Impact of Panax Against Cypermethrin Hepatotoxicity

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Abstract:

The involvement of (ROS) has been linked in toxicity of various pesticides. Our study was designed to investigate the induction of oxidative stress and hepatotoxicity by cypermethrin type II synthetic pyrethroids in male rats and discussed the role of Panax ginseng supplementation in reducing the hepatic oxidative stress and liver damage. Rats were given either Panax mixed with diet (0.1%diet/day) or cypermethrin (9.4mg/kg/b.wt) orally (5times/week) or both of them for a period of 3 months. Serum and liver tissue samples were collected at one month intervals during the period of experiment for biochemical assay, oxidative stress biomarkers and histopathological examination. Analysis of variance (ANOVA) added revealed that oral administration of cypermethrin significantly reduced the level of glutathione (GSH) and the activity of antioxidant enzymes superoxide dismutase and catalase (SOD and CAT), while the level of lipid peroxidation (MDA) was elevated indicating the presence of oxidative stress. Regarding biochemical analysis cypermethrin exposure significantly raise the activities of aminotransferases enzymes, ALP, total bilirubin, total cholesterol, triglycerides, LDL from the beginning (first month) except total bilirubin increased from 2nd month of treatment. Meanwhile, total protein, albumin and HDL are significantly depleted at the beginning of the experiment to reach the highest changes at the end of experiment (third months) in a time dependent manner. That correspond to the extensive liver damage and histopathological findings in liver. On the other hand administration of Panax significantly reduced the toxic effect of cypermethrin on the biochemical constituents, histo-architecture of liver and restored the antioxidant capacity in liver.

Keywords: cypermethrin, hepatotoxicity, oxidative stress, Panax ginseng.

Introduction:

Agrawal and Sharma (2010) were described cypermethrin as a type II synthetic pyrethroid that is widely used in agriculture as a foliar spray on food and feed crops. It is also used in commercial, industrial, and residential settings to control pests and insects like fleas, cockroaches, and ants ***(EPA, 2020).*** Cypermethrin residues are frequently found in the environment, food, human urine, and breast milk ***(Tang et al., 2018)***. It tends to accumulate in tissues and organs, especially the central and peripheral nervous systems, because of its lipophilic qualities ***(Starr et al., 2012).*** Because of how frequently it is exposed to the general public, even at low environmental concentrations, there is cause for concern regarding its toxicity. The major way that pesticide-contaminated food affects humans indirectly is through consumption. Alpha-cypermethrin bioaccumulation and persistence in mammalian tissues are important from a toxicological perspective, even if literature data suggests that it is not very hazardous ***(Singh et al., 2012; Yuan et al., 2013)***. Pyrethroids primarily target the nervous system, but research has shown that exposure to cypermethrin may cause hepatotoxicity ***(Sharma et al., 2013)***. This has been observed in numerous studies using animal models ***(Sami et al., 2018; Afolabi et al., 2019; Abdou and Sayed,2019; Nessrin Kheirallah et al., 2021).*** Alpha-cypermethrin toxicity has been linked to the induction of intracellular reactive oxygen species (ROS) and oxidative stress, according to research ***(Abdou et al., 2012).*** When cytochrome enzymes break down cypermethrin, a lot of free radicals are produced ***(Gokhan Eraslan et al., 2015).***

These extremely potent substances cause lipid peroxidation and oxidative stress ***(Mignini et al., 2013).***

Because of their antioxidant ability to prevent oxidative stress brought on by free radicals, it has been discovered that natural products have medicinal potential ***(Hassan et al., 2014)***.

Traditional herbal medicines such as Panax ginseng roots are frequently used as dietary supplements to preserve and improve human health ***(Park et al., 2012)***; they include liver disease patients ***(Chung et al., 2016).***

Previous research utilizing animal models have demonstrated the hepatoprotective impact of Panax ginseng on cirrhosis and ischemia injury ***(Mustafa et al., 2012; Yao et al., 2019; Hao Liu et al., 2020; Shaima, 2020; In-Hee Baik et al., 2021).*** Along with its many other advantageous biological qualities, panax ginseng also possesses anti-inflammatory, anti-diabetic, antioxidant, immunomodulatory ***(Wei Chan, 2019; Shaima, 2020;***

Zubair et al., 2021) and neuroprotective qualities ***(In-Hee Baik et al., 2021).***

Phenolic acids, triterpenoids, saponines, and flavonoids are generally responsible for the pharmacological actions of ginseng ***(kim et al., 2010).***

Strong antioxidants like panax ginseng saponines can reduce tissue damage and inflammation brought on by free radicals ***(Sun-Hye et al., 2015)***.

