# Antioxidant Role of both Propolis and Ginseng against Neurotoxicity of Chlorpyrifos and Profenofos in Male Rats

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**Abstract:** The present study was an attempt to evaluate the toxic effect of both Chlorpyrifos and profenofos (organophosphorous insecticides) each alone and in their combinations with either propolis or ginseng and as well known that propolis and ginseng have been reported to be effective antioxidant, therefore, the present study was aimed to elucidate the possible ameliorative role of propolis and ginseng in alleviating the toxicity of both Chlorpyrifos and profenofos when given to male rats. This was done through studying the effects of both Chlorpyrifos and profenofos on some antioxidant enzymes in liver, Kidney and brain homogenates and by measuring acetylcholinesterase as well as histopathological changes in vital organ like Brain. Animals were divided into nine groups; The 1st (Control group): Animals received 1ml of distilled water orally daily for 8 weeks, The 2nd (Chlorpyrifos treated group)Animals were daily received oral doses of Chlorpyrifos (6.75 mg/Kg b.wt.) for 60 days , The 3rd (Profenofos treated group)Animals were received orally Profenofos (20 mg/Kg b.wt.) daily for 8 weeks , The 4th (Propolis treated group)Animals were received orally Propolis extract (70mg/kg) daily for 8 weeks,The 5th (Ginseng treated group)Animals were given orally Ginseng extract (200mg/Kg b.wt.) for 8 weeks daily, The 6th (Chlorpyrifos + Propolis treated group)Animals were given orally Chlorpyrifos (6.75 mg/Kg) and then co-administered with Propolis extract (70mg/kg b.wt.) for 8 weeks daily, The 7th (Chloropyrifos+Ginseng treated group)Animals were given orally Chlorpyrifos (6.75 mg/Kg b.wt.) and then co-administered with Ginseng extract (200mg/Kg b.wt.) for 8 weeks daily , The 8th (Profenofos +Propolis treated group)Animals were given orally Profenofos (20 mg/Kg b.wt.) and then co-administered with Propolis extract (70mg/kg b.wt.) for 8 weeks daily, The 9th (Profenofos +Ginseng treated group)Animals were given orally Profenofos (20 mg/Kg) and then co-administered with Ginseng extract (200mg/Kg) as mentioned above for 8 weeks daily . Results showed that there was a correlation between CPF and PRF administration and the highly significant increase of the antioxidant enzymes, Cortisol and neurotransmitter (Acetylcholinesterase). In contrary to these actions, co-administration of propolis and ginseng to CPF and PRF-treated rats retrieved almost most of these biochemical parameters to normal levels. On the other hand, CPF and PRF showed histopathological alterations in brain of male rats like hemorrhage and mild degeneration, while administration of both propolis and ginseng highly ameliorate these dangerous neurotoxicity markers.

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**Keywords:** Chlorpyrifos, Profenofos, Propolis, Ginseng, neurotoxicity, antioxidant enzymes, Acetylcholinesterase.

**Abbreviations**: CPF, Chlropyrifos; PRF, Profenofos; MDA, Malondialdhyde enzyme; SOD, Superoxide dismutase; CAT, Catalase; NO; Nitric oxide, GPX;Glutathione peroxidase, GSH; Glutathione reduced, G-6-Ph; Glucose-6-phosphate

## 1. Introduction

Exposure to pesticides may involve large segments of population which include agriculture workers and their families, besides the general population who may be exposed through home application of pesticides or via residues on food **[1]**. There is an urgent need for the use of pesticides to protect economic plants and animals against pests infesting them. Several organophosphorus insecticides are widely used in various purposes. The unavoidable increased use of many new pesticides may cause great hazards to the living organisms, carelessly or wrongly application lead to pollution for the total ecosystem (i.e., air, earth, plant, water, animal and human ecosystem). A considerable numbers of these pesticides were reported to have acute, chronic, histopathologic and teratogenic activities **[2].**

Chlorpyrifos (CPF) is an effective organophosphate; (OP) pesticide used heavily throughout the world for agriculture and domestic purposes. The main target of OP pesticides is acetylcholinesterase (AChE), which hydrolyse acetylcholine (ACh) in cholinergic synapses and at neuromuscular junctions **[3]** this results in the accumulation of ACh in the synapses which in turn induces hyperactivity in cholinergic pathways. Besides, CPF elicits a number of other effects including hepatic dysfunction, immunological abnormalities,

embryotoxicity, genotoxicity, teratogcnicity, neurochemical, and neurobehavioral changes **[4].**

The organophosphorus (OP) insecticide Profenofos (o-4-bromo -2- chlorophenyl-O- ethyl S-propyl) phosphorothioate is used heavily in cotton-growing areas of wide area of the world such as; Eastern Australia, Northern Africa and various areas of America **[5]**. Besides Profenofos is a broad-spectrum organophosphate insecticide and acaricide used widely used for agricultural and household purposes **[6]**.Profenofos caused different symptoms of toxicity and revealed some biochemical changes especially in the enzymes activity of the liver and brain following two sublethal doses of profenofos in mice **[7].**

To control the level of reactive oxygen species (ROS) and to protect cells under stress conditions, mammalian tissues contain several enzymes scavenging ROS such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-PX) and glutathione S-transferase (GST), and reduced glutathione (GSH) Some compounds also contribute to detoxification process from ROS such as propolis **[8].**

Natural products are a promising source for the discovery of new pharmaceuticals. In the last decades, several works dealing with propolis' composition and biological properties have been published, revealing the interest of researchers on this bee product and its potential for the development of new drugs **[9].**

Propolis is a resinous hive product collected by honeybees from plants, showing a very complex chemical composition **[10]**. It has been used in folk medicine since ancient times, due to its many biological properties, such as antibacterial **[11]**, antitumor **[12]**, and immunomodulatory **[13]**.

Propolis also contains more than 300 biochemical constituents, including mostly a mixture of polyphenols, flavonoid aglycones, phenolic acid and their esters, and phenolic aldehydes and ketones, terpenes, sterols, vitamins, amino acids **[14]**.

Ginseng is a well-known medicinal herb in traditional Asian medicine and is considered an adaptogen. *Panax ginseng* C.A. Meyer (Araliaceae), which grows in China and Korea, has a variety of beneficial biological actions that include anti-carcinogenic, anti-diabetic-inflammatory effects, as well as cardiovascular protection and neuroprotection **[15].**

## 2. Materials and Methods

### 2.1. Test insecticide

**2.1.1 Chlorpyrifos** was produced by Misr for Agricultural Development Company, Cairo, Egypt. Under trade name Dursban and was stored at 4°C until stock solution preparation. The insecticide (CPF) was orally administered at a dose level equivalent to 1/20 $LD_{50}$ (6.75 mg/kg b.wt.) in distilled water for 60 successive days, this selected dose of the insecticide was based on previous studies in which 1/20 $LD_{50}$ of CPF induced biochemical alterations in rats without morbidity **[16]**. Stock solution was prepared by bringing Chlorpyrifos to room temperature then taking a certain amount by pipette from the Chlorpyrifos bottle and dilute it in distilled water (**0.25 ml of Chlorpyrifos was dissolved in 250 ml dist. water**) and diluting it in tween 80 to ensure rapid and complete absorption and we prepare 250 ml only to prepare the working solution freshly for each day of dosing **[17, 18].**

**2.1.2 Profenofos** is a pale yellow liquid; it was produced by Ciba-Geigy, Pharmacological Company, Scientific office Cairo, Egypt. under trade name: Selecron 72% EC , Profenofos was given at a dose of (20mg/Kg b.wt.) which represent 1/10 $LD_{50}$, where the $LD_{50}$ value of Profenofos is (200 mg/Kg) according to Weil**[19]** and this selected dose of the insecticide was based on Weil studies in which 1/10 $LD_{50}$ of Profenofos induced biochemical alterations in rats without morbidity. Tap water was used for preparing emulsion of Profenofos immediately before use, Stock solution was prepared by bringing Profenofos to room temperature then taking a certain amount by pipette from the Profenofos bottle and diluting it in distilled water (1.97 ml of Profenofos was diluted in 250 ml dist.water) we prepare 250 ml only of working solution freshly for each day of dosing **[20]**.

### 2.2. Extracts

**2.2.1Propolis extract preparation:**

In this study, Propolis powder extract (70% ethanolic extract) was obtained from (Dosic IMP &EXP. Co, Ltd) China .Propolis was dissolved in dist. water and administered orally for 60 successive days via gastric tube at dose 70 mg/ Kg **[21,22]**

**2.2.2Ginseng extracts preparation*:***

Red Ginseng powder (Supplied by Tsumura Pharmaceutical Co., Tokyo, Japan) was administered orally at dose (200 mg/Kg b.wt.) **[23]** for 60 successive days via a gastric tube. The Ginseng extract was suspended in tap water just before use and the dose was calculated according to the animal's body weight on the week before using.

### 2.3. Animals

The present study was carried out at Zoology Department, Faculty of Science - Zagazig University, using (one hundred and ten) (110) clinically healthy mature adult male albino rats. The animals were obtained from the Animal House of Faculty of Veterinary Medicine, Zagazig University, Their weights ranged from (200-250gm) each. The animals were housed in standard conditions, where the animals were housed in metal cages and bedded with wood shavings and kept under standard laboratory conditions of aeration and room temperature at about 25°C. The animals were allowed to free access of standard diet and water *ad libitum*.The animals were accommodated

to the laboratory conditions for two weeks before being experimented.

**2.4. Experimental design**

After the period of acclimation, animals were divided into nine groups with 10 animals in each as :

**I) The 1st (Control group):** Animals received 1ml of distilled water orally daily for 8 weeks.

**II) The 2nd (Chlorpyrifos treated group):** Animals were daily received oral doses of Chlorpyrifos (6.75 mg/Kg) for 8 weeks using metallic stomach tube.

**III) The 3rd (*Profenofos treated group*):** Animals were received orally Profenofos (20 mg/Kg) daily for 8 weeks using metallic stomach tube.

**IV) The 4th (Propolis treated group):** Animals were received orally *Propolis* extract (70mg/kg) daily for 8 weeks using metallic stomach tube.

**V) The 5th (*Ginseng treated group*):** Animals were given orally Ginseng extract (200mg/Kg) for 8 weeks daily using metallic stomach tube.

**VI) The 6th (Chlorpyrifos + Propolis treated group):** Animals were given orally Chlorpyrifos (6.75 mg/Kg) and then co-administered with *Propolis* extract (70mg/kg) for 8 weeks daily.

***VII)* The 7th (Chloropyrifos+Ginseng treated group*):*** Animals were given orally Chlorpyrifos (6.75 mg/Kg) and then co-administered with *Ginseng* extract (200mg/Kg) for 8 weeks daily.

