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## Haematological changes by combined exposure of cypermethrin and deltamethrin and their amelioration by *Withania somnifera* and resveratrol in male rats

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### Abstract

The combined exposure of cypermethrin and deltamethrin was given in adult male Wistar rats and their amelioration by *Withania somnifera* and resveratrol on haematological alterations was investigated up to 28 days. The combined treatment of cypermethrin and deltamethrin caused significant decrease in total erythrocyte count, total leucocyte count, haemoglobin, packed cell volume, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration. It caused increase in neutrophil count and decrease in lymphocyte count. In the cypermethrin plus deltamethrin plus *Withania somnifera* group and cypermethrin plus deltamethrin plus resveratrol group, both *Withania somnifera* and resveratrol co-treatment restored the changes to normal observed following combined cypermethrin and deltamethrin exposure in rats. The present study showed that combined cypermethrin and deltamethrin exposure cause haematological alterations in rats which is reversed and restored to normal values following co-treatment with *Withania somnifera* and resveratrol. This indicates the ameliorating effects in rats exposed to cypermethrin and deltamethrin.

**Keywords:** Cypermethrin, deltamethrin, resveratrol and *Withania somnifera*

### 1. Introduction

Cypermethrin, a synthetic pyrethroid insecticide is used to kill insects especially on cotton. It behaves as a fast-acting neurotoxin in insects. It interacts with transportation system of sodium ions through cellular membrane. It is easily degraded on soil and plants but can be effective for weeks when applied to indoor inert surfaces. Exposure to sunlight, water and oxygen accelerates its decomposition. According to the National Pesticides Telecommunications Network (NPTN), cypermethrin is highly toxic to fish, bees and aquatic insects. It is used in agriculture to control ectoparasites which infest cattle, sheep and poultry [1]. In veterinary medicine, it is effective in controlling ticks on dogs. Pyrethroids cause oxidative stress and alteration in antioxidant enzymes in erythrocytes of pyrethroid intoxicated rats [10].

Deltamethrin, a synthetic pyrethroid insecticide is used in agriculture, home pest control and disease vector control. It is able to pass from a woman's skin through her blood and into breast milk [4]. Since deltamethrin is a neurotoxin, it temporarily attacks the nervous system of any animal with which it comes into contact. Skin contact can lead to tingling or reddening of the skin. Neurotoxic mechanisms of deltamethrin include, prolonging the opening of voltage sensitive sodium channels and inhibition of voltage gated chloride channels and GABA receptors [23].

Resveratrol is a fat soluble compound that occurs in *trans* and *cis* configuration. Resveratrol (*trans*-3, 5, 4-trihydroxystilbene), a polyphenolic phytoalexin abundantly found in grapes and red wine is a potent antioxidant and cytoprotective agent. Resveratrol was originally isolated by Takaoka from the roots of hellebore in 1940 and later in 1963 from the roots of Japanese knotweed. It attracted wider attention only in 1992 when its presence in wine was suggested as the explanation for cardio protective effects of wine [2]. Resveratrol has been found to exert a number of potentially cardio protective effects *in vitro*, including promotion of vasodilation by enhancing the production of nitric oxide (NO) [8] and inhibition of inflammatory enzymes. Resveratrol also possesses antidiabetic and neuroprotective effects for inflammation and neuro protection [2].

*Withania somnifera* is a plant in the Solanaceae or nightshade family and used as a herb in ayurvedic medicine. The species name *somnifera* means "sleep-inducing" in Latin and its main chemical constituents are alkaloids and steroid lactones,

which include tropine and cuscohygrine. The leaves contain the steroid lactones, withanolides, notably withering A, which was the first to be isolated from the plant. Bioactive constituent withaferin A has shown potential in therapy for glioblastomas, although this is not a traditional use of the plant. In ayurveda, the berries and leaves are applied externally to tumors, tubercular glands, carbuncle, and ulcers [15]. *Withania somnifera* possesses anti-inflammatory, antitumor, antistress, antioxidant, immunomodulatory, hemopoetic, and rejuvenating properties [16]. Pharmacological experiments in a number of *in-vitro* and *in-vivo* models have demonstrated the ability of *Withania somnifera* to exhibit anti-inflammatory, antiulcer, antidiabetic, central nervous system depressants and hepatoprotective activities leading support to the rationale behind several of its traditional uses [13]. The present study was undertaken to investigate the protective effects of *Withania somnifera* and resveratrol on combined cypermethrin and deltamethrin exposure induced haematological changes in adult male rats.

