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Ameliorative effect of resveratrol against thiacloprid induced acute and subacute toxicity in rats: Liver markers, renal markers and total protein

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Abstract
Thiacloprid, a neonicotinoid insecticide is known to target the nicotinic acetyl choline receptors (nACHRs) in insects and potentially in mammals. The aim was to ascertain the effect of acute (24h) and subacute (28 days) toxicity of thiacloprid and its amelioration by resveratrol in male Wistar rats. Liver and kidney function tests viz. ALT, AST, GGT, BUN, creatinine, were significantly increased while reduction in total protein levels were resulted from thiacloprid treatment which were significantly restored with resveratrol co-treatment in rats. The study revealed that thiacloprid possesses mild to moderate toxicity potential for hepatic and renal profile of adult male rats. Resveratrol possesses potential to sufficiently ameliorate the toxicity produced by thiacloprid and as such do not have any toxic effect at therapeutic doses in adult male wistar rats.

Keywords: thiacloprid, toxicity, Liver markers, renal markers, total protein

1. Introduction
Insecticides fall into two categories-inorganic and organic. The organic insecticides are further divided into different groups such as organophosphorus compounds (OP), organochlorine compounds (OC), carbamates (C), pyrethrins/synthetic pyrethroids (SP), neonicotinoids, insect growth regulators (IGR), etc. The neonicotinoids are the only major new class of insecticides developed in the past three decades, mainly because they show reduced toxicity compared to the previously used organophosphate and carbamate insecticides. The neonicotinoids are the fastest growing chemical class of insecticides, accounting for over 15% of the total insecticide market [22]. Thiacloprid [3-(6-chloro-3-pyridylmethyl)-1, 3-thiazolidin-2-ylidenecyanamide] is neurotoxic and a new neonicotinoid insecticide that belongs to a new group of active ingredients, the cyanoamidine [20] and is effective on contact and also via stomach action. The selective toxicity of thiacloprid to insects and not to mammals is attributed to differences in the binding affinity or potency at nicotinic acetylcholine receptors.
Resveratrol is a fat soluble compound that occurs in *Trans* and *cis* configuration. Resveratrol was originally isolated by Takaoka from the roots of hellebore in 1940 and later in 1963, from the roots of Japanese knotweed. *Pediomelum cuspidatum* root has been used for long in traditional Asian medicine, as a circulatory tonic, is a source of resveratrol [9].

2. Materials and Methods
2.1 Drugs and chemicals
Thiacloprid was purchased from Bayer Crop Science Ltd., India. Resveratrol was procured from Sigma-Aldrich Company

2.2 Animals and Experimental design
Adult male Wistar rats weighing 100-120g were procured from Disease Free Small Animal House (DFSAH), Lala Lajpat Rai University of Veterinary and Animal Sciences (LUVAS), Hisar. A total of 112 rats were used in the study. Rats were housed in polyacrylic cages in a group of 6 rats per cage in the departmental animal house. Bedding material (rice husk) was changed on alternate days. The animals were provided with feed and water *ad libitum* and maintained at room temperature with a natural light-dark cycle. Rats were acclimatized to laboratory conditions for 7 days before the experiment was conducted. Animal house temperature varied between 22 to 27 ºC throughout the study. The prior approval of institutional animal ethics committee was obtained for the use of experimental animals in this study.

2.3 Experimental design
Acute and subacute toxicity of thiacloprid and its amelioration by resveratrol was studied in adult male Wistar rats weighing 100-120g.

2.3.1 Experiment 1: Rats were divided in 6 groups for study of acute toxicity (24hrs), each comprising of 6 rats.
Group 1: Naive control: 3% gum acacia suspension was given orally in a single dose.

Group 2: Resveratrol (20mg/kg): Resveratrol (20mg/kg) in 3% gum acacia was administered orally in a single dose.

Group 3: Thiacloprid (40% of MTD): Thiacloprid suspension (40% of MTD) in 3% gum acacia was administered orally in a single dose.

Group 4: Thiacloprid (20% of MTD): Thiacloprid suspension (20% of MTD) in 3% gum acacia was administered orally in a single dose.

Group 5: Thiacloprid (40% of MTD) +Resveratrol (20mg/kg): Resveratrol (20mg/kg) and thiacloprid suspension (40% of MTD) in 3% gum acacia were administered separately in a single dose by oral route.

Group 6: Thiacloprid (20% of MTD) +Resveratrol (20mg/kg): Resveratrol (20mg/kg) and thiacloprid suspension (20% of MTD) in 3% gum acacia were administered separately in a single dose by oral route.