The research interest in cypermethrin related hepatic injury was inspected by biochemical enzymatic liver biomarkers oxidative stress and hepatic histopathological analysis and to evaluate the role of Panax ginseng as an antioxidant and hepatoprotective agent to relieve cypermethrin hepatotoxicity in adult male rats.

Despite the vast amount of literature supporting the role of free radicals-mediated oxidative stress in the pathogenesis of cypermethrin mediating injury, the use of antioxidants as possible therapeutic agents has not been well studied. The present study was carried out to evaluate the hepatotoxic effect of cypermethrin in adult male rats as well as potential inhibition of the induced hepatotoxicity by using Panax ginseng as a powerful antioxidant and hepatoprotective agent.

Materials and methods:

Cypermethrin: (Cyperguard 10%EC ®) made in the Arab Company for Chemical Industry, weighed 100 grams per liter was administered orally after being dissolved in distilled water.

Panax ginseng: (Imtenan health company) was made from roots of genuine ginseng which imported from East Asian countries that described by company.

Experimental animals: We used eighty mature male rats weighing between 120 and 150 grams. Water and food were available all the times.

Experimental design: The acute oral LD_{50} was established using twenty adult male rats.

Four groups of fifteen adult male rats each were created from the sixty animal.

Group 1: maintained as a negative control, untreated.

Group 2: served daily as a positive control group, Panax powder was added to feed at a concentration of 0.1%. ***(Srour, Sahar., 2004).***

Group 3 received five oral doses of cypermethrin per week at a concentration level of 9.4 mg/kg.bw, or 1/40 of the anticipated LD_{50}.

Group 4 received oral cypermethrin dosages of 1/40 LD_{50} five times per week along with a diet containing 0.1% Panax per day.

The trial was carried out for an additional three months. 24 hours after the last dose, all of the animals were sacrificed. following the first, second, and third months of the trial.

Sampling: Retro-orbital venous plexus was used to collect blood samples from each group of five rats ***(Halperin et al., 1953)***. Serum was

separated by centrifugation at 3000 r.p.m. over the course of three experiment periods (1st, 2nd, 3rd months), and the serum was utilized to estimate certain biochemical parameters.

Cervical dislocation was used to scarify the animals under diethyl ether anesthesia, and liver samples were collected. Part of the liver tissue was frozen at -20°C to examine oxidative stress biomarkers, and the liver tissues were preserved in 10% formal saline for histological observation.

Biochemical studies: to estimate the levels of liver enzymes globulin, total protein according to ***(Kaplan and Szalbo 1983),*** albumin according to ***(Walker et al., 1990)***, serum bilirubin according to the method of ***(Tietz, 1986)***, AST, ALT, and ALP according to ***(White et al., 1970)***, and globulin Usually, the albumin is subtracted from the total protein to find the total globulin fraction. For the lipid profile serum cholesterol according to **Deeg and Ziegenohrm (1983),** triglycerides according to **Fossati and Prencip*s (1982)***, *HDL according to* ***(Lopes - Virella et al., 1977)***, *and LDL by computation*: LDL: Total cholesterol - (triglycerides/5) - HDL cholesterol equals LDL cholesterol (mg/dl).

Liver tissues were dissected to measure oxidative stress indicators SOD calculated by ***(Kakkar et al., 1984),*** CAT measured by ***(Sinha, 1972)***, and lipid peroxidation (MDA) assessed by ***(Okhawa et al., 1979*)** and GSH calculated using ***(Ellman's, 1959)*** methodology.

Histopathological examination: The liver tissues were taken and preserved in 10% buffered formaline. They were then treated using the standard paraffin embedding method, and sections five microns thick were stained with Eosin and Meyer's Hematoxyline ***(Bancroft et al., 1996)***.

Statistical analysis: After statistical analysis of the collected data, the Duncan test was used to establish significance, and the Analysis of Variance (ANOVA) software was used to compute the results.

Results:

LD_{50} of cypermethrin

The acute oral LD_{50} of cypermethrin was calculated as 374.633 ±12.187 mg/kg in adult male.

Results concerning the effect of oral administration of cypermethrin (9.4mg/kg b.wt equvilant to 1/40 (LD_{50}) 5 times /week either alone or in combination with Panax ginseng (0.1%) containing diet /day at all treatment periods (1st, 2nd and 3rd months) to adult male rats, on certain serum constituents, antioxidant parameters and liver peroxidation in addition to histopathological examination of the liver.

Effect on liver function: table (1) indicates significant elevation at ($P<0.05$) in serum liver integrity biomarkers enzymes (AST, ALT and ALP) along with rises in serum bilirubin levels, meanwhile serum total protein and albumin were

significantly decreased at ($P<0.05$) in cypermethrin intoxicated rats in comparable to –ve and +ve control groups from the beginning (1st month) till the end of experiment (3rd months) in a time dependent status .on the contrary ,no significant change were observed in all treated parameters of Panax containing diet group(+ve control) in relation to –ve control .

