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# Phytoprotective and Antioxidant Effects of German Chamomile Extract against Dimpylate-Induced Hepato-Nephrotoxicity in Rats

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**Abstract**
Dimpylate is one of the most organophosphorus widely used insecticides in agriculture. This study aims to investigate the ameliorative effect of German chamomile (*Matricaria recutita*) on the hepato-nephrotoxicity induced by Dimpylate in male Wistar rats. Rats were divided into 4 groups: Control group, received corn oil alone; Chamomile group, orally given water extract of Chamomile (300 mg/kg b.wt./day for 30 days); Dimpylate group, orally given 15 mg/kg b.wt./day for 30 days of Dimpylate; and Dimpylate and chamomile group, orally given Dimpylate (15 mg/kg b.wt./day) with Chamomile extract (300 mg/kg b.wt./day) for 30 days. Oxidative stress and antioxidant status were estimated in the liver and kidney of all groups. In the liver and kidney of the Dimpylate-intoxicated rats, there was an increase in malondialdehyde (MDA) concentration and a significant decrease in the activities of superoxide dismutase (SOD), total antioxidant capacity (TCA), glutathione-peroxidase (GPx), glutathione reductase (GSH-R) and Glutathione–S-transferase (GST). In addition, significant increases in serum liver function marker enzymes (AST, ALT, ALP) were recorded in Dimpylate intoxicated rats as compared to control group. Moreover, significant increase in serum total lipid, triglyceride and total cholesterol levels was observed in Dimpylate group as compared to control group. Serum total protein was decreased significantly in Dimpylate intoxicated rats as compared to the control group. Renal products; urea and creatinine were significantly elevated in in Dimpylate group compared to the control group. Dimpylate treated animals also revealed a significant increase in serum biochemical parameters as well as hepatic and renal lipid peroxidation but caused an inhibition in antioxidant biomarkers. normalized the elevated serum levels of AST, ALT, APL, uric acid, urea and creatinine. Furthermore, it reduced dimpylate-induced lipid peroxidation and oxidative stress in a dose dependent manner. Therefore, it could be concluded that Chomomile extract administration able to minimize the toxic effects of dimpylate by its free radical-scavenging and potent antioxidant activity. Co-administration of the Chamomile aqueous extract with Dimpylate could attenuate the all the disrupted measured parameters in liver and kidney tissued. Therefore, it could be concluded that the chamomile aqueous extract has antioxidant and protective property againsit Dimpylate hepato-nephrotoxicity
**Keywords**: Dimpylate, Chamomile, hepato-nephrotoxicity, Antioxidants

## Introduction

Dimpylate or Diazinon is a synthetic organophosphorous (Ops) compound with a broad-spectrum insecticide which kills insects by altering normal neurotransmission within the nervous system of the insect (Govindwar and Dalvi, 1990). It seems that the lipophilic nature of organo-phosphorous compound facilitates their penetration through the cell membrane to induce changes in cell membrane phospholipids, production of free radical of reactive oxygen species and a generation of oxidative stress in different tissues (West et al., 2013).

The main mechanism of action of diazinon is acetyl-cholinesterase enzyme inhibition (Kamanyire and Karalliedde, 2004), however, it may induce imbalance in the free radical production/elimination processes with consequent induction of cellular damage (Gokcimen et al., 2007). Because of Dimpylate or Diazinon (DZN) is one of the widely used organo-phosphorous (Ops) in agriculture. Only a few reports are available about Dimpylate effects on human after long-term exposure to low levels of Dimpylate insecticide. Several experimental and clinical studies have reported Dimpylate induced toxicities on several organs. Some studies have shown that may induce hepatic toxicity. It has been shown that insecticide may increase the enzyme activities of alkaline phosphatase (ALP), alanine transaminase (ALT) and aspartate transaminase (AST) and induce histopathological and biochemical alterations in the liver organ in a dose-dependent behavior (Rush et al., 2010). Also, the renal oxidative stress was observed following exposure to Dimpylate and other organophosphorous compounds (Ozbek, 2012).

At the present time, herbal treatment including the use of supplement and total extract is usual around the world. An increasing number of patients uses medicinal plants or searches the advice of their physicians regarding their use. More than one-third of Americans use medicinal plants for health ambitions, yet patients (and physicians) often lack accurate information about the safety and efficacy of medicinal plant remedies

 

(O'Hara et al., 1998).

