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RESEARCH ARTICLE

RESTITUTIVE PROPERTIES OF CURCUMA LONGA ON CYPERMETHRIN INDUCED SWISS-ALBINO MICE (MUS MUSCULUS)

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Abstract

The present investigation delves into the reparative efficacy of Curcuma longa extract in mitigating the deleterious effects induced by varying concentrations of cypermethrin in Swiss albino mice (Mus musculus). A significant increase was observed at the highest dose of cypermethrin (200 mg/kg of body weight of Swiss albino mice) in biochemical parameters namely Aspartate Aminotransferase (AST), 49 %; Alanine Aminotransferase (ALT), 58 %; Blood Urea Nitrogen (BUN), 108 %; Creatinine 247 %. The discernible outcome is evidenced by a gradual recovery in the damage inflicted by cypermethrin. Significant changes were observed, including an approximate 16% decrement in AST, 7% reduction in ALT, substantial 45% decline in BUN levels, and a pronounced 76.16% decrease in creatinine levels. Further, haematological indices demonstrate a commendable recovery pattern, with a 10% resurgence in neutrophils, 3% restitution in lymphocytes, 6% recuperation in basophils, 2% restoration in monocytes, and 10% revival in eosinophils. These findings substantiate a promising therapeutic role for C. longa extract within the realm of pharmaceutical industries, signifying its potential utility in countering cypermethrin-induced physiological disbalance.

Introduction:-

Agriculture has long stood as the cornerstone of our nation, supporting over half of the population. To maximize yields, the farming community relies heavily on insecticides. In their quest to combat the pervasive threat of harmful insects in agricultural lands, which significantly diminishes crop yields, farmers resort to various insecticides readily available in the open market. Among them, Cypermethrin has emerged as a valuable asset for realizing optimal crop yields. However, its widespread use comes at a cost, unleashing sweeping consequences on non-target organisms, including humans.

Cypermethrin, classified as a fourth-generation type II synthetic pyrethroid (WHO) poses toxicity risks in mammals due to accidental or intentional exposure through inhalation, skin contact, or ingestion [14]. Owing to its lipophilic structure, it accumulates in body fat, skin, liver, kidneys, adrenal glands, ovaries, and brain. Toxic oral doses range from 100 to 1000 mg/kg of body weight, with potentially lethal acute oral doses at 10–100 g [10,11,22]. Despite pyrethroid insecticides having modest toxicity, their persistence in mammalian tissues raises concerns [10].

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Cypermethrin adversely affects mammalian immune systems, functioning as a neurotoxic agent, leading to clinical and/or behavioural issues [4,12,22,24]. Furthermore, the haematological profiles of rodents are significantly altered due to cypermethrin toxicosis [17,18,19,22,23]. Numerous studies have demonstrated cypermethrin's potential to induce hepatotoxicity [2,8,32,35] and nephrotoxicity [15,16,21,25] in mice and rats. In India, cypermethrin's indiscriminate and unregulated use in agriculture and public health has dramatic effects on various non-target species, including humans [1].

Curcuma longa (turmeric) is a rhizomatous perennial herb from the Zingiberaceae family, known for its yellow powder. Its active compound, curcumin, exhibits diverse chemical, biological, and pharmacological properties, including anti-inflammatory and antioxidant effects [7,29]. Moreover, curcumin has documented anticarcinogenic properties against chemically induced cancers, spanning from skin malignancies to digestive system cancers [13,31], even extending to cell lines [5,26,33]. Numerous studies highlight curcumin's promising remedial roles against chemically exposed mammals [30].The present investigation aims to assess the potential of C. longa extract in mitigating the effects of cypermethrin exposure on Swiss albino mice (Mus musculus), focusing on clinic-haematological endpoints.

Materials and Methods:-

Test Chemicals:
Cypermethrin was procured from the local market of Bhagalpur with the trade name Cypren manufactured by Swisston insecticides Private ltd, India.

