STUDY THE PROTECTIVE EFFECT OF GINGER AGAINST THE TOXICITY OF DIMETHOATE ON HORMONES IN RABBITS

ABSTRACT

Organophosphorus insecticides have been widely classified as a health dangerous and high toxicity compounds due to their widespread use and release into the environment. Ginger (Zingiber officinale) has been used as a medicinal plant since antiquity and is known to play diverse biological roles including anti oxidation, anti-inflammation, hypolipidemia, anti-carcinogenesis, anti-nausea, anti-thrombosis, and antibacterial process. The purpose of these experiments was to study decreasing the toxicity effect of Dimethoate by ginger. All animals in this study were assigned to one of four treatment groups: 0 mg ginger and 0 mg dimethoate /kg BW (control); 100 mg ginger/kg BW; 43.2 mg dimethoate /kg BW;and43.2 mg dimethoate plus 100 mg ginger/kg BW. Rabbits were orally managed the particular measurements each other day for 12 weeks. Results indicated that treatment with ginger alone caused significant (P<0.05) increase in body weight (BW) and relative weight of testes compared to control animals. Whereas the rabbits treated with dimethoate showed significant (P<0.05) decrease in BW and relative weight of testes compared with control. Results showed that treatment with DM caused significant (P<0.05) decrease activity of testosterone, T_3 and T_4. While, increase the levels of FSH and LH in plasma. Ginger caused significant (P<0.05) increase in the activity of testosterone, T_3 and T_4 in plasma compared to control. While, decrease the levels of FSH and LH in plasma. The **presence of ginger with DM caused significant (P<0.05) decrease in the reduction of T_3 and T_4,while caused an improvement in the levels of testosterone as compared to control** and **the presence of ginger with DM caused increase in the levels of FSH and LH as compared to control, and this means that ginger counteracted the toxic effects of DM.**

Keywords:{ *dimethoate, ginger, testosterone and rabbits* }

1. INTRODUCTION

Dimethoate is the ISO common name for O,O-dimethyl S methylcarbamoylmetyl phosphorodithioate or 2 Dimethoate belong to class of aliphatic amide organothiophsphoate insecticides such as omethoate and mecarbam which consider a members of organothiophsphoate also[1]. The chemical structure of dimethoate is illustrated in Image1 [2] .

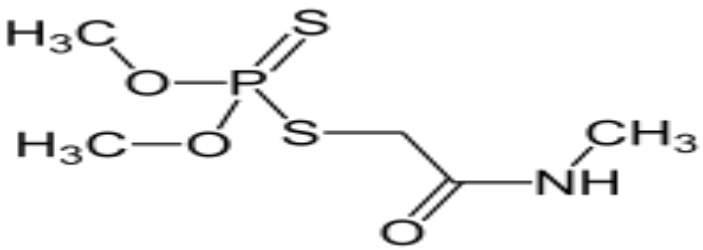

Image 1. Chemical structures of dimethoate[1,2] [2]**.**

A total of 91 pesticides have been reported as the endocrine glands deactivate. However, the disorders that are generated by the endocrine disruptive pesticides can be temporary or permanent. It may produce reproductive abnormalities or congenital malformations[3]. It has previously been shown that the farmers and allied people who have been exposed to the pesticides possess more risks for thyroid cancer[4]. In fact, investigators have shown that repeated exposure to DM decreases serum testosterone levels, testicular weight, and sperm motility and increases the percentage of dead and

abnormal sperm in rats and rabbits. Moreover, it accumulates in the testes where it persists for weeks even after its oral administration is stopped[5]. Since spermatogenesis and fertility are critically dependent upon the maintenance of adequate levels of testosterone, the ability of DM to reduce serum testosterone levels might contribute to the reduction in spermatogenesis and fertility observed in animals exposed to this pesticide. Although DM has a low environmental persistence, it has been confirmed to cause developmental toxicity as well as reproductive failures in organisms upon repeated exposures[6]. Developmental toxicity of DM includes decreased number of implantations and live fetuses, increased incidences of resorptions, and decreased fetal body weights[7]. Reproductive toxicity of this pesticide on adult rodents of both gender has been demonstrated. Irregularities of estrous cycle and altered level of serum gonadotrophins have been reported in females[8], while impairment of fertility, suppressed libido, semen quality deterioration, altered testosterone levels, and testicular degeneration are few of the reports available in males[9]. Although organophosphates may reduce serum steroid hormone levels by increasing steroid catabolism and elimination, several studies have demonstrated that these compounds can directly inhibit steroid hormone production. In addition, dichlorvos, dursban, diazinon, chlorpyrifos, furadan, and isopropyl bicyclic phosphate have all been shown to inhibit steroidogenesis in adrenal cells[10].