2.3.2 Experiment 2: Rats were divided in 6 groups for study of subacute toxicity (28days), each comprising of 6 rats.
Group 1: Naive control: 3% gum acacia suspension was given once daily orally for 28 days.

Group 2: Resveratrol (2mg/kg): Resveratrol (2mg/kg) in 3% gum acacia was administered orally in a single dose for 28 days.

Group 3: Thiacloprid (MTD/10): Thiacloprid suspension (MTD/10) in 3% gum acacia was administered once daily orally for 28 days.

Group 4: Thiacloprid (MTD/20): Thiacloprid suspension (MTD/20) in 3% gum acacia was administered once daily orally for 28 days.

Group 5: Thiacloprid (MTD/10) +Resveratrol (2mg/kg): Resveratrol (2mg/kg) and thiacloprid suspension (MTD/10) in 3% gum acacia were administered separately once daily orally for 28 days.

Group 6: Thiacloprid (MTD/20) +Resveratrol (2mg/kg): Resveratrol (2mg/kg) and thiacloprid suspension (MTD/20) in 3% gum acacia were administered separately once daily orally for 28 days.
A gap of 12 hours was maintained between resveratrol and thiacloprid administration

2.4 Sampling and Biochemical assay
Blood samples were taken by sterile hypodermic syringe directly from heart after anaesthetizing animals with ether in vials for blood parameters in sterile tubes for serum extraction which was used for analysis of biochemical constituents. Different biochemical parameters *viz.* BUN, Creatinine, Total protein and various enzymes like AST, ALT and GGT were determined by autoanalyzer using Erba kits.

2.5 Statistical Analysis
Data were expressed as mean ± SE. Statistical analysis of data were performed using SPSS v16 software. Data were analyzed by analysis of variance and difference between the means was compared with Duncan's multiple comparison post hoc test. A value of $p<0.05$ was considered statistically significant.

3. Results
3.1 Effect of 24h study of thiacloprid toxicity on ALT, AST and GGT levels (IU/L), BUN (mg/dl), creatinine (mg/dl) and total protein (g/dl) in serum and its amelioration by resveratrol in male rats
Effect of 24 h study of thiacloprid on ALT, AST and GGT levels (IU/L), BUN (mg/dl), creatinine (mg/dl) and total protein (g/dl) in serum of male rats and its amelioration by resveratrol in male rats is shown in Table 1 and Fig. 1. Thiacloprid treatment at higher dose increased the serum ALT level significantly ($p<0.05$) as compared to naive animals while non-significant increase in ALT level was observed at lower dose. Resveratrol co-treatment in thiacloprid treatment groups decreased the elevated ALT values non-significantly ($p<0.05$) in both higher and lower dose treatment groups. AST values were found significantly ($p<0.05$) elevated in both higher dose (40% THIA) and lower dose (20% THIA) treatment groups as compared to naive control group. Resveratrol co-treatment in thiacloprid treatment groups decreased the elevated AST values in both the higher and lower dose treatment groups non-significantly ($p<0.05$). GGT values were found elevated significantly ($p<0.05$) in higher dose treatment group compared to naive while no change was observed in lower dose treatment group. Resveratrol co-treatment with higher dose of thiacloprid treatment group decreased the elevated serum values of GGT significantly ($p<0.05$) while no change was observed on resveratrol co-treatment in lower dose thiacloprid treatment group. BUN levels were also found significantly ($p<0.05$) increased in both the higher and lower dose treatment groups of thiacloprid as compared to naive group of animals, while resveratrol co-treatment decreased the elevated BUN levels in both the higher and lower dose treatment groups of thiacloprid non-significantly ($p<0.05$) compared to groups treated with thiacloprid only. Creatinine levels were found elevated significantly ($p<0.05$) in higher dose treatment group of thiacloprid as compared to naive. Resveratrol co-treatment in thiacloprid treatment groups decreased the elevated Creatinine values non-significantly ($p<0.05$) in both higher and lower dose treatment groups compared to groups treated with thiacloprid alone. No significant ($p<0.05$) changes were observed in total protein levels in between the various treatment groups.

Table 1: Effect of thiacloprid on ALT, AST and GGT levels (IU/L), BUN (mg/dl), creatinine (mg/dl), and total protein (g/dl) in serum and its amelioration by resveratrol in male rats for 24h.

