

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, hyperlipidemia, 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; and 43.2 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 ; rabbits

1. INTRODUCTION

Dimethoate is the ISO common name for O,O-dimethyl S methylcarbamoylmethyl phosphorodithioate or 2 Dimethoate belong to class of aliphatic amide organothiophosphate insecticides such as omethoate and mecarbam which consider a members of organothiophosphate also¹. The chemical structure of DM is illustrated in figure1².

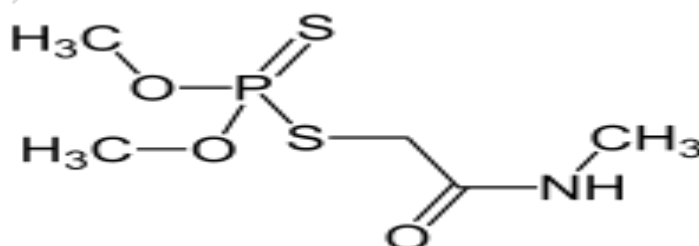


Fig. 1. Chemical structures of dimethoate[1,2]².

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 malformations³. It has previously been shown that the farmers and allied people who have been exposed to the pesticides possess more risks for thyroid cancer⁴. 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 stopped⁵. 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 exposures⁶. Developmental toxicity of DM includes decreased number of implantations and live fetuses, increased incidences of resorptions, and decreased fetal body weights⁷. Reproductive toxicity of this pesticide on adult rodents of both genders has been demonstrated. Irregularities of estrous cycle and altered level of serum gonadotropins have been reported in females⁸, while impairment of fertility, suppressed libido, semen quality deterioration, altered testosterone levels, and testicular degeneration are few of the reports available in males⁹. 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 cells¹⁰.

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 disease¹¹.

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) 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 diabetes¹². 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 plant¹³. 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 agent¹⁴. 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 radicals¹⁵. It is considered a safe herbal medicine with only few and insignificant adverse/side effects¹⁶. 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) radicals¹⁷. 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 properties¹⁵. 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 gingerols increase the motility of the gastrointestinal tract and have analgesic, sedative, antipyretic and antibacterial properties¹⁸. A study at the University of Michigan demonstrated that gingerols can kill ovarian cancer cells¹⁹. The chemopreventive potentials of [6]-gingerol present a promising future alternative to expensive and toxic therapeutic agents²⁰.

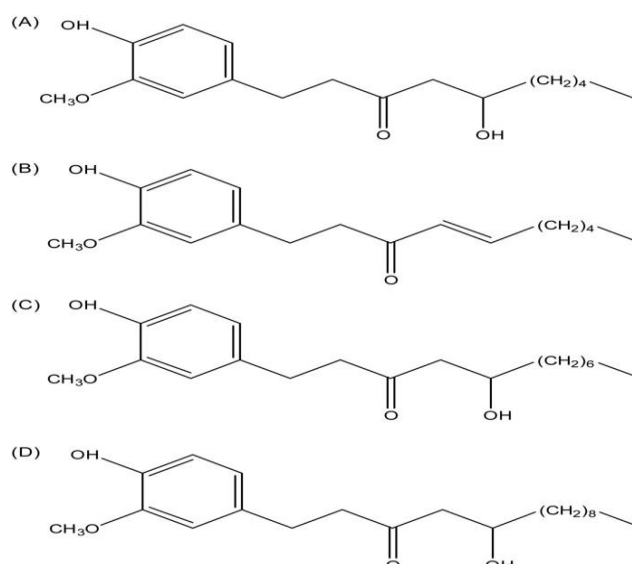


Fig.2. Chemical structures of 6-gingerol (A), 6-shogaol (B), 8-gingerol (C), and 10-gingerol (D)²¹

Both of the gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are important synthesized by the pituitary gland and play an important role control in reproductive and growth functions²². FSH and LH have specific mechanism by binding to receptors in the testis and ovary and regulate gonadal function to start stimulating sex steroid production and gametogenesis²³. In addition, Thyroid hormones are two hormone synthesized and released by the thyroid gland, called Triiodothyronine T₃ and thyroxin T₄²⁴. They are tyrosine -based hormones that are control the regulation of metabolism. Both of T₃ and T₄ are composed of Iodine in their structures, that why any deficiency of iodine leads to decreased production of T₃ and T₄. The major form of thyroid hormone in the blood is thyroxin (T₄), which has a longer half-life than T₃²⁵.

