Assessment of permethrin induced subacute toxicity following dermal application in rats

ABSTRACT

Permethrin is an insecticide in the pyrethroid family, used for control of pests in veterinary and agriculture sector. Present study was designed to investigate the toxicity of permethrin following daily dermal application in Albino rats for 28 days. Rats were divided in to three groups having six animals in each group. Group I was treated as control and rats in group II and III were dermally applied with permethrin at dose 100 and 200mg/Kgbwt. respectively daily for 28 days. Hematological and biochemical parameters were assessed at 0, 14th and 28th day of exposure. Significant changes in level of haemoglobin, total erythrocyte count and packed cell volume was observed at both the doses of permethrin during exposure period. The present investigation also resulted in significant elevation in aspartate amino transaminase, alanine amino transaminase, alkaline phosphatase, lactate dehydrogenase activities in permethrin treated rats at both dose levels, indicated liver damage, permethrin also induced kidney damage as evidenced by significant increase in blood urea nitrogen and creatinine level. Present study suggests that permethrin is harmful when repeated dermal exposure occurs.

Keywords: Permethrin, dermal application, hematological parameters, biochemical parameters, rats.

1. INTRODUCTION

A pesticide is any substance used to kill, repel, or control certain forms of plant or animal life that are considered to be pests. Insecticides are of chemical and biological origins, used in agriculture, horticulture, forestry, gardens, homes and offices. They are also used to control vectors such as mosquitoes and ticks, that are involved in spreading human and animal diseases [1]. Pesticides have become an area of intense research due to its diverse properties and related effects. The demand for pesticide products and the concentration that they make towards agriculture efficiency are clear, but the volume of production indicates that the potential for misapplication and accidental exposure is very high. Besides being beneficial for increased crop

yield and in vector/pest control program, it has resulted in the manifestation of several health-related problems.

Pyrethroids are synthetic derivatives of natural pyrethrins from the plant *Chrysanthemum cinerariaefolium.* Synthetic pyrethroid insecticides are widely used in controlling various insect pests in agriculture, veterinary practice, and the public health arena. Permethrin belongs to the first group of pyrethroids. It is primarily a neurotoxin, acting on the nervous system of insects. The mechanism of pyrethroid action is interaction with sodium channels and the induction of prolonged depolarization in neurons causing repetitive nerve impulses, culminating in paralysis and death [2,3]. Exposure of insecticides may occur through oral, inhalation and dermal route and may cause toxic effects in man, animal and aquatic organism. Many previous oral/dermal toxicity studies have been performed for other pyrethroids insecticides [4,5,6,7], however, effect of repeated dermal exposure of permethrin on hemato-biochemistry is yet to be investigated. Therefore, present study was undertaken to conduct the subacute dermal toxicity of permethrin in rats.

2. MATERIALS AND METHODS

2.1 Experimental animals

Eighteen healthy male Wistar albino rats (6-8 weeks) weighing 150-200 (g) were used for the experiment. They were housed under normal environmental conditions of temperature and humidity and allowed to adapt to the new environment for 2 weeks before starting the experiment. Animal rooms (23±2°C) with a relative humidity of 45.0 (±15) % was maintained on a 12:12 h light/dark photoperiod. Animals were provided with food with free access standard pellet diet and

water *ad libitum*. Rats were divided into three groups, each having six animals. The maintenance of experimental rats and all the procedures implemented are in accordance with standard guidelines issued by CPCSEA followed with approval of the Institutional Animal Ethics Committee (IAEC) of the institute.

Ful form

2.2 Dose and administration

Acute dermal LD_{50} of permethrin is more than 2000 $mg.kg^{-1}$b.wt. in rats [8]. Therefore, $1/10^{th}$ dose of 2000 $mg.kg^{-1}$b.wt. (200 $mg.kg^{-1}$b.wt.) and $1/20^{th}$ dose of 2000 $mg.kg^{-1}$b.wt.(100 $mg.kg^{-1}$b.wt.) was selected for sub-acute dermal toxicity study of permethrin.

