

Protective Effects of Curcumin for Oxidative Stress and Histological Alterations Induced by Pyrethroid Insecticide in Albino Rats

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ABSTRACT

Background: esfenvalerate(esfen) is a type II of synthetic pyrethroid that has replaced other groups of insecticides due to its improved insecticidal potency. The objective of this study was to investigate the toxicity of pyrethroid insecticides on liver tissues of rats and the possible role of antioxidant plant (curcumin) as a protective agent against oxidative stress and histological alterations.

Material and methods: forty male albino rats were divided into 8 groups of 5 rats /each: G1: served as control and G2: served as positive control received (100mg/kg curcumin), G3,G4 and G5 had oral administration (1/20 LD50, 1/40 LD50 and 1/60 LD50 of esfenvalerate) respectively and the last three groups(G6,G7and G8) were received the same doses of pesticide plus 100mg /kg curcumin for 28 days daily.

Results: exposure of rats to (esfen) induced significant increase in the levels of MDA and significant decrease in total protein, GSH, SOD and catalase whilst the insecticides doses plus curcumin showed decrease in MDA for high and medium dose and ameliorated the reduction of total protein concentration in low dose. We showed that curcumin acts as an effective antioxidant for esfen pesticide toxicity by reducing oxidative stress burden and histological damage.

Keywords: esfenvalerate, pyrethroid, curcumin, oxidative stress.

INTRODUCTION

Pyrethroid pesticides such as cypermethrin and Fenvalerate show high toxicity to a wide range of insects, including some pesticide resistant strains and low toxicity to mammals and birds but when administered at a high dose, pyrethroids produce evident neurotoxicity in mammals. However, the current information is not sufficient to adequately assess the risk posed by fenvalerate to non-target organisms, though some work has been done to assess its toxicity to non target species.¹ Synthetic pyrethroids, a group of neurotoxic insecticides have emerged as a new class of agricultural pesticides showing high toxicity to a wide range of insects including resistance strains and low toxicity to mammalian and birds.² Fenvalerate is the most widely used compound of the cyanophenoxy-benzyl group of the synthetic pyrethroid pesticides and it is used in agriculture to protect a wide variety of crops including cotton, soybeans, corn, vegetables, apples, peaches, pears and nuts from insect pests.³ Oxidative stress is ultimately defined as "the

imbalances in the equilibrium between pro-oxidants/antioxidants status in cellular systems, which results in damaging the cells." Cells have an intact oxidation process to detoxify the cellular environment from oxidants, and thus create the equilibrium in oxidants and antioxidants from aerobic metabolism. The formation of pro-oxidants is readily balanced by antioxidants by a similar rate. The failure in the neutralization events of oxidative status result in oxidative stress which leads to the cell death by lipid peroxidation, carbohydrates oxidation, protein oxidation and nucleic acid oxidation.⁴ Reactive oxygen species (ROS) are formed and degraded by all aerobic organisms, leading to either physiological concentrations required for normal cell function, or excessive quantities, the state called oxidative stress. As the term ROS implies, intracellular production of those oxygen intermediates threatens the integrity of various biomolecules including proteins⁵ lipids as well as lipoproteins involved in atherosclerosis⁶ and DNA⁷. Oxidative stress is also proposed to be involved in the process of aging both by

inducing damage to mitochondrial DNA and by other mechanisms.⁸

Oxidative stress causes damage to cellular macromolecules such as nucleic acids, proteins, and lipids. Among these targets, the peroxidation of lipids is particularly more damaging because the formation of lipid peroxidation products leads to a facile propagation of free radical reactions. Abstraction of a hydrogen atom from the Poly Unsaturated Acid (PUFA) moiety of membrane phospholipids initiates the process of lipid peroxidation. It can be categorized into primary antioxidants and secondary antioxidants. SOD, Catalase and Glutathione peroxidase are the primary antioxidant enzymes which inactivate the ROS into intermediates. Besides the antioxidant enzymes, primary antioxidants are water soluble and lipid soluble.⁹ Antioxidant enzymes, mainly Superoxide dismutase(SOD) and Catalase (CAT) are the first line of defence against free radical induced oxidative stress. SOD is responsible for catalytic dismutation of highly reactive and potentially toxic superoxide radicals to hydrogen peroxide, and CAT is responsible for the catalytic decomposition of hydrogen peroxide to molecular oxygen and water.¹⁰ The reduced glutathione is also involved in the detoxification of many toxic peroxides, by supplying these compounds with protons, transforming them into primary alcohols in the presence of glutathione peroxidase.¹¹ In the process of these detoxifying reactions, the reduced glutathione (GSH) oxidizes into the oxidized form (GSSG), so its level in the cells decreases.¹² Curcumin (CMN), a phenolic phytochemical responsible for the yellow colour of turmeric(*Curcuma longa*), has been designated to be a forceful anti-inflammatory, anti-cancer and antioxidant agent, and is under preclinical trial for cancer prevention.¹³ It also has potential therapeutic effects against neurodegenerative, cardiovascular, pulmonary, metabolic and autoimmune diseases.¹⁴ In addition, CMN exerted hepatoprotective effects in various animal models of liver injury such as carbon tetrachloride.¹⁵ The present study aim to investigate the toxic effects of esfenvelerate on liver and the possible amelioration effect of curcumin.