Extract Preparation of Curcuma longa:
After drying at 37℃ for 24 hrs, the rhizomes were grounded into powder. Exposure to sunlight was avoided to prevent any loss of active components. One litre of double distilled water was mixed with 200 g of powdered C. longa rhizome, filtered with nitrocellulose membrane and the extracted liquid was subjected to water bath evaporation at 70℃ for 7-10 hrs daily for 2-3 days until a semi solid state of liquid extract was obtained. The semisolid extract was kept in the deep freezer at -20℃ overnight and then subjected to freeze drying. Extract obtained by this method was then weighted and stored at 22℃ in desiccators until further use [30].

Animals:
Twenty-five mature Swiss albino mice of same cohort with average body weight ranging from 22-25 gm which were reared in animal house of PG Department of Zoology, Bhagalpur University, Bhagalpur, Bihar were taken. Food and water to mice were provided ad libitum (prepared mixed formulated feed by the laboratory itself). Animals were housed in colony rooms with 12 hrs light/dark cycle at 22 ± 2 ℃ during the period (Jan-March, 2023) of experimentation.

Experiment Protocol.
Swiss albino mice were randomly divided into 5 groups, (5 mice in each group) exposed to different concentration of cypermethrin (for the first 7 days). Group I was given tap water and standard feed (control group). Group II was given 50 mg/kg body weight (b.w) of cypermethrin and standard feed. Group III was given 100 mg/kg b.w of cypermethrin and standard feed. Group IV was given 50 mg/kg b.w of cypermethrin and standard feed. Group V was given 200 mg /kg b.w of cypermethrin and standard feed. For the next 28 days all the groups except control group i.e., Group I, were given a similar treatment dose of C. longa extract (50 mg/kg b.w of mice) along with tap water and the standard feed.

During the experiment, clinical symptoms of all animals such as different activities and mortality were monitored daily. Feed and water intakes were also noted. Any abnormal clinical symptoms were observed daily in all groups of mice. At the end of 35 days blood samples were collected from the retro-orbital plexus for further investigation.

Haematology
At the end of the exposure period of one week, blood samples were collected aseptically from the retro-orbital plexus of the mice, under controlled conditions (Hoff et al., 2000) in heparinized 70ml microhematocrit capillary vials, each containing an anticoagulant of 0.5mL Ethylene diamine tetra acetate (EDTA). The peripheral blood cell indicators, viz. total erythrocyte (RBC) count (TEC, 10^6 cells/mm^3), total leucocyte (WBC) count (TLC, 10^3 cells/mm^3), differential leucocyte count (DLC, which included numbers of basophils, eosinophils, lymphocytes, monocytes, and neutrophils per 100 cells), total thrombocyte count (TTC, 10^4 cells/mm^3) and

haemoglobinconcentration (Hb, g/dL) were evaluated. These tests were conducted according to Schalm method [28]. Similarly, blood samples were again collected from the retro-orbital plexus of the mice after the period of treatment from C. longa. Parallel investigations were made for the corresponding samples to observe the degree of cure in the cypermethrin exposed mice.

Statistical Analysis

The data were analysed for significancy by using Statistica 8.0 and SPSS software. ANOVA and the t-test were used to determine significant differences among groups. The results were expressed as mean ± standard error (SE). Values of $p < 0.05$ were considered significant.

Result and Discussion:-

Clinical manifestations

Control mice remained highly energetic with voracious appetite throughout the experiment. Though cypermethrin did not elicit death, salivation, and seizures in the experimental mice; however, they showed few characteristic symptoms such as decrease in the feed intake, hind limb jerking, laboured breathing, loss in body weight under different doses of cypermethrin. (Table-1)

Table 1:- Clinical manifestations in mice after exposure with cypermethrin.

Clinical and behavioural signs	Group I	Group II	Group III	Group IV	Group V
Death	×	×	×	×	×
Decrease in feed intake	×	√	√	√	√
Hind limb jerking	×	√	√	√	√
Laboured breathing	×	√	√	√	√
Salivation	×	×	×	×	×
Seizures	×	×	×	×	×

Physiological parameters.