***VIII)* The 8th (Profenofos +Propolis treated group*):*** Animals were given orally Profenofos (20 mg/Kg) and then co-administered with *Propolis* extract (70mg/kg) for 8 weeks daily.

***XI)* The 9th (Profenofos +Ginseng treated group*):*** Animals were given orally Profenofos (20 mg/Kg) and then co-administered with *Ginseng* extract (200mg/Kg) as mentioned above for 8 weeks daily.

**2.5 Biochemical Assays**

Blood samples were collected after the end of the experiment from the retro-orbital vein, which is a simple, convenient and successful procedure that allows bleeding of the same animal more than one time with minimal stress **[24]** .After the last administration of the drug at the end of 8th week, individual blood samples were drawn by orbital puncture (from eye plexus) using microhematocrit capillary tubes (Lancer, Athy, County-Kildare, Republic of Ireland), Serum was harvested from blood without EDTA and then blood samples were transferred into Eppendorf tubes and subsequently used for the determination of the following biochemical parameters , The biochemical measurements were performed according to the details given in the kit's instructions.

**2.5.1 Determination of serum Cortisol concentration:**

Serum cortisol was determined using by biodiagnostic kit method (Biodiagnositc Company, Dokki, Giza, Egypt). The electro chemiluminescence's immunoassay (ECLIA) is intended for immunoassay analyzer of cobas according to Arakawa et al.**[25].**

**2.6 Preparation of Tissue Homogenate for antioxidant enzymes:**

The remainder tissues of liver were used for the analyses of oxidative stress parameters. They were washed with saline and distal water for the removal of blood, and later the fatty parts were removed and blotted over a piece of filter paper. Prior to dissection, tissue was perfused with a 50 mM (sodium phosphate buffer saline (100 mM $Na_2HPO_4$ / $NaH_2PO_4$) (PH 7.4) in an Ice containing medium containing 0.16 mg / ml heparin or containing 0.1 mM ethylene di amine tetra acetic acid (EDTA)to remove any red blood cells and clots. Then tissues were homogenized in 5 – 10 ml cold buffer per gram tissue and Centrifuged at 5000 r.p.m for ½ hour. The resulting supernatant was transferred into Eppendorf tubes, and preservedat -80°C in a deep freezer until used for various biochemical Assays **[26].**

**2.6.2 Determination of Catalase activity:**

Catalase (CAT) activity was determined by biodiagnostic kit method (Biodiagnositc Company, Dokki, Giza, Egypt), according to the method of Aebi **[27]**.

**2.6.3 Determination of Superoxide dismutase activity:**

Superoxide dismutase (SOD) activity was determined by biodiagnostic kit (Biodiagnositc Company, Dokki, Giza, Egypt), according to the method of Nishikimi et al.**[28].**

**2.6.4 Determination of Reduced Glutathione (GSH) activity:**

Glutathione reduced (GSH) activity was determined by biodiagnostic kit (Biodiagnositc Company, Dokki, Giza, Egypt), according to the method of Beutler et al.**, [29].**

**2.6.5 Determination of Glutathione Peroxidase (GPX) activity:**

Glutathione peroxidase activity was determined using biodiagnostic kit (Biodiagnositc Company, Dokki, Giza, Egypt), according to the method of Paglia and Valentine **[30]**.

**2.6.6 Determination of Lipid peroxide (Malondialdhyde) activity:**

Malondialdehyde (MDA) was determined by using Biodiagnostic kit (Biodiagnostic Company, Dokki, Giza, Egypt), according to the method of **[31].**

**2.6.7 Determination of Serum Nitric Oxide (NO):**

Nitric oxide (NO) level was determined by using Biodiagnostic kit method (Biodiagnostic Company, Dokki, Giza, Egypt), according to the method of Montgomery and Dymock **[32].**

**2.6.8 Determination of Glucose -6-Phosphate Dehydrogenase:**

The enzyme activity is determined by measurement of the rate absorbance change at 340 nm due to the reduction of NADP+ by using Biodiagnostic

kit method (Biodiagnostic Company, Dokki, Giza, Egypt), according to the method of Kornberg **[33].**

**2.7 Estimation of brain neurotransmitters:**

**(Estimation of Dopamine, Epinephrine, nor epinephrine and serotonin content)**

Dopamine as well as catecholamines (Epinephrine, nor epinephrine and dopamine) was determined in rat's brain according to the method of Ciarlone **[34].**

**2.8 Estimation of acetylcholinesterase:**

Acetylcholinesterase was determined by biodiagnostic kit (Biodiagnositc Company, Dokki, Giza, Egypt), according to the method of Ellman et al**[35]**.

**2.9 Preparation of tissues for histopathological examination**

After 8 weeks post drug administration, animals were sacrificed and samples from heart, liver, brain, kidney and testis were fixed in 10% formalin for histopathological studies. Parts of liver were transferred into 10% buffered formalin for histopathological examination, and the remainder tissue was used for the analysis of oxidative stress parameters. Tissue samples were taken from the liver of the necropsied animals and fixed in 10% formalin saline. The trimmed tissues were first washed with tap water followed by dehydration through a graded alcohol series and then passed through xylol and paraffin series before finally blocked in paraffin. The paraffin blocks were cut into 5-6 µm sections using a microtome stained using hematoxylin and eosin and examined under a light microscope **[36]**.

**2.10 Statistical analysis**

Data were collected, arranged and reported as mean ± standard error of mean (S.E.M) of nine groups (Each group was considered as one experimental unit), summarized and then analyzed using the computer program SPSS/ version 15.0) The statistical method was one way analyzes of variance ANOVA test (F-test), and if significant differences between means were found, Duncan's multiple range test (Whose significant level was defined as ($P$<0.05) was used according to Snedecor, and Cochran, **[37]** to estimate the effect of different treated groups.

**3. Results**

**3.1 Morbidity and mortality:**

Male rats orally administered Chlorpyrifos, profenofos in doses of (6.75 mg/kg) and (200 mg/Kg) respectively for 60 days have shown signs of toxicity (Diarrhea, myosis, increased urination, diaphoresis,nose and eye bleeding and salivation) and no deaths were recorded throughout the experimental groups.

**3.2 Effect on serum Cortisol:-**

It was clearly evident from (Table 1) and (Fig. 1) that the administration of Chlorpyrifos and/or Profenofos each alone in their recommended doses daily for successive 60 days afforded a highly significant increase ($P$< 0.05) in serum cortisol level after the end of the experiment when compared with control group. Concerning the effect of either Propolis or Ginseng, the same table and figure revealed that Propolis and/or Ginseng treated groups showed non significant changes in serum cortisol level when compared with control group. A non significant increase in serum cortisol level was also recorded in response to treatment of male rats with combinations of either Chlorpyrifos or Profenofos with either Propolis or ginseng compared with normal control group.

**3.3 Effect on Antioxidant enzymes:**

**3.3.1 Effect on Catalase:**

Regarding the effect of profenofos and Chlorpyrifos on catalase activity of normal rats, Chlorpyrifos and profenofos afforded a marked decrease ($P$<0.05) in liver homogenates catalase after the end of the study when compared with control group, whereas, Treatment of normal rats with either propolis or Ginseng alone exhibited non significant changes in Catalase of liver after the end of the experiment when compared with control group (Table 2) and (Figs. 2,3)While combinations of Chlorpyrifos, Profenofos with either Propolis or ginseng exhibited a significant decrease in Catalase activity of liver after the end of the study compared with normal control group.

**3.3.2 Effect on Superoxide dismutase (SOD):**

The results of the study revealed that treatment of normal rats with either of Chlorpyrifos and/or profenofos elicited a highly significant decrease ($P$<0.05) in liver SOD level after the end of the study when compared with control group. Treatment of normal rats with either propolis or ginseng for 8 weeks elicited a significant increase in SOD activity of the liver after the end of the study. Whereas, the combinations of the plant extracts with the test insecticides afforded non significant changes in the SOD activity of the liver compared with normal control group .Table (3) and Figs. (4,5).

**3.3.3 Effect on Malondialdhyde (MDA):**

The MDA content of the liver was significantly elevated ($P$<0.05) in response to treatment of normal male rats with either Chlorpyrifos and/or profenofos for 8 weeks compared with normal control group. The same previous response was reported with propolis, ginseng and their combinations with either Chlorpyrifos or profenofos compared with control group (Table 4) and (Figs. 6,7**)**.

**3.3.4 Effect on Glutathione reduced:**

It was apparent from (Table 5) and (Figs. 8,9**)** that treatment of rats with Chlorpyrifos, Profenofos each alone afforded a significant decrease ($P$<0.05) in liver reduced glutathione after the end of the study when compared with normal control group. On the other hand, the results revealed that Ginseng and/or Propolis induced a non significant change in reduced

Glutathione content of the liver compared with control group.

**3.3.5 Effect on Glutathione Peroxidase:**

The plasma Glutathione peroxidase level was significantly reduced (P<0.05) in all groups treated with Chlorpyrifos, Profenofos each alone, propolis, ginseng and their combinations for successive 60 days when compared with normal control group. Whereas, a non significant change to slight decrease was reported in response to treatments with all combinations used except combination of Chlorpyrifos with propolis which showed a significant decrease compared with normal control group (Table 6) and (Figs.10,11 ).

**3.3.6 Effect on serum Nitric oxide (No) &Glucose-6-Phosphate Dehydrogenase (G6PH):**

The serum Nitric oxide and glucose – phosphate dehydrogenase levels were significantly elevated (*P*<0.05) in groups treated with Chlorpyrifos and /or Profenofos each alone .Whereas, Treatment of normal rats with Ginseng, Propolis and their combinations with both Chlorpyrifos and Profenofos afforded non significant changes (P<0.05) after the end of the study when compared with normal control group (Table 7) (Fig.12).

**3.4 Effect on Acetylcholinesterase:**

It was clear from (Table 8) and (Fig.13) that the administration of either Chlorpyrifos or Profenofos each alone to normal rats for successive 60 days afforded a marked decrease (*P*<0.05) in serum acetylcholinesterase activity after two monthes post administration. Whereas, a non significant change in serum Acetylcholinesterase activity was observed in the groups treated with either Propolis or Ginseng. At the meantime , a significant decrease (*P*<0.05) was recorded in the groups treated with the combinations of the insecticides used with either Propolis or ginseng after 8 weeks post administration except the combination of Profenofos with Propolis which showed a non significant change with control group . Yet the results of the drugs combinations were much higher than that produced with the insecticide alone indicating a good ameliorating effect with the used plant extracts.