Approximately 24 hours before the test, fur was removed by shaving the dorsal area of the trunk of animals from scapulae to the wing of ilium extending the lateral midline on either side. This area represents approximately 10% of the body surface [9]. Later the animals were shaved at weekly intervals without injuring the skin. During the exposure period the test substance was held in contact with the skin with a porous gauze dressing covered with non-irritating tape to retain the gauze for at least 6 hrs. per day exposure throughout the study period of 28 days.

2.3 Collection of blood samples

Blood samples were collected from rats of different groups at 0, 14^{th} and 28^{th} day of study period from medial canthus with the help of 1ml tuberculin syringe in clean and dry vial which was coated with anticoagulant (EDTA) for estimation of hematological parameters, another vial without anticoagulant for biochemical parameters.

About 1ml blood was collected in sterile vial containing anticoagulant EDTA @ 2mg/ml of blood for hematology and remaining 1ml of blood was collected in a centrifuge tube without

anticoagulant for serum separation. After clotting of blood the vial was centrifuged @ 2000 rpm for 5 minutes and serum was collected in a sterile vial and was preserved at -20ºC for biochemical estimation.

2.4 Hematological parameters

All the hematological parameters, Hemoglobin (Hb), Packed cell volume (PCV), Total erythrocyte count (TEC), Total leukocyte count (TLC), Erythrocyte sedimentation rate (ESR), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), were estimated by method as described by [10].

2.5 Serum Biochemical Parameters

Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN) and creatinine were determined by method described by [11].

2.6 Experimental design

After acclimatization to the laboratory conditions, the animals were randomly divided into three groups (6 rats each) placed in individual cages and classified as follow:

Group I (**normal control group**): Rats received no drugs, served as control.

Group II (**Permethrin treated group**): Rats received permethrin at dose rate of 100 $mg.kg^{-1}$ b.wt. dermally daily for 28 days.

Group III(Permethrin treated group): Rat received permethrin at dose rate 200 $mg.kg^{-1}$ b.wt. dermally daily for 28 days.

2.7 Statistical Analysis

Data were reported as mean ± SE. The data were subjected to one-way analysis of variance and further subjected to Tukey's test for post hoc analysis by defining the significance level at $p<0.05$. All statistical analyses were performed using SPSS software (Version 20.0).

3. RESULT AND DISCUSSION

3.1 Behavioral signs of toxicity and mortality

No mortality or behavioural signs of toxicity were recorded in rats of group I (control) and in groups II and III during dermal exposure to permethrin. No clinical and behavioral alterations were exhibited by rats dermally applied with 100 and 200 $mg.kg^{-1}$ b.wt. of alpha-cypermethrin [12]. [13] also did not observe any signs of toxicity or mortality when administered 25 $mg.kg^{-1}$ b.wt. of cypermethrin orally in rats for 90 days.

3.2 Body weight

Non-significant increase in body weight of rats was observed on 7^{th},14^{th} and 21^{st} day of study period which increased significantly ($P<0.05$) on 28^{th} day in control group compare to '0' day value. However, body weight of rats reduced significantly ($P<0.05$) on 21^{st} day of dermal application in group II and III which differed non-significantly with values of body weight on 28^{th} day (Table no. 1),

The data showed that body weight of rats in control group increased during study period which indicates normal weight gain of rats, but in groups treated with permethrin at dose 100 $mg.kg^{-1}$

b.wt. and 200 mg.kg^{-1} b.wt. body weight decreased 21day onwards which may be due to oxidative stress induced by the insecticide which hamper the growth of rats, also the reduction in body weight may be due to the overall increased degradation of lipids and proteins [14]. Similar results were recorded by [6] in rats dermally applied with bifenthrin at dose 45 mg.kg^{-1} b.wt. for 30 days.