The effects of cypermethrin on selected physiological parameters in Swiss albino mice are shown in Table 2. The highest body weight gain (+ 6.10 g) was measured in the control group as compared to the treated group. The greatest reduction in body weights (1.93 times) among the cypermethrin-administered groups was observed in Group V. These decreases were statistically significant by ANOVA ($p < 0.05$). The decrease observed in body weight is thought to be due to the decrease in feed intake of mice in the cypermethrin treated groups. It was observed that the body weight decreased considerably in male rats when administered cypermethrin at a dose of 500 mg/kg of body weight [14]. The digestive, behavioural, morphological, and histopathological effects of male and female albino rats (Rattus norvegicus) exposed to cypermethrin at doses of 5 and 20 mg/kg/day orally for 30 days were also observed [12]. However, it was also reported that in rats exposed to cypermethrin at 50 mg/kg body weight for 2 to 4 weeks, had no effect on the feed and water intake of the rats compared to the control group, but caused significant changes in body and various organ weights. [27]

Table 2:- Effects of cypermethrin on certain physiological parameters and its remedy by administration of C. longa extract. F.C = Feed consumption.

Parameters	Group I	Group II	Group III	Group IV	Group V
Initial body weight	22.68±0.62	23.58±0.95	22.98±0.65	23.56±0.61	23.65±0.63
Final body weight	28.78±0.81	28.60±0.68	27.52±0.77	27.01±0.78	26.81±0.80
Body weight gain	+6.10	+5.02	+4.54	+3.45	+3.16
F.C. 7^{th} day(g)	149.00	144.50	139.00	134.60	128.50
F.C. 14^{th} day(g)	153.20	145.40	142.10	137.70	133.30
F.C. 21^{st} day(g)	152.40	145.90	143.70	140.5	137.40
F.C. 28^{th} day(g)	153.70	146.60	145.00	142.80	140.60
F.C 35^{TH} day(g)	153.30	148.20	147.6	144.4	141.9

Serum Parameters:

The effect of cypermethrin on selected biochemical parameters (Table 3). Aspartate Aminotransferase (AST) and Alanine Aminotransferase ALT enzyme activities, Blood Urea Nitrogen (BUN) and Creatinine levels increased significantly compared to the control group, depending on the increase in the dosages of cypermethrin administered.

The highest increase in all 4 parameters (AST, 49%; ALT, 58%; BUN, 108%; Creatinine, 247%) was detected in Group V. It was reported that serum AST and ALT activities were increased in wistar rats fed on escalating doses of cypermethrin [6]. It was also observed that serum AST and ALT enzyme activities, BUN and creatinine levels increased considerably in rats exposed to cypermethrin at a dose of 12 mg/kg by oral gavage for 30 consecutive days [2]. Statistically significant increases were found in serum AST, ALT and ALP enzyme activities in male albino rats weighing approximately 120–50 g exposed to cypermethrin at 30 mg/kg dose for 28 consecutive days. [3]

The two enzymes AST and ALT are the most significant markers of liver injury. The activity of these two enzymes in the blood increases when the liver is affected by a disease, medication, chemical, or radioactive harm. Kidney injury is indicated by the levels of BUN and creatinine. When proteins are digested, ammonia is created as a byproduct. Muscle cells naturally produce a chemical called creatinine, which is also excreted by kidney. Blood levels of urea and creatinine rise because of renal damage. The increase in AST and ALT enzyme activity, as well as the blood levels of BUN and creatinine in mice given cypermethrin, are indications of liver and kidney cell death or damage

Table 3:- Serum analysis of different groups of Swiss albino mice after cypermethrin exposure of 7 days.