Treatment	ALT (IU/L)	AST (IU/L	GGT (IU/L)	BUN (mg/dl)	Creatinine (mg/dl)
Naive	34.20^{a} ±0.86	85.95^{a} ±2.98	1.88^{a}±0.12	16.08^{a}±1.13	0.50^{a}±0.03
RT	34.40^{a}±1.02	84.45^{a}±3.13^{a}	1.66^{a}±0.14	16.7^{a}±1.48	0.51^{a}±0.03
40% THIA	47.25^{c} ±2.87	109.52^{c} ±3.68	3.67^{c}±0.30	24.85^{d}±1.11	0.64^{b}±0.03
20% THIA	39.95^{ab}±2.19	102.40^{bc}±2.81	2.22^{a}±0.20	20.28^{bc}±1.12	0.58^{ab}±0.03
40%THIA +RT	43.77^{bc}±2.78	105.17^{bc}±3.70	3.01^{b}±0.23	21.43^{cd}±1.01	0.55^{ab}±0.04
20%THIA +RT	37.22^{a}±1.46	96.70^{b}±3.36	2.07^{a}±0.15	17.32^{ab}±1.20	0.53^{a}±0.02

Values are Mean ± S.E; n=6; Values bearing common superscripts within a column do not differ significantly (p<0.05).

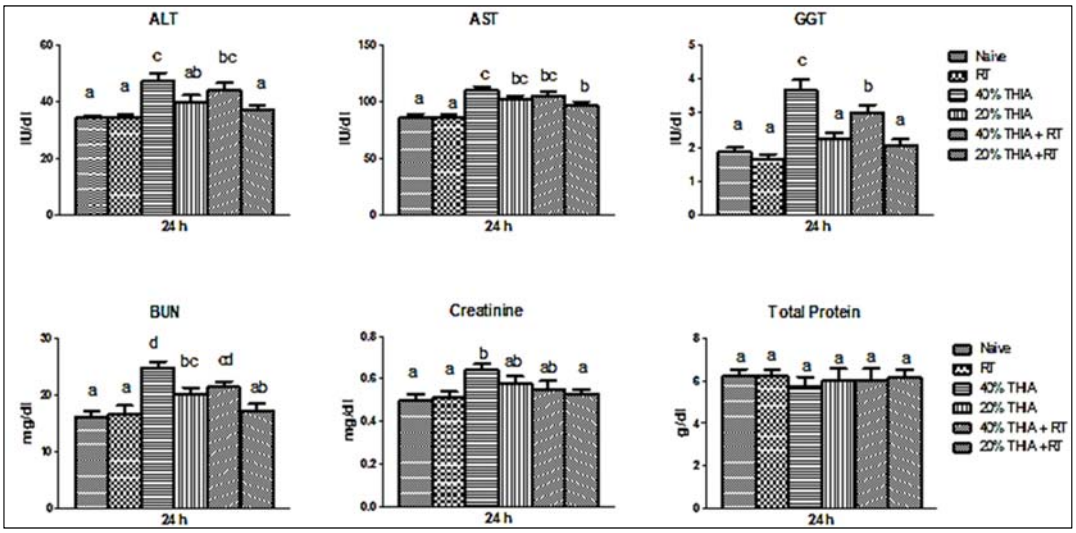

Fig 1: Effect of thiacloprid on ALT, AST and GGT levels (IU/L), BUN (mg/dl), creatinine (mg/dl) and total protein in serum and its amelioration by resveratrol in male rats for 24 h.
Bars are Mean ± S.E; n=6; Bars bearing common superscripts do not differ significantly (p<0.05).

3.2 Effect of 28 days study of thiacloprid toxicity on ALT, AST and GGT levels (IU/L), BUN (mg/dl), creatinine (mg/dl) and total protein (g/dl) in serum and its amelioration by resveratrol in male rats