**3.4.1 Effect on brain Dopamine:**

Treatment of normal rats with either Chlorpyrifos or Profenofos for 60 successive days in their recommended doses elicited a marked decrease (*P*<0.05) in plasma dopamine level after 8 weeks post administration when compared with normal control group. Propolis and Ginseng treated groups showed non significant changes in plasma dopamine activity after two monthes of administration when compared with normal control group. yet their combinations with either Chlorpyrifos or profenofos elicited a significant increase in plasma dopamine concentration when they were compared with each insecticide alone reverting their values to nearly control values (Table 9) & (Fig. 14).

**3.4.2 Effect on brain Serotonin:**

The administration of Chlorpyrifos and/or Profenofos in their recommended doses for successive 60 days into normal rats elicited a significant decrease (*P*<0.05) in plasma serotonin level compared to normal control group. Whereas a significant increase (*P*<0.05) was observed in the groups treated with either Propolis or Ginseng alone. Whereas, the combinations of either propolis or ginseng with either Chlorpyrifos or profenofos afforded non significant changes when compared with normal control group, indicating that they reverted the serotonin level to nearly it's normal control level (Table 9) and (Fig 14).

**3.4.3 Effect on brain Epinephrine:**

Concerning the effect of Chlorpyrifos and Profenofos on serum epinephrine, Chlorpyrifos and/or Profenofos each alone afforded a significant decrease (*P*<0.05) in serum epinephrine level when compared with normal control group after 8 weeks of the insecticides administration. Meanwhile, treatment with either Propolis or Ginseng and their combinations with either chlorpyrifos or profenofos revealed non significant changes after 8th weeks when compared with normal control group (Table 9) and (Fig. 14).

**3.4.4 Effect on brain nor-Epinephrine:**

The administration of either Chlorpyrifos and/or Profenofos each alone in their recommended doses for successive 60 days into normal rats elicited a significant decrease (P<0.05) in neither plasma nor epinephrine content when compared with normal control group. Meanwhile, non significant changes were reported in groups treated with either Propolis or Ginseng each alone and their combinations with either Chlorpyrifos and/or Profenofos after the end of the experiment when compared with normal control group (Table 9) and (Fig. 14).However, these values were significantly elevated (*P*<0.05) when compared with the groups given the insecticides used alone, indicating a potent ameliorative effect of the test plant extracts.

**3.5 Histopathology:**

**(Group 1): Control group**

**The Brain:** Microscopically: normal gyri and sulci of brain tissue (Fig. 15). Normal brain tissue formed of round and pyramidal shaped neurons surrounded by eosinophilic glial fibers.

**(Group 2): Chlorpyrifos treated group**

**The Brain:** Showed fragments of brain tissue separated by large areas of haemorrhage (Fig. 16). Also seen in (Fig. 17) atrophic brain tissue showing few atrophic neurons with pyknotic nuclei and surrounded by excessive glial tissue.

**(Group 3): Profenofos treated group**

**The Brain:** Dilated congested vascular space filled with red blood cells and compressing brain tissue (Fig. 18).

**(Group 4): Propolis treated group**

**The Brain :**The brain of Propolis treated group showing normal gyri and sulci of brain tissue, (Fig. 19).

**(Group 5): Ginseng treated group**

**The Brain :**Normal brain tissue formed of round and pyramidal shaped neurons surrounded by eosinophilic glial fibers (Fig. 20).

**(Group 6): Chlorpyrifos + Propolis treated group**

**The Brain:** The brain of this group showed dilated mild congested vascular space filled with few red blood cells (Fig. 21).

**(Group 7): Chlorpyrifos + Ginseng treated group**

**The Brain:** Photomicrograph of brain tissue showing normal appearance of sulci of brain tissues with very mild haemorrhage in between the compartments of brain tissues (Fig. 22).

**(Group 8): Profenofos+Propolis treated group**

**The Brain:** Brain tissue showing mild congestion with mild haemorrage in the area between the compartments of brain tissues (Fig. 23).

**(Group 9): Profenofos + Ginseng treated group**

**The Brain:** Photomicrograph of normal brain tissue fragment separated by very mild congested area (Fig. 24).

Table (1): Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Cortisol in male albino rats (mean ± SE). (N = 7).

| | Cortisol (µg/dL) |
|---|---|
| Control group | 1.90±0.23$^{bc}$ |
| Chlorpyrifos | 7.85±0.64$^{a}$ |
| Profenofos | 7.54±0.89$^{a}$ |
| Propolis | 1.81±0.36$^{bc}$ |
| Ginseng | 1.81±0.17$^{bc}$ |
| Chlorpyrifos + Propolis | 2.98±0.72$^{b}$ |
| Chlorpyrifos + Ginseng | 2.81±0.51$^{b}$ |
| Profenofos+ Propolis | 2.96±0.39$^{b}$ |
| Profenofos+Ginseng | 2.86±0.58$^{b}$ |

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test, where the highest mean value has symbol (a) and decreasing in value were assigned alphabetically.

Table (2): Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Catalase in male albino rats (mean ± SE). (N = 7).

| Groups | Antioxidant defense system | | | |
|---|---|---|---|---|
| | plasma Catalase (U/ml) | Liver Catalase (U/g) | Brain Catalase (U/g) | Kidney Catalase (U/g) |
| Control group | 159.92±2.21$^{bc}$ | 4.19±0.01$^{a}$ | 8.18±0.01$^{c}$ | 5.49±0.05$^{b}$ |
| Chlorpyrifos | 77.60±7.16$^{d}$ | 0.50±0.09$^{c}$ | 2.57±0.02$^{f}$ | 12.96±0.05$^{a}$ |
| Profenofos | 64.87±17.73$^{d}$ | 0.41±0.13$^{c}$ | 2.52±0.01$^{f}$ | 12.91±0.05$^{a}$ |
| Propolis | 155.07±0.99$^{c}$ | 4.33±0.03$^{a}$ | 8.23±0.01$^{b}$ | 4.61±0.01$^{c}$ |
| Ginseng | 158.53±1.08$^{c}$ | 4.43±0.04$^{a}$ | 9.24±0.03$^{a}$ | 4.68±0.07$^{c}$ |
| Chlorpyrifos +Propolis | 163.93±1.45$^{b}$ | 3.72±0.03$^{b}$ | 7.42±0.02$^{d}$ | 4.36±0.07$^{d}$ |
| Chlorpyrifos +Ginseng | 167.37±2.47$^{ab}$ | 3.57±0.04$^{b}$ | 6.45±0.02$^{e}$ | 4.41±0.04$^{d}$ |
| Profenofos + Propolis | 175.75±2.25$^{a}$ | 3.72±0.05$^{b}$ | 7.37±0.04$^{d}$ | 4.77±0.07$^{c}$ |
| Profenofos + Gensing | 179.90±3.84$^{a}$ | 3.69±0.02$^{b}$ | 7.41±0.01$^{d}$ | 4.74±0.08$^{c}$ |

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test, where the highest mean value has symbol (a) and decreasing in value were assigned alphabetically.

Table (3): Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Super oxide dismutase (SOD) in male albino rats (mean ± SE). (N = 7).

| Groups | Antioxidant defense system | | | |
|---|---|---|---|---|
| | Plasma SOD (U/ml) | Liver SOD (U/g) | Brain SOD (U/g) | Kidney SOD (U/g) |
| Control group | 108.06±3.70$^{b}$ | 83.32±0.87$^{c}$ | 105.13±0.17$^{c}$ | 102.41±0.79$^{i}$ |
| Chlorpyrifos | 22.91±3.77$^{d}$ | 20.61±1.52$^{de}$ | 194.03±0.23$^{b}$ | 281.59±0.22$^{a}$ |
| Profenofos | 20.22±4.02$^{d}$ | 24.14±2.98$^{e}$ | 196.75±0.15$^{a}$ | 277.76±0.51$^{b}$ |
| Propolis | 100.07±2.26$^{b}$ | 98.82±0.91$^{a}$ | 100.93±0.21$^{e}$ | 110.66±0.18$^{h}$ |
| Ginseng | 120.80±2.03$^{a}$ | 92.94±1.66$^{b}$ | 102.35±0.36$^{d}$ | 112.62±0.22$^{g}$ |
| Chlorpyrifos +Propolis | 81.27±1.90$^{d}$ | 80.92±1.59$^{c}$ | 99.07±0.23$^{e}$ | 147.05±0.24$^{c}$ |
| Chlorpyrifos +Ginseng | 92.90±2.20$^{c}$ | 79.91±0.88$^{c}$ | 95.25±0.09$^{f}$ | 140.25±0.03$^{d}$ |
| Profenofos + Propolis | 95.80±3.92$^{b}$ | 81.18±1.68$^{c}$ | 100.40±0.22$^{e}$ | 130.73±0.16$^{e}$ |
| Profenofos + Gensing | 99.77±10.79$^{b}$ | 82.99±1.10$^{c}$ | 104.64±0.37$^{c}$ | 125.70±0.21$^{f}$ |

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test, where the highest mean value has symbol (a) and decreasing in value were assigned alphabetically.

Table (4): Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Malondialdhyde (MDA) in male albino rats (mean ± SE). (N = 7).

| Groups | Oxidative stress markers | | | |
|---|---|---|---|---|
| | Plasma MDA (nmol/ml) | Liver MDA (nmol/g) | Brain MDA (nmol/g) | Kidney MDA (nmol/g) |
| Control group | 16.50±0.63$^{h}$ | 1.74±0.10$^{d}$ | 10.39±0.05$^{g}$ | 13.27±0.02$^{h}$ |
| Chlorpyrifos | 55.47±1.60$^{a}$ | 8.35±0.26$^{a}$ | 19.53±0.12$^{a}$ | 23.68±0.42$^{b}$ |
| Profenofos | 46.30±1.64$^{b}$ | 8.50±0.66$^{a}$ | 18.51±0.09$^{b}$ | 26.60±0.18$^{a}$ |
| Propolis | 18.04±0.45$^{G}$ | 2.81±0.12$^{c}$ | 14.44±0.07$^{f}$ | 14.42±0.01$^{g}$ |
| Ginseng | 18.39±0.16$^{G}$ | 3.30±0.25$^{c}$ | 15.15±0.02$^{e}$ | 14.79±0.03$^{g}$ |
| Chlorpyrifos +Propolis | 25.52±0.67$^{de}$ | 5.38±0.38$^{b}$ | 17.34±0.10$^{c}$ | 19.27±0.15$^{d}$ |
| Chlorpyrifos +Ginseng | 22.18±0.56$^{f}$ | 5.04±0.26$^{b}$ | 17.43±0.16$^{c}$ | 18.59±0.05$^{e}$ |
| Profenofos + Propolis | 31.69±1.18$^{c}$ | 3.66±0.26$^{c}$ | 16.25±0.07$^{d}$ | 20.10±0.08$^{c}$ |
| Profenofos + Ginseng | 27.74±0.61$^{d}$ | 5.05±0.06$^{b}$ | 17.32±0.14$^{c}$ | 17.75±0.11$^{f}$ |

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test, where the highest mean value has symbol (a) and decreasing in value were assigned alphabetically.