Parameters	Group I	Group II	Group III	Group IV	Group V	F value
AST (U/L)	76.00±1.56	81.00±2.51	89.00±1.99	99.00±2.03	105.00±1.87	1.37
ALT (U/L)	48.00±1.18	53.00±1.66	59.00±1.18	68.00±2.33	74.00±1.67	10.50
BUN (mg/L)	124.00±2.99	148.00±1.76	173.00±1.12	217.00±1.34	258.00±1.56	0.41
Creatinine (mg/L)	4.16±0.49	7.28±0.69	9.64±0.70	11.35±0.98	14.45±1.32	38.8

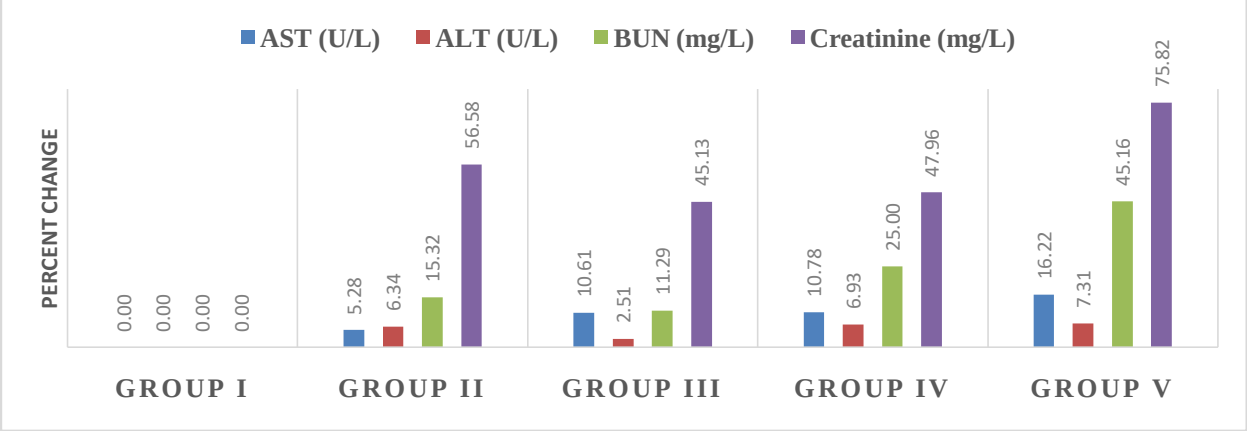
With the administration of C. longa extract there has been a considerable amount of improvement in the figures (Table 4). The highest recovery in all four measured biochemical parameters (AST,16%; ALT, 7 %; BUN, 45%; Creatinine, 76%) was detected in Group V.

Relative decrease in enzyme AST, ALT, BUN and creatinine can be attributed to the hepatoprotective role of C. longa extract (Fig-1). Curcumin plays a pertinent role in reducing the oxidative stress induced by the exposure of cypermethrin. It can modulate various signaling pathways involved in the cellular response to oxidative stress, thus attenuating the levels of enzymatic activity caused by different dosage of cypermethrin

Table 4:- Serum analysis of different groups of Swiss albino mice after treatment of cypermethrin exposed mice with C. longa extract.

Parameters	Group I	Group II	Group III	Group IV	Group V	F value
AST (U/L)	77.00±1.08	78.00±1.46	82.00±1.35	92.00±1.93	102.00±1.43	1.13
ALT (U/L)	49.00±0.96	51.00±1.85	59.00±1.09	65.00±2.02	74.00±1.37	9.86
BUN (mg/L)	124.00±1.35	129.00±1.18	159.00±0.99	186.00±1.14	202.00±1.45	0.63
Creatinine (mg/L)	4.18±0.86	4.95±0.54	7.80±0.91	9.40±0.63	11.35±1.12	32.65

Fig 1:- Relative Change in Activity of Different Enzymes after recovery from Curcuma longa extract.



Hematological profile

Table 5:- Haematological analysis in different groups of Swiss albino mice after cypermethrin exposure of 7 days.