*Matricaria recutita L.* (Family *Asteraceae*, commonly known as German chamomile) is one of the most widely used and well-documented medicinal plants in the world. Chamomile powder is yellowish green in color, aromatic and acrid taste. Its essence called chamazulene is the reason of smelling. The components of apigenin and Trihydroxyflavone in Chamomilla are glycosides that cause bitter taste. They also contain two important flavonoids called Pituitrin and Cyranosid (Nouri and Abad, 2012). It seems that flavonoids are important in anti-spasmodic effects and main parts of the essence such as sesquiterpenes, chamazulene, α– Bisabolol and bisabolol have anti-inflammatory influences (Baghalian et al., 2011). Chamomile is also extensively consumed as a tea or tonic. Chamomile is used both internally and externally to treat an extensive list of conditions. It is used externally for ulcers, gout, eczema, skin irritations, sciatica, neuralgia, hemorrhoids, and rheumatic pain (Newall et al., 1996). Also, the chamomile is the herb that is used for antioxidant agent, pain management, anti-spasmodic, anti-inflammatory, anti-convulsant, anti-pyretic, sedation, and wound healing in traditional medicine (Namvaran-Abbas-Abad and Khayat-Nouri, 2011).

Upon of these, the present study is aimed to investigate the role of chamomile extract in ameliorating the physiological disorders and oxidative stress associated with the injection of Dimpylate on the hepato-nephrotoxicity in rats.

## Materials and Methods

### Experimental animals

Twenty eight adult male Sprague Dawley rats, weighing 180–200g, were obtained from the Experimental Animal Unit, Faculty of Science, King Khalid University, Saudi Arabia. All rats received food and water *ad libitum* and were kept in a room with the temperature regulated to 22±1°C. The experiment was approved by the Animal Ethical Committee, Faculty of Science, King Khalid University.

### The extract of chamomile plant:

A dry flower of chamomile plant was purchased from the local market, Abha, Saudi Arabia, and the flowers were subjected to pulverize to get coarse powder and then passed through sieve #44 to get uniform powder. The sieved powder will be stored in airtight high density polyethylene container before extraction. The powdered (600 g) will be subjected to successive extraction with petroleum ether (40–60°C) and subsequently with methanol (64–65.5°C). After the residue extraction, solvent will be distilled off and excess solvent will be completely removed by using a rotating flash evaporator to get concentrated, then completely dry in freeze drier and will be stored in airtight container under refrigeration. The obtained extract (64 g, percentage yield-10.67%) then will be used for the hepato-nephroprotective activity (Chandrashekhar et al., 2010).

### Animal grouping

The protocol was designed to investigate the physiological, oxidative stress changes associated with the exposure of experimental animals to the dimpylate (0, 0-diethyl-0-[2-isopropyl-6-methyl-4-pyrimidine-yl] phosphorothionate) pesticide for 28 days. After determination of the $LD_{50}$ dose (600 mg/kg b. wt.) we used the quarter (150 mg/kg. b. wt.) orally administered to the animals using gavage for the experiment period. The animal groups were divided into four groups: Control group: rats were received corn oil alone as a vehicle for dimpylate; chamomile extract (25 mg/kg, oral administration) group; dimpylate group that received intrapersonal 150 mg/kg. b. wt of dimpylate; dimpylate and chamomile extract that received 150 mg/kg of dimpylate and treated with chamomile extract (25 mg/kg).

### Physiological investigation

Blood samples were individually collected from the inferior vena cava in non-heparinized tube. Blood serum was separated by centrifugation at 3000 rpm for 10 min and then stored at -20°C. Liver and kidney tissues were homogenized in a phosphate buffer solution, pH 7.4, centrifuged at 3000 r/min for 10 min at 4°C, and the supernatant was stored at -80°C until measurement of the parameters.

Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were determined according to the method described by Reitman and Frankel (Reitman and Frankel, 1957). Serum alkaline phosphatase (ALP) was calorimetrically estimated by randox kit according to the method described by Belfield and Goldberg (Belfield and Goldberg, 1971). Serum total protein concentration was calorimetrically determined by the biuret method as described by Koller (Koller and Kaplan, 1989). Using the urease-Berthelot reaction, urea level (mg/dl) was estimated by a test reagent kit (Biodiagnostics, Egypt). Urea is hydrolysed by urease enzyme giving ammonium ions which are then measured by the Berthelot reaction. The formed blue dye indophenols product was measured calorimetrically at 550 nm. Protein concentration in tissue homogenates of was determined using the standard method of Bradford (Bradford, 1976). The level of Triglycerides was determined by the method of McGowan (McGowan et al., 1983) using commercially available kit (Human, Germany). An aliquot (1.0ml) of reagent solution was added to 10µl of homogenate or standard, vortex-mixed and incubated at 25oC for 10 min before reading the absorbance at 500nm against the reagent blank. Total cholesterol (TC) level; The method described by Allain (Allain et al., 1974) was used for determination of total