Material and Methods:

Chemicals pesticide Esfenvelerate (purity 5%) was obtained from Kafr EL Zayate Pesticides & Chemicals and antioxidant material Curcumin (purity 98% total curcuminoid content) was obtained from Alfa Aesar Tumeric rhizome (C₁₂ H₂₀ O₆) and was dissolved in corn oil . animals

Forty Animals. Healthy male Wistar rats were obtained from Animal Breeding House of the Research Institute of Ophthalmology ,Giza, Egypt. Rats were housed in clean plastic cages with free access to food (standard pellet diet) and tap water *ad libitum*, under standardized housing conditions(12 h light/dark cycle, the temperature was 23 ± 2°C, and a minimum relative humidity of 44%) in the laboratory animal room, body weight range of 145–155 g before being used for this study.

Experimental Design

Animals were caged in 8 groups(5 animals for each group), they had oral administration of insecticide or curcumin by gastric tube daily for 28 days. G1 [negative control], G2 [positive control (100mg/ kg curcumin)], G3[1/ 20 LD50 of esfenvelerate], G4[1/ 40 LD50 of esfenvelerate], G5[1/ 60 LD50 of esfenvelerate], G6[1/ 20 LD50 of esfenvelerate+ (100mg/ kg curcumin)], G7[1/ 40 LD50 of esfenvelerate+ (100mg/ kg curcumin),] and G8 [1/ 60 LD50 of esfenvelerate+ (100mg/ kg curcumin)].

Samples preparation

Blood was collected from the retro-orbital plexus vein according to Schermer¹⁶ on heparinized tubes at 28 days of treatment periods . plasma samples were separated by centrifugation of the blood samples at 3600 rpm for 15 min . Plasma samples were kept at – 20°C for determination of total protein and malondialdehyde levels . At the end of the experiment , animals were scarified and samples of liver tissue washed with saline solution, weighed, cut in small parts, homogenized in 10% (w/v) ice cold 100 mmol/L phosphate buffer (pH 7.4) and centrifuged at 4 500 r/min for 15 min at 4 °C, then the supernatant was obtained and used for antioxidant enzyme measurements (SOD, catalase) and GSH.

Total protein

Plasma total protein concentration was determined calorimetrically according to methods adopted by Domas.¹⁷

Lipid Peroxidation.

Lipid peroxidation was determined according to methods Buege and Aust.¹⁸ It was estimated by measuring thiobarbituric acid reactive substances (TBARS) and was expressed in terms of malondialdehyde (MDA) content by a colorimetric method according to Satoh.¹⁹

Antioxidant Enzymes and GSH

Superoxide dismutase activity was determined according to the method of Nishikimi *et al.*²⁰

Catalase activity was determined according to the method of Aebi²¹

GSH level in the liver was assessed according to the method of Beutler.²²

Histological study

Autopsy samples were taken from the liver of rats in different groups and fixed in 10% formal saline for twenty four hours. Washing was done in tap water then serial dilution of alcohol (methyl, ethyl and absolute ethyl) were used for dehydration. Specimens were cleared in xylene and embedded in paraffin at 56 degree in hot air oven for twenty four hours. Paraffin bees wax tissue block were prepared for sectioning at microns thickness by sledge microtome. The obtained tissue sections were collected on glass slides, deparaffinized, stained, stained by hematoxylin & eosin stain for routine examination then examination was done through the light electric microscope Banchroft *et al.*²³

Statistical Analysis

The results were expressed as mean \pm standard error of means. The data were statistically analyzed using (ANOVA ONE WAY) the program statistical package for social sciences (SPSS) version 17. The data means were considered different at $p < 0.05$.

RESULTS

Total protein concentration

The data presented in Table (1) showed that esfenverlate treatment alone caused significant decrease in all doses when compared with control. Esfenverlate combined with curcumin showed significant decrease in high and medium doses and had no statistically significant in low dose among treatment groups

and control. Comparing between esfenverlate treatment alone and esfenverlate combined with curcumin revealed that antioxidant material ameliorated the reduction of total protein concentration in low dose to reach level to normalize.

The obtained data in table (1) recorded that esfenverlate induced significant increment in high and medium doses but no significant change in low dose compared to control, while esfenverlate combined with curcumin caused no significant change in all doses in comparison with control rats, which was indicated that curcumin modulated the increment of MDA in high and medium doses to nearly normal value.

Glutathione (GSH) levels

The data present in table (2) showed that esfenverlate alone caused significant decrease in high dose and non significant change in medium and low doses compared with control. Esfenverlate plus curcumin showed no significant change in all doses. Comparing between esfenverlate treatment alone and esfenverlate combined with curcumin reflected that curcumin improved in high dose to reach normal level.

Catalase (CAT) activity

The present study in table (2) revealed significant decrement in catalase activity in all doses for esfenverlate treatment and the same significant decrease in high and medium doses with esfenverlate plus curcumin which reflected that curcumin did not achieve good treatment for esfenverlate in both doses and improved low dose only superoxide dismutase (SOD) activity.

The obtained data in Table (2) indicated significant decrease in all doses of esfenverlate treatment when compared with control groups in SOD activity while comparing between esfenverlate plus curcumin treatment showed non-significant change when compared with control in all doses which recorded that antioxidant material ameliorated the decrement SOD activity to reach normal control.