Table (5): Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Glutathione reduced in male albino rats (mean ± SE). (N = 7).

| Groups | Oxidative stress markers | | | |
|---|---|---|---|---|
| | Serum Glutathione reduced (U/L) | Liver Glutathione reduced (U/g) | Brain Glutathione reduced (U/g) | Kidney Glutathione reduced (U/g) |
| Control group | 15.60±0.66$^{e}$ | 26.11±0.75$^{a}$ | 72.38±0.13$^{c}$ | 96.41±0.50$^{a}$ |
| Chlorpyrifos | 8.62±0.47$^{f}$ | 6.12±0.48$^{c}$ | 37.84±0.14$^{G}$ | 44.62±0.30$^{e}$ |
| Profenofos | 3.91±1.34$^{G}$ | 2.99±0.58$^{d}$ | 35.33±0.05$^{h}$ | 39.50±0.43$^{f}$ |
| Propolis | 15.67±0.73$^{e}$ | 28.30±0.94$^{a}$ | 80.49±0.10$^{b}$ | 97.31±0.38$^{a}$ |
| Ginseng | 26.37±0.38$^{c}$ | 27.01±0.82$^{a}$ | 81.42±0.18$^{a}$ | 96.25±0.92$^{a}$ |
| Chlorpyrifos +Propolis | 29.20±0.68$^{b}$ | 26.03±1.56$^{a}$ | 72.55±0.14$^{c}$ | 92.41±0.29$^{b}$ |
| Chlorpyrifos +Ginseng | 31.20±0.37$^{a}$ | 22.77±1.19$^{b}$ | 71.48±0.09$^{d}$ | 97.20±0.53$^{a}$ |
| Profenofos + Propolis | 26.85±0.48$^{c}$ | 24.47±1.70$^{ab}$ | 65.13±0.05$^{e}$ | 89.97±0.20$^{c}$ |
| Profenofos + Ginseng | 23.40±1.01$^{d}$ | 23.48±2.45$^{ab}$ | 62.36±0.11$^{f}$ | 87.99±0.45$^{d}$ |

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test, where the highest mean value has symbol (a) and decreasing in value were assigned alphabetically.

Table (6): Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Glutathione peroxidase in male albino rats (mean ± SE). (N = 7).

| Groups | Oxidative stress markers | | | |
|---|---|---|---|---|
| | plasma Glutathione Peroxidase | Liver Glutathione Peroxidase | Brain Glutathione Peroxidase | Kidney Glutathione Peroxidase |
| Control group | 34.53±0.67$^{a}$ | 33.04±0.74$^{a}$ | 77.22±0.09$^{c}$ | 55.13±0.36$^{h}$ |
| Chlorpyrifos | 5.61±0.47$^{h}$ | 4.99±0.51$^{c}$ | 26.79±0.17$^{f}$ | 143.47±0.36$^{a}$ |
| Profenofos | 9.90±1.19$^{g}$ | 2.64±0.44$^{d}$ | 24.23±0.01$^{G}$ | 138.32±0.40$^{b}$ |
| Propolis | 32.14±0.45$^{b}$ | 34.50±1.34$^{a}$ | 88.46±0.38$^{a}$ | 66.27±0.43$^{g}$ |
| Ginseng | 30.33±0.39$^{c}$ | 35.89±0.82$^{a}$ | 80.20±0.03$^{b}$ | 65.25±0.92$^{g}$ |
| Chlorpyrifos +Propolis | 26.46±0.84$^{d}$ | 22.83±1.00$^{b}$ | 71.24±0.30$^{e}$ | 81.41±0.29$^{d}$ |
| Chlorpyrifos +Ginseng | 28.37±0.45$^{d}$ | 35.70±1.13$^{a}$ | 70.45±0.13$^{e}$ | 96.20±0.53$^{c}$ |
| Profenofos + Propolis | 23.86±0.49$^{e}$ | 29.33±1.68$^{ab}$ | 74.43±0.20$^{d}$ | 78.97±0.20$^{e}$ |
| Profenofos + Ginseng | 20.42±1.02$^{ef}$ | 32.34±2.46$^{a}$ | 71.26±0.03$^{e}$ | 77.00±0.44$^{f}$ |

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test, where the highest mean value has symbol (a) and decreasing in value were assigned alphabetically.

Table (7): Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Nitric oxide (NO) & Glucose -6-Phosphate hydrogenase (G-6-PH) in male albino rats (mean ± SE). (N = 7).

| Groups | Oxidative stress markers | |
|---|---|---|
| | Serum NO (µmol/L) | Serum G-6-PH (µmol/L) |
| Control group | 0.77±0.11$^{bc}$ | 2.18±0.01$^{a}$ |
| Chlorpyrifos | 4.52±0.05$^{a}$ | 0.005±0.001$^{c}$ |
| Profenofos | 5.30±0.21$^{a}$ | 0.006±0.001$^{c}$ |
| Propolis | 0.80±0.25$^{b}$ | 2.16±0.05$^{a}$ |
| Ginseng | 0.85±0.31$^{b}$ | 2.17±0.1$^{a}$ |
| Chlorpyrifos +Propolis | 0.83±0.22$^{b}$ | 2.09±0.003$^{ab}$ |
| Chlorpyrifos +Ginseng | 0.86±0.15$^{b}$ | 2.10±0.002$^{ab}$ |
| Profenofos + Propolis | 0.90±0.35$^{b}$ | 2.07±0.002$^{ab}$ |
| Profenofos + Ginseng | 0.89±0.18$^{b}$ | 2.08±0.005$^{ab}$ |

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test, where the highest mean value has symbol (a) and decreasing in value were assigned alphabetically.

Table (8): Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on plasma Acetylcholinesterase (mmol/min/ml) in male albino rats (mean ± SE). (N = 7).

| Groups | Acetylcholinesterase (mmol/min/ml) |
|---|---|
| Control group | 1486.00±3.52$^{a}$ |
| Chlorpyrifos | 612.60±25.04$^{d}$ |
| Profenofos | 530.80±15.14$^{e}$ |
| Propolis | 1481.80±13.73$^{a}$ |
| Ginseng | 1476.80±7.54$^{a}$ |
| Chlorpyrifos + Propolis | 1363.20±12.13$^{b}$ |
| Chlorpyrifos + Ginseng | 1042.00±16.77$^{c}$ |
| Profenofos + Propolis | 1444.80±14.06$^{a}$ |
| Profenofos + Ginseng | 1059.80±17.48$^{c}$ |

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test, where the highest mean value has symbol (a) and decreasing in value were assigned alphabetically.

Table (9): Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on plasma monamines in male albino rats (mean ± SE). (N = 7).

| Groups | Dopamine (DA) (µg/ml) | Serotonin (5-HT) (µg/ml) | Epinephrine (µg/ml) | Nor-Epinephrine (µg/ml) |
|---|---|---|---|---|
| Control group | 1.09±1.092[a] | 0.66±0.011[b] | 0.66±0.01[ab] | 0.95±0.021[a] |
| Chlorpyrifos | 0.35±0.060[c] | 0.48±0.075[c] | 0.42±0.096[c] | 0.63±0.098[c] |
| Profenofos | 0.45±0.045[c] | 0.47±0.098[c] | 0.40±0.081[c] | 0.60±0.097[c] |
| Propolis | 1.07±0.032[ab] | 0.78±0.030[a] | 0.65±0.096[ab] | 0.98±0.011[a] |
| Ginseng | 1.09±0.030[ab] | 0.77±0.019[a] | 0.66±0.082[ab] | 0.96±0.001[a] |
| Chlorpyrifos + Propolis | 1.10±0.099[a] | 0.67±0.029[b] | 0.69±0.097[a] | 0.87±0.052[ab] |
| Chlorpyrifos + Ginseng | 1.11±0.033[a] | 0.60±0.090[b] | 0.68±0.015[ab] | 0.83±0.043[ab] |
| Profenofos+ Propolis | 0.92±0.018[ab] | 0.68±0.092[ab] | 0.67±0.011[ab] | 0.85±0.032[ab] |
| Profenofos+Ginseng | 1.06±0.044[ab] | 0.66±0.022[b] | 0.70±0.079[a] | 0.88±0.016[ab] |

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test, where the highest mean value has symbol (a) and decreasing in value were assigned alphabetically.