## 2. Materials and Methods

### 2.1 Animals and treatment

A total of 84 adult male Wistar rats weighing 100-120 g were procured from Disease Free Small Animal House (DFSAH), Lala Lajpat Rai University of Veterinary and Animal Sciences (LUVAS), Hisar and housed in polyacrylic cages in a group of 7 rats per cage in the departmental animal house. 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 start of the experiment. Animal house temperature varied between 22 to 27° C throughout the study. The prior approval of institutional animal ethics committee was obtained for the use of experimental animals in this study. Forty two rats were used for 14 days study, while remaining 42 rats were used for 28 days study. Cypermethrin and Deltamethrin formulations were purchased from Bayer Crop Science Ltd., India. Resveratrol was procured from Sigma-Aldrich Company. Methanolic extract of *Withania somnifera* roots were prepared in the departmental laboratory.

The rats were randomly divided into six groups, each comprising of seven rats. Group 1 was Naive (control) group which received 3% gum acacia suspension orally. Group 2 was given cypermethrin (75 mg/kg) plus deltamethrin (4 mg/kg) as suspension in 3% gum acacia orally. Group 3 animals received cypermethrin (75 mg/kg) plus deltamethrin (4 mg/kg) as suspension in 3% gum acacia and separately *Withania somnifera* (12.5 mg/kg) suspension in 3% gum acacia orally. Group 4 animals were administered cypermethrin (75 mg/kg) plus deltamethrin (4 mg/kg) as suspension in 3% gum acacia and separately resveratrol (5mg/kg) as suspension in 3% gum acacia orally. In group 5

*Withania somnifera* (12.5 mg/kg) in 3% gum acacia suspension was administered orally. In group 6 animals, resveratrol (5 mg/kg) in 3% gum acacia suspension was administered orally. Experiment groups were same for 14 days as well as for 28 days study.

### 2.2 Statistical Analysis

Statistical analysis of data was performed using Graph Pad prism 5.03 and Microsoft Excel. Data were analyzed by ANOVA along with Bonferroni multiple comparison post hoc test. A value of  $p < 0.05$  was considered statistically significant.

### 2.3 Sampling

Blood samples were taken by sterile hypodermic syringe directly from heart after anaesthetizing animals with ether in heparin coated vials for blood parameters in sterile tubes.

### 2.4 Haematological assay

Various hematological parameters *viz.* hemoglobin concentration (Hb), total erythrocyte count (TEC), total leukocyte count (TLC), differential leukocyte count (DLC), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were determined using automated haematology analyzer.

## 3. Results

### 3.1 Effect of combined treatment of cypermethrin and deltamethrin on hematological parameters (TEC, Hb and PCV) and their amelioration by *Withania somnifera* and resveratrol in adult male rats in 14 and 28 days study

Effect of combined treatment of cypermethrin and deltamethrin on hematological parameters (TEC, Hb and PCV) and their amelioration by *Withania somnifera* and resveratrol in adult male Wistar rats in 14 and 28 days study is presented in Table 1 and 2 respectively. Combined treatment of cypermethrin and deltamethrin significantly ( $p < 0.05$ ) reduced the TEC, Hb and PCV values as compared to naive group in both 14 and 28 days study. *Withania somnifera* co-treatment along with combined treatment of cypermethrin and deltamethrin significantly ( $p < 0.05$ ) increased the TEC, Hb and PCV values as compared to combined treatment of cypermethrin and deltamethrin in both 14 and 28 days study. Resveratrol co-treatment along with combined treatment of cypermethrin and deltamethrin significantly ( $p < 0.05$ ) increased TEC, Hb and PCV values as compared to combined treatment of cypermethrin and deltamethrin in both 14 and 28 days study. *Withania somnifera* treatment alone and resveratrol treatment alone did not have any effect on TEC, Hb and PCV values as compared to naive group in both 14 days and 28 days study.