3.6 Histological results

Microscopically, liver of control (G1) showed no histopathological alterations and normal histological structure of the portal vein in the portal area and hepatocytes apparent (fig .6).

While in (G3) was noticed degenerative change in the hepatocytes in diffuse manner associated with dilatation and congestion were noticed. Few inflammatory cells infiltration in the portal area (Fig.7).and In (G4) The hepatocytes showed degenerative change associated with sever congestion in the portal vein and oedema in the portal area (Fig.8). Sever dilatation and congestion were detected in the central and portal veins in Low doses (G5)in (Fig9).

On the other hand , rat treated curcumin (G2) only revealed no histopathological alteration as recorded in (Fig.10). and 1/20 LD50 of esfenvelerate plus curcumin(G6) was showed Diffuse kupffer cells proliferation was detected in between the hepatocytes associated with dilatation in the central vein (Fig.11).whilst (G7) and (G8) was showed vacuolar degeneration in the hepatocytes(Fig.7)

DISCUSSION

Most toxic chemical are metabolized in liver and these may lead to liver injuries.²⁴ Decrease in antioxidant enzyme activity was concomitant with decrease in the total protein content in the rat brain. Decrease in total protein contents may be due to the inhibition of protein synthesis and low cell survival due to defective antioxidant enzyme²⁵. Curcumin reduces the oxidative stress in animals, by its high ROS scavenging capacity and by protecting the antioxidant enzymes from being denatured.²⁶ Similar studies indicated the reduction of total protein concentrations when use pyrethroids.^{27 28 25}

Lipid peroxidation is a chemical mechanism capable of disrupting the structure and function of the biological membranes that occurs as a result of free radical attack on lipids.²⁹ The induction of oxidative stress and alteration of antioxidant system by pyrethroids in animals and fishes have been reported.³⁰ Curcumin was shown to inhibit lipid peroxidation in rat liver microsomes preparation as well as in rat brain homogenate where Curcumininiod actually exhibited more potent antioxidant activity than alpha tocopherol.³¹ Several studies agreed with our results which reported increment in malondialdehyde when used pyrethroid as toxic material in rats.^{32 33 34 35}

GSH acts as a direct free radical scavenger as well as co-substrate for Glutathione peroxidase

(GPx) and GST to react with the highly reactive free radicals and organic peroxides.³⁶ The level of GSH was reduced in liver of rats treated with Fenvalerate.³⁷ Curcumin has also been recorded to raise the levels of the significant antioxidant, glutathione . A low dose administration of curcumin elicited the dual adaptive response of an instant enhancement in GSH and the knack for producing an increased amount glutathione .The effects of curcumin can be attributed to its affinity for inducing Messenger RNA (mRNA) of the GSH biosynthetic genes. ³⁸ Our data are in line with several studies which reported a reduction in GSH content of rats exposed to a mixture of synthetic pyrethroids and organophosphate insecticides.

Some investigations indicated that mammalians have a good defense mechanism for lipid peroxidation because it can increase the hepatic CAT activity when needed. However, CAT is generally localized in peroxisomes and therefore its role in the other parts of cell is limited. In particular, H₂O₂ at low concentration is destroyed by this enzyme.³⁰ Cells had several biological defense mechanisms against intracellular oxidative stress. Enzymatic antioxidant defense system includes superoxide edismutase (SOD), catalase (CAT), glutathioneperoxidase (GPx), glutathione reductase (GR) and glutathione transferase (GST) and non-enzymatic antioxidants such as reduced glutathione (GSH),vitamins C and E.³⁹ According to WHO⁴⁰, pyrethroids indirectly generates various ROS such as superoxide radical and hydroxyl radical, and reactive nitrogen species (RNS) such as peroxy nitrite and nitric oxide . This depression of antioxidant enzyme activities reflects failure of the antioxidant defense mechanisms to overcome the influx of ROS induced by Lambda-cyhalothrin (exposure that leads to accumulation of free radicals and facilitate the enhancement of Lipid peroxidation , which in turn increases the oxidative damage to the brain tissue.⁴¹ Similar studies were reported on experimental animals showing significant decrease in catalase and superoxide dismutase activity as a result of exposure pyrethroid. For instance , Kale *et al.*,³² found a decrease in catalase and superoxide dismutase activity when treated rats at a single dose of the pyrethroids

cypermethrin (25g /kg) and fenvalerate (4.5g/kg) and Sakr and Al-Amoudi,³³ reported that deltamethrin doses caused a significant decrement in the activities of SOD and CAT. Also Ali⁴² administered orally male rats Lambda-cyhalothrin at a dose of 4.2 or 8.4 mg/Kg b.w for 4 weeks daily.who showed significant inhibition in antioxidant defense enzymes (superoxide dismutase SOD and catalase CAT activity).

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Table 1. Effect of esfenvelerate alone and esfenverate with curcumin on total protin (g /100ml) and malondialdehyde (nmol/ml) in plasma male rat.