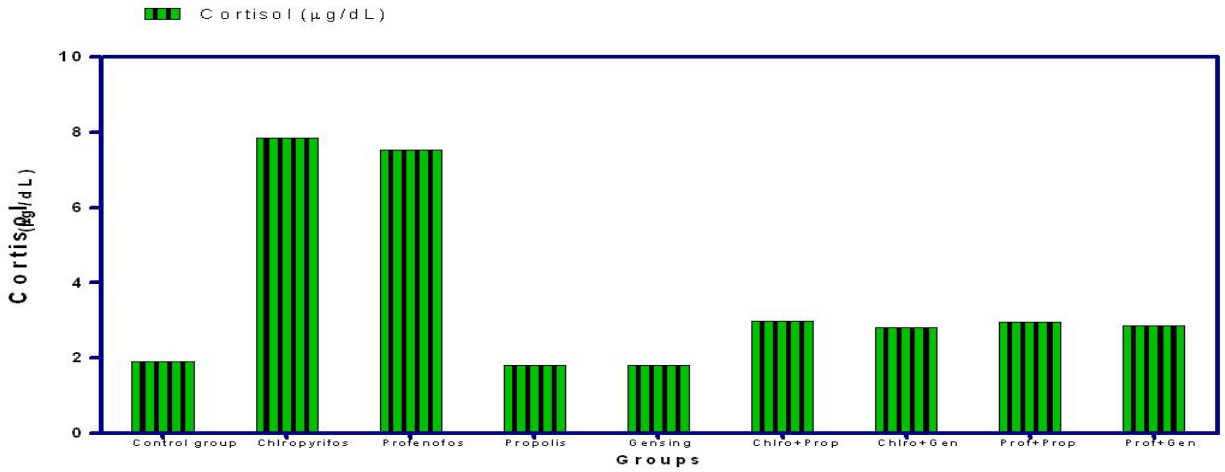



**Fig (1) :** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on monoamines in male albino rats .

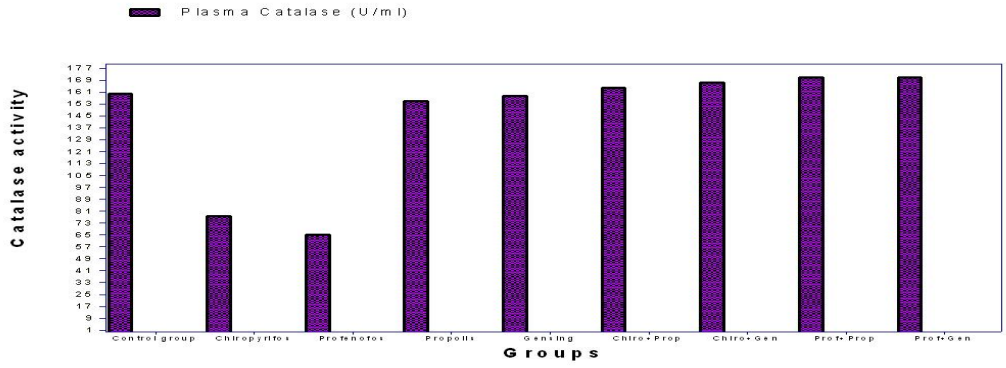



**Fig. (2):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Catalase activity (in plasma) in male albino rats .

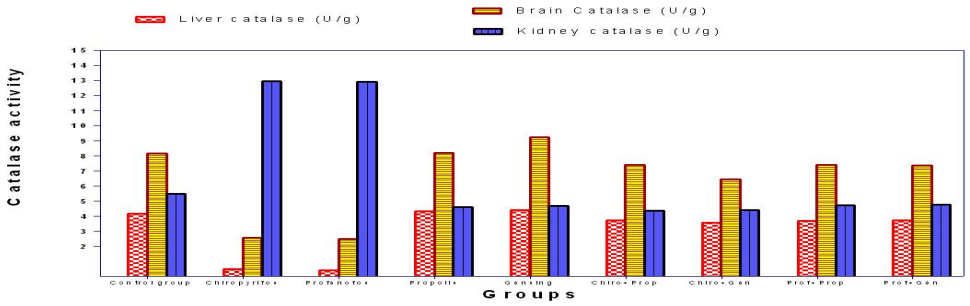



**Fig (3):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Catalase activity (in tissue homogenates) in male albino rats .

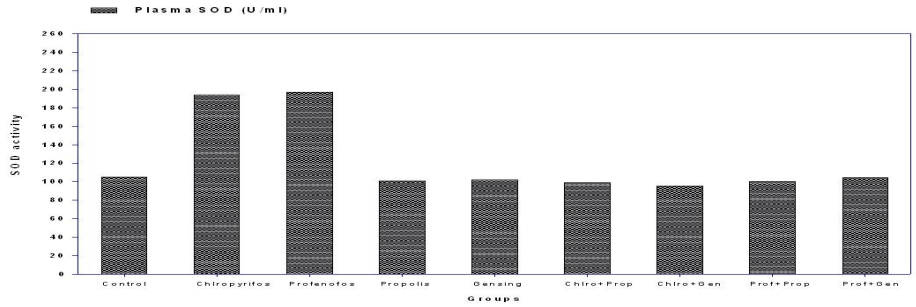



**Fig (4):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on SOD (in plasma) activity in male albino rats .

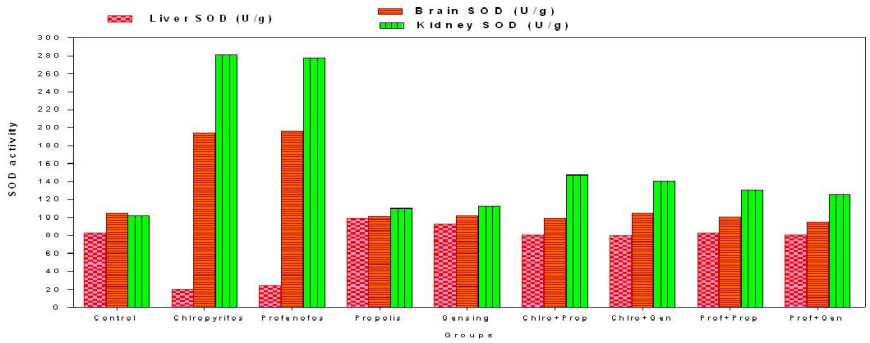



**Fig (5):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on SOD activity (in tissue homogenates)in male albino rats .

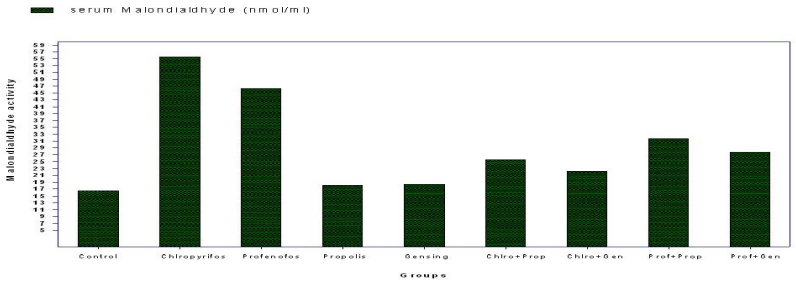



**Fig (6):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Malondialdhyde (MDA) (in plasma) in male albino rats.

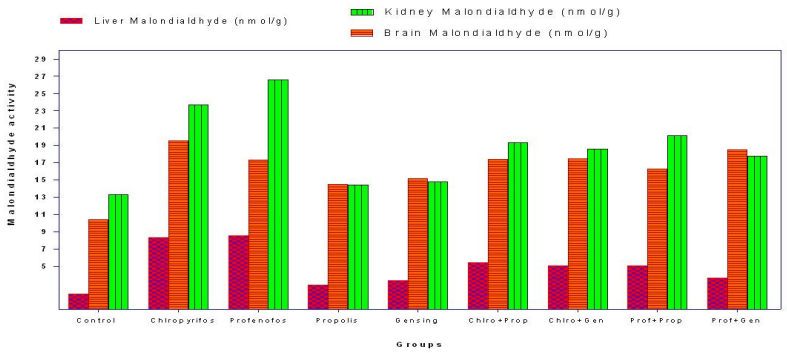



**Fig (7):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Malondialdhyde (MDA) (in tissue homogenates) in male albino rats.

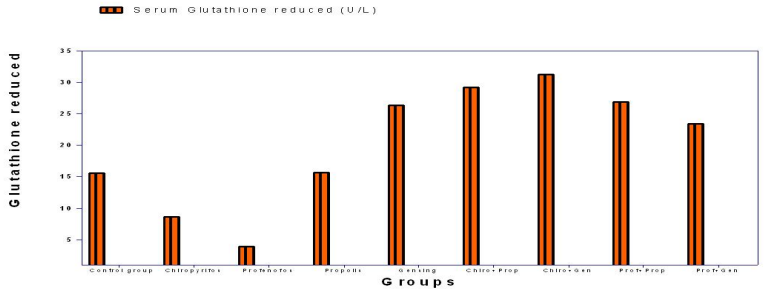



**Fig (8):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Glutathione reduced (in serum) in male albino rats.

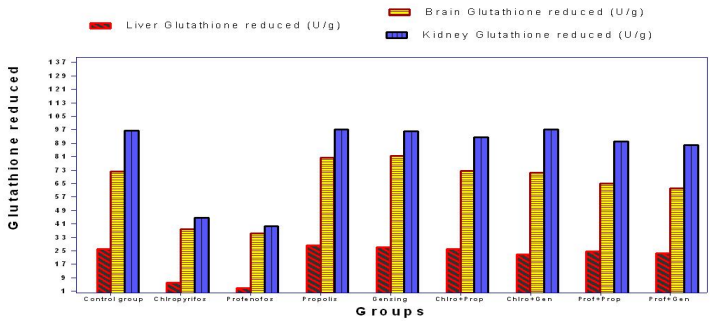



**Fig (9):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Glutathione reduced (in tissue homogenates) in male albino rats.

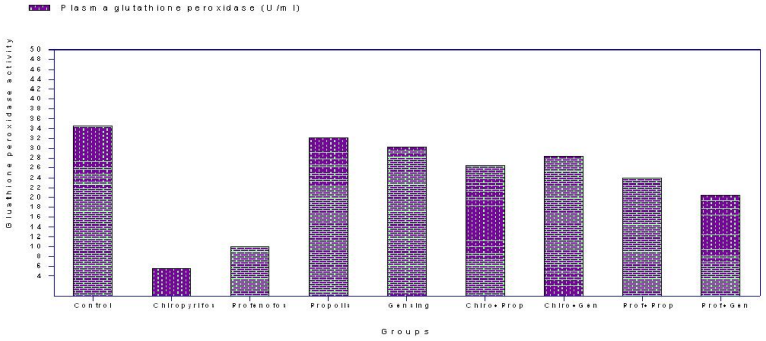



**Fig (10):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Glutathione peroxidase (in plasma) in male albino rats

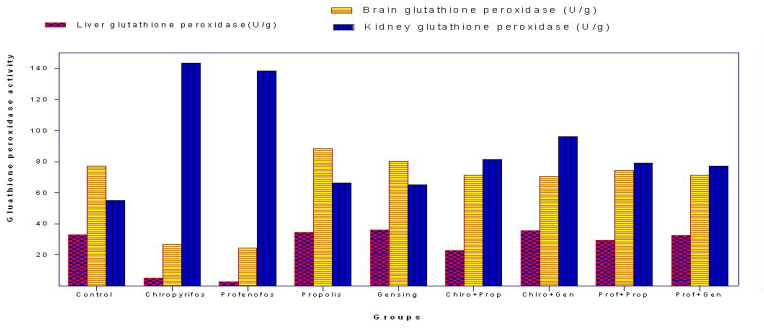



**Fig (11):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Glutathione peroxidase (in tissue homogenates) in male albino rats

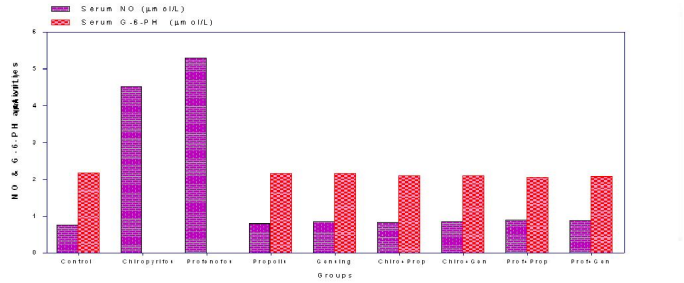



**Fig (12):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on NO & G-6-PH activities in male albino rats.

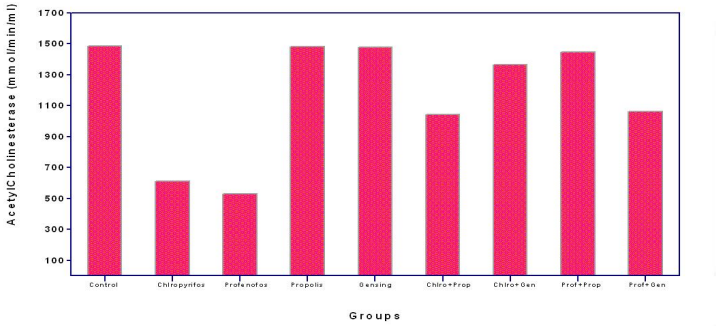



**Fig (13):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on Acetylcholinesterase (mmol/min/ml) in male albino rats.