Antioxidant applications are important for protecting the human body from various sources of oxidative damage and are used extensively for prevention of a variety of diseases. It has many bio-functions including anti-allergenic, anti-inflammatory, anti-bacterial and anti-viral activities, and the prevention of carcinogenesis, diabetes and heart disease[11].

Ginger (Zingiber officinale Roscoe, Zingiberacae) is widely used around the world in foods as a spice. For centuries, it has been an important ingredient in Chinese, Ayurvedic and Tibb-Unani as herbal medicines for the treatment of catarrh, rheumatism, nervous diseases, gingivitis, toothache, asthma, stroke, constipation and diabetes[12]. Several reviews have appeared in the literature about this plant, and this may reflect the popularity of the subject and its common use as a spice and a medicinal plant[13]. Many studies have been devoted to specific aspects of ginger's actions. For example, the review of Grzanna *et al* was on the use of ginger as an anti-inflammatory agent[14].for more, previous study confirmed the cancer prevention properties of the crude drug. Ginger is a strong anti-oxidant substance and may either mitigate or prevent generation of free radicals[15]. It is considered a safe herbal medicine with only few and insignificant adverse/ side effects[16]. Its major pungent constituent, [6]-gingerol has been reported to exhibit antioxidative activity against linoleic acid autoxidation and peroxidation of phospholipid liposomes and to scavenge trichloromethylperoxyl- and 1,1- diphenyl-2-picrylhydrazyl (DPPH) radicals[17]. The major bioactive constituents of ginger are [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol having various pharmacological properties including antioxidant, anti inflammatory, anticancer and anti-ulcer properties[15] .The characteristic odor and flavor of ginger is caused by a mixture of zingerone, shogaols and gingerols, volatile oils that compose one to three percent of the weight of fresh ginger. In laboratory animals, the gingerrols increase the motility of the gastrointestinal tract and have analgesic, sedative, antipyretic and antibacterial properties[18]. And a study at the University of Michigan demonstrated that gingerols can kill ovarian cancer cells[19]. The chemopreventive potentials of [6]-gingerol present a promising future alternative to expensive and toxic therapeutic agents[20].

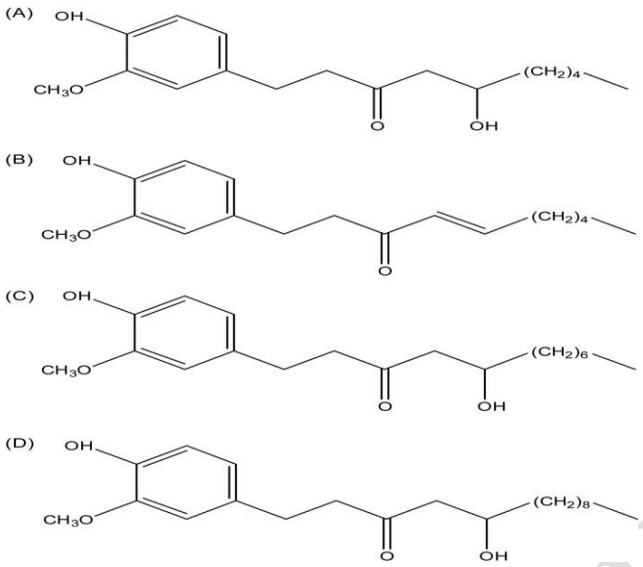

Image (2): Chemical structures of 6-gingerol (A), 6-shogaol (B), 8-gingerol (C), and 10- gingerol (D)[21]

2. MATERIALS AND METHODS

In this study dimethoate (DM) and ginger were used in this study. DM (purity 400g/L) was purchased from B &W agrochemichals (China) and ginger was obtained from Superior Nutrition and Formulation by Jarrow Formulas, Los Angeles, USA. All other chemicals used in the experiment were of analytical grade.

Mature male New Zealand White rabbits (age of 6 months and initial weight of (1.641 $\pm$ 27.2 Kg) were used. Animals were individually housed in cages and weighed weekly throughout 12-weeks experimental period. The objective of this study was to determine the protective role of ginger (100 mg/kg BW) according to *fayrouz et al*[22].on hormones of male New Zealand White rabbits given sublethal measurements (43.2 mg/kg BW each other day for 12 weeks) of dimethoate (DM)[23]. The LD50 of DM when given orally to rabbits was reported to be 10 000 mg/kg BW respectively[24]. Rabbits were orally administered their respective doses for 3 month. At the conclusion of the exploratory period body weight of rabbits were recorded. Animals were sacrificed by decapitation and testes were immediately removed and weighed then the organs weight ratio was calculated. The relative weight of organs (%) was calculated as g/100 g body weight. Serum was obtained by centrifugation of blood samples at 860×g for 20 min, and was stored at (-20^{oC}) until used for analysis testosterone hormone concentration were assayed by using commercial kit that was supplied by Coat – A – Count testosterone RIA, from Diagnostic Systems Laboratories (DSL), from Texas, USA. Follicle Stimulating Hormone (FSH), Luteinizing hormone (LH) levels, Thyroxine (T_4) and Triiodothyronine (T_3) hormone concentrations were assayed by using commercial kit that was supplied by Coat - A - Count, from Los Angeles, USA.