Treatment	Total protein	MDA
G1 negative control	7.53± 0.15	3.25±0.18
G2 positivecontrol	6.33±0.25	4.03±0.32
G3 1/20 LD50 of esfenvelerate	4.78±0.44 a	7.79±0.09a
G4 1/40 LD50 of esfenvelerate	5.15±0.42 a	4.93±1.21a
G5 1/60 LD50 of esfenvelerate	5.56±0.43 a	3.69±0.26
G6 1/20 LD50 of esfenvelerate+curcumin	5.64± 0.76 b	4.51±0.88 c
G7 1/40 LD50 of esfenvelerate+curcumin	5.83±0.52 b	4.01±0.06
G8 1/60 LD50 of esfenvelerate+curcumin	6.15±0.87 c	3.57± 0.15

All data are expressed as means±SE; a significant different between esfenverate treatment alone and control(p<0.05). b significant different between esfenverate treatment with curcumin and control(p<0.05).c significant different between esfenverate treatment alone and esfenverate treatment with curcumin(p<0.05).

Table 2. Effect of esfenvelerate alone and esfenverate with curcumin on glutathione reduced (mg/g.tissue) , catalase activity(U/g) and superoxide dismutase (U/ ml)in liver male rat.

TREATMENT	GSH	CAT	SOD
G1 negative control	12.82± 0.17	4.48±0.17	312.71± 3.72
G2 positivecontrol	14.27±0.15	4.10±0.14	306.88±2.63
G3 1/20 LD50 of esfenvelerate	10.63±0.06 a	2.63± 0.28a	195.21±2.30 a
G4 1/40 LD50 of esfenvelerate	13.07±0.72	2.98±0.03a	258.15±8.73 a
G5 1/60 LD50 of esfenvelerate	12.65±0.36	2.95±0.08a	248.00±8.60 a
G6 1/20 LD50 of esfenvelerate+curcumin	12.88±0.51 c	2.99±0.05b	280.27±7.24c
G7/40 LD50 of esfenvelerate+curcumin	13.81±0.35	3.11±0.03b	262.48± 1.02c
G81/60 LD50 of esfenvelerate+curcumin	13.13±0.36	3.57± 0.08c	264.99±1.63c

All data are expressed as means±SE; a significant different between esfenverate treatment alone and control(p<0.05). b significant different between esfenverate treatment with curcumin and control(p<0.05).c significant different between esfenverate treatment alone and esfenverate treatment with curcumin(p<0.05).

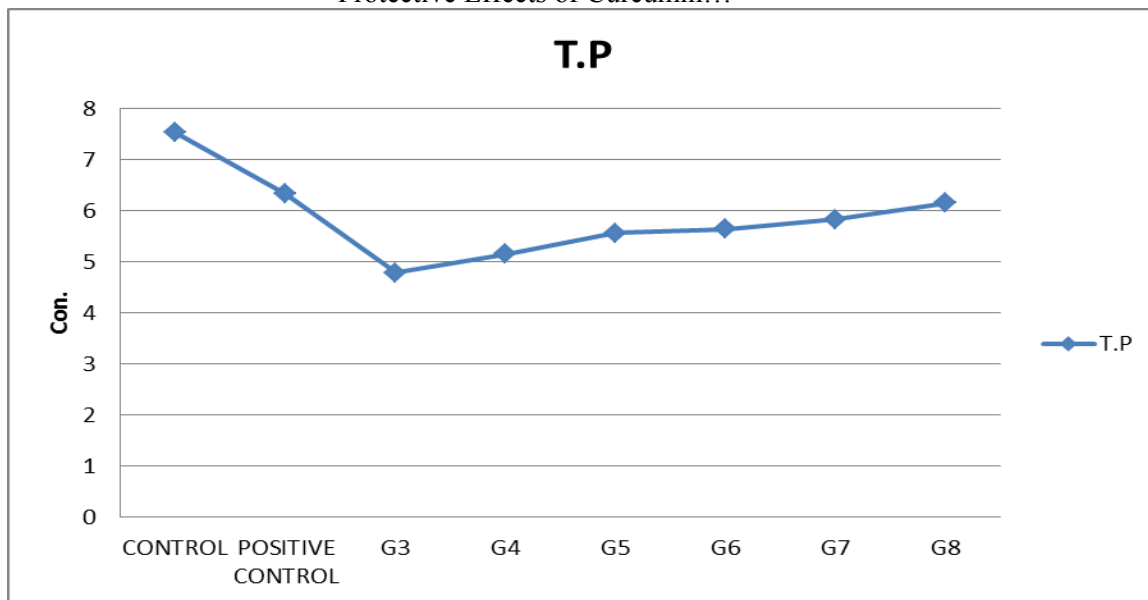


Fig .1. Effect of esfenvelerate and /or curcumin on total protein concentration in albino rats.