2. MATERIALS AND METHODS

The 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 this experiment were of analytical grade.

The research was carried out on 20 Mature male New Zealand White rabbits, the rabbits were 6 months and initial weight of (1641 ± 27.2 g). 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*²⁶ on hormones of male New Zealand White rabbits, dimethoate was given as measurements of sublethal (43.2 mg/kg BW each other day for 12 weeks)²⁷. The LD50 of DM when given orally to rabbits was reported to be 10 000 mg/kg BW respectively²⁸. Rabbits were orally administered their respective doses for 3 month. At the conclusion of the exploratory period body weight of rabbits recorded. Animals 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 before rabbits were killed, after that 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, Thyroxin (T₄) and Triiodothyronine (T₃) hormone concentrations examined by using commercial kit that was supplied by using Coat - A - Count, from Los Angeles, USA.

Statistical analysis: statistical analysis were 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 DISCUSSION

Table 1 presented 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 level 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 1 to 2 and Figs 3 to 6).

Table 1. The overall means (\pm 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 \pm 27.19 ^{ab}	1705.3 \pm 48.65 ^a	1541.5 \pm 49.24 ^b	1628.1 \pm 25.50 ^{ab}
RTW (g/100g BW)	3.100 \pm 0.535 ^a	4.050 \pm 0.690 ^a	2.760 \pm 0.656 ^a	3.320 \pm 0.645 ^a
Testosteron (ng/ml)	1.542 \pm 0.065 ^c	2.439 \pm 0.34 ^a	0.987 \pm 0.155 ^d	1.976 \pm 0.145 ^b

Values are expressed as means \pm 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 thyroxin (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 \pm 0.030 ^b	1.348 \pm 0.056 ^a	0.936 \pm 0.077 ^c	1.121 \pm 0.038 ^b
T_3 (ng/dl)	1.705 \pm 0.075 ^{ab}	1.803 \pm 0.088 ^a	1.419 \pm 0.129 ^c	1.643 \pm 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.

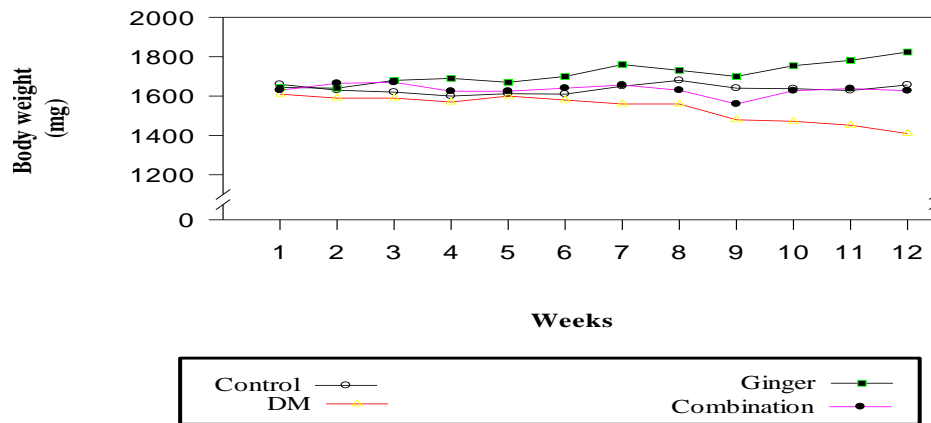


Fig. 3. Change in body weight (gm), treatment of male rabbits with ginger, DM (DM) and/or their combination.