Parameters/ Groups	Group I	Group II	Group III	Group IV	Group V	F value
TLC (× 10^3 cells / mm^3)	5.91 ± 0.26	6.23± 0.27	8.99± 0.13	11.56± 0.32	17.25± 0.08	9.46
TEC (× 10^6 cells / mm^3)	5.7± 0.23	4.5± 0.22	3.9± 0.13	3.1± 0.41	2.8± 0.09	1.33
Platelets (× 10 cells / mm3)	9.43 ± 0.48	8.45± 0.52	8.102± 0.23	7.953± 0.29	7.65± 0.91	3.43
Haemoglobin (gm/dl)	13.2± 0.34	11.9± 0.27	10.3±0.25	9.5± 0.12	7.7± 0.31	0.98

Total leucocyte count (TLC,) increased significantly compared to the control group, depending on the increase in the dosages of cypermethrin administered (Table-5) highest increase (TLC, 113%) being recorded for group V when compared to control. This can be owed to sequestration of foreign toxic element in the blood of Swiss albino mice. Correspondingly there was a significant lowering in the other parameters as compared to control group, highest decrease being recorded for group V (TEC, 50.8 %; Platelets 18.8%; Hb, 41.6%). This can be attributed to the increasing oxidative stress caused by escalating doses of cypermethrin.

With the administration of C. longa extract there were perceived changes in the above parameters. The highest decrease for TLC (27%) was detected in Group V. Similarly highest increase in (TEC, 39.2%; Platelets, 5.2%; Hb,15.5%) in other parameters was also found in group V when compared to parallel groups of exposed mice (Fig 2). These results can be attributed to the anti-oxidative role of curcuma longa extract, which neutralizes the free radicals produced due to consumption of different dosage of cypermethrin.

Table 6:- Haematological analysis of different groups of Swiss albino mice after treatment of cypermethrin exposed mice with Curcuma longa extract.

Groups / Parameters	Group I	Group II	Group III	Group IV	Group V	F value
TLC (× 10^3 cells / mm^3)	5.89± 0.29	6.04± 0.27	7.26± 0.13	8.12± 0.32	12.56± 0.08	10.87
TEC (× 10^6 cells / mm^3)	5.8± 0.26	5.1± 0.21	4.8± 0.14	4.3± 0.32	3.9± 0.08	1.67
Platelets (× 10^5 cells / mm^3)	9.455± 0.58	8.756± 0.52	8.482± 0.21	8.253± 0.31	8.056± 0.94	3.23
Haemoglobin (gm/dl)	13.1± 0.33	12.6± 0.11	11.4± 0.26	10.5± 0.25	8.9± 0.29	1.08

Anti-oxidant properties of C. longa were reported [29]. The role of C. longa in combatting inflammation of arthritis in by collagen in wistar rats is widely known [7]. The protective role of C. longa was also reported in CCl_4 induced liver damage in Swiss albino mice.[20]

Differential leucocyte counts for groups of mice both under the exposure of cypermethrin and after treatment with C. longa extract has shown incessant decrease in leucocyte components, lowest recorded in group V (Neutrophils, 62%; Lymphocyte, 19%; Basophils, 45%; Monocyte 77.9%; Eosinophils, 26%). Similar biochemical observation in albino mice was stated under cypermethrin toxicity.[34] Comparable figures were also testified while assessing immunomodulatory properties of Tinospora in CCl_4 induced rats.[9]

Fig 2:- Relative Change in haematological profile after recovery from C. longa extract.