3.3 Hematological parameters

A significant (P<0.05) variation in values of haemoglobin, PCV and TEC was observed in group II and III on 28th day of dermal application of insecticides compare to '0' day values. The percent (%) decrease in mean values of haemoglobin on 28th day of exposure day when compared to '0' day in group II and III was 11.7 and 21.5, respectively and the percent (%) decrease in mean values of packed cell volume on 28th day of dermal exposure as compared to '0' day in group II and III, was 13.1, 14.3, respectively. Similarly, percent (%) decrease in mean values of total erythrocyte count on 28th day as compared to '0' day in group II, III was 13.1 and 22.6, respectively. The findings revealed significant changes in Hb, TEC and PCV values at both dose level of permethrin compare to 0 day values (table No. 2-4) However values of TLC, MCV, MCH and MCHC did not differ significantly at both doses. The decrease in TEC, Hb concentration, and PCV observed in this study could be due to the disruptive action of the permethrin on the erythropoietic tissue as a result of which the viability of the cells might have been affected. The important factors to be considered in reduction of TEC is the production of the hormone erythropoietin. This correlate with the kidney damage caused by permethrin [15]. Significant (P<0.05) decrease in Hb, PCV and TEC was reported by [6] when bifenthrin was administered dermally at dose 45 mg.kg^{-1} b.wt. for 30 days in rats. [16] also reported significant (P<0.05) changes in hematological parameters when administered lambda-cyhalothrin in rabbit

for seven days. Similar results were observed when rats were treated with 50 $mg.kg^{-1}$ b.wt. of cypermethrin orally for six weeks [7].

3.4 Biochemical parameters

3.41 Liver function biomarkers

Values of AST, ALT ALP and LDH in control group did not vary significantly ($P<0.05$) at 0, 14^{th} and 28^{th} days compare to '0' day. Activity of AST, significantly ($P<0.05$) increased in groups II, III on 14^{th} and 28^{th} day of exposure compare to '0' day. The percent decrease in mean values of aspartate aminotransferase on 28^{th} day as compared to '0' day, in groups II and III was 31.9 and 41.9, respectively (table no. 5).

ALT level was significantly ($P<0.05$) increased in group III on 14^{th} and 28^{th} day compare to '0' day and the values differed significantly ($P<0.05$) in group II on 28^{th} day of exposure compare to 0' day values. The percent increase in mean values of alanine aminotransferase on 28^{th} day as compared to '0' day in group II and III was 18.4 and 35.1, respectively (table no. 6).

The activity of ALP, significantly ($P<0.05$) increased in groups II, III on 14^{th} and 28^{th} day of exposure compare to '0' day values. The percent increase in mean values of alkaline phosphatase on 28^{th} day as compared to '0' day in groups II and III was, 34.7 and 56.4, respectively (table no. 7).

The activity of LDH, significantly ($P<0.05$) increased in groups II, III on 14^{th} and 28^{th} day of exposure compare to '0' day values. The percent increase in mean values of lactate dehydrogenase on 28^{th} days as compared to '0' day in groups II and III was 12.6 and 18.6, respectively (table no. 8).

The results of the present study indicate that permethrin induced liver damage at selected doses (100 $mg.kg^{-1}$ b.wt. and 200 $mg.kg^{-1}$ b.wt.) when applied dermally daily for 28 days, as shown by significant ($P<0.05$) increase in serum marker enzymes AST, ALT, ALP and LDH and the effect was dose dependent. A significant ($P<0.05$) increase in AST and ALT activities in rabbit administered with 8 $mg.kg^{-1}$ b.wt. of lambda-cyhalothrin for seven days orally, was reported by [16]. In different studies also pyrethroids induced significant increase in AST, ALT, ALP and LDH activities [6,13,17].