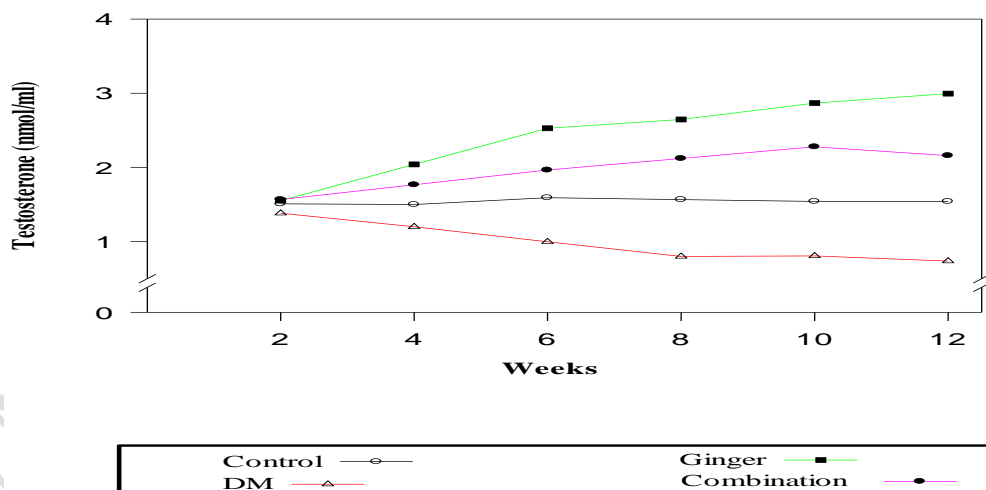


Fig. 4. Changes in plasma testosterone during treatment of male rabbits treated with ginger, DM and/or their combination

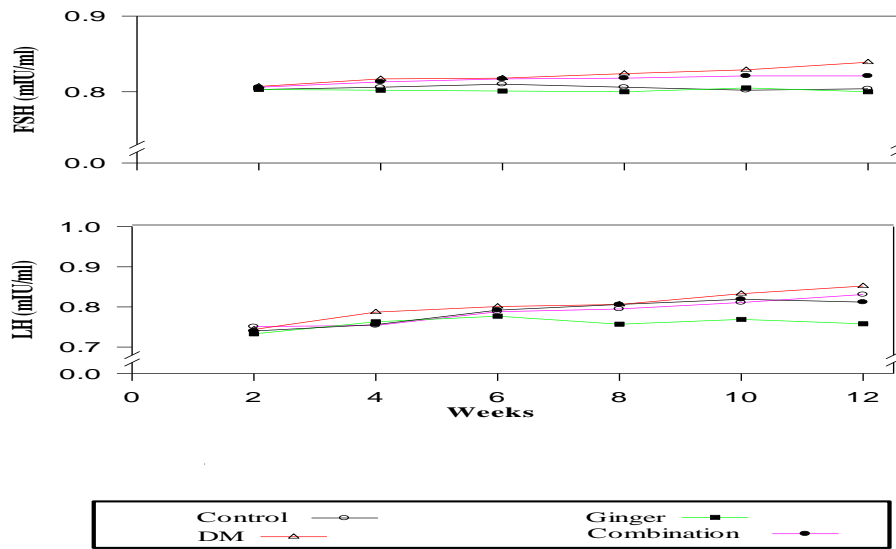


Fig. 5. Changes in the activity of plasma follicular stimulating hormone (FSH) and luenizing hormone (LH) during treatment of male rabbits with ginger, DM and/or their combination.