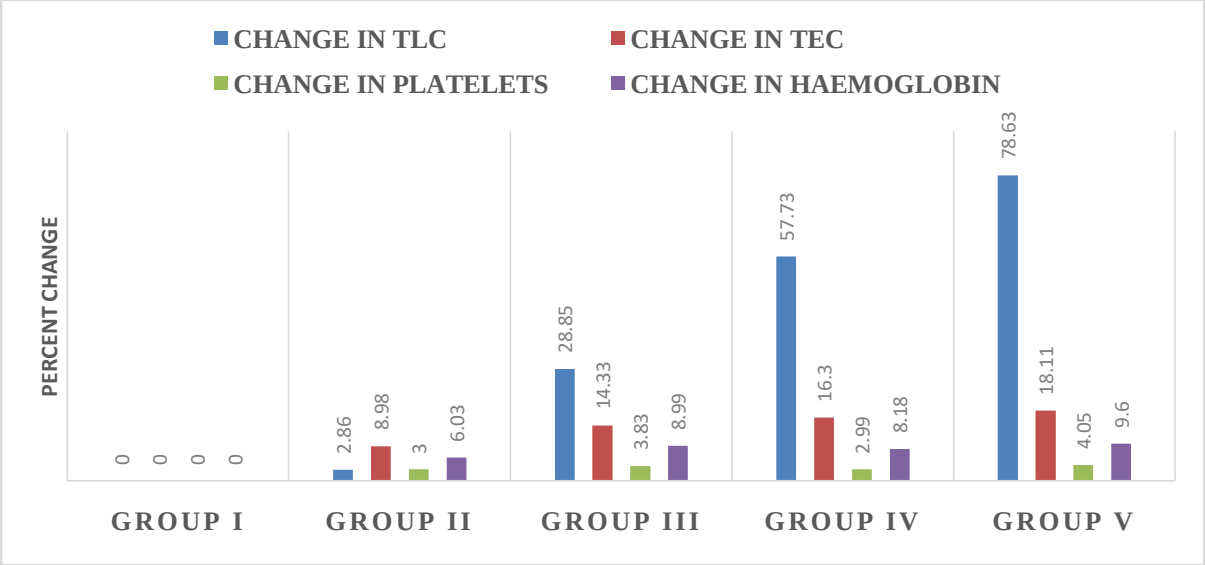


Table 7:- Differential Leucocyte Count of different groups of Swiss albino mice on cypermethrin exposed mice.

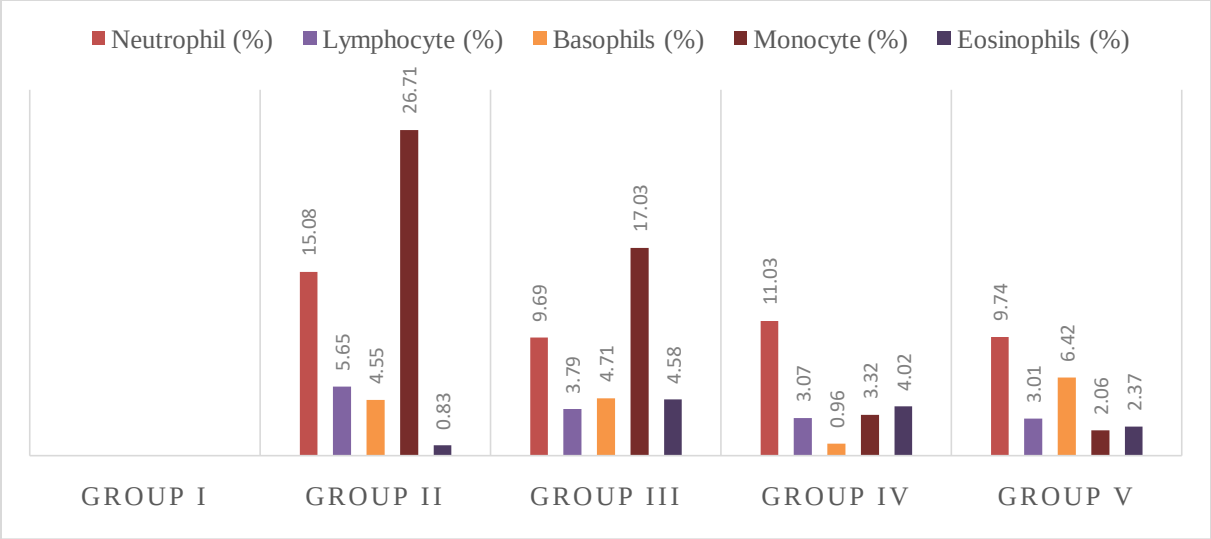
Groups /	Neutrophil (%)	Lymphocyte (%)	Basophils (%)	Monocyte (%)	Eosinophils (%)	F value
GROUP I	18.51 ± 0.23	74.60 ± 0.38	1.24 ± 0.25	4.62 ± 0.37	1.03 ± 0.08	7.34
GROUP II	13.60 ± 0.32	83.20 ± 0.23	0.98 ± 0.28	1.23 ± 0.15	0.99 ± 0.10	1.34
GROUP III	12.56 ± 0.47	84.60 ± 0.17	0.83 ± 0.19	1.04 ± 0.04	0.97 ± 0.21	2.09
GROUP IV	10.93 ± .07	86.30 ± 0.21	0.78 ± 0.14	1.10 ± 0.34	0.89 ± 0.11	56.9
GROUP V	8.95 ± 0.10	88.50 ± 0.25	0.67 ± 0.12	1.02 ± 0.27	0.76 ± 0.07	0.36