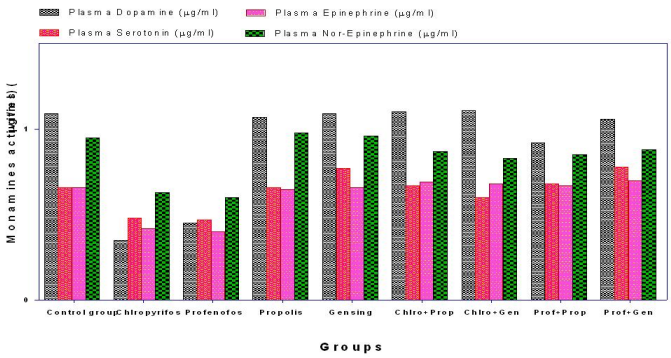
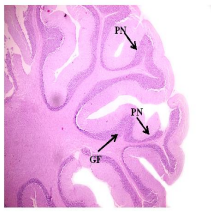
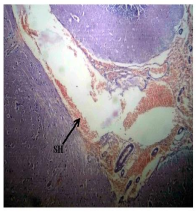



**Fig (14):** Effect of Chlorpyrifos (6.75 mg/kg), Profenofos (20mg/Kg) , Propolis (70 mg/ Kg), Ginseng (200 mg/Kg) and their combinations on plasma monoamines in male albino rats.



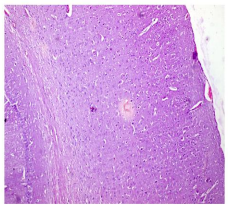

(B)

**Fig. (15):** Cross section of control rat brain of (Group 1) showing normal brain tissues formed of round and pyramidal shaped neurons surrounded by eosinophilic glial fibers (H and E x 400) (PN: Pyramidal neurons, GF: Glial fibers).




(A)

**Fig. (16):** Cross section of rat brain of group (2) treated with chlorpyrifos (6.75 mg/kg) showing fragments of brain tissue separated by large areas of haemorrhage (H and E x 200) (SH: Severe haemorrhage).



(B)

**Fig. (17):** Cross section of rat brain of group (2) treated with chlorpyrifos (6.75 mg/kg) showing atrophic brain tissues with few atrophic neurons with pyknotic nuclei and surrounded by excessive glial tissue (H and E x 400) (ABT: Atrophic brain tissue, PN: pyknotic nuclei ).

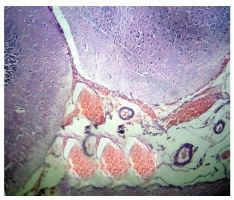


**Fig. (18):** Cross section of rat brain from group (3) treated with profenofos (20 mg/ Kg) showing dilated congested vascular space filled with red blood cells and compressing brain tissue (H&E.X200) (DCVR: Dilated congested vascular space failed with redblood cells).

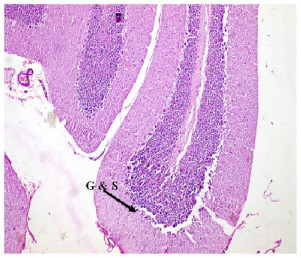



**Fig. (19) :**Cross section of rat brain of group (4) treated with propolis (70 mg/ Kg) with normal gyri and sulci of brain tissue (H and E x 100) (**G & S: gyri and sulci**).

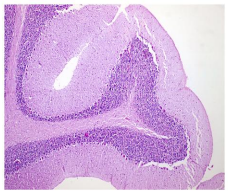


**Fig. (20) :**Cross section of rat brain of group(5) treated with ginseng (200 mg/ Kg) showing normal brain tissue formed of round and pyramidal shaped neurons surrounded by eosinophilic glial fibers (H and E x 200) (PN: Pyramidal neurons).

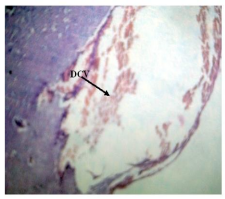
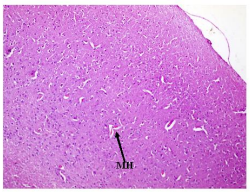
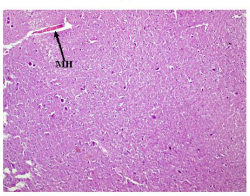



**Fig. (21):** Cross section of rat brain of group (6) treated with (Chlorpyrifos +Propolis) (6.75 mg/kg) & (70 mg/kg) respectively showing dilated mild congested vascular space filled with few red blood cells (H&EX200) (DCV: Dilated congested vein).




(A)




(B)

**Fig.(22):** Cross section of rat brain of group (7) treated with (Chlorpyrifos +ginseng) (6.75 mg/kg) & (200 mg/kg) respectively showing normal appearance of sulci of brain tissues with very mild haemorrhage in between the compartments of brain tissues (H an E x 200) (MH: Mild haemorrhage)..

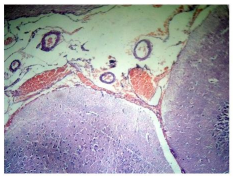


Fig.(23): Cross section of rat brain of group (8) treated with (profenofos + propolis) (20 mg/kg) & (70 mg/kg) respectively showing mild congestion with mild area of haemorrage between the compartments of brain tissues (H&EX200) (MC: Mild congestion).

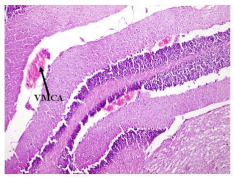



Fig. (24): Cross section of rat brain of group (9) treated with (profenofos + ginseng) (20 mg/kg) & (200 mg/kg) respectively showing normal brain tissues fragment separated by very mild congested area (H and E X 100) (Veri mild congested area).

## 4. Discussion:

Chlorpyrifos (CPF) is an effective organophosphate ( OP) pesticide used heavily throughout the world for agriculture and domestic purposes. The main target of OP pesticides is acetylcholinestcrase (AChE), which hydrolyses acetylcholine (ACh) in cholinergic synapses and at neuromuscular junctions **[38].**This results in the accumulation of ACh in the synapses which in turn induces hyperactivity in cholinergic pathways.

Profenofos caused different symptoms of toxicity and revealed some biochemical changes especially in the enzymes activity of the liver and brain following two sublethal doses of profenofos in mice **[39].**

Natural products are a promising source for the discovery of new pharmaceuticals. In the last decades, several works dealing with propolis' composition and biological properties have been published, revealing the interest of researchers on this bee product and its potential for the development of new drugs **[9].**

The low cost of traditional medicinal plants also raise significant interest to prevent morbidity and mortality from chronic diseases in countries where low or middle income populations are important **[40].**

Increased utilization of medicinal plants became a World Health Organization (WHO) policy in 1970. Plants and herbs are chemical factories that directly provide about 25% of currently used drugs and another 25% of drugs comprise chemically altered natural products **[41]**.

Propolis is a resinous hive product collected by honeybees from plants, showing a very complex chemical composition **[10]**. It has been used in folk medicine since ancient times, due to its many biological properties, such as antibacterial **[11]**, antitumor ***[42,43]***, and immunomodulatory **[44]**, among others.

Ginseng is a well-known medicinal herb in traditional Asian medicine and is considered an adaptogen. *Panax ginseng* C.A. Meyer (Araliaceae), which grows in China and Korea, has a variety of beneficial biological actions that include anti-carcinogenic, anti-diabetic-inflammatory effects, as well as cardiovascular protection and neuroprotection **[45, 46].**

**Effect on Cortisol level:**

It was clearly evident that the administration of Chlorpyrifos and/or Profenofos each alone in their recommended doses daily for successive 60 days afforded a highly significant increase in serum cortisol level after the end of the experiment when compared with control group. Concerning the effect of either Propolis or Ginseng, our results revealed that Propolis and/or Ginseng treated groups showed non significant changes in serum cortisol level when compared with control group. A non significant increase in serum cortisol level was also recorded in response to treatment of male rats with the combinations of either Chlorpyrifos or Profenofos with either Propolis or ginseng compared with normal control group.

Cortisol, a corticosteroid hormone, is considered to be an important physiological effector of homeostasis in all vertebrates, through its effects on metabolism and immune function. **[47]** stated that the decrease of normal cortisol secretion is due to the effects of Organophosphorous on cortisol biosynthesis pathway **[48]** found that an increase in gonadal oxidative stress is generally coincident with decreased levels of β-estradiol.

One of the characteristics of organophosphorous pesticides is induction of stress. Stress is a response to every situation which threatening homeostasis and result in activation of hypothalamic-pituitary-adrenal (HPA) axis and sympathetic autonomic nervous system which conesquently lead to hyperglycemia **[49]**.

Activation of HPA (Hypothalmic–pituitary adrenal) axis causes secretion of glucocorticoids from adrenal cortex. Cortisol increases blood glucose by induction of gluconeogenesis pathway as a result of organophosphorous exposure **[50]**.

**Effect on antioxidant activity:**

Regarding the effect of profenofos and chlorpyrifos on catalase activity of normal rats, chlorpyrifos and profenofos afforded a marked decrease in plasma, liver and brain catalase after the end of the study when compared with control group, whereas, a significant increase in the enzyme activity was recorded in kidney. Treatment of normal rats with either propolis or Ginseng alone exhibited non significant changes in Catalase of liver and plasma after the end of the experiment when compared with control group ,

Whereas , a significant increase was reported in brain and kidney tissues respectively compared with control group .While combinations of Chlorpyrifos, Profenofos with either Propolis or ginseng exhibited a significant decrease in Catalase activity of liver, kidney, plasma and brain after the end of the study except combinations of Chlorpyrifos with either propolis and/or ginseng in the plasma which showed a non significant increase compared with normal control group.The results of our study revealed that treatment of normal rats with either Chlorpyrifos or profenofos elicited a highly significant decrease in serum and liver SOD level after the end of the study together with a marked increase in SOD activity of kidney and brain when compared with control group. Treatment of normal rats with either propolis or ginseng for 8 weeks elicited a significant increase in SOD activity of the liver, Kidney and serum after the end of the study except with ginseng in serum which showed a significant increase compared with control group. Whereas, the combinations of the plant extracts with the test insecticides afforded a significant decrease in SOD activity of the brain and serum, beside a significant increase and non significant changes in the SOD activity of the kidney and liver respectively compared with normal control group. The MDA content of the serum, liver, kidney and brain were significantly elevated in response to treatment of normal male rats with either Chlorpyrifos or profenofos for 8 weeks compared with normal control group. The same previous response was reported with propolis, ginseng and their combinations with either Chlorpyrifos or profenofos compared with control group.