Liver is the first organ to face any foreign molecule that is carried out through portal circulation and it is subjected to most damage. AST, ALT, ALP and LDH are mainly used in the assessment of hepatic damage. Transaminases (AST and ALT) are responsible for detoxification processes, metabolism and biosynthesis of energetic macromolecules for different essential functions and used as specific indicators for liver damage. The increase in these enzymes may be due to liver dysfunction and disturbance in the biosynthesis of these enzymes with alteration in the permeability of the liver membrane. Being liver-specific enzyme, ALT activity is elevated due to extensive hepatic damage as a result of free radicals production and degenerative changes in hepatocytes as a result of pyrethroid metabolism [16]. The elevation in LDH activity may be due to the hepatocelluar necrosis and leakage of the enzyme into the blood [18,19]. Assay of ALP can be used for the prognosis of liver and lung disorder. ALP, cytoplasmic marker enzyme, is a known indicator of cell and tissue damage by toxic compounds [20].

first time write full form than write short form.

3.42 Kidney function biomarkers

The values of BUN and creatinine in control group varied non-significantly at 14th and 28th day compare to '0' day. Level of BUN was significantly ($P<0.05$) increased at 28th day compare

to ‘0’ day in group II and III.The percent (%) increase in mean values of blood urea nitrogen on 28th day as compared to ‘0’ day in group II and III was 18.3 and 26.8, respectively (table no. 9). Level of creatinine was significantly (P<0.05) increased in group III, on 14th and 28th day of exposure, compare to ‘0’ day, but in group II significant (P<0.05) increase in creatinine level was recorded on 14th day which differed non significantly with values on 28th day.The percent (%) decrease in mean values of creatinine on 28th day as compared to 0th day in groups II and III was 30.4 and 43.3, respectively (table no. 10).

The results revealed renal damage by permethrin, as evident from significant (P<0.05) elevation of BUN and creatinine level. [13] obtained significant (P<0.05) increase in BUN and creatinine level when administered cypermethin at dose 25 $mg.kg^{-1}$ b.wt. orally for 90 days in rats.

Deamination of amino acids in the liver leads to formation of urea at the end. Urea is a nitrogenous waste product.It is transported in the blood to the kidneys where it is excreted in the urine [21]. Elevated level of urea in blood is correlated with increase protein catabolism in mammalian body. It may also be due to more efficient conversion of ammonia to urea as a result of increased synthesis of enzyme involved in urea production [13]. Creatinine is a metabolite of creatine and is excreted completely in urine via glomerular filtration. Increase in plasma creatinine and BUN levels probably indicate renal damage, which may be attributed to urinary obstruction, which potentiates decreased secretion of urea from the body [15].

4. CONCLUSION

The findings of present investigation suggest that during long term dermal exposure, permethrin may produce adverse effect at selected doses. Permethrin may be toxic to bone marrow as evidenced by decrease in hematological parameters during exposure period and may impair

liver and kidney function, supported by significant changes in biochemical data. So, it can be concluded that permethrin is harmful at selected doses when applied dermally for 28 days. A great care should be taken during application of permethrin in agriculture, veterinary, household sectors.

Table 1: Effect of repeated 28-days dermal exposure of permethrin on body weight (g) of rats

Groups	0 day	7th day	14th day	21st day	28th day
I	141.73 ± .43^{b}	143.80 ± 2.86^{b}	146.68 ± 2.81^{ab}	149.71 ± .24^{ab}	152.66 ± .37^{a}
II	157.01 ± .66^{a}	153.61 ± .42^{ab}	150.63 ± 2.30^{ab}	148.31 ± 2.53^{b}	146.73 ± .83^{b}
III	140.48 ± .44^{a}	137.51 ± .58^{ab}	133.66 ± 3.74^{ab}	130.58 ± 3.42^{b}	128.03 ± .21^{b}

Mean values bearing common superscripts within rows (within groups) did not differ significantly (P<0.05)

WHAT IS MEANT FOR SUPERSCRIPT a, b, and ab.