In addition, co-treatment of rats with Panax ginseng significantly counteracted the hepatotoxic effect of cypermethrin as compared to cypermethrin treated group. However, values of AST, ALT, ALP and bilirubin were still significantly higher than –ve and +ve controls values all over the experimental periods (1st, 2nd and 3rd months) in a time dependent.

Effect on lipid profile:

Table (2) indicated a noticeable extensive alteration in serum lipid profiles in cypermethrin exposed group as compared to -ve and +ve controlled groups at different periods of experiment in a time – dependent effects. As serum total cholesterol , LDL and triglycerides were found to be raised significantly at ($P<0.05$) from the beginning of experiment (1st month) up to maximum level following 3rd month of cypermethrin intoxication to all group, with a substantial decline in HDL values served at ($P<0.05$) in respective to –ve and +ve control values. Meanwhile, all the affected values of lipid profile could be partially improved in cypermethrin with Panax group as compared to cypermethrin intoxicated rats, but it still significantly differ over the + ve and –ve levels along the time of experiment. On the other hand +ve control group treated with Panax alone showed non-significant variation in lipid profile values as evaluated to –ve control group.

Effect on liver lipid peroxidation and oxidative stress biomarkers:

As reported in table (3) the activities of SOD, CAT and GSH of cypermethrin treated rats were extensively reduced ($P<0.05$) along with a significant increase ($P<0.05$) in hepatic level of MDA in relation to controlled groups from the beginning until the termination of the experiment.

The pronounced effects of cypermethrin intoxication on oxidative stress biomarkers were significantly counteracted by concomitant treatment of rats with Panax containing diet , however , SOD ,CAT and GSH , and MDA still significantly differ over –ve and +ve values. Moreover, giving Panax alone didn't produce any significant variations in MDA and GSH levels. Meanwhile, it significantly increase at ($P<0.05$), the activities of SOD and CAT as compared to –ve control from first month till third month of experiment.

Effect on hepatic histopathology:

Be revealing Fig. (10): liver section at 1 month of the experimental period normal hepatic architecture in both of -ve control and +ve control group with some activation of

kupffer cells. However Cyprmethrin treated group showed significance level of sporadic hepatocyte necrosis; meanwhile combination of cypermethrin with Panax group illuminated reduction in the sporadic cell necrosis and invasion of necrotic area by inflammatory cells.

As shown in Fig. (11): Liver section at 2nd months of the experimental period reveled necrotic foci associated with activation of inflammatory cells and von-kupffer cells in Cypermethrin treated group, meanwhile cypermethrin with Panax showing activation of kupffer-cells and infiltration of inflammatory cells surrounding necrotic foci.

Seen in fig. (12): Liver tissue at 3rd months of the experimental showed Congested blood vessels with wide area of hepatic degeneration in form of areas with hepatocytes lysis surrounded by adjacent hepatocytes necrosis hyperplasia in cypermethrin group (c). cypermethrin combined with Panax group (d) exhibiting small necrotic foci infiltrated by inflammatory cells.

Table (1): *Effect of oral administration of cypermethrin (9.4mg/kg.b.wt equivalent to 1/40 of the estimated LD_{50} 5times/week) either alone or in combination with Panax (0.1%feed/day) on serum liver enzymes (AST, ALT and ALP), Total protein and albumin level of adult male rats for a period of experiment at (1st, 2nd and 3rd months).*