It was apparent from our results that treatment of rats with Chlorpyrifos, Profenofos each alone afforded a significant decrease in serum, liver, kidney and brain reduced glutathione after the end of the study when compared with normal control group. On the other hand, the results revealed that Ginseng and/or Propolis induced a non significant change in reduced Glutathione content of the kidney, liver and serum together with a significant increase in the reduced glutathione content of the brain compared with control group.

The plasma Glutathione peroxidase level was significantly reduced in all groups treated with Chlorpyrifos, Profenofos each alone, propolis, ginseng and their combinations for successive 60 days when compared with normal control group. Whereas, a significant increase was recorded in the enzyme activity of the kidney of all treated groups when compared with control group. The enzyme activity was significantly decreased and increased in the brain tissue in response to treatment with the insecticides and plant extracts used compared with the control group. Together with a significant decrease in the enzyme activity in response to combinations of propolis and/or ginseng with either Chlorpyrifos or profenofos.The enzyme activity in the plasma was markedly decreased in response to treatment with either Chlorpyrifos or profenofos compared with control group. Beside a non significant increase in response to treatments with either propolis or ginseng. Whereas, a non significant change was reported in response to treatments with all combinations used except combination of Chlorpyrifos with propolis which showed a significant decrease compared with normal control group. The serum Nitric oxide and glucose – phosphate dehydrogenase level were significantly elevated in serum , liver , brain and kidney in groups treated with Chlorpyrifos and /or Profenofos each alone .Whereas, Treatment of normal rats with Ginseng, Propolis and their combinations with both Chlorpyrifos and Profenofos afforded non significant changes after the end of the study when compared with normal control group.

Pesticides may also affect the biochemical and physiological functions in living organisms, thereby affecting the membrane integrity **[51]** and may induce in vivo and in vitro generation of reactive oxygen species (ROS)leading to oxidative stress.

Oxidative injury, resulting from excessive release of free radicals, likely contributes to the initiation and progression of brain injury. Therefore, antioxidant therapies as propolis treatment aimed at reducing oxidative stress have received considerable attention **[52]**.

Lipid peroxidation (LPO) is one of the molecular mechanisms involved in pesticide toxicity. Living organisms have a complex antioxidant (enzymatic and non-enzymatic) system to protect against the deleterious effects of free radicals. Activity of the antioxidant defense system can be increased or inhibited under chemical stress, and antioxidant parameters therefore represent biomarkers of interest **[53]**. The enzymes that provide the first line of defense include superoxide dismutase (SOD), catalase (CAT) and glutathione reductase (GR). Reduced glutathione (GSH) is the primary cellular antioxidant (non-enzymatic) and plays an important role in the antioxidation of ROS and free radicals and, as a thiol- containing co-enzyme, in the detoxification of xenobiotic compounds. Glutathione-S transferase (GST) is a group of multifunctional enzymes that catalyze the conjugation of GSH with a variety of electrophilic metabolites that are involved in the detoxification of both reactivintermediates and oxygen radicals **[54]**.

Our results are reinforced by ***Verma & Srivastava (55)***. They reported that Chlorpyrifos is known to produce oxidative stress resulting in the accumulation of lipid peroxidation products in different organs of rats, also authors ***Shadina et al., (56)*** reported that CPF and other OP pesticides have been shown to damage DNA also .The generation of free

radicals constitutes one of the underlying mechanisms of Chlorpyrifos and Profenofos intoxication. Changes in blood MDA levels and SOD, CAT, and GSH-Px activities have been determined to develop due to the generation of free radicals. Since the generation of free radicals also causes red blood cell damage, damage occurs in tissues, primarily in the liver**.** Pesticides are reported to inhibit the enzymatic defense also in rat tissues **[57]**. Thus it can be concluded that these OP pesticides generate oxidative stress by inhibiting both enzymatic and non enzymatic antioxidant defenses. The generated oxidative stress may contribute substantially in the overall toxicity of OP pesticides.

CPF exposure caused an increase in levels of lipid peroxidation in the liver, kidney, spleen, and brain of rats as measured by estimation of thiobarbituric acid reactive substances (TEARS). The increase in the level of TEARS ranged from 30% to 74% in different tissues of rats treated with l00mg CPF/kg body weight for 3 days. When rats were exposed to CPF following the treatment with vitamins, the TEARS level remained almost unaltered in the liver and kidney but was slightly elevated in the brain and spleen of the same animals **[55].**

The results of ***Ehrhart and Zeevalk, (58)*** suggest that ginseng root extract could protect astrocytes from oxidant stress generated by $H_2O_2$ which is consistent with the reports of antioxidant effects observed in ginseng root extracts in other cellular types. Panax ginseng saponins have shown a suppressive action on the lipid peroxidation caused by radical generating systems in tissue preparations, and attenuate lipid peroxidation in the rat liver homogenate.In addition***, Yousef and Salama. (59)*** found that propolis water extract can protect brain cells against oxidative stress-induced death and may exert neuroprotective effects through their antioxidant actions.

***Naval et al., (60)*** have demonstrated the protective effect of a normalized aqueous Panax ginseng root extract on hydrogen peroxide-induced oxidative damage in astrocytic primary cultures. Their results showed that the root of Korean ginseng is endowed with significant antioxidant properties and this is the base for its glioprotection against acute oxidant stress.

**SOD and CAT:**

Our results were in complete accordance with previous findings, but our results showed significant increase in Catalase enzyme in kidney homogenates and as it is well known fact that CAT is the enzyme involved in the breakdown of $H_2O_2$ so this explain the reason of increasing CAT in kidney as the elevation of CAT may be due to a counteraction to scavenge the damaging toxic free radicals which may cause tissues injury and damage. CAT is mainly located in the peroxisomes and is responsible for the reduction of hydrogen peroxide produced from the metabolism of long chain fatty acids in peroxisomes to water and oxygen **[61]**.

In contrary to our result, CAT and SOD activities in liver were increased in chlorpyrifos treated mice probably to dismutate superoxide anions and to decompose $H_20_2$ according to ***(Nagat Aly, et al., [62]***. These data are parallel with ***Yu et al.[63]***. In contrast. ***Bindhumol et al., (64), Banudevi et al.(2006)*** found that bisphenol A and PCB's decreased the activity of both CAT and SOD. Also, our results revealed that CAT enzyme was decreased in brain tissues and this disagrees with ***Verma et al.,(65)*** as they reported that the activities of SOD and CAT were significantly inhibited in all the tissues tested (except SOD in brain) to varying extents, however, pre-treatment with vitamins prevented CPF induced changes. In addition, ***Sayeed et al., (66)*** reported that organophosphorous exposure also causes significant decreases in CAT activities in liver, kidney and gill tissues of *Channa punctatus.*

Our results coincide with ***Kono and Fridovich, (67)***.They reported that the inhibition of CAT activity could be due to the flux of superoxide radicals, resulting in $H_2O_2$ increase in the cell

SOD help to dismutase superoxide radical $0^2$ to hydrogen peroxide ($H_2O_2$) **[68] ,**Thus the increase in CAT activities in the kidney may be in response to $H_20_2$ produced by SOD activity since CAT is responsible for the detoxification of $H_2O_2$ to water .

Our results were greatly reinforced by ***Mates, (69)*** who reported that SOD has been strongly inhibited in brain, this may be due to over production of free radicals .Moreover, the brain is especially vulnerable to oxidative damage because of its high abundance of polyunsaturated fatty acids, and has a relatively low antioxidant defense system. The cause of tissue differences could be due to different rates of free radical generation and different antioxidant potentials in the tissues. At the same time, the results of ***Lin et al.,*** **[70]** were in full agreement with our results (increasing the levels of SOD in brain and kidney) as they reported that profenofos increased the antioxidase activities (SOD, CAT,) earlier than the decease of ChE activity. They suggested that profenofos can result in the increase of the antioxidant enzyme activities which may be earlier diagnostic index in profenofos poisoning.

In accordance with our results, Propolis also induces the activation of antioxidant enzymes such as Superoxide dismutase and catalase (CAT) against free radicals.The antioxidant activity seemed to relate with total flavonoid contents of the extract. Flavonoids are reported to be the most abundant and most effective antioxidant in propolis **[71].**

Our results were in full agreement with ***Naval et al., (60).*** They reported that Ginseng extract had a significant effect on the reduction of astrocytic death

induced by $H_2O_2$.Dose–response experiments revealed that this ginseng extract increased cell viability at a wide range of concentrations. Therefore, they investigated the effects of this extract on antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidases (GPx) and glutathione reductase (GR), on glutathione content (reduced and oxidized forms and red/ox index) and on the intracellular reactive oxygen species (ROS) formation. Exposure of astrocytes to $H_2O_2$ decreased the activities of antioxidant enzymes, and increased ROS formation. Ginseng root extract reversed the effect of almost all of these parameters in $H_2O_2$-injured primary cultures of rat astrocytes.

It was shown that administration of ginseng in humans for 8 weeks decreased MDA while increased SOD and CAT activities. ***Hyunghee et al., (72)*** suggested that ginseng administration elevated antioxidant potential by decreasing MDA level and by increasing SOD and CAT activities as scavengers.

**MDA:**

Levels of MDA, a major oxidation product of poly-unsaturated fatly acids, have been considered to be the most significant indicator of membrane lipid peroxidation arising from the interaction of reactive oxygen types with cellular membranes **[73].**

***Kumar and Ramakrishna (5)*** have reported an increase in MDA levels in chronic Chlorpyrifos intoxication and these findings were in complete accordance with our results.

Increasing level of MDA in our study as a result of treatments with both Chlorpyrifos and profenofos go hand in hand with the results of ***Mecdad et al (74).*** They revealed statistically significant reduction of antioxidant defense enzymes, total antioxidant capacity, while MDA levels showed significant elevations in MDA in insecticides exposed workers.

Furthermore, Exposure of rats to Chlorpyrifos through drinking water resulted in a significant increase in lipid peroxidation and protein oxidation as indicated by the significant increase in MDA content, protein carbonyls and apoptosis levels suggesting that Chlorpyrifos activated the formation of free radicals in cerebral cortex tissue. This is corroborated with the findings which demonstrated that Chlorpyrifos exposure stimulated the generation of reactive oxygen species (ROS) in the brain **[75].**

Our results weren't in agreement with some authors who have underlined the occurrence of alterations in enzyme activities and MDA levels upon the administration of propolis. ***Jasprica et al.,(76)*** have reported Propolis to cause reduction in MDA levels.