Effect of acute toxicity of thiacloprid on ALT, AST and GGT levels (IU/L), BUN (mg/dl), creatinine (mg/dl) and total protein (g/dl) in serum of male rats and its amelioration by resveratrol in male rats is shown in Table 2 and Fig. 2 respectively. Thiacloprid treatment at both higher and lower dose increased the serum ALT, AST and GGT level significantly (p<0.05) compared to naive. Resveratrol co-treatment in thiacloprid treatment groups decreased the elevated ALT, AST and GGT values significantly (p<0.05) in both higher and lower dose treatment groups. BUN levels were also found significantly (p<0.05) increased in both the higher and lower dose treatment groups of thiacloprid as compared to naive group of animals, while resveratrol co-treatment decreased the elevated BUN levels significantly (p<0.05) in higher dose group and in lower dose treatment groups of thiacloprid non-significantly (p<0.05) compared to groups treated with thiacloprid only. Creatinine levels were found elevated significantly (p<0.05) in higher and lower dose treatment group of thiacloprid as compared to naive. Resveratrol co-treatment in thiacloprid treatment groups decreased the elevated creatinine values significantly (p<0.05) in higher and non-significantly (p<0.05) in lower dose treatment groups compared to groups treated with thiacloprid alone. Thiacloprid treatment at both higher and lower dose decreased the serum Total protein level significantly (p<0.05) compared to naive. Resveratrol co-treatment in thiacloprid treatment groups increased the serum Total protein values significantly (p<0.05) in both higher and lower dose treatment groups.

Table 2: Effect of thiacloprid on ALT, AST, GGT levels (IU/L), BUN (mg/dl), creatinine (mg/dl), and total protein (g/dl) in serum and its amelioration by resveratrol in male rats in 28 days study.

Treatment	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	BUN (mg/dl)	Creatinine (mg/dl)	Total Protein (g/dl)
Naive	36.48^{a} ±1.19	86.39^{a} ±3.06	1.89^{a} ±0.10	18.57^{a} ±1.02	0.51^{a} ±0.03	6.86^{a} ±0.37
RT	37.32^{a} ±1.55	88.33^{a} ±3.72	1.62^{a} ±0.12	18.91^{a} ±1.67	0.53^{a} ±0.03	6.67^{a} ±0.27
10% THIA	71.18^{d} ±2.36	184.5^{d} ±6.67	7.58^{d} ±0.49	31.71^{c} ±2.80	0.74^{c} ±0.03	5.14^{c} ±0.30
5% THIA	60.55^{c} ±1.74	151.43^{c} ±7.17	6.39^{c} ±0.48	27.63^{bc}±2.23	0.65^{bc} ±0.04	5.26^{c}±0.31
10%THIA+RT	61.72^{c} ±1.53	153.80^{c} ±6.48	4.33^{b} ±0.38	26.57^{bc} ±1.10	0.57^{ab} ±0.04	5.72^{b} ±0.28
5%Thia +RT	54.50^{b} ±3.25	126.57^{b} ±4.7	3.79^{b} ±0.33	24.90^{b} ±1.46	0.62^{ab} ±0.04	5.91^{b} ±0.43

Values are Mean ± S.E; n=6; Values bearing common superscripts within a column do not differ significantly (p<0.05).

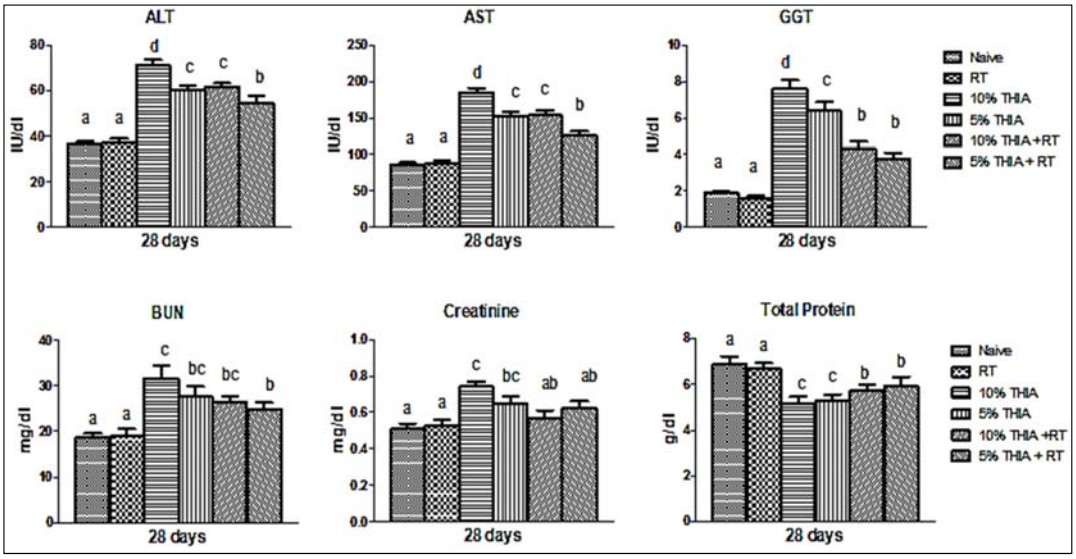

Fig 2: Effect of thiacloprid on ALT, AST and GGT levels (IU/L), BUN (mg/dl), creatinine (mg/dl), and total protein (g/dl)) in serum and its amelioration by resveratrol in male rats in 28 days study
Bars are Mean ± S.E; n=6; Bars bearing common superscripts do not differ significantly (p<0.05).).

