداخلها مع الادوية العقاقير التى يتعاطها الانسان وذلك على جرذان التجارب. و تهدف ايضا هذه الدراسة لدراسة قدرة السيلينيوم على تقليل التأثيرات السلبية مما فيها الاكسدة الهدامة الذى يحدث بسبب الديكفول والدايمثوايت والفولتارين ومخاليطهم .

واوضحت النتائج عدم ظهور اى اعراض سمية او حالات موت . واستخدمت فى هذه الدراسة ذكور جرذان الالبينو (110±10) جرام وتم تقسيم الفئران الى 16 مجموعة كل مجموعة تحتوى 8 فئران : المجموعة الاولى تمثل المجموعة الضابطة، المجموعة الثانية عوملت بمبيد الديكفول ((LD50 100/1) 662,12ملجم/كجم)، المجموعة الثالثة عوملت بمبيد الديمثوايت ((LD50 100/1) 481,65ملجم/كجم)،المجموعة الرابعةعوملت بالسيلينيوم (400ميكروجرام/كجم 66, 6ملجم / كجم), المجموعة الخامسة عوملت بالفولتارين (0,83مجم/كجم)، المجموعة السادسة عوملت بالديكفول+الفولتارين ، المجوعة السابعة عوملت بالدايمثوايت + الفولتارين ، المجموعة

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الثامنة عوملت بالديكفول+ بالدايمثوايت، المجموعة التاسعة عوملت الديكفول + بالدايمثوايت+ الفولتارين، المجموعة العاشرة عوملت الديكفول +السيلينيوم، المجموعة الاحدى عشر عوملت بالدايمثوايت + السيلينيوم، المجموعة الثانية عشر عوملت بالديكفول+الفولتارين+ السيلينيوم، المجموعة الثالثة عشر عوملت بالدايمثوايت+ الفولتارين + السيلينيوم، المحموعة الرابعة عشر عوملت بالديكفول+ بالدايمثوايت+ السيلينيوم، الخامسة عشر عوملت بالديكفول+ الدايمثوايت+ الفولتارين + السيلينيوم، المجموعة السادسة عشر عوملت الفولتارين + السيلينيوم. أدت المعاملة بالديكفول، الدايمثوايت، الديكفول+الفولتارين، الديمثوايت+الفولتارين، الدايمثوايت+الديكفول، الدايمثوايت+الديكفول + الفولتارين الى حدوث زيادة معنوية مرتفعة فى مستوى الدهون المؤكسدة فى مصل الحيوانات المعاملة. وأدت أيضا هذه المجاميع الى حدوث زيادة معنوية مرتفعة فى نشاط انزيم ال catalase بينما ادت هذه المجاميع حدوث انخفاض معنوى مرتفع فى نشاط انزيمات superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-s-transferase (GST) and cytochrome P450 . واوضحت الدراسة ان للسلينيوم دور فعال فى الوقاية من الاثار الضارة للمركبات المختبرة.