**G6PD:**

In contrary to our results, Sub-lethal exposure to Chlorpyrifos caused a significant inhibition in G6PD activity. It is an important enzyme of hexose monophosphate shunt and its function in the mature cells is to generate NADPH, while it is required for conversion of oxidized glutathione to reduced glutathione form that in turn is necessary for membrane integrity of cell membranes. This might be the possible reason for the increased fragility of cells upon treatment with different pesticides. It is well documented in literature that treatment with Organophosphorous insecticides such as Chlorpyrifos results in a decrease in GSH levels, thereby decreasing G6PD activity **[65]**.

**Glutathione:**

GSH is an important naturally occurring antioxidant, which prevents free radical damage and helps detoxification by conjugating with chemicals. In addition, GSH is central to the cellular antioxidant defenses and acts as an essential cofactor for antioxidant enzymes including GPx, GR and GST. Under oxidative stress, GSH is consumed by GSH related enzymes to detoxify the peroxides produced due to increased lipid peroxidation **[77].**

Our results showed marked decrease in glutathione enzyme and these results were in full agreement with ***Rana et al., (78).*** They reported that glutathione deficiency contributes oxidative stress, which plays a key role in aging and the pathogenesis of many diseases including seizures, Alzheimer's disease, Parkinson's disease, liver disease, cystic fibrosis, sickle cell anemia, AIDS, cancer, heart attack, stroke and diabetes. GSH is also a substrate of enzymes, glutathione peroxidase and glutathione-S-transferase.

It has been reported also that the long-term treatment with OP causes a gradual depletion of GPx, and GST **[79].**

Our results were compatible also with ***Fang et al., (80).*** They reported that a considerable decline in GSH content in the tissue may be due to its utilization to challenge the prevailing oxidative stress under the influence of ROS generated from MP and CPF oxidative stress. However, oxidative stress can induce GSH rising by protective role in the organisms exposed to chemicals. Reduced GSH and its metabolizing enzymes provide the foremost defense against ROS-induced cellular damage**.**

Meanwhile, the administration of profenofos caused a significant decrease in the levels of glutathione peroxidase (GPx) and reduced glutathione (GSH), and an increase in the lipid peroxidation (LPO) level **[81]**.

Similar results were recorded by **[82].**They reported that inhibition of GST was observed in brain

Furthermore, a reduction in GSH levels led to a significant induction of GST activity during most of the exposure period. GST has been strongly inhibited by exposure to profenofos, whereas GST was induced in fish after exposure to profenofos **[83].**

Similar kind of results (inhibitionin GR) and GSH depletion were observed in fish after exposure to profenofos. Glutathione was depleted in all the tissues,

an indication of severe oxidative stress, and may lead to lipid peroxidation and tissue damage. Glutathione is the major low-molecular-weight, non-enzymatic antioxidant **[23].**

**Nitric oxide (NO):**

Concering the effect on No production.our results are greatly reinforced by ***Orsi et al.,(84).*** They demonstrated that caffiec acid (The main component of propolis) can acts as a prooxidant and an effective irreversible inhibitor of glutathione S-transferases that causes a decrease of generation of NO by activated macrophage.

**Effect on Acetylcholinesterase enzyme activity:**

It was clear from our results that the administration of either Chlorpyrifos or Profenofos each alone to normal rats for successive 60 days afforded a marked decrease in serum acetylcholinesterase activity after two monthes post administration. Whereas, a non significant change in serum Acetylcholinesterase activity was observed in the groups treated with either Propolis or Ginseng.

At the meantime, a significant decrease was recorded in the groups treated with the combinations of the insecticides used with either Propolis or ginseng after 8 weeks post administration except the combination of Profenofos with Propolis which showed a non significant change compared with control group. Yet the results of the drugs combinations were much higher than that produced with the insecticide alone indicating a good ameliorating effect with the used plant extracts.

OP pesticides compounds are known to induce toxicity in mammals by inhibiting acetylcholinesterase (AChE), which leads to the accumulation of acetylcholine and the subsequent activation of cholinergic muscarinic and nicotinic receptors. OP pesticides are also known to inhibit pseudocholinesterase activity. Other systems that may be affected by OP pesticide exposure are the immune system **[85]**, pancreas **[86],** liver, Kidney **[87]**, hematological system **[88]** and reproductive system **[89].**

The main target to OP pesticides is Acetylcholinesterase (ACHE) which hydrolyses acetylcholine (Ach) in cholinergic synapse and in neuromuscular junctions where this enzyme plays a key role in cell to cell communication, **[90].**

Our results were in full agreement with ***Abbassy et al., (91).*** They showed that plasma cholinesterase activity of rats fed single doses of Chlorpyrifos (32 mg/kg body) was significantly reduced after 24 hours post feeding, CPF also inhibits ACHE irreversibly. It can cause acute poisoning and well known symptoms include myosis, increased urination, diarrhea, diaphoresis, lacrimation and salivation.

On the same basis, CPF is metabolized by microsomal mixed function oxidase system to active oxon metabolites which are more potent inhibitor of acetylcholinesterase. Besides being potent anticholinestrase compound, CPF is reported to affect adversely the membrane signal transduction, brain development, neurotransmitter receptor and release of neurotransmitters. CPF is also a potent anticholinergic agent and affects other metabolic events, like changes in membrane lipid physicochemical properties, monoaminergic system, and reproductive system and DNA damage **[92].**

The toxicity of Chlorpyrifos is attributed to inhibition of the enzyme acetylcholinesterase and it is well known that the classical role of acetylcholinesterase is to hydrolyze the neurotransmitter acetylocholine, effectively clearing it from the synapse and terminating impulse conduction. There is, however, a growing body of literature suggesting a role for acetylcholinesterase and butrylcholinesterase in development **[93].**

**Effect on plasma monoamines activity:**

Treatment of normal rats with either Chlorpyrifos or Profenofos for 60 successive days in their recommended doses elicited a marked decrease in plasma dopamine level after 8 weeks post administration when compared with normal control group. Propolis and Ginseng treated groups showed non significant changes in plasma dopamine activity after two monthes of administration when compared with normal control group. Yet their combinations with either Chlorpyrifos or profenofos elicited a significant increase in plasma dopamine concentration when they were compared with each insecticide alone reverting their values to nearly control values.

The administration of Chlorpyrifos and/or Profenofos in their recommended doses for successive 60 days into normal rats elicited a significant decrease in plasma serotonin level compared to normal control group. Whereas a significant increase was observed in the groups treated with either Propolis or Ginseng alone. Whereas, the combinations of either propolis or ginseng with either Chlorpyrifos or profenofos afforded non significant changes when compared with normal control group, indicating that they reverted the serotonin level to nearly it's normal control level .Concerning the effect of Chlorpyrifos and Profenofos on serum epinephrine, Chlorpyrifos and/or Profenofos each alone afforded a significant decrease in serum epinephrine level when compared with normal control group after 8 weeks of the insecticides administration.

Meanwhile, treatment with either Propolis or Ginseng and their combinations with either Chlorpyrifos or profenofos revealed non significant changes after $8^{th}$ weeks when compared with normal control group.The administration of either Chlorpyrifos and/or Profenofos each alone in their recommended doses for successive 60 days into normal rats elicited a

significant decrease in plasma norepinephrine content when compared with normal control group.

Meanwhile, non significant changes were reported in groups treated with either Propolis or Ginseng each alone and their combinations with either Chlorpyrifos and/or Profenofos after the end of the experiment when compared with normal control group.

However, these values were significantly elevated when compared with the groups given the insecticides used alone, indicating a potent ameliorative effect of the test plant extracts.On the same basis, our results were supported by ***Parvez & Raisuddin (94)*** Changes in plasma neurotransmitter levels of the treated groups might be due to the selective block plasma membrane reuptake of these amines. It is known that, plasma membrane uptake process is the key for termination of many neurotransmitters as well as, the allowance for their reuse. As recorded by several investigators, catecholamine are 12 TMD (transmembrane-spanning domain) protein that driven by inward of gradient $Na^+$ and the transporters for NE and DA require $Na^+$ which may be altered by Organophosphorous including Chlorpyrifos **.** Concerning the MAO activity, the present study revealed that chlorpyrifos treatment caused a decrease in MAO activity in most of animals. Furthermore, several lines of evidence indicate that organophosphorous compounds are strong inducers for catecholamine release.

In contrary to our results, the significant increase in brain serotonin observed following Chlorpyrifos administration might be attributed to the fact that liver damage induced by organophosporous insecticides evidenced in our study increased ammonia concentrations which could lead to increased brain uptake of the aromatic amino acid as tryptophan. Since tryptophan is the amino acid precursor of serotonin, its hydroxylation is the rate-limiting step in serotonin synthesis and in turns increased brain serotonin synthesis **[95]**.

Our results also were consistent with ***Aldridge et al., (96).***They showed that Chlorpyrifos exposure during early and late gestation have also shown to elicit both short- and long-term changes in serotonin (5HT) systems, disrupting the ability of 5HT to modulate adenylyl cyclase.The elevated levels in plasma catecholamines (DA & NE) could be attributed to the effect of Chlorpyrifos on chromaffin cells which secrete catecholamines (DA & NE) that might be increased after Chlorpyrifos treatment and this disagree with our obtained results. Moreover, Chlorpyrifos can elicit vigorous autonomic and neuroendocrine response due to an indirect action on the hypothalamic-pituitary adrenal axis leading to increased plasma corticosteroid levels and, catecholamines content.In contrast to our obtained results, ***Santoni et al., (97)*** reported that organophosphorous compounds induced marked and long lasting increase in epinephrine and nor epinephrine plasma concentrations.

At the same time, Ginsenoside Rgi was shown to interrupt dopamine-induced elevation of reactive oxygen species (ROS) or NO generation **[98]**.

Our results were supported by ***Kim et al., (99).*** They reported that ginsenosides Rb1, Rg1, Rc, and Re inhibited tyrosine hydroxylase activity and exhibited anti-dopaminergic action since they reduced the availability of dopamine at presynaptic dopamine receptors.

## 5. Conclusions

From the obtained results, we report that both organophosphorous insecticides either Chlorpyrifos or profenofos have very dangerous and toxic effects, since they showed many side effects represented by high level of antioxidant enzymes and decreasing acetylcholinesterase enzyme. Moreover, the damage in tissues of brain.

## 6. Recommendations

So we recommend the use of the combination of propolis and ginseng which is known as antioxidants compounds in order to ameliorate the possible side effects caused by insecticides that we exposed to them to avoid the proven hazardous effect of insecticides on biochemical parameters and to overcome the side effects of both Chlorpyrifos and profenofos on liver.

## Conflict of interest

The authors declare that there are no conflicts of interest.

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