 

cholesterol using Randox kit. Briefly, 1ml reagent solution was added to 10µl sample, standard cholesterol (standard) and distilled water (blank) respectively in disposable tubes, mixed and then incubated at 25oC for 10min. The absorbance was read at 500nm within 1 hour. Creatinine level (mg/dl) was determined by colorimetric kinetic assay using a test reagent kit (Biodiagnostics, Egypt). Creatinine reacts with picric acid in an alkaline solution to form a yellow colored complex. The intensity of the formed yellow dye increases by time and measured colorimetrically at 495 nm.

**Antioxidant and Oxidative stress investigations**

To analyse lipid peroxidation in liver and kidney tissues, 2-Thiobarbituric Acid-Reactive Substances (TBARS) were measured according to Ohkawa et al., and Yagi (Ohkawa et al., 1979, Yagi, 1998) method at 532 nm in nanomoles per gram of tissue. Total glutathione content was measured according to the method described by Beutler (Beutler et al., 1963)using glutathione reduced colorimetric method. Superoxide dismutase (SOD) activity was determined in the sample according to the method of Woolliams (Woolliams et al., 1983)using Randox superoxide dismutase kit. Glutathione peroxidase (GSH-px) activity in the sample was measured according to the Paglia and Valentine's method (Paglia and Valentine, 1967) using Randox GSH-px kit. Determination of Glutathione reductase (GSH-R) and Glutathione–S-transferase (GST) activities were done by the method of Habig (Habig and Jakoby, 1981). The total antioxidant capacity (TAC) was measured according to Koracevic (Koracevic et al., 2001).

**Statistical analysis**

The results data were expressed as mean±SD and statistical and correlation analyses were performed using the one-way ANOVA followed by a post-hoc least significant difference (LSD) test. *P*-values ≤0.05 were considered as statistically significant. Statistical analyses were performed with the statistical package for the social sciences for Windows (SPSS, version 16.0, Chicago, IL, USA.

**The results**

The current study was undertaken to determine the possible protective effect of German Chamomile on the physiological, the antioxidant and the oxidative stress status during Dimpylate-toxicity in rats. During the treatment, an important daily decrease in water consumptions and food has been shown. These behavioural perturbations could be resulted from Dimpylate stress.

**Physiological changes**

In table 1, the non-significant changes of liver functions, Creatinine and urea ($p > 0.05$) in Chamomile group (G2) when compared with the normal control group (G1) were shown. But this relation showed a very high significant ($p < 0.001$) increase in the levels of AST, ALT, ALP, protein, Creatinine and urea in the Dimpylate-treated group (G3) when compared with the control group. The levels of AST, ALT, ALP, protein and Creatinine are significantly decreased in the rats that were treated with Dimpylate and treated with German Chamomile extract group. But in urea, the insignificant was done in group 4 when compared with the control.

**Table (1): The biochemical investigations in different animal groups:**

| Parameters | Control | Chammomile extract | Dimpylate pesticide | Dimpylate with Chamomile extract |
|---|---|---|---|---|
| **AST (U/L)** | 56±13.6 | 49±18.9 | 75.8±10.2** | 70.5±2.8* |
| **ALT (U/L)** | 42.9±6.5 | 36.3±5.5 | 130.6±15.7** | 73.5±7.1* |
| **ALP (U/L)** | 89.2±11.4 | 60.2±9.5 | 386.4±52.9** | 85.9±51.3* |
| **T. protein (g/dl)** | 6.4±0.3 | 6.7±0.5 | 4.4±0.4** | 5.1±0.5* |
| **Creatinine (mg/dl)** | 0.3±0.05 | 0.2±0.03 | 1.2±0.2** | 0.9±0.13* |
| **Urea (mg/dl)** | 39.5±5.9 | 33.2±3.4 | 57.4±5** | 45±7.4 |

Values were expressed as means ±SD of five animals in each group.
* = P<0.05 (significant), ** = P≤0.001 (highly significant), when all groups compared with control group.