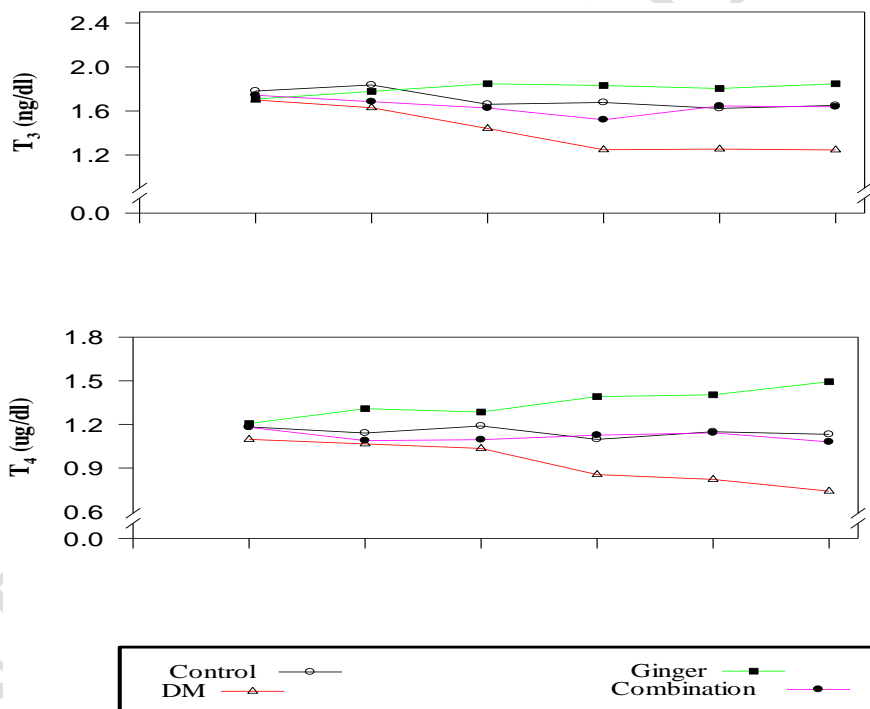


Fig. 6. Changes in the activity of plasma triiodothyronine (T_3) and thyroxine (T_4) treatment of male rabbits with ginger, DM and/or their combination

The present results indicate that treatment with (DM) caused significant reductions in body weight (BW) and relative organs weight (ROW) (Table 1 and 2 and [Figure 3 to 6](#)). In previous studies have established the reduction in BW and ROW of the (DM) treated rabbits^{29, 30, 31}. 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^{32,33,34}. The increase body weight observed in the present study due to treatment with ginger is

agreements with *Okoye et al* results³⁵. 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^{36,37}.

The present study showed that DM decrease plasma testosterone concentration in rabbits (Table1 to 2) and (figure3 to 6). Endocrine toxicity of pesticides has been well recognized, and many studies have reported their adverse effects on the reproductive axis of animals, including humans^{38,39}. 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^{40, 7,41,42}. 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 vitro⁴³. The observed reproductive endocrine toxicity might be due to direct interference of the pesticide of the pituitary-testicular axis^{44,7,45}. 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 model⁴⁶. The oral administration of technical DM also produces adverse effects on male reproductive performance in mice⁷. It was previously reported that DM decreases serum testosterone levels and testicular weight of rabbits and mice^{47,7, 5 , 43}. Moreover, a previous work from our lab demonstrates that, DM displays a complex mechanism of action involving disturbances in the hormone production⁴⁶. Treatment with ginger caused an increase in plasma testosterone concentration (Table 1) and (Figure4), these results are in agreement with the finding in the study of Saeid who suggested that ginger administration also increased the level of testosterone⁴⁸. 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 tumors 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 hormones⁴⁹.

The current study investigated the effects of pesticide exposure on T₃ and T₄ 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. The exposure to pesticides has also been shown to enhance the chances for thyroid cancer. However, the results of *Toft*⁵⁰ are conflicted with our current findings. They showed a decrease in T₃ hormone level, due to this variation in the results causes changes in environmental factors, differences in immunity of the selected population and differences in the use of pesticides⁵¹.

4. conclusion:

our results have indicated that the dimethoate, as widely use organophosphate insecticide, caused decrease the hormones level concentration. In contrast, Using ginger caused significant increase in the activity testosterone, T₃ and T₄. In addition, presence of ginger with dimethoate showed decreasing in the levels of testosterone, T₃ and T₄ as compared to control and the presence of ginger with dimethoate caused increase in the levels of FSH and LH as compared to control, which make a ginger as a promising protective compound against toxicity of DM.

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