Statistical analysis: Where applicable, statistical analysis was carried out in Minitab software (version17) statistical significance was assessed using ANOVA analysis with Tukey multiple comparison test after detection normal distribution to the information and suitable $P < 0.05$ consider critical.

3. RESULTS AND DISCUTION

Table 1: The changes in body weight (BW), relative testicles weight (RTW) and the concentrations of blood plasma testosterone all through the 12-week exploratory period of bucks treated with ascorbic acid caused increment ($p<0.05$) in BW and testosterone levels. Treatment with dimethoate caused significant ($P<0.05$) decrease activity of testosterone, T_3 and T_4. While, increase the levels of FSH and LH in plasma. Ginger caused significant ($P<0.05$) increase in the activity testosterone, T_3 and T_4. While, decrease the levels of FSH and LH in plasma compared to control. The presence of ginger with dimethoate caused significant ($P<0.05$) decrease in the reduction of testosterone ,T_3 and T_4 as compared to control and the presence of ginger with dimethoate caused increase in the levels of FSH and LH as compared to control, and this means that ginger counteracted the toxic effects of dimethoate (Table 1to 2 and Figs 1to 4) .

Table 1. The overall means (±SE) of body weight, relative testes weight and blood plasma testosterone concentration during treatment of male rabbits with ginger , dimethoate (DM) and their combination.

Parameter	Experimental groups			
	Control	**Ginger**	**DM**	**Ginger + DM**
BW (g)	1641.0 ±27.19^{ab}	1705.3±48.65^{a}	1541.5±49.24^{b}	1628.1± 25.50^{ab}
RTW (g/100g BW)	3.100 ± 0.535^{a}	4.050 ± 0.690^{a}	2.760 ± 0.656^{a}	3.320 ± 0.645^{a}
Testosteron (ng/ml)	1.542 ± 0.065^{c}	2.439 ± 0.34 ^{a}	0.987 ±0 .155^{d}	1.976 ±0.145^{b}

Values are expressed as means ± SE; n = 5 for each treatment group. Mean values within a row not sharing a common superscript letters (a, b, c, d) were significantly different, p<0.05.

Table 2. Changes in thyroxine (T_4), Triiodothyronine (T_3), Luteinizing Hormone (LH)and Follicle Stimulating hormone (FSH), of male rabbits treated with ginger, dimethoate (DM) and their combination

Parameter	Experimental groups			
	Control	**Ginger**	**DM**	**Ginger + DM**
T_4 (ng/dl)	1.149± 0.030^{b}	1.348± 0.056^{a}	0.936 ± 0.077^{c}	1.121 ± 0.038^{b}
T_3 (ng/dl)	1.705± 0.075^{ab}	1.803 ± 0.088^{a}	1.419 ± 0.129^{c}	1.643 ± 0.126^{b}
LH (mIU/ml)	0.788 ± 0.022^{ab}	0.759 ± 0.037^{b}	0.804 ± 0.026^{a}	0.787± 0.022^{ab}
FSH(mIU/ml)	0.019±0.804^{a}	0.021± 0.802^{a}	0.019 ±0.028^{a}	0.012 ± 0.814^{a}

Values are expressed as means ± SE; n = 5 for each treatment group. Mean values within a row not sharing a common superscript letters (a, b, c, d) were significantly different, p<0.05.

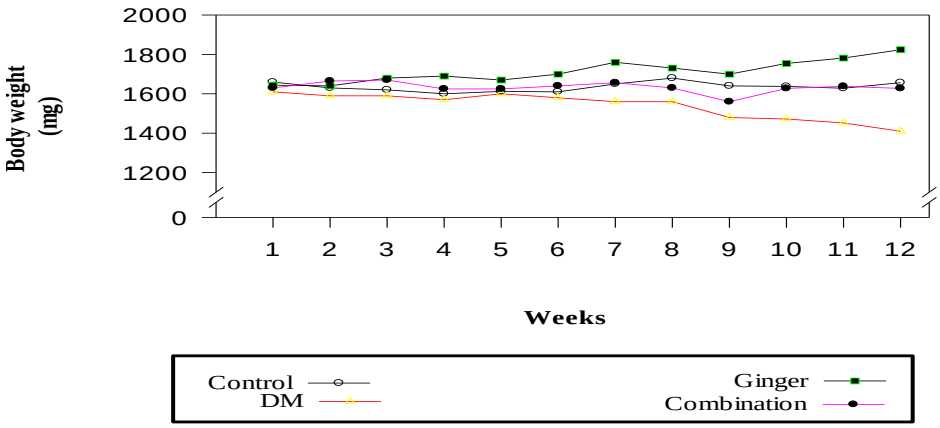

Fig. 1. Change in body weight (gm), treatment of male rabbits with ginger, DM (DM) and/or their combination.