Table 8:- Differential Leucocyte Count of different groups of Swiss albino mice after treatment of cypermethrin exposed mice with C. longaextract.

Groups/ Parameters	Neutrophil (%)	Lymphocytes (%)	Basophils (%)	Monocyte (%)	Eosinophils (%)	F value
GROUP I	18.35± 0.2	74.90 ± 0.33	1.34 ± 0.28	4.35 ± 0.19	1.06 ± 0.03	7.95
GROUP II	16.25±0.31	79.30 ± 0.21	1.12 ± 0.27	2.32 ± 0.16	1.01 ± 0.13	1.09
GROUP III	14.23± 0.44	82.10 ± 0.18	0.96 ± 0.16	1.72 ± 0.36	0.99 ± 0.24	2.97
GROUP IV	12.86± 0.88	84.35 ± 0.21	0.83 ± 0.17	1.18 ± 0.07	0.93 ± 0.12	45.8
GROUP V	10.66± 0.11	86.6 ± 0.23	0.81 ± 0.13	1.05 ± 0.26	0.88 ± 0.09	0.67

There was a notable recovery with the administration of C. longa extract, peak being noticed in group V (Neutrophils, 10%; lymphocyte, 3%; basophils, 6%; monocyte, 2%; eosinophils, 10) as compared to parallel group infused with similar dosage (Fig-3). This can be explained by the redressal of oxidative stress caused by cypermethrin toxicosis. C. longa extract regulates ROS levels by countering chronic stress and by controlling enhanced ROS signalling.

Fig 3:- Relative Change in Differential Leucocyte Count of different groups after recovery from C. longa extract.



It was reported increase in TLC and decrease in TEC, Platelets and Hb in similar studies conducted on haematological parameters of rat model.[31] Hepatoprotective and immunomodulatory properties of aqueous extract of C. longa in CCl_4 intoxicated Swiss albino mice was also conducted in similar studies.[31] It was also testified that the C. longa extract mitigates the effect of liver damage induced by CCl_4.[20]

Conclusions:-

The observed changes in physiology, clinical markers, and behaviour may be attributed to cypermethrin-induced oxidative stress on haematological profiles, leading to degenerative alterations in the liver and kidneys of experimental mice. The fluctuations in peripheral blood parameters such as TEC, TLC, platelets, and haemoglobin, along with differential leukocyte count, can be linked to the toxic impact of cypermethrin. These irregularities were effectively mitigated by the administration of C. longa extract, which normalized the variations and restored the values toward baseline levels. Consequently, it can be inferred that curcumin, the primary component in C. longa extract, exhibits promising potential in preserving its inherent therapeutic properties. This study serves as an initial exploration into the maintenance of the efficacy of C. longa extract, whether in its hepatoprotective capacities or in reinstating peripheral blood parameters. Its noteworthy to predict the radical implications of curcumin (C. longa extract) as far as mammals are concerned.

Conflict Of Interest

We declare that there is no conflict of interest with any other authors regarding the content of this paper.

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