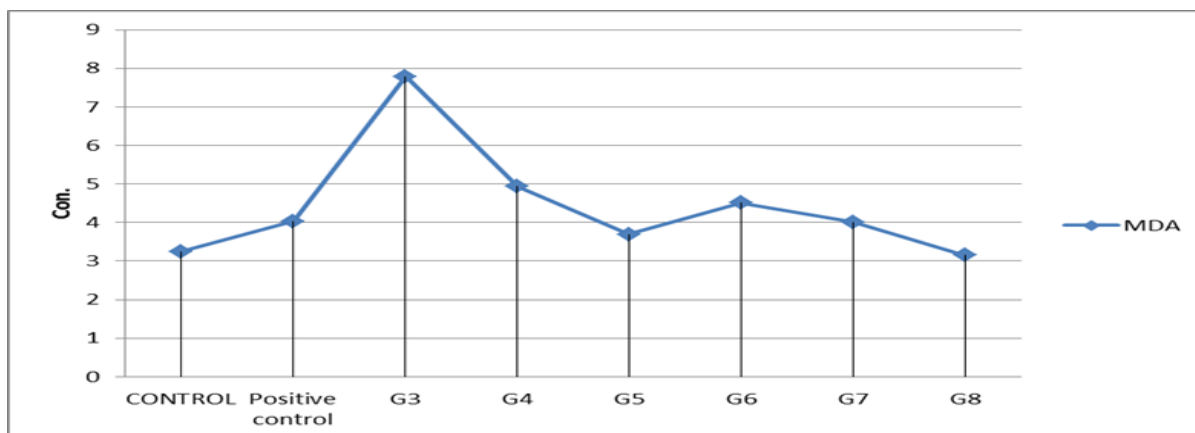


Fig .2. Effect of esfenvelerate and curcumin on malondialdehyde concentration in albino rats.

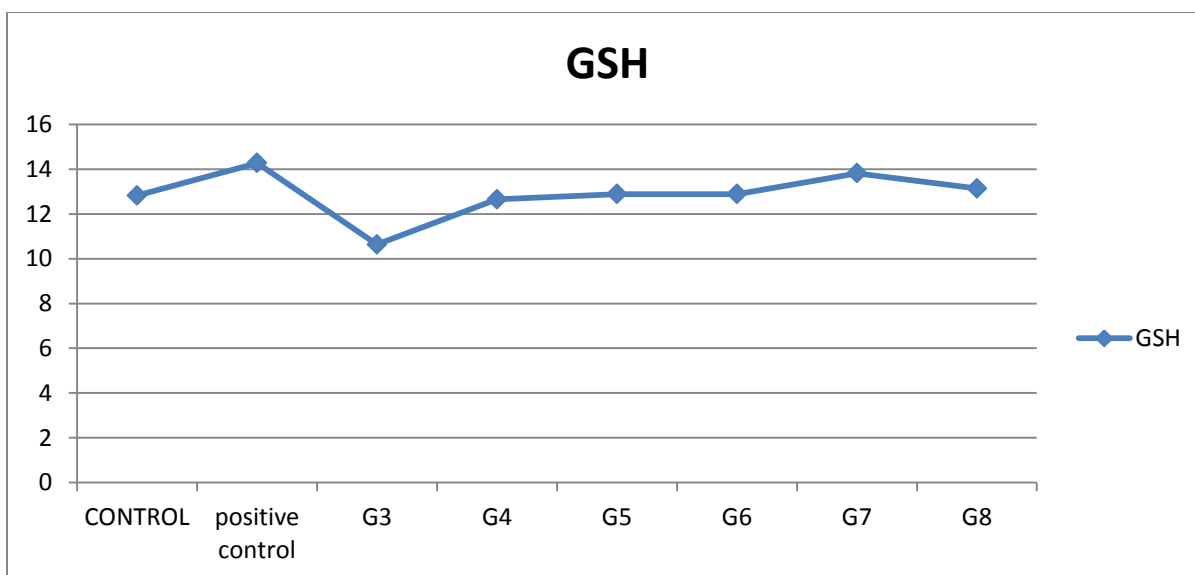


Fig.3.Effect of esfenvelerate and curcumin on glutathione reduce concentration in albino rats