The administration of rats with Dimpylate injected caused high significant elevation in serum total lipids, triglycerides, and total cholesterol levels as compared with control group. The treatment with chamomile extract induced significant decrease in serum lipid profile when compared with dimpylate administered groups when compared to their matched groups (**Figure 1**).

 

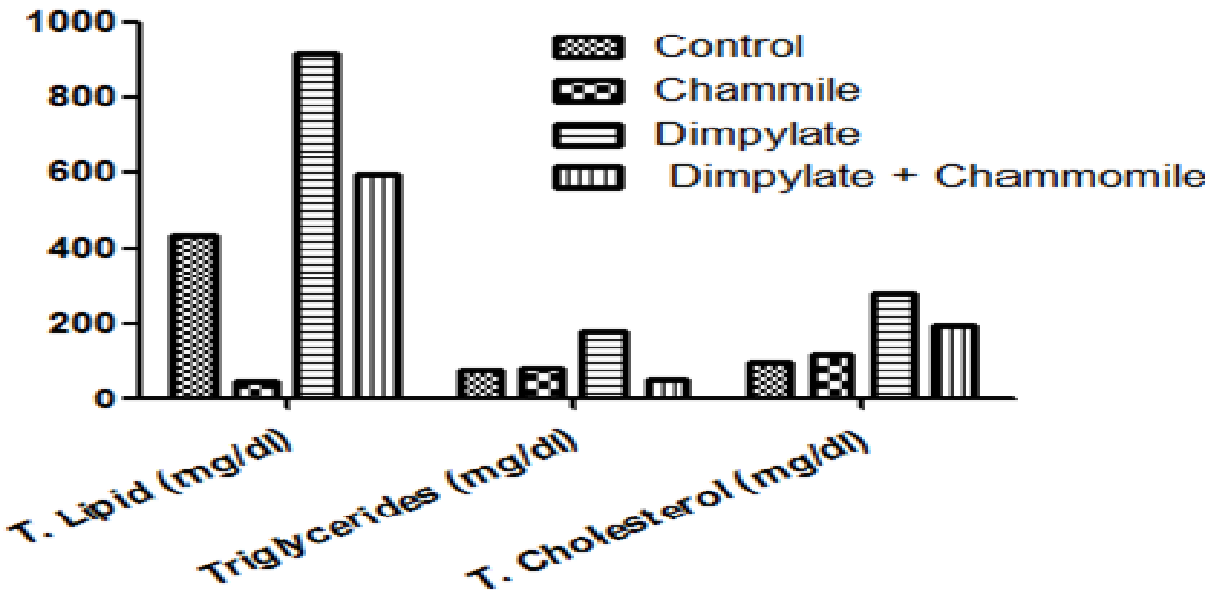


Fig. (1): Lipids profile in different experimental groups

**Superoxide dismutase (SOD), total antioxidants capacity (TAC) and lipid peroxidation**

In figures (2-4) show the activity of superoxide dismutase (SOD), total antioxidant capacity and the lipid peroxidation (malondialdehyde (MDA) level) of all groups of rats. Rats administered with Dimpylate showed high significant decrease in the activity of SOD in kidney and liver tissues compared to the rats in the control group. However, rats administered with Dimpylate along with chamomile (300 mg/kg b. wt.) showed a significant improvement in the imbalance of SOD in kidney and liver tissues compared to the dose of Dimpylate group. The total antioxidants capacity in kidney and liver was depleted significantly in the Dimpylate group as compared to the control one. Oral administration of watery extracts of chamomile able to restore the total antioxidant capacity in the investigated tissue in the all treated groups when compared to their matched ones. Lipid peroxidation (measured by MDA level) was high significant increase in Dimpylate group when compared to the control group. This increase of MDA leads to augmentation of oxidative stress in all tissues, the administration of aqueous tested extract of chommile alleviated this increase.