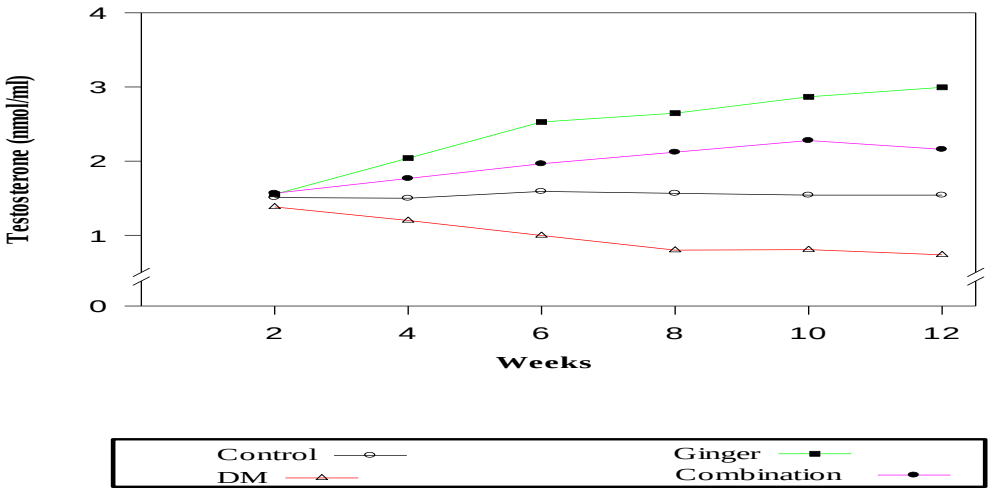

Fig. 2. Changes in plasma testosterone during treatment of male rabbits treated with ginger, DM and/or their combination

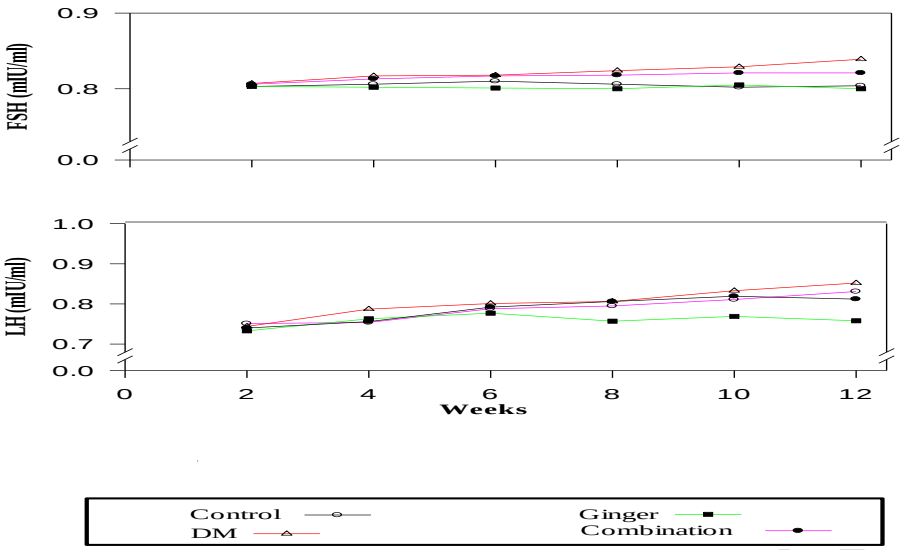

Fig. 3. Changes in the activity of plasma follical stimulating hormone (FSH) and luenizing hormone (LH) during treatment of male rabbits with ginger, DM and/or their combination.