4. Discussion

4.1 Effect of toxicity of thiacloprid on liver biomarker enzyme levels and its amelioration by resveratrol in male rats in 24 hours study

The liver functional transaminase (ALT and AST) enzyme activity in plasma are most frequently measured for diagnosis of liver diseases particularly infective hepatitis, alcoholic cirrhosis, biliary obstruction, toxic hepatitis and liver cancer [1, 21, 23].

AST is similar to alanine transaminase (ALT) in that both enzymes are associated with liver parenchymal cells. The difference is that ALT is found predominantly in the liver, with clinically negligible quantities found in the kidney, heart, and skeletal muscle, while AST is found in the liver, heart (cardiac muscle), skeletal muscle, kidneys, brain, and red blood cells. As a result, ALT is a more specific indicator of liver inflammation than AST, as AST may be elevated also in diseases affecting other organs, such as myocardial infarction, acute pancreatitis, acute hemolytic anemia, severe burns, acute renal disease, musculoskeletal diseases, and trauma.

GGT catalyzes the transfer of gamma-glutamyl moiety of glutathione to an acceptor that may be an amino acid, a peptide or water molecule. GGT plays a key role in the gamma-glutamyl cycle, a pathway for the synthesis and degradation of glutathione and xenobiotic detoxification [7]. GGT is predominantly used as a diagnostic marker for liver disease. Elevated GGT activity can be found in diseases of the liver, biliary system and pancreas.

Biochemical analysis performed in our 24 hours experiment showed that the oral intake of thiacloprid resulted in rise in liver functional enzymes activities in serum of treated animals. The elevation rate was increased significantly with increasing oral intake dose of thiacloprid. Aydin [4] have also reported a significant increase in ALT values in serum of male Wistar rats on single acute dose of thiacloprid @ 112.5mg/kg body wt. administered through oral route.

In present study, resveratrol co-treatment @ 20mg/kg b.wt. in thiacloprid administered rats slightly reduced the serum levels of liver biomarker enzymes.

4.2 Effect of toxicity of thiacloprid on creatinine and BUN levels and its amelioration by resveratrol in 24 hours study

Creatinine is derived mainly from the catabolism of creatine found in muscle tissue and its catabolism to creatinine occurs at a steady rate. Increase in creatinine levels may be the indicator of the degeneration of the kidney, heart muscle and other muscles. Creatinine is useful in early detection of nephrotoxicity induced by exogenous compounds.

The elevation of plasma levels of BUN and creatinine are considered as significant markers of renal dysfunction [2]. BUN and creatinine are waste products of protein metabolism that need to be excreted by the kidney, therefore, marked increase in plasma BUN and creatinine, as noticed in this study, confirms an indication of degenerative changes in the kidney. These changes cause disturbance in the transport system of biochemical constituents in the kidney [10, 12].

Pesticide induced increase in BUN level observed in the present study may be due to the effect of pesticides on liver function, as urea is the end product of protein catabolism. Elevated BUN is correlated with an increased protein catabolism in mammalian body or from more efficient conversion to urea as a result of increased synthesis of enzyme involved in urea production [17].A significant increase was found in creatinine and BUN levels in present study which is a classical sign that kidney was affected by thiacloprid administration.

In the present study, resveratrol co-treatment in thiacloprid treated animals failed to reduce the increased levels of urea and creatinine significantly as compared to rats treated with thiacloprid alone.

4.3 Effect of toxicity of thiacloprid on total protein level and its amelioration by resveratrol in 24 hours study

Plasma protein level is a significant indicator of health condition, metabolic and production features of the organism because of numerous roles in the patho-physiology. Therefore, plasma proteins have an exceptional significance in homeostasis as they play important roles in maintenance of colloid osmotic pressure. No significant change in total protein level in animals of thiacloprid administered groups

was observed in the present study. Resveratrol co-treatment also not resulted in any deviation of serum protein in thiacloprid administered rats.