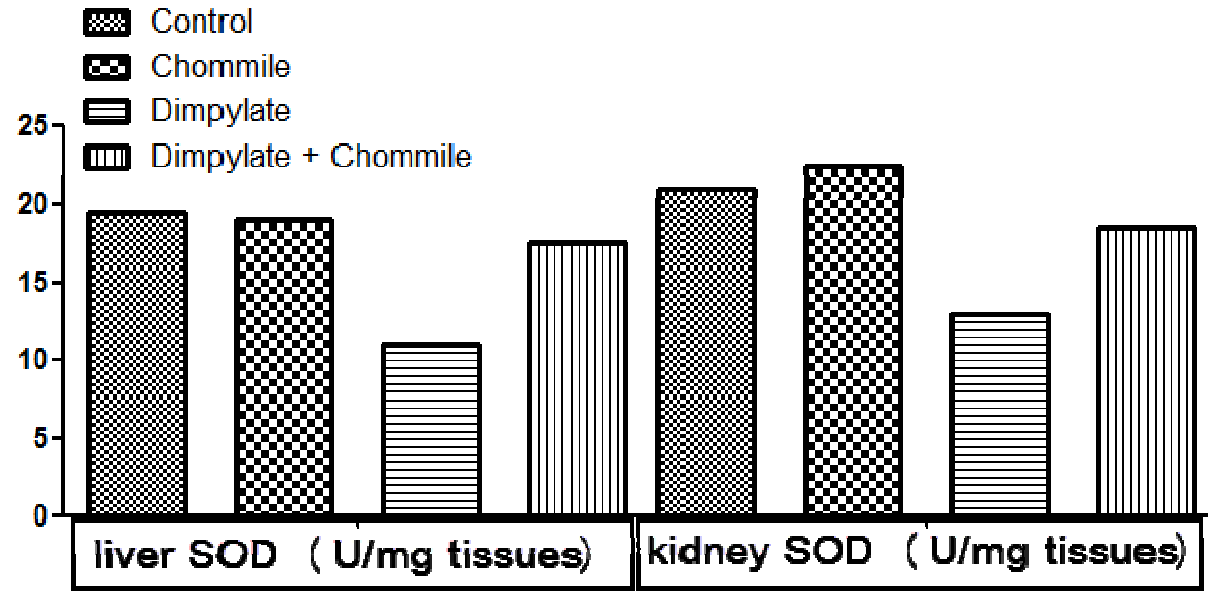


Figure (2): Superoxide dismutase (SOD) in liver and kidney tissues of the different animal groups.

 

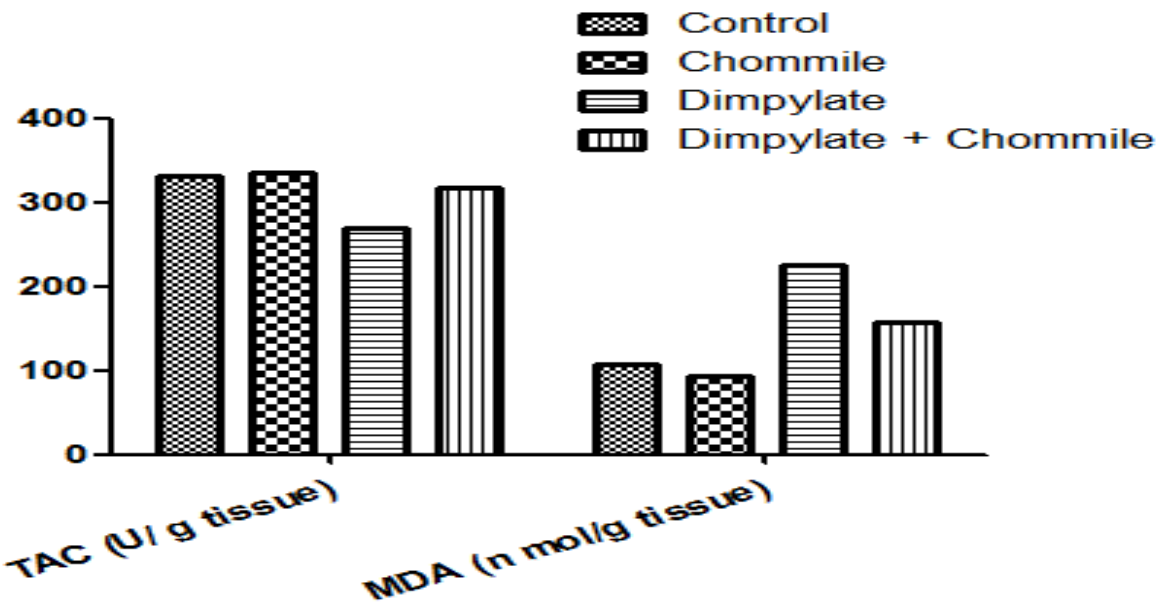


Figure (3): Total antioxidants capacity (TAC) and lipid peroxidation in the renal tissues of the different animal groups