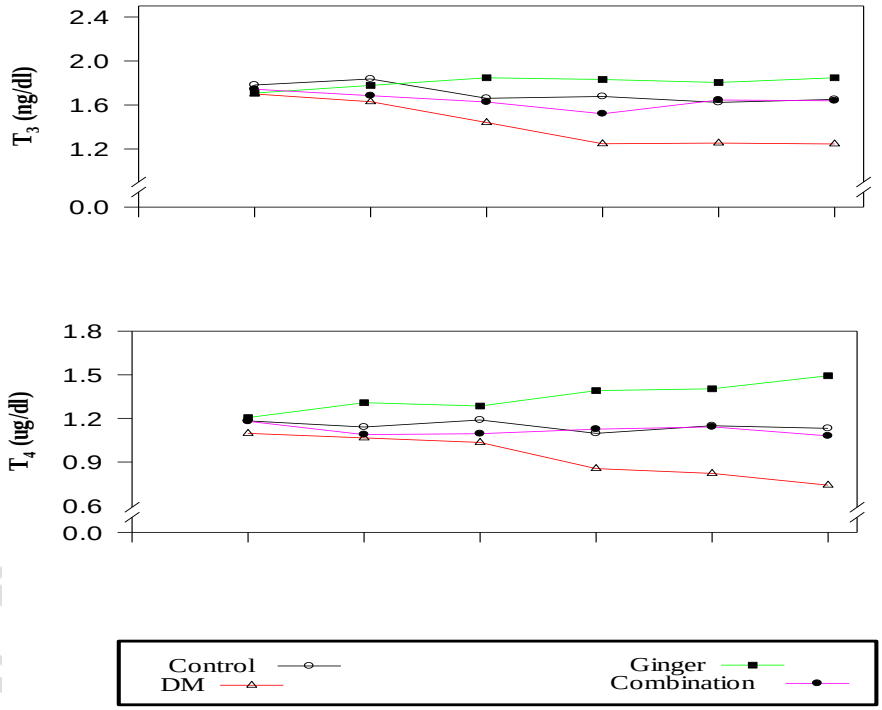

Fig. 4.Changes in the activity of plasma triiodothyronine (T_3) and thyroxine (T_4) treatment of male rabbits with ginger, DM and/or their combination

The present results indicate that treatment with (DM) caused significant reductions in body weight (BW) and relative organs weight (ROW) (Table 1and 2 and Figure 1 to 4). In previous studies have established the reduction in BW and ROW of the (DM) treated rabbits [25, 26, 27]. The reduction in body weight in response to DM intake may be a result of the combined action of cholinergic and oxidative stress and/or due to increase degradation of lipids and proteins as a direct effect of Organophosphorus compound exposure[28,29,30]. The increase body weight observed in the present study due to treatment with ginger is

agreements with *Okoye et al* results [31]. Also, reported significant increase in body weight gain (14.4%) of broilers fed ginger. They reported that increase in body weight gain of the broilers fed ginger indicates the positive nutritive effects of this natural feed additive[32,33].

The present study showed that DM decrease plasma testosterone concentration in rabbits (Table1 to 2) and (figure1 to 4). Endocrine toxicity of pesticides has been well recognized, and many studies have reported their adverse effects on the reproductive axis of animals, including humans [34,35]. Organophosphorus pesticides such as malathion, dichlorvos, chlorpyrifos, and DM have been reported to affect male reproductive system of adult rodents, inducing histopathological alterations in testes, spermatogenic disturbances, as well as altered testosterone levels[36, 7,37,38]. The low-testosterone levels might also be due to direct toxic effects of the pesticide on testicular Leydig cells, the steroidogenic component, DM might have inhibited the steroidogenesis in Leydig cells as demonstrated in vitro[39] . The observed reproductive endocrine toxicity might be due to direct interference of the pesticide of the pituitary-testicular axis. Being a neurotoxic pesticide, DM [40,7,41]. DM by itself inhibits testosterone biosynthesis in interstitial (Leydig) cells by a mechanism that involves COX-2 and StAR expression, even at the low doses used in our experimental model [42]. The oral administration of technical DM also produces adverse effects on male reproductive performance in mice[7]. It was previously reported that DM decreases serum testosterone levels and testicular weight of rabbits and mice [43 ,7, 5 , 39]. Moreover, a previous work from our lab demonstrates that, DM displays a complex mechanism of action involving disturbances in the hormone production[42]. Treatment with ginger caused an increase in plasma testosterone concentration (Table 1) and (Figure2), these results are in agreement with the finding in the study of Saeid who suggested that ginger administration also increased the level of testosterone[44]. Ginger was also found to possess a strong androgenic activity, which is reflected by increased testosterone levels. Thyroid hormones homeostasis can be disrupted by variety of xenobiotic, this disruption was found to be associated with thyroid follicular cell hypertrophy, hyperplasia, and the development of thyroid tumours in rats. Thyroid toxicants affect circulating concentrations of thyroid hormones by either direct action on the thyroid gland or by increasing peripheral elimination of the thyroid hormones[45].

The current study investigated the effects of pesticide exposure on T_3 and T_4 hormone level of rabbits . The function of both of these hormones is to stimulate the metabolism. The disturbances in the production of these hormones can impair metabolism and can lead to several developmental disorders and diseases. It has already been shown that exposures to pesticides adversely affect human health, producing hormonal disorders . The exposure to pesticides has also been shown to enhance the chances for thyroid cancer . However, the results of *Toft* are conflicted with our current findings. They showed a decrease in T3 hormone level, this variation in the results may be due to changes in environmental factors, differences in immunity y of the selected population and differences in the use of pesticides [46].