Table 2: Effect of repeated 28-days dermal application of permethrin on haemoglobin (g/dl) in rats of different groups (n=6)

Groups	0 day (Mean ± S.E)	14th day (Mean ± S.E)	28th day (Mean ± S.E)	Percent decrease
I	13.16 ± 0.33^{a}	12.75 ± 0.38^{a}	12.83 ± 0.35^{a}	-
II	12.75 ± 0.38^{a}	12.50 ± 0.28^{a}	11.25 ± 0.48^{b}	11.7
III	13.58 ± 0.23^{a}	12.91 ± 0.23^{a}	10.65 ± 0.55^{b}	21.5

Mean values bearing common superscripts within rows (within groups) did not differ significantly (P<0.05)

FROM WHERE IT IS COME, YOU HAVE NOT MENTIONED IT IN THE TEST CHEMICALS

Table 3: Effect of repeated 28-days dermal application of fipronil and permethrin on Packed cell volume (%) in rats of different groups (n=6)

Groups	0 day (Mean ± S.E)	14th day (Mean ± S.E)	28th day (Mean ± S.E)	Percent decrease
I	42.10 ± 1.82[a]	41.83 ± 1.98[a]	39.18 ± 2.30[a]	-
II	46.10 ± 2.66[a]	44.28 ± 1.70[a]	40.05 ± 1.11[b]	13.1
III	38.65 ± 1.68[a]	36.83 ± 1.43[a]	33.11 ± 1.14[b]	14.3

Mean values bearing common superscripts within rows (within groups) did not differ significantly (P<0.05)

Table 4: Effect of repeated 28-days dermal application of fipronil and permethrin on Total erythrocyte count (10^6/µl) in rats of different groups (n=6)

Groups	0 day (Mean ± S.E)	14th day (Mean ± S.E)	28th day (Mean ± S.E)	Percent decrease
I	7.48 ± 0.18[a]	7.11 ± 0.09[a]	7.16 ± 0.22[a]	-
II	7.96 ± 0.36[a]	7.70 ± 0.21[a]	6.91 ± 0.14[b]	13.1
III	7.90 ± 0.17[a]	7.13 ± 0.21[a]	6.11 ± 0.15[c]	22.6

Mean values bearing common superscripts within rows (within groups) did not differ significantly (P<0.05)

Table 5: Effect of repeated 28-days dermal application of fipronil and permethrin on Aspartate aminotransferase (IU/L) in rats of different groups (n=6)

Groups	0 day (Mean ± S.E)	14th day (Mean ± S.E)	28th day (Mean ± S.E)	Percent increase
I	52.53 ± 1.98[a]	50.38±2.58[a]	50.66 ± 1.14[a]	-
II	53.45 ± 1.93[c]	60.96±2.13[b]	70.51 ± 1.62[a]	31.9
III	53.06 ± 2.82[c]	62.18±1.39[b]	75.30 ± 2.06[a]	41.9

Mean values bearing common superscripts within rows (within groups) did not differ significantly (P<0.05)

Table 6: Effect of repeated 28-days dermal application of fipronil and permethrin on Alanine aminotransferase (IU/L) in rats of different groups (n=6)

Groups	0 day (Mean ± S.E)	14th day (Mean ± S.E)	28th day (Mean ± S.E)	Percent increase
I	37.65 ± 1.24[a]	38.48 ± 1.53[a]	38.31 ± 0.97[a]	-
II	39.58 ± 1.07[b]	42.96 ± 0.72[b]	46.88 ± 2.71[a]	18.4
III	36.45 ± 1.75[c]	44.91 ± 1.64[b]	49.28 ± 1.45[a]	35.1

Mean values bearing common superscripts within rows (within groups) did not differ significantly (P<0.05)

Table 7: Effect of repeated 28-days dermal application of fipronil and permethrin on Alkaline phosphatase (IU/L) in rats of different groups (n=6)