4.4 Effect of subacute toxicity of thiacloprid on liver bio-marker enzyme levels and its amelioration by resveratrol in in 28 days study

Biochemical analysis performed in our experiment showed that the oral intake of thiacloprid resulted in rise in liver functional enzymes activities in serum of treated animals. The elevation rate was increased significantly with increasing oral intake dose of thiacloprid. Our findings are in accordance with Hendawi *et al* [11] who stated that sub-acute thiacloprid intoxication at 22.5mg/kg body wt. for 30 days induced a significant increase serum biochemical parameters related to hepatic injury: alanine aminotransferase (ALT) and alkaline phosphatase (ALP). Similarly, a significant increase in ALT, AST and GGT in animals exposed to imidacloprid at 20mg/kg b.wt./day dose has been reported [6].

In a separate study, Mohany *et al.* [14] reported that oral administration of imidacloprid at 0.21mg/kg b. wt. for 28 days in male albino rats resulted in elevation of AST, ALT, ALP and MDA levels. Also another study, subacute toxicity of repeated oral administration of imidacloprid in male white Leghorn chicks showed significant increase in AST level at 14 and 28 days of experiment, while no significant change in ALT, total protein, albumin and creatinine was seen [5].

In the present study, resveratrol co-treatment in thiacloprid administered rats reduced the serum levels of liver bio-marker enzymes. Atmaca *et al.* [3] observed a similar decrease in AST and ALT enzyme activity in the animals that received resveratrol with fluoride suggesting that resveratrol had a protective effect on the liver. The administration of resveratrol has been able to protect against the increased activity of ALT, AST, and GGT, thus demonstrating the protective effect of this polyphenol against hepatic damage [18].

4.5 Effect of toxicity of imidacloprid on creatinine and BUN levels and its amelioration by resveratrol in 28 days study

A significant increase in creatinine and BUN levels was observed in present study which is a classical sign that kidney was affected by thiacloprid administration in rats.

Likewise, in other studies increased levels of BUN and creatinine concentration have been reported in experimental animals after exposure to organophosphorus and carbamate insecticides [8, 16].

Sener *et al.* [19] also observed decrease in values of BUN and creatinine indicating its renoprotective effects. In the present study also, resveratrol reduced the increased BUN and creatinine levels due to imidacloprid exposure in rats.

4.6 Effect of subacute toxicity of thiacloprid on total protein level in serum and its amelioration by resveratrol in male rats

Significant decrease in total protein level in animals of thiacloprid administered groups was observed in the present study. Our results are similar to that of Hendawi *et al* [11] who stated that subacute thiacloprid intoxication at 22.5mg/kg body wt. for 30 days induced a significant reduction in serum total protein levels.

Qadir *et al.* [15] also found similar results. There was significant hypoprotonemia in fresh water fish *Labeorohita* at 15mg/kg dose level of imidacloprid. Decreased protein levels may be attributed to stress mediated immobilization of proteins to fulfil an increased demand for energy for the detoxification process [13]. Decreased protein level in blood may also be due to excessive loss through nephrosis [16] as kidney is mainly affected in the present study.

In the present study, decrease in total protein level may be due to their degradation and possible utilization of degraded products for metabolic purpose or hepatic dysfunction or possible loss through kidney.

Decreased protein level in imidacloprid administered group may be due to more production of free radicals that can damage DNA and proteins, either through oxidation of DNA bases (primarily guanine via lipid peroxyl or alkoxyl radicals) or through covalent binding to DNA resulting in strand breaks and cross-linking. Reactive oxygen species can also induce oxidation of critical Sulfhydryl (SH) groups in proteins and DNA, which will alter cellular integrity and function [9]. This finding is supported by previous finding of this study, which states an increased protein carbonyl levels after imidacloprid exposure.

Resveratrol co-treatment resulted in reversal of decreased values of plasma proteins in imidacloprid administered groups. This may be because of the hepato-protective and reno-protective effects of resveratrol that resulted in restoration of normal liver and kidney functions. Resveratrol also inhibited the tissue inflammation and injury which prevented the migration of proteins from plasma to tissues.

5. Conclusions

Hepatic biomarkers like serum ALT, AST and GGT were significantly increased in thiacloprid administered animals as compared to naive animals indicating its hepatotoxicity which was slightly restored by resveratrol co-treatment in thiacloprid administered groups.

Serum levels of BUN and creatinine were significantly increased in thiacloprid administered animals as compared to naive animals indicating its nephrotoxicity which were reduced to some extent by resveratrol co-treatment in thiacloprid administered groups.

No significant changes in serum protein levels were observed in various treatment groups of thiacloprid, resveratrol and their combination.

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