peri	Parameter / Group	AST U/L	ALT U/L	ALP U/L	Total protein gm/dl	Albumin(A) gm/dl
1st month	Control-ve	42±0.82^{a}	40±1.14^{a}	182±2.95^{a}	6.86±0.27^{a}	4.21±0.26^{a}
	Control+ve	41±0.79^{b}	39.7±1.11^{b}	180±2.98^{b}	7.13±0.26^{b}	4.26±0.29^{b}
	Cypermethrin	52±1.04^{abc}	50±1.52^{abc}	199±2.77^{abc}	5.66±1.04^{abc}	3.2±0.17^{abc}
	Cypermetrhin +Panax	47±1.14^{abc}	46±2.21^{abc}	189±2.83^{abc}	6.63±0.21^{c}	4.02±0.18^{c}
2nd month	Control-ve	42±0.85^{a}	41±1.51^{a}	181.7±2.59^{a}	6.9±0.29^{a}	4.26±0.26^{a}
	Control+ve	41.4±0.93^{b}	40±1.82^{b}	180±2.51^{b}	7.19±0.26^{b}	4.37±0.23^{b}
	Cypermethrin	66±1.3^{abc}	60±2.35^{abc}	305.8±1.77^{abc}	4.8±0.27^{abc}	2.48±0.15^{abc}
	Cypermerhin + Panax	53±1.58^{abc}	51±2.35^{abc}	274.4±2.36^{abc}	5.93±0.19^{abc}	3.4±0.29^{abc}
3rd month	Control –ve	42.2±0.66^{a}	41.5±1.06^{a}	182±2.61^{a}	6.85±0.36^{a}	4.07±0.24^{a}
	Control +ve	41±1^{b}	40±1.25^{b}	179.5±2.55^{b}	7.02±0.23^{b}	4.15±0.15^{b}
	Cypermethrin	92±2.34^{abc}	88.5±1.52^{abc}	396±3.36^{abc}	3.93±0.31^{abc}	2.07±0.15 ^{abc}
	Cypermethrin + Panax	74±1.87^{abc}	70±2.98^{abc}	299±4.18^{abc}	4.84±0.25^{abc}	2.76±0.19^{abc}

Data expressed as means± S.E

Different superscript indicates significance at ($P<0.05$).

Table (2): *Effect of oral administration of cypermethrin (9.4mg/kg.b.wt equivalent to 1/40 of the estimated LD_{50} 5times/week) either alone or in combination with Panax (0.1%feed/day) on lipid profile (Cholesterol, Triglycerides, LDL and HDL) of adult male rats for a period of experiment at (1^{st}, 2^{nd} and 3^{rd} months). (Mg/dl)*

Period	Parameter / Group	Cholesterol	Triglycerides	LDL	HDL
1st month	Control-ve	107±2.7^{a}	139±2.43^{a}	40±2.12^{a}	60±2.55^{a}
	Control+ve	106±2.02^{b}	137.2±2.78^{b}	42±1.7^{b}	62±1.92^{b}
	Cypermethrin	127±2.81^{abc}	154.2±1.9^{abc}	60±1.64^{abc}	44±1.52^{abc}
	Cypermetrhin +Panax	117±3.62^{abc}	146.8±2.03^{abc}	51±2.03^{abc}	51±2.28^{abc}
2nd month	Control-ve	105.6±2.84^{a}	139±2.35^{a}	45±2.12^{a}	60±1.92^{a}
	Control+ve	105.2±2.56^{b}	137.6±1.57^{b}	43.5±1.91^{ab}	62±1.84^{b}
	Cypermethrin	166±2.65^{abc}	180±2.12^{abc}	81.2±2.37^{abc}	37±1.52^{abc}
	Cypermerhin + Panax	130±2.58^{abc}	163.2±1.85^{abc}	70±2.55^{abc}	45.5±2.37^{abc}
3rd month	Control –ve	105.8±2.69^{a}	138.5±2.02^{a}	44.5±2.31^{a}	60±1.92^{a}
	Control +ve	105.2±3.12^{b}	137.5±1.86^{b}	43.5±2.19^{b}	61±2.28^{b}
	Cypermethrin	213±2.83^{abc}	209±2.55^{abc}	127.4±1.74^{abc}	29±1.98^{abc}
	Cypermethrin + Panax	168±3.86^{abc}	185±2.21^{abc}	96±1.92^{abc}	36±2.12^{abc}

Data expressed as means± S.E

Different superscript indicates significance at (P<0.05).

Table (3): *Effect of oral administration of cypermethrin (9.4mg/kg.b.wt equivalent to 1/40 of the estimated LD_{50} 5times/week) either alone or in combination with Panax (0.1%feed/day) on oxidative stress biomarkers of adult male rats for a period of experiment at (1^{st}, $2^{nd}$and 3^{rd} months).*