Groups	0 day (Mean ± S.E)	14th day (Mean ± S.E)	28th day (Mean ± S.E)	Percent increase
I	48.93 ± 1.95[a]	50.16 ± 1.21[a]	51.65 ± 2.49[a]	-
II	50.45 ± 3.23[c]	57.15 ± 2.15[b]	67.98 ± 2.11[a]	34.7
III	49.28 ± 1.08[c]	60.41 ± 1.71[b]	77.08 ± 2.11[a]	56.4

Mean values bearing common superscripts within rows (within groups) did not differ significantly (P<0.05)

Table 8: Effect of repeated 28-days dermal application of fipronil and permethrin on Lactate dehydrogenase (IU/L) in rats of different groups (n=6)

Groups	0 day (Mean ± S.E)	14th day (Mean ± S.E)	28th day (Mean ± S.E)	Percent increase
I	214.08 ± 1.78[a]	215.05 ± 2.40[a]	211.46 ± 1.44[a]	-
II	207.43 ± 1.25[c]	214.11 ± 1.38[b]	233.73 ± 2.93[a]	12.6
III	207.03 ± 1.37[c]	219.63 ± 1.06[b]	245.61 ± 3.24[a]	18.6

Mean values bearing common superscripts within rows (within groups) did not differ significantly (P<0.05)

Table 9: Effect of repeated 28-days dermal application of fipronil and permethrin on Blood urea nitrogen (mg/dl) in rats of different groups (n=6)

Groups	0 day (Mean ± S.E)	14th day (Mean ± S.E)	28th day (Mean ± S.E)	Percent increase
I	35.83 ± 1.19[a]	35.81 ± 1.31[a]	36.03 ± 1.11[a]	-
II	35.65 ± 1.21[b]	38.93 ± 1.24[ab]	42.20 ± 1.34[a]	18.3
III	36.81 ± 1.19[b]	38.61 ± 1.30[b]	46.71 ± 1.20[a]	26.8

Mean values bearing common superscripts within rows (within groups) did not differ significantly (P<0.05)

Table 10: Effect of repeated 28-days dermal application of fipronil and permethrin on Creatinine (mg/dl) in rats of different groups (n=6)

Groups	0 day (Mean ± S.E)	14th day (Mean ± S.E)	28th day (Mean ± S.E)	Percent increase
I	1.03 ± 0.05[a]	1.08 ± 0.06[a]	0.97 ± 0.02[a]	-
II	0.92 ± 0.04[b]	1.09 ± 0.05[a]	1.20 ± 0.02[a]	30.4
III	1.06 ± 0.04[c]	1.20 ± 0.05[b]	1.52 ± 0.12[a]	43.3

Mean values bearing common superscripts within rows (within groups) did not differ significantly (P<0.05)

References:

1. Gupta, R. C. and D. Milatovic.. Insecticides. Biomarkers Toxicol, 2014; 389-407.
2. Garg, S.K. Vety toxicol*: (a textbook as per VCI syllabus)*. CBS Publishers and Distributors Pvt. Ltd. New delhi,178; 2018 .
3. Chrustek, A., I. Hołyńska-Iwan, I. Dziembowska, J. Bogusiewicz, M. Wróblewski, A. Cwynar, and D. Olszewska-Słonina. Current Research on the Safety of Pyrethroids Used as Insecticides. Medicina. 2018; 54(4):61.
4. Gabbianelli, R., M.L. Falcioni, C. Nasuti, F. Cantalamessa, I. Imadaand M. Inoue.. Effect of permethrin insecticide on rat polymorphonuclear neutrophils. Chemico-Biol Interactions. 2009; 182(2-3):245-252.
5. Yavuz, O., A. Aksoy, Y.K. Das, M.Y. Gulbahar, G.F. Yarim, M. Cenesiz, E. Atmaca and D.Guvenc. Repeated-dose 14-day dermal toxicity of different combinations of some synthetic pyrethroid insecticides, piperonylbutoxide, and tetramethrin in rats. Cutan and Ocular Toxicol. 2010; 29(1):16-25.