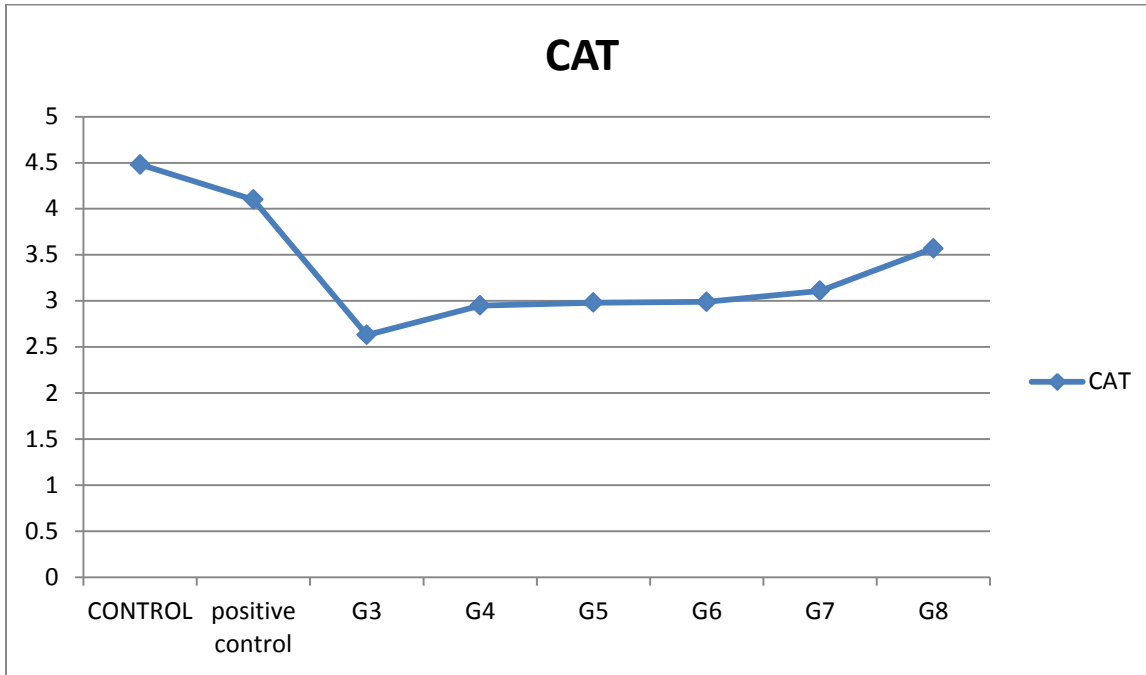


Fig.4.Effect of esfenvelerate and curcumin on catalase activity in albino rats.

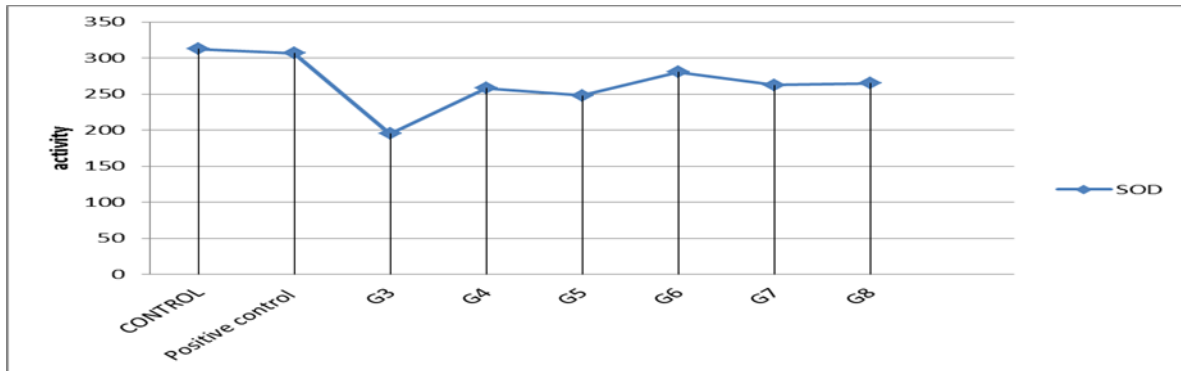


Fig.5.Effect of esfenvelerate on superoxide dismutase(SOD) activity. activity in albino rats.

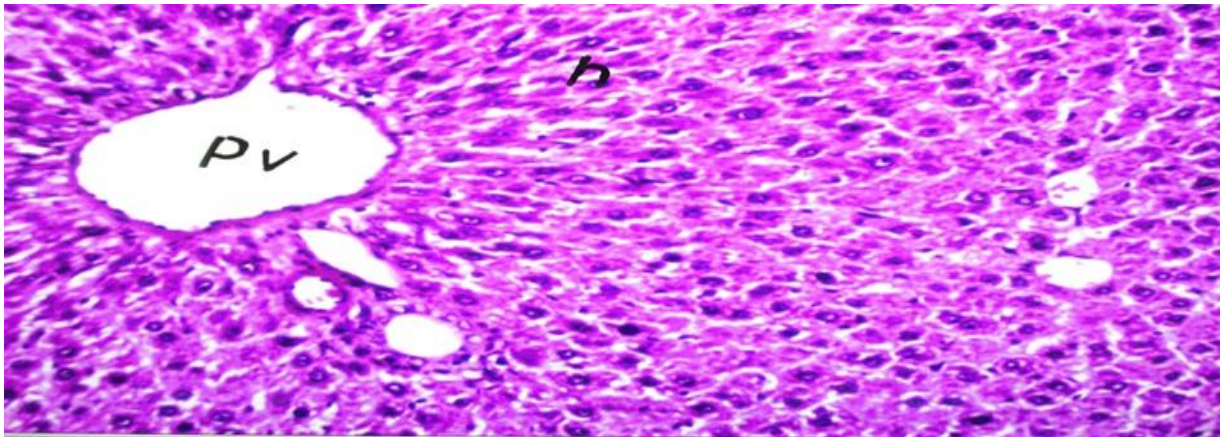


Fig6. A photomicrograph of control mouse showing that There was no histopathological alteration and the normal histological structure of the portal vein in the portal area and surrounding hepatocytes .(Hand E X 40).