4. CONCLUTION:

Our results have showed that the dimethoate, as widely use organophosphate insecticide, by oral route to adult male rabbits at the dose of 43.2mg/kg/day during 3 month caused decrese the hormones level . Using ginger capability to alleviate the harmful effect of dimethoate on hormones. Finally, it is recommended that the use of dimethoate must be limited due to its hazardous effects.

REFERENCES

(1) Fischer, E.; Farkas, S.; Hornung, E.; Past, T. Sublethal Effects of an Organophosphorous Insecticide, Dimethoate, on the Isopod Porcellio Scaber Latr. *Comp. Biochem. Physiol. - C Pharmacol. Toxicol. Endocrinol.* **1997**. https://doi.org/10.1016/S0742-8413(96)00164-8.

(2) Williams, A. J. Public Chemical Compound Databases. *Current Opinion in Drug Discovery and Development*. 2008. https://doi.org/10.6084/m9.figshare.654769.v1.

(3) Alavanja, M. C. R.; Sandler, D. P.; McMaster, S. B.; Zahm, S. H.; McDonnell, C. J.; Lynch, C. F.; Pennybacker, M.; Rothman, N.; Dosemeci, M.; Bond, A. E.; et al. The Agricultural Health Study. *Environ. Health Perspect.* **1996**. https://doi.org/10.1289/ehp.96104362.

(4) Ejaz, S.; Akram, W.; Lim, C. W.; Lee, J. J.; Husain, I. Endocrine Disrupting Pesticides: A Leading Cause of Cancer among Rural People in Pakistan. *Experimental Oncology*. 2004.

(5) Afifi, N. A.; Ramadan, A.; el-Aziz, M. I.; Saki, E. E. Influence of Dimethoate on Testicular and Epididymal Organs, Testosterone Plasma Level and Their Tissue Residues in Rats. *Dtsch. Tierarztl. Wochenschr.* **1991**.

(6) Roy, W. R. Pesticide Profiles: Toxicity, Environmental Impacts, and Fate. *J. Environ. Qual.* **1998**. https://doi.org/10.2134/jeq1998.00472425002700040038x.

(7) Farag, A. T.; El-Aswad, A. F.; Shaaban, N. A. Assessment of Reproductive Toxicity of Orally Administered Technical Dimethoate in Male Mice. *Reprod. Toxicol.* **2007**. https://doi.org/10.1016/j.reprotox.2006.12.003.

(8) Kaur, S.; Dhanju, C. K. Biochemical Effects of Some Organophosphorus Pesticides on the Ovaries of Albino Rats. *Indian J. Physiol. Pharmacol.* **2005**.

(9) Sayim, F. Histopathological Effects of Dimethoate on Testes of Rats. *Bull. Environ. Contam. Toxicol.* **2007**. https://doi.org/10.1007/s00128-007-9196-5.

(10) Civen, M.; Lifrak, E.; Brown, C. B. Studies on the Mechanism of Inhibition of Adrenal Steroidogenesis by Organophosphate and Carbamate Compounds. *Pestic. Biochem. Physiol.* **1977**. https://doi.org/10.1016/0048-3575(77)90029-3.

(11) Chen, B. H.; Chang, H. W.; Huang, H. M.; Chong, I. W.; Chen, J. S.; Chen, C. Y.; Wang, H. M. (-)-Anonaine Induces DNA Damage and Inhibits Growth and Migration of Human Lung Carcinoma H1299 Cells. *J. Agric. Food Chem.* **2011**. https://doi.org/10.1021/jf103488j.

(12) Tapsell, L. C.; Hemphill, I.; Cobiac, L.; Patch, C. S.; Sullivan, D. R.; Fenech, M.; Roodenrys, S.; Keogh, J. B.; Clifton, P. M.; Williams, P. G.; et al. Health Benefits of Herbs and Spices: The Past, the Present, the Future. *The Medical journal of Australia*. 2006. https://doi.org/10.5694/j.1326-5377.2006.tb00548.x.

(13) Chrubasik, S.; Pittler, M. H.; Roufogalis, B. D. Zingiberis Rhizoma: A Comprehensive Review on the Ginger Effect and Efficacy Profiles. *Phytomedicine* **2005**. https://doi.org/10.1016/j.phymed.2004.07.009.

(14) Grzanna, R.; Lindmark, L.; Frondoza, C. G. Ginger - An Herbal Medicinal Product with Broad Anti-Inflammatory Actions. *Journal of Medicinal Food*. 2005. https://doi.org/10.1089/jmf.2005.8.125.

(15) Shukla, Y.; Singh, M. Cancer Preventive Properties of Ginger: A Brief Review. *Food and Chemical Toxicology*. 2007. https://doi.org/10.1016/j.fct.2006.11.002.

(16) Ali, B. H.; Blunden, G.; Tanira, M. O.; Nemmar, A. Some Phytochemical, Pharmacological and Toxicological Properties of Ginger (Zingiber Officinale Roscoe): A Review of Recent Research. *Food and Chemical Toxicology*. 2008. https://doi.org/10.1016/j.fct.2007.09.085.