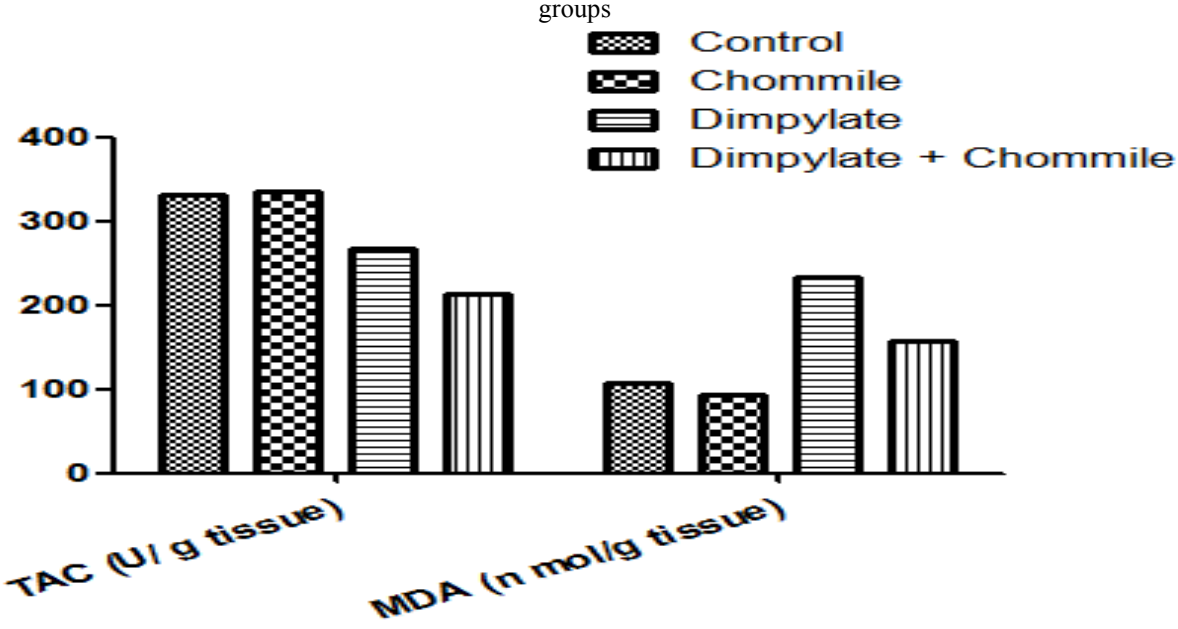


Figure (4): Total antioxidants capacity (TAC) and lipid peroxidation in the hepatic tissues of the different animal groups

**Glutathione contents and their relative antioxidant enzymes**

In figures (5, 6) the enzymatic antioxidants such as glutathione-S-transferase (GST), glutathione peroxidase (GSH-Px) and glutathione reductase (GSH-R) and non-enzymatic antioxidant such as glutathione (GSH) were adversely changed in all investigated tissues in treated groups when compared with the control. The Kidney and liver tissues were more sensitive to the Dimpylate as represented by the high significant decrease in GST, GSH-Px and GSH-R activity in Dimpylate group. Administration of aqueous extracts of chamomile is effective mediators as it alleviates the inhibition of these antioxidant enzymes when compared to the pesticide administered group. The decrement of the above enzymes may be due to the significant decrease in GSH of kidney and liverof the Dimpylate rats' groups.

 