Period	Parameter / Group	MDA n.moles/g	GSH U/g	SOD U/g	CAT U/g
1stmonth	Control-ve	6.79±0.21^{a}	5.2±0.3^{a}	31.42±0.61^{a}	3.91±0.43^{a}
	Control+ve	6.54±0.27^{b}	5.32±0.18^{b}	33.35±0.83^{b}	3.96±0.41^{b}
	cypermethrin	7.26±0.27^{c}	4.64±0.41^{c}	26.75±0.7^{abc}	3.27±0.28^{c}
	Cypermetrhin +Panax	7.05±0.22	4.85±0.27	29.24±0.78^{abc}	3.59±0.27
2ndmonth	Control-ve	6.72±0.28^{a}	5.32±0.36^{a}	32.72±0.76^{a}	4.07±0.36^{a}
	Control+ve	6.49±0.23^{b}	5.42±0.34^{b}	34.13±0.47^{b}	4.5±0.35^{b}
	Cypermethrin	8.43±0.20^{abc}	3.75±0.17^{abc}	22.58±0.62^{abc}	2.54±0.21^{abc}
	Cypermerhin + Panax	7.63±0.28^{abc}	4.3±0.16^{abc}	26.73±0.69^{abc}	3.49±0.28^{abc}
3rdmonth	Control –ve	6.57±0.31^{a}	5.29±0.36^{a}	33.33±0.65^{a}	4.14±0.35^{a}
	Control +ve	6.42±0.22^{b}	5.4±0.29^{b}	35.16±0.49^{b}	4.39±0.25^{b}
	Cypermethrin	9.48±0.27^{abc}	3.38±0.2^{abc}	18.23±0.91^{abc}	2.33±0.23^{abc}
	Cypermethrin + Panax	7.87±0.4^{abc}	4.16±0.17^{abc}	23.63±0.66^{abc}	3.31±0.23^{abc}

Data expressed as means± S.E

Different superscript indicates significance at (P<0.05).

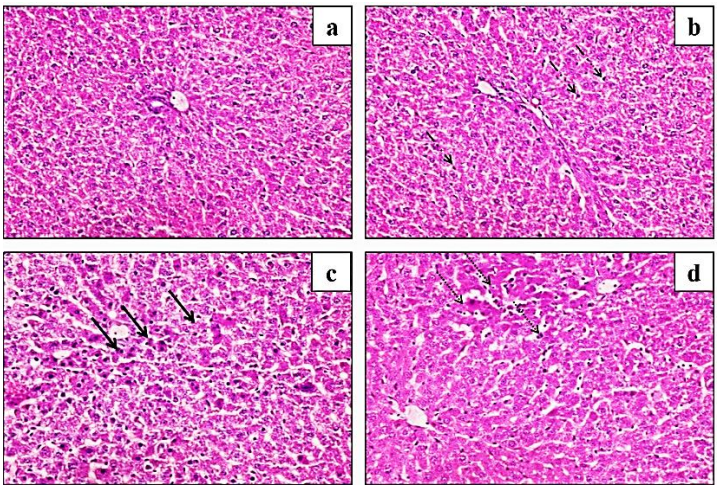

Fig. (1): Liver at 1st month of the experimental period revealing normal hepatic architecture in both of; (a) -ve control group and (b) +ve control group with some activation of kupffer cells (dashed arrows). (c) Cyprmethrin treated group showing significance level of sporadic hepatocyte necrosis (solid arrows); meanwhile (d) cypermethrin with Panax group showing reduction in the sporadic cell necrosis and invasion of necrotic area by inflammatory cells (spotted arrows). H&E X 400.

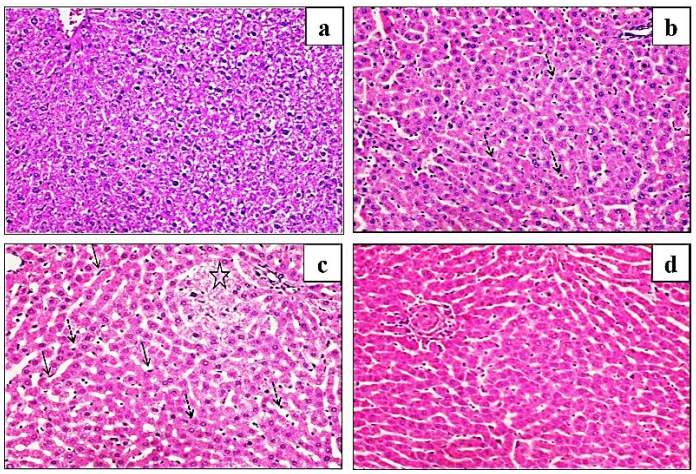

Fig. (2): Liver at 2nd months of the experimental period showing normal architecture in (a) –ve control group. Noticeable activation of von-kupffer cells (dashed arrows) could be detected in (b) +ve control group (b). Appearance of necrotic foci (asterisk) associated with activation of Ito (solid arrows) and von-kuppfer cells (dashed arrows) in (c) Cypermethrin group, initiation of immune response in activation of kupffer- cells and infiltration of inflammatory cells surrounding necrotic foci was detected in (d) group. H&E X 400.