(17) Sekiwa, Y.; Kubota, K.; Kobayashi, A. Isolation of Novel Glucosides Related to Gingerdiol from Ginger and Their Antioxidative Activities. *J. Agric. Food Chem.* **2000**. https://doi.org/10.1021/jf990674x.

(18) O'Hara, M.; Kiefer, D.; Farrell, K.; Kemper, K. A Review of 12 Commonly Used Medicinal Herbs. *Archives of Family Medicine*. 1998. https://doi.org/10.1001/archfami.7.6.523.

(19) Choudhury, D.; Das, A.; Bhattacharya, A.; Chakrabarti, G. Aqueous Extract of Ginger Shows Antiproliferative Activity through Disruption of Microtubule Network of Cancer Cells. *Food Chem. Toxicol.* **2010**. https://doi.org/10.1016/j.fct.2010.07.020.

(20) Oyagbemi, A. A.; Saba, A. B.; Azeez, O. I. Molecular Targets of [6]-Gingerol: Its Potential Roles in Cancer Chemoprevention. *BioFactors*. 2010. https://doi.org/10.1002/biof.78.

(21) Wohlmuth, H.; Leach, D. N.; Smith, M. K.; Myers, S. P. Gingerol Content of Diploid and Tetraploid Clones of Ginger (Zingiber Officinale Roscoe). *J. Agric. Food Chem.* **2005**. https://doi.org/10.1021/jf050435b.

(22) Khaled, F.; Shoaib, A.; Attia, M. Hepatoprotective Effect of Ginger Induced Experimentally by Dimethoate And Liver Injury in Adult Male Rabbits. 24–30.

(23) El-Sharaky, A. S.; Newairy, A. A.; Kamel, M. A.; Eweda, S. M. Protective Effect of Ginger Extract against

Bromobenzene-Induced Hepatotoxicity in Male Rats. *Food Chem. Toxicol.* **2009**. https://doi.org/10.1016/j.fct.2009.04.005.

(24) Ahmed, M. S.; Massoud, A. H.; Derbalah, A. S.; Al-Brakati, A.; Al-Abdawani, M. A.; Eltahir, H. A.; Yanai, T.; Elmahallawy, E. K. Biochemical and Histopathological Alterations in Different Tissues of Rats Due to Repeated Oral Dose Toxicity of Cymoxanil. *Animals* **2020**. https://doi.org/10.3390/ani10122205.

(25) Hassan, A. A. M.; Minatogawa, Y.; Hirai, T.; Kido, R. Changes of Some Serum Parameters and Amino Acids Content in Rats after Chronic Sublethal Doses of Dimethoate. *Arch. Environ. Contam. Toxicol.* **1994**. https://doi.org/10.1007/BF00214271.

(26) Farag, A. T.; Karkour, T. A. Z.; El Okazy, A. Developmental Toxicity of Orally Administered Technical Dimethoate in Rats. *Birth Defects Res. Part B - Dev. Reprod. Toxicol.* **2006**. https://doi.org/10.1002/bdrb.20066.

(27) AHMED M. ALI, M.D., A. A. E. M. D. .; BASMA Z. MOSTAFA, M.Sc., A. Y. A. E.-N. M. D. .; EMAN M.A. ABDELGHANY, M.D., A. E. A. M. D. .; H. HASSAN, M.D., N. Beneficial Effect of Quercetin Against Dimethoate Induced Cerebellar Cortex Injury in Adult Male Albino Rat: Histological and Immunohistochemical Study. *Med. J. Cairo Univ.* **2019**. https://doi.org/10.21608/mjcu.2019.88800.

(28) Saafi, E. B.; Louedi, M.; Elfeki, A.; Zakhama, A.; Najjar, M. F.; Hammami, M.; Achour, L. Protective Effect of Date Palm Fruit Extract (Phoenix Dactylifera L.) on Dimethoate Induced-Oxidative Stress in Rat Liver. *Exp. Toxicol. Pathol.* **2011**. https://doi.org/10.1016/j.etp.2010.03.002.

(29) M. Heikal, T. Protective Effect of a Synthetic Antioxidant "Acetyl Gallate Derivative" Against Dimethoate Induced DNA Damage and Oxidant/Antioxidant Status in Male Rats. *J. Environ. Anal. Toxicol.* **2012**. https://doi.org/10.4172/2161-0525.1000155.

(30) Valko, M.; Morris, H.; Cronin, M. Metals, Toxicity and Oxidative Stress. *Curr. Med. Chem.* **2005**. https://doi.org/10.2174/0929867053764635.

(31) Okoye, F. C.; Ugwuene, M. C.; Mbarah, J. U. Effects of Local Spices on the Utilization of Cassava Peel Meal-Based Diets by Weaner Rabbits. *Pakistan J. Nutr.* **2006**. https://doi.org/10.3923/pjn.2006.203.205.