6. Dar, M.A., Raina, R., Pankaj, N.K., Sultana, M., Verma, P.K. and Mehraj, A. Sub-acute dermal toxicity of bifenthrin with special reference to haemato-biochemical changes in rat. J Vety Pharmacol and Toxicol. 2012; 11(1-2):62-64.
7. Omonona, A.O. and T.A. Jarikre. Comparative toxicity of cypermethrin following oral and dermal routes in guinea pigs and the ameliorative effect of ascorbic acid. Res J pharmaceut, Biol and Chem Sci. 2015; 6(1):1552-1556.
8.
9. U.S. EPA (United states Environmental Protection Agency) HED Records centre series 361 science reviews file R099687. United States Environmental Protection Agency Washington D.C, pp 1-41; 2003.
10. Michael, J.D. and A.H. Mannfred. Hand book of Toxicology 2nd edition, CRC press, Newyork, USA. 2001; 98-99.
11. Wills, T.B. Hematology of water buffalo (*Bubalisbubalis*). In: Weiss D.J. and Wardrop K.J. (eds.). Schalm's Veterinary Hematology, 6thEdition.,Blackwel publishing, Oxford, England. 2010; 927-93.
12. Teitz, N.W. Textbook of clinical chemistry. Publ. W.B. Saunders Co. Philadelphia. 1999; 582-584.
13. Yavuz, O.,H. Kayir, I. Yilmaz, G. Ulusoy,G. Cakir and I.T. Uzbay. Subacute neurobehavioral effects of dermally-applied alphacypermethrin in rats. Revue de médecine vétérinaire. 2009; 160(4):184-91.
14. Abbassy, M.A. and A.H. Mossa. Hematobiochemical effects of formulated and technical cypermethrin and deltamethrin insecticides in male rats. J Pharmacol and Toxicol. 2012; 7(7):312-321.
15. Mossa, A.H. and M.A. Abbassy. Adverse haematological and biochemical effects of certain formulated insecticides in male rats. Res J Environ Toxicol. 2012 ,6(4):160-168.
16. Dar, S.A. and R. Kaur. Hematobiochemical Evaluation of Dermal Subacute Cypermethrin Toxicity in Buffalo Calves. Toxicol Int. 2014; 21(3): 283-287
17. Basir, A., A Khan, R. Mustafa,M. Z. Khan, F. Rizvi, F. Mahmood and A. Yousaf. Toxicopathological effects of lambda-cyhalothrin in female rabbits (Oryctolaguscuniculus). Human & Exp Toxicol. 2011; 30(7):591-602.
18. Dar, M.A.,A.H. Mir, A.A. Dev ,A.A. Bhat, N. Sharma, N.Pagrut and S.A. Choudhary. An assessment of toxicological profile of pyrethroids in animals - A Review, Int J current res in biosci and plant biol. 2015; 2(11):19-26.
19. Mossa, A.T.H., E.S. Swelamand S.M.M.Mohafrash. Sub-chronic exposure to fipronil induced oxidative stress, biochemical and histopathological changes in the liver and kidney of male albino rats.Toxicol Reports. 2015; 2:775-784
20. Al-Harbi, M.S. Fipronil Induced hepatotoxicity, genotoxicity, oxidative stress and the possible ameliorative effect of ginseng. Brit Pharmaceut Res. 2016; 14(5):1-14.
21. Al-Anany, M.G.E.,A.M. Kamal and K.E. Saied. Effects of curcumin and/or quercetin on nicotine-induced lung and liver toxicity in adult male albino rat. Al-azharAssiut Medi J. 2015; 13(2):93-103.
22. Khan, A., L. Ahmad and M.Z. Khan. Hemato-Biochemical Changes Induced by Pyrethroid Insecticides in Avian, Fish and Mammalian Species. *Int Agri & bio*. 2012; 14(5).