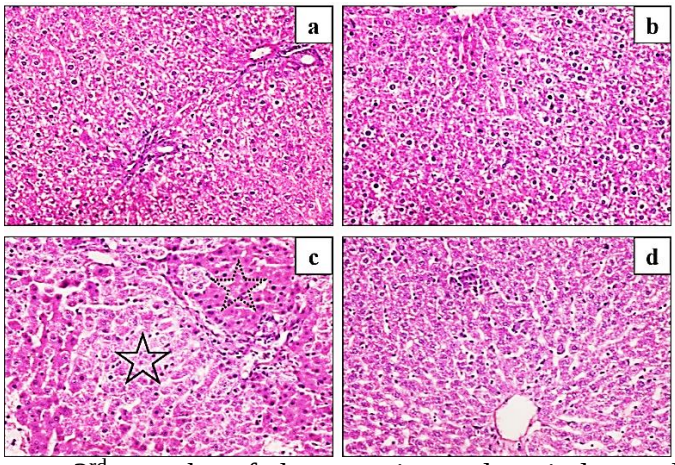

Fig (3) Liver at 3rd months of the experimental period revealing, normal hepatic architecture in both of (a) -ve control group and (b) +ve control group. Wide area of hepatic degeneration in form of; areas with hepatocytes lysis (solid asterisk) surrounded by adjacent hepatocytes necrosis (dashed asterisk) could be seen in (c) cypermethrin group. (d) cypermethrin with Panax group revealing small necrotic foci infiltrated by inflammatory cells (dashed asterisk). H&E X 400**.**

Discussion:

A worldwide synthetic pyrethroids was a cypermethrin which has been used for several purposes and recognized to be toxic in acute and chronic manner for animals and human ***(Grewal et al., 2010).***

As liver is the major organ for cypermethrin metabolism so it could be inflamed and damaged through reactive oxygen species mediated by cypermethrin intoxication ***(Gomaa et al., 2011).***

Oxidative stress and reactive oxygen species have been implicated of various toxicosis ***(Abdou et al., 2012).***

The acute oral LD_{50} of cypermethrin was calculated as 374.633 ±12.187 mg/kg in adult male

Results concerning the effect of oral administration of cypermethrin (9.4mg/kg b.wt equivalent to 1/40 LD_{50}) 5 times/week either alone or in combination with Panax ginseng (0.1%) containing diet /day at all treatment periods (1st, 2nd and 3rd months) to adult male rats, on certain serum constituents, antioxidant parameters and liver peroxidation in addition to histopathological examination of the liver.

The most phytotherapy drugs in Asian and many parts of the world is Panax ginseng, it can be absorbed in the systemic circulation, could be and serve as potent pharmaceutical agents to prevent and treat inflammatory diseases and enhance overall health through its antioxidant and anti-inflammatory character ***(Ji Hye kim et al., 2017; In-Hee Baik et al., 2021).***

The present study was aimed to investigate the chronic toxic impact and induction of hepatic oxidative stress induced through oral administration of 9.4mg/kg b.wt cypermethrin equivalent to 1/40 LD_{50} (5times /week) to adult male rats. In addition, the ameliorative role of Panax containing diet (0.1%/diet/day) as a detoxifying agent against the cypermethrin hepatotoxicity was evaluated compared to control at one month interval during periods of treatment (3 months).

Results of the present study, elucidated that chronic exposure to cypermethrin increased liver biomarkers enzymes (AST, ALT and ALP) leakage into the serum of treated cypermethrin rats as comparable to -ve and +ve controls groups over the experimental periods; it also raised total bilirubin from the 2nd month of the treatment. Meanwhile total proteins and albumin were significantly drop in cypermethrin exposed group, these results in accordance with that reported by ***(Gokhan Eraslan et al., 2015; Abdou and Sayed 2019 and Lyiola et al., 2019)*** in rats.

The elevation of all hepatic indices reflect to the drastic conditions caused by cypermethrin and are usually associated with impaired hepato-cellular function and disintegration of hepatic cell membrane ***(Abdel-Daim et al.,2015; Abdou et al., 2015)*** lead to hepatocellular injury which was confirmed by our histopathological findings in the liver .

Furthermore , the reduction of total protein and albumin in cypermethrin treated rats indicates increased inflammation , hepatoxicity and liver damage , that lead to liver become unable to produce proteins ***(Kumar et al., 2007)*** .

Concerning lipid profile the obtained data showed that cypermethrin administration causing a significant elevation in serum total cholesterol, LDL and triglycerides associated with a significant depletion of HDL. These results were in agreement with ***(Nessrin Kheirallah et al., 2021)*** who stated that.

The increased cholesterol level in serum of cypermethrin stressed rats might be an outcome of cholestasis , along with endogenous synthesis of cholesterol ***(Brijender et al.,2013)*** while, the increase in serum triglycerides could be discussed by ***(Bhushan, 2011)*** who stated that triglycerides are esters of free fatty acids with glycerol, which considered an important cause of excess carbohydrates in the blood so any alteration in carbohydrate metabolism or protein as reflected by cypermethrin intoxication could lead to conversion of it to fats including triglycerides via intermediatory metabolism.