(32) Omage, J. J.; Onimisi, P. A.; Adegbite, E. K.; Agunbiade, M. O. The Effect of Ginger (Zingiber Officinale Roscoe) Waste Meal on Growth Performance, Carcass Characteristics, Serum Lipid and Serum Cholesterol Profiles of Rabbit. *Pakistan J. Nutr.* **2007**. https://doi.org/10.3923/pjn.2007.359.362.

(33) Ademola, S.; Farinu, G.; Adewolo, O.; Lawal, T.; Babatunde, G. Antimicrobial Activity of Garlic and Ginger Mixtures, Serum Lipid Profile and Growth Performances of Broilers Fed the Mixtures. *Bowen J. Agric.* **2008**. https://doi.org/10.4314/bja.v4i1.41934.

(34) Akingbemi, B. T.; Ge, R. S.; Klinefelter, G. R.; Gunsalus, G. L.; Hardy, M. P. A Metabolite of Methoxychlor, 2,2-Bis(p-Hydroxyphenyl)-1,1,1- Trichloroethane, Reduces Testosterone Biosynthesis in Rat Leydig Cells through Suppression of Steady-State Messenger Ribonucleic Acid Levels of the Cholesterol Side-Chain Cleavage Enzyme. *Biol. Reprod.* **2000**. https://doi.org/10.1095/biolreprod62.3.571.

(35) Rignell-Hydbom, A.; Rylander, L.; Giwercman, A.; Jönsson, B. A. G.; Nilsson-Ehle, P.; Hagmar, L. Exposure to CB-153 and p,P′-DDE and Male Reproductive Function. *Hum. Reprod.* **2004**. https://doi.org/10.1093/humrep/deh362.

(36) Choudhary, N.; Goyal, R.; Joshi, S. C. Effect of Malathion on Reproductive System of Male Rats. *J. Environ. Biol.* **2008**.

(37) Huang, L. G.; Lin, P.; Gong, C. Y.; Zhang, J.; Zhou, Q.; Gong, X. De; Zeng, L. Pathological Changes in the Testes of the Rats with Hypospadia Induced by Dichlorvos. *Zhonghua Nan Ke Xue* **2006**.

(38) Joshi, S. C.; Mathur, R.; Gulati, N. Testicular Toxicity of Chlorpyrifos (an Organophosphate Pesticide) in Albino Rat. *Toxicol. Ind. Health* **2007**. https://doi.org/10.1177/0748233707080908.

(39) Walsh, L. P.; Webster, D. R.; Stocco, D. M. Dimethoate Inhibits Steroidogenesis by Disrupting Transcription of the Steroidogenic Acute Regulatory (StAR) Gene. *J. Endocrinol.* **2000**. https://doi.org/10.1677/joe.0.1670253.

(40) Colborn, T. A Case for Revisiting the Safety of Pesticides: A Closer Look at Neurodevelopment. *Environmental Health Perspectives*. 2006. https://doi.org/10.1289/ehp.7940.

(41) Walker, C. H. Neurotoxic Pesticides and Behavioural Effects upon Birds. *Ecotoxicology*. 2003. https://doi.org/10.1023/A:1022523331343.

(42) Astiz, M.; Hurtado De Catalfo, G. E.; De Alaniz, M. J. T.; Marra, C. A. Involvement of Lipids in Dimethoate-Induced Inhibition of Testosterone Biosynthesis in Rat Interstitial Cells. *Lipids* **2009**. https://doi.org/10.1007/s11745-009-3323-5.

(43) Salem, M. H.; Abo-elezz, Z.; Abd-Allah, G. A.; Hassan, G. A.; Shaker, N. Effect of Organofhosphorus (Dimethoate) and Pyrethroid (Deltamethrin) Pesticides on Semen Characteristics in Rabbits. *J. Environ. Sci. Heal. Part B* **1988**. https://doi.org/10.1080/03601238809372604.

(44) Saeid, J. M.; Shanoon, A. K.; Marbut, M. M. Effects of Zingiber Officinale Aqueous Extract on Semen

Characteristic and Some Blood Plasma, Semen Plasma Parameters in the Broilers Breeder Male. *Int. J. Poult. Sci.* **2011**. https://doi.org/10.3923/ijps.2011.629.633.

(45) Pickrell, J. A. Casarett and Doull's Toxicology: The Basic Science of Poisons. *Toxicol. Lett.* **1996**. https://doi.org/10.1016/s0378-4274(96)90054-5.

(46) Toft, G.; Flyvbjerg, A.; Bonde, J. P. Thyroid Function in Danish Greenhouse Workers. *Environ. Heal. A Glob. Access Sci. Source* **2006**. https://doi.org/10.1186/1476-069X-5-32.