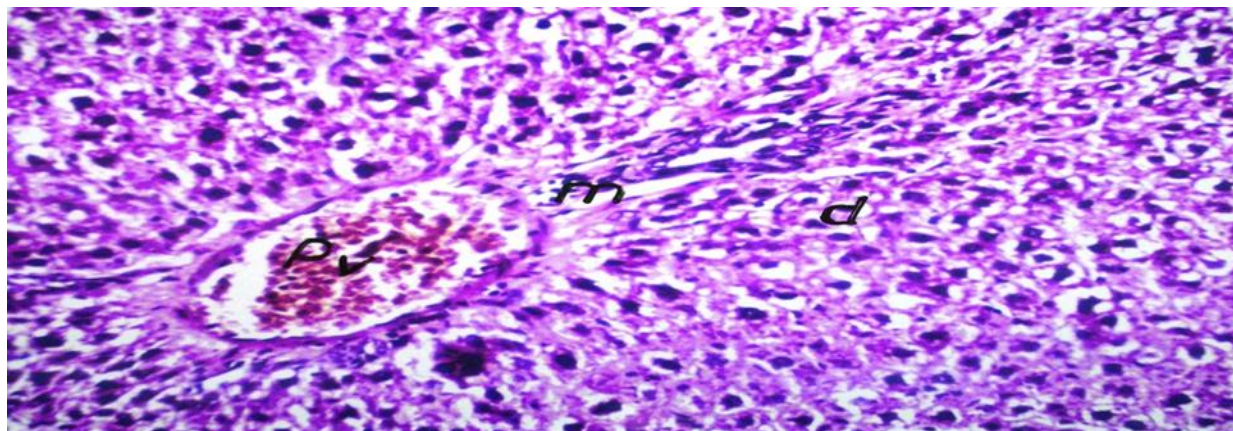


Fig7. A photomicrograph of G3(1/20 LD50) mouse showing that Degenerative change was noticed in the hepatocytes in diffuse manner associated with dilatation and congestion in the portal vein with few inflammatory cells infiltration in the portal area . (Hand E X 40).

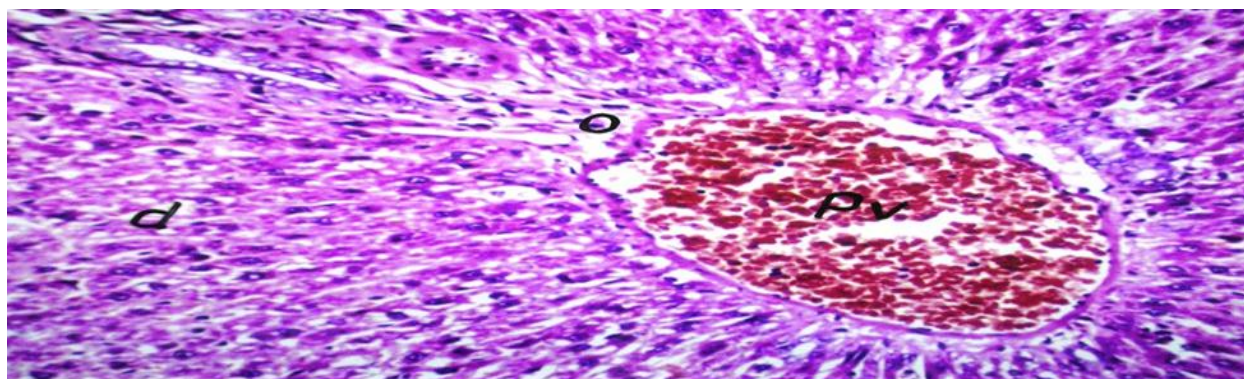


Fig 8. . A photomicrograph of G4(1/40LD 50) mouse showing that The hepatocytes showed degenerative change associated with sever congestion in the portal vein and oedema in the portal. (H and E X 40)

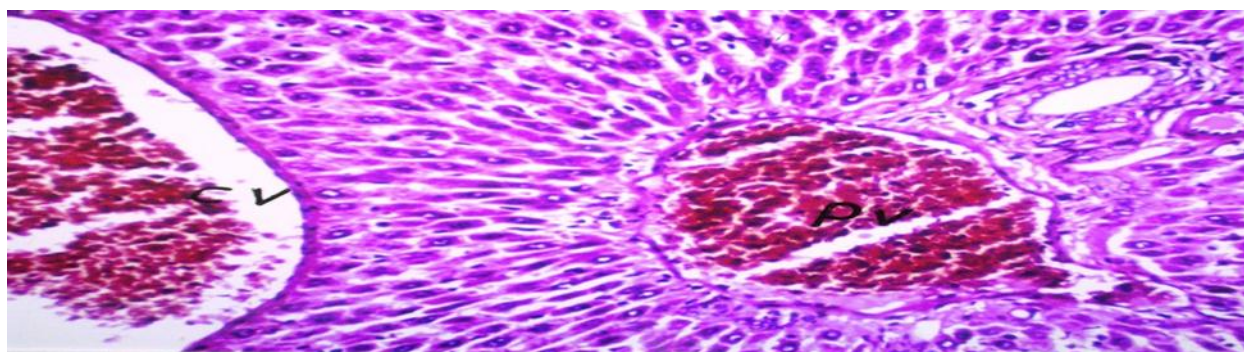


Fig 9. . A photomicrograph of G5(1/60LD50) mouse showing that Sever dilatation and congestion were detected in the central and portal veins (H and E X 40)