In addition**, *(Sadeghi –Hashjin et al., 2011)*** reported that the increased triglycerides levels may be due to the activation of sympathetic nervous system by cypermethrin, resulting in release of epinephrine and

norepinepherine by adrenal medulla which in turn stimulate hormone sensitive triglycerides lipase in tissue, resulting in hydrolysis of stored triglycerides from fats stores and mobilization of free fatty acids in the blood stream caused raising in serum total lipid values.

Moreover, an increase in circulating LDL is almost due to lack of LDL uptake via receptor dependent pathways however, the decreased HDL levels could be related to impairment in the biosynthesis of HDL in hepatic and intestinal cells ***(Brijender et al., 2013)***.

Several clinical studies have suggested that the potential to induce oxidative stress is one of the toxic mechanism of action of pesticides ***(Agrawal and Sharma, 2010)***. in the present work , the oxidative stress that caused the free radicals production may be resulted in hepatic damage by cypermethrin ***(Gokhan Eraslan ,2015)*** .Our analyzed data revealed that cypermethrin intoxication induces lipid peroxidation and oxidative stress associated with a significant increase at ($P<0.05$) in the level of oxidative biomarkers (MDA) and decreased the (GSH) antioxidant capacity in hepatic tissues as well as decreasing the activities of hepatic SOD and CAT at ($P<0.05$) in liver tissues as compared to –ve and +ve controlled groups from 2nd month except SOD decreased from the 1st month of the experiment to reach to the highest hazardous values at the termination of the experiment (at 3 months). These effects are incriminated in hepatic oxidative stress and toxicity. These findings are in agreement with those obtained by many other researches ***(Gomaa et al., 2011; Gokhan Eraslan 2015).***

The possible explanation of the cypermethrin lipid peroxidation and oxidative stress could be discussed by ***(Gokhan Eraslan et al, 2015)*** who stated that cypermethrin lead to the generation of high levels of free radicals , which could not be fully inactivated by the cellular antioxidant defense system , and thus , resulted in lipid peroxidation , oxidative stress. Meanwhile, decreased GSH levels, SOD and CAT activities as compared to controls, could be related to the highly consumption of these markers during the detoxification of the generated free radicals at high levels in the cells. The impact of cypermethrin was more sever at the tissue levels at last month of experiment, this was attributed to the level of free radicals mediated by cypermethrin being higher in the chronic stage.

In addition, the present investigation showed that Panax co-treatment with cypermethrin decreased the chronic harmful effect of cypermethrin as evidenced by reducing the negative effect on the liver enzymes, total bilirubin, total protein and albumin as well as on lipid profile.

These results may be due to maintaining of hepatocytes integrity or regeneration of injured hepatocyte **(*He Zhu et al., 2015)***. Also,

handling with ginseng Panax inhibits oxidative damage, including lipid peroxidation reduced MDA levels and elevated GSH contents as well boosted quantities of self-antioxidant enzymes and strengthened the antioxidant defense system (SOD and CAT) in liver tissues in (cypermethrin with Panax) compared with cypermethrin group , also, restored these affected values to be nearly towards the controls. These observations verify the restorative effects of Panax ginseng on liver tissues that may be explained by the primary and bioactive components of saponines from Panax ginseng recognized as ginsenoides ***(Choi, 2008)***. Its advantageous preventive qualities against organ damage give it antioxidant activity. ***(Lobna et al., 2014)*** through reductive of free radical chain reactions ***(Hassan et al., 2015)***. The antioxidant activity of Panax ginseng against hepatic damage was established by other published data ***(He Zhu et al.,2015 .; Weidong et al., 2018 .; Manal Abdul-Hamid et al.,2020.; Fatma, M. El-Demerdash et al., 2021; Heba Ghamry et al., 2022)***. Many studies attributed the potential protecting effects of Panax ginseng against oxidative stress and inflammation due to its scavenging capacity ***(Heba Ghamry et al., 2022)***.

Regarding the histopathological alteration observed in cypermethrin treated group time- subordinate change ranged from sporadic hepatocyte necrosis at the 1st month of cypermethrin treatment, infiltration of inflammatory cells surrounding necrotic foci at the 2nd month, progression of lesion severity to include wide area of hepatic degeneration, areas with hepatocytes lysis surrounded by adjacent hepatocytes necrosis, congestion of blood vessels, activation of kupffer cells and hyperplasia of bile duct at 3rd month of cypermethrin exposure.