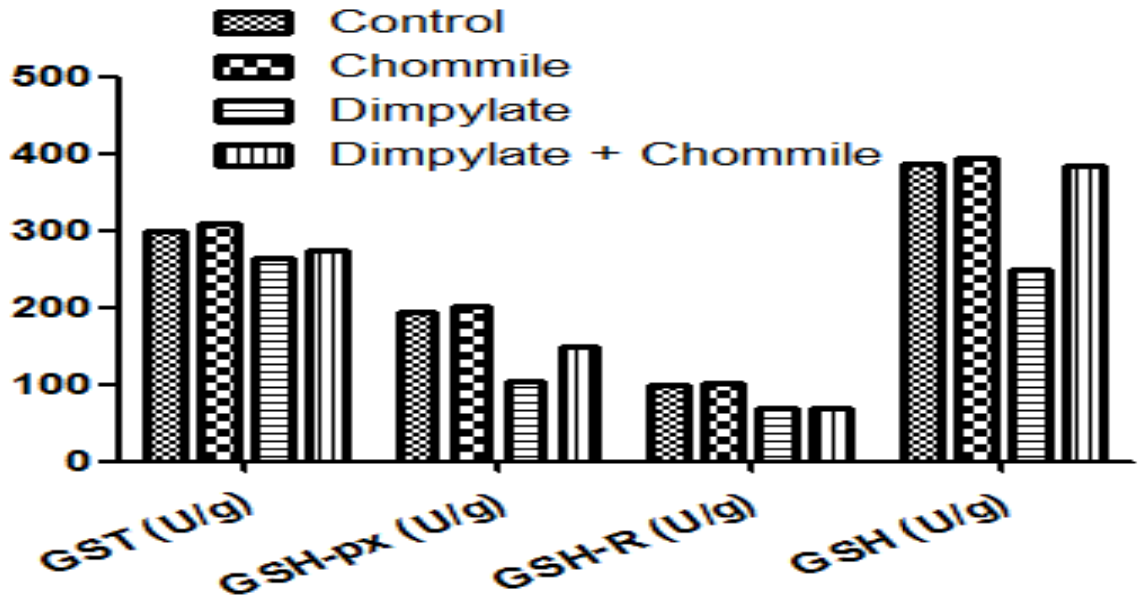


Figure (5): Glutathione contents and their relative antioxidant enzymes in the renal tissues of the different animal groups

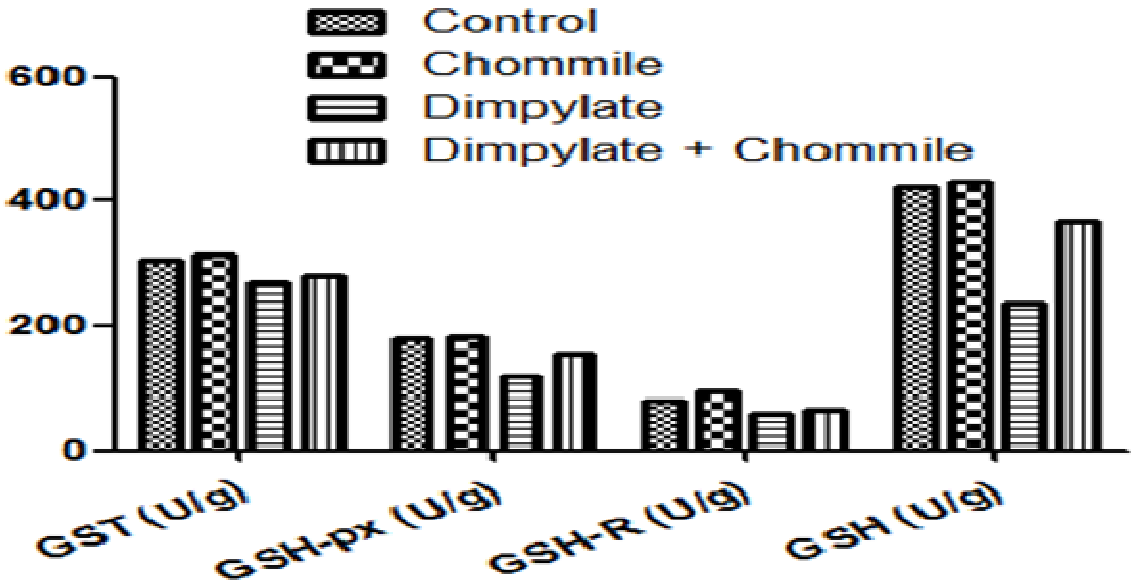


Figure (6): Glutathione contents and their relative antioxidant enzymes in the kidney of the different animal groups

**Discussion**

Diazinon (Dimpylate), the organophosphorous pesticide, was reported to cause toxic effects in man (Messarah et al., 2013). Dimpylate is well known to show its toxic effects by inhibiting cholinesterase activity in plasma, erythrocytes and brain (Katsumaro and Tohru, 1985). Other studies showed that Dimpylate had affected the expression of neurotrophic factors that coordinate neuronal cell differentiation and brain assembly (Slotkin and Seidler, 2007). In the present study, We reported that Dimpylate caused degeneration in hepatocytes and changes of liver enzymes (ALT, AST, TP and ALP) and kidney functions (Creatinine and Blood Urea). Also, Dimpylate caused high significant increase in the activity of liver enzymes. The administration of chamomile improve the hepatic biochemistry may be due to their antioxidant action (Newall et al., 1996). Moreover, as the liver is the main detoxifying organ in the body, serum aminotransferases activities are used as toxicity markers in studying hepatotoxicity caused by chemicals. Therefore, a significant increase in the activities of serum AST, ALT, ALP, protein, creatinine and urea was verified.