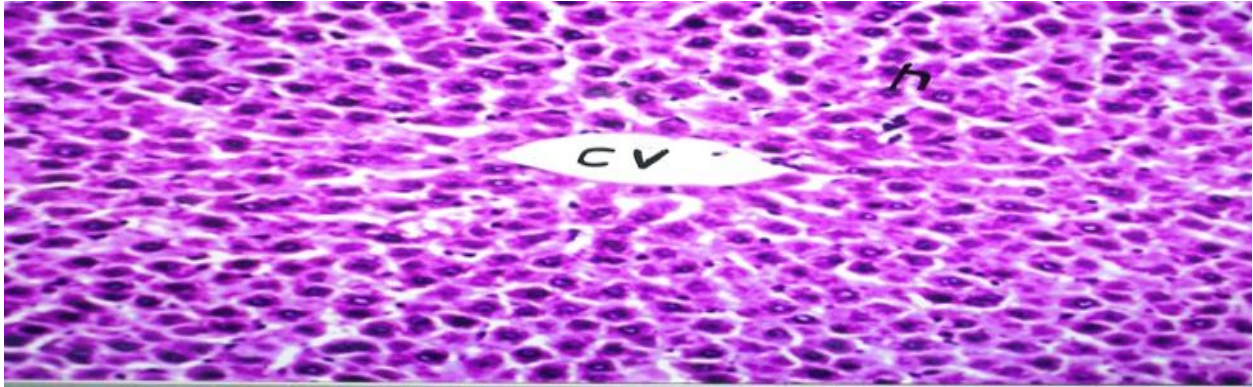


Fig 10. . A photomicrograph of positive control mouse showing that There was no histopathological alteration in hepatocytes (H and E X 40)

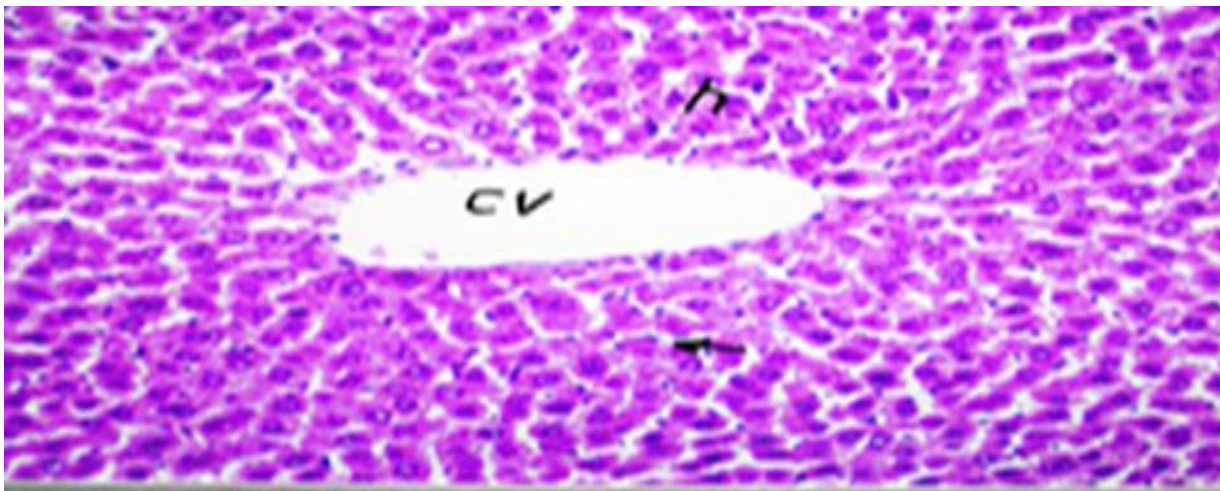


Fig 11. . A photomicrograph of G6 (1/20 LD50 plus curcumin) mouse showing that dilation in central vein (cv) with diffuse kuffer cells proferation between the hepatocytes(H and E X 40) .

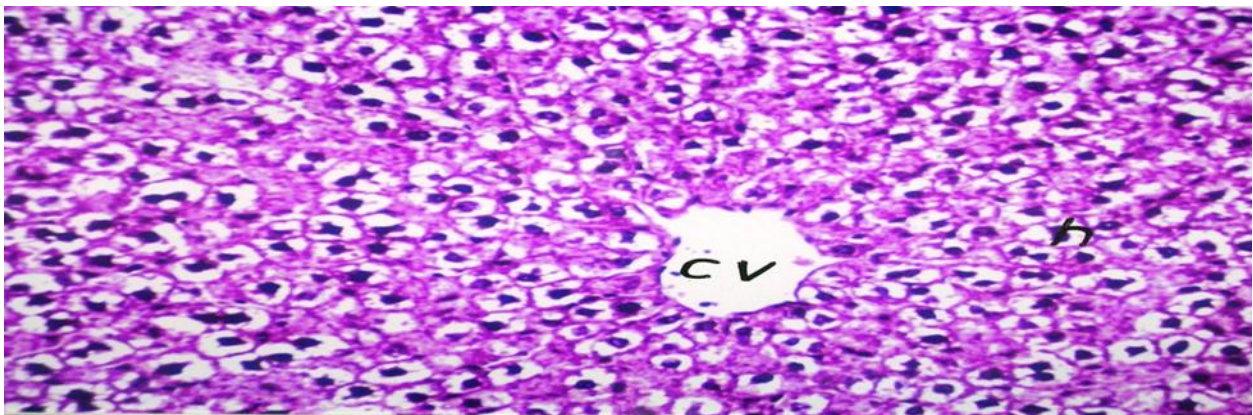


Fig 12. . A photomicrograph of G7(1/40 LD50 plus curcumin) and G8 (1/60LD50 plus curcumin)mouse showing that vacuolar degeneration in hepatocytes (h) . (H and E X 40) .