The rat hepatic tissues treated with Panax ginseng (+ve control) showed no signs of pathology. Liver sections in rats treated with cypermethrin with Panax ginseng showed significantly less damage and degeneration of the hepatic cells displaying small necrotic foci infiltrated by inflammatory cells at the termination of experiment.

The histopatholoigcal findings supported the biochemical analysis and were in line with the observed activity of the serum liver enzymes, this can be discussed by components of Panax ginseng that are free radicals scavengers prevent the peroxidation of lipid and preventing oxidative stress that free radicals cause to cells and tissues. ***(Shaima, 2020)***.

The positive control group (Panax treated rats) showed similar results to that of –ve controls and recorded better results in some antioxidant values as SOD and CAT.

Conclusion:

The result of the current study indicates that the administration of Panax ginseng to cypermethrin treated rats led to an enhancement of the morphological pictures of the liver in addition to biological factors, primarily by inhibiting oxidative stress and inflammation via its antioxidant and inflammatory properties.

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تأثير البانكس جينسنج ضد التسمم الكبدي بالسيبرميثرين

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الملخص

إن الأستخدامات المكثفة والمتزايدة للمبيدات بمختلف أنواعها تكون عادة مرتبطة بمشاكل التلوث و الخطورة علي الصحة العامة بوجه عام. لذلك استهدفت في هذه الدراسة تقييم التأثير السام لواحد من المبيدات البروثيريدية النامية – علي وظائف الكبد و بعض المعاملات البيو كيميائية و المؤشرات الحيوية للأجهاد التأكسدي و التغيرات المرضية في كبد ذكور الفئران البالغة. و كذلك دراسة دور البانكس جنيسنج كعامل طبيعي مضاد للأكسدة في مقاومة و تثبيط الآثار السلبية الناشئة عن المبيد. بادئ ذي بدء تم تقدير و حساب الجرعة النصف مميتة لذكور الفئران البالغة . و تم استخدام عدد 80من ذكور الجرذان (20 فأر لتحديد الجرعة النصف المميتة ،60 فأر تم تقسيمهم بالتساوي إلي 4 مجموعات كالآتي مجموعة ضابطة سلبية تركت بدون أي علاج تتغذي علي العليقة العادية ، المجموعة الضابطة الإيجابية تتغذي علي نفس العليقة العادية مع إضافة مسحوق البانكس عند مستوي تركيز (0.1% جرام) ممزوجة مع العليقة يوميا ، المجموعة تم تجريعها مبيد السيبرميثرين عن طريق الفم بجرعة (9.4ملجم / كجم من وزن الجسم و هي جرعة تكافئ 40/1 من الجرعة النصف المميتة) 5 مرات أسبوعيا، ومجموعة تم علاجها بنفس جرعة السيبرميثرين كما في المجموعة الثالثة (9.4 ملجم/ كجم من وزن الجسم) 5مرات / أسبوعيا مع إضافة البانكس ممزوج بالعليقة (0.1% جرام) يوميا . و قد استمرت التجربة لمدة ثلاثة لأشهر تم خلالها تجميع عينات من سيرم الدم وأنسجة الكبد في نهاية كل شهر وذلك لإجراء التحاليل الكيمائية الحيوية و فحص الباثولجي لأنسجة . فقد أظهر الفحص البيوكيميائي عن ارتفاع معنوي في مستوي أنزيمي اسبرتيت أمينو ترانسفيريزو ألنين أمينو ترانسفيرز و كذلك أنزيم الفوسفاتيز القلوي و مستوي الجلوكوز و البيليروبين و الكوليسترول ومستوي الدهون الثلاثية و البروتين الدهني منخفض الكثافة في المصل مقارنة بالمجموعة الضابطة السلبية و الإيجابية من الشهر الأول في التجربة إلي الشهر الثالث فيما عدا مستوي البيلروبين سجل الزيادة من الشهر الثاني في التجربة الي الشهر الثالث , كما سجلت النتائج انخفاض معنوي في مستويات كلا من البروتين الكلي و الالبيومين و الجلوبيولين و أيضا انخفاض مستوي البروتين الدهني عالي الكثافة خلال فترة التجربة (3 شهور) مقارنة بالمجموعتين الضابطة السلبية و الإيجابية و كانت هذه التغيرات متزامنة مع وقت التجربة في نمط يعتمد علي الوقت . و فيما يتعلق بالمؤشرات الحيوية للإجهاد التأكسدي فقد أوضحت النتائج زيادة مستوي فوق أكسدة الدهون مالونالدهيد و إنخفاض مستوي الجلوتاثيون وأنزيمي السوبر اوكسيد ديسميوتاز و الكتاليز في المجموعة المعالجة بالسيبرميثرين مقارنة مع المجموعتين الضابطتين السلبية و الإيجابية .