 

Oxidative stress refers to the cytotoxic consequences of ROS, which are generated as byproducts of normal and aberrant metabolic processes that utilize molecular oxygen. GSH is a major player in cellular defense against ROS, because it non-enzymatically scavenges both singlet oxygen and hydroxyl radicals, and is utilized by glutathione peroxidase and glutathione-S-transferase to limit the levels of certain reactive aldehydes and peroxides within the cell. When ROS production exceeds the antioxidant defense capacity of the cell, oxidative stress ensues, leading to damage of DNA, proteins and membrane lipids, which result in cell death (Giordano et al., 2007). In the renal and hepatic tissues, the glutathione contents and their relative antioxidant enzymes (GST, GSH-px, GSH R, and GSH) were delayed in dimpylate animal treated group when compare the control and dimpylate with German chamomile treated groups.

The key enzymes for the detoxification of reactive oxygen species in all organisms are superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). Enzymatic degradation of $O^{2-}$ to $H_2O_2$ is ensured by SOD (Oruç and Usta, 2007). Oxidative stress following OP exposure has also been reported in humans and increased lipid peroxidation and decreased levels of total antioxidant capacity (TAC) were found in acutely organophosphorus poisoned individuals (Ranjbar et al., 2005). So, in the present study the levels of SOD were increased in the Dimpylate experimental animal groups and the improvement was occurred in German chamomile animals group. On another, the total antioxidant capacity (TAC) concentrations were significant decreased in dimpylate treated animals and recover the levels in dimpylate group with treated German chamomile extract in different brain tissues.

Malondialdehyde, the end product of lipid peroxidation, has also been measured to indicate the presence of lipid peroxidation and free radicals induced tissue toxicity. Organophosphorus compounds cause increase of lipid peroxidation level (Hazarika et al., 2003). Recent studies indicate that pesticide intoxication produce oxidative stress by the generation of free radicals and induce tissue lipid peroxidation in mammals and other organisms (Hazarika et al., 2003). Malondialdehyde (MDA) is increased MDA content is an important indicator of lipid peroxidation and a major oxidation product of peroxidized polyunsatured fatty acids (Kalender et al., 2004). Many insecticides are hydrophobic molecules, which bind extensively to biological membranes, especially to the phospholipids bilayers (Lee et al., 1991). The increase of MDA level is an indicator of free radical formation of Dimpylate in rats. So, reactive oxygen species (ROS), such as singlet oxygen, hydroxyl radical, superoxide anion and peroxyl radical can be generated from normal metabolism in the human or animal body, and can cause DNA damage, cancer, cardiovascular disease and aging. Antioxidants can reduce the damage tissue induced by ROS; therefore, intake of vegetables could significantly decrease the death rate of cardio- and cerebrovascular diseases, immune dysfunction and cancer (Verlangieri et al., 1985). Since reactive oxygen species are involved in stress and pathogenesis of cancer, diabetes mellitus, atherosclerosis and dementia, the use of these natural products especially German chamomile may be beneficial in preventing initiation or progress of such disorders. So the hepato-nephrotoxicity was documented here by the increase in lipid peroxidation especially with the exposure to Dimpylate in different brain tissues.

The decrease in total antioxidant capacity of all tissues in the Dimpylate group can lead reactive metabolites of Dimpylate cruelty attack the biomolecules such as DNA, protein and lipids. These DNA adducts can then, in case no reparation mechanisms start, cause tumorigenesis. The oral administration with chamomile has anticancer action as they restoring the level markers nearly to the control group. Oxidative stress is responsible for an increase in the accumulation of the reactive oxygen species in cells, which may subsequently lead to an increase in the expression of genes encoding antioxidant enzymes (Michiels et al., 1994).

## Conclusions

Dimpylate organophosphates pesticide, Diazinon has high toxic effect on the kidney and liver in rats. The hepato-nephrotoxicity effect of Dimpylate comes from their ability to initiate the oxidative stress by increasing the high levels of lipid peroxidation. Moreover the inhibition of most enzymatic antioxidants and non-enzymatic antioxidants play a vital role in the malfunction of reno-hepatic functions. The administration of chamomile extract ameliorates the biochemical, antioxidants and lipid profile changes associated with Dimpylate exposure.

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