**Table 1:** Effect of combined treatment of cypermethrin and deltamethrin on TEC, Hb and PCV and their amelioration by *Withania somnifera* and resveratrol in adult male Wistar rats in 14 days study

Treatment	TEC ( $\times 10^6/\mu\text{L}$ )	Hb (g/dL)	PCV (%)
Naive	$7.64 \pm 0.11$	$16.40 \pm 0.40$	$49.20 \pm 1.20$
C + D	$4.67^a \pm 0.25$	$8.97^a \pm 0.46$	$26.91^a \pm 1.40$
C + D + W	$5.94^{ab} \pm 0.24$	$13.55^{ab} \pm 0.02$	$40.67^{ab} \pm 0.61$
C + D + R	$5.92^{ab} \pm 0.42$	$13.64^{ab} \pm 0.24$	$40.92^{ab} \pm 0.72$
W	$7.61^{bcd} \pm 0.20$	$16.05^{bcd} \pm 0.35$	$48.17^{bcd} \pm 1.07$
R	$7.31^{bcd} \pm 0.10$	$15.95^{bcd} \pm 0.47$	$47.87^{bcd} \pm 1.41$

Values are expressed as Mean  $\pm$  SE of seven animals in each group.

a, b, c, d, e, f ( $p \leq 0.05$ ) vs. control, C + D, C + D + W, C + D + R, W and R respectively.

C + D mean 10% of MTD of cypermethrin and deltamethrin individually used in combination.

**Table 2:** Effect of combined treatment of cypermethrin and deltamethrin on TEC, Hb and PCV and their amelioration by *Withania somnifera* and resveratrol in adult male Wistar rats in 28 days study

Treatment	TEC ( $\times 10^6/\mu\text{L}$ )	Hb (g/dL)	PCV (%)
Naive	8.05 $\pm$ 0.16	17.35 $\pm$ 0.29	52.07 $\pm$ 0.89
C + D	4.95 <sup>a</sup> $\pm$ 0.36	8.20 <sup>a</sup> $\pm$ 0.31	24.60 <sup>a</sup> $\pm$ 0.93
C + D + W	6.72 <sup>ab</sup> $\pm$ 0.08	14.44 <sup>ab</sup> $\pm$ 0.28	43.32 <sup>ab</sup> $\pm$ 0.85
C + D + R	6.67 <sup>ab</sup> $\pm$ 0.09	14.90 <sup>ab</sup> $\pm$ 0.31	44.70 <sup>ab</sup> $\pm$ 0.94
W	7.90 <sup>bcd</sup> $\pm$ 0.08	17.00 <sup>bcd</sup> $\pm$ 0.25	51.00 <sup>bcd</sup> $\pm$ 0.77
R	7.74 <sup>bcd</sup> $\pm$ 0.16	16.97 <sup>bcd</sup> $\pm$ 0.32	50.91 <sup>bcd</sup> $\pm$ 0.98

Values are expressed as Mean  $\pm$  SE of seven animals in each group.  
a, b, c, d, e, f ( $p \leq 0.05$ ) vs. control, C + D, C + D + W, C + D + R, W and R respectively.

C + D mean 10% of MTD of cypermethrin and deltamethrin individually used in combination.

### 3.2 Effect of combined treatment of cypermethrin and deltamethrin on hematological parameters (TLC, HCH and MCHC) and their amelioration by *Withania somnifera* and resveratrol in adult male rats in 14 and 28 days study

Effect of treatment toxicity of cypermethrin and deltamethrin on hematological parameters (TLC, MCH and MCHC) and their amelioration by *Withania somnifera* and resveratrol in adult male Wistar rats in 14 and 28 days study is shown in Table 3 and 4 respectively. Combined treatment of cypermethrin and deltamethrin significantly ( $p < 0.05$ ) reduced the TLC, MCH and MCHC values as compared to naive group in both 14 days and 28 days study. *Withania somnifera*

co-treatment along with combined treatment of cypermethrin and deltamethrin significantly ( $p < 0.05$ ) increased the TLC, MCH and MCHC values as compared to combined treatment of cypermethrin and deltamethrin in both 14 days and 28 days study. Resveratrol co-treatment along with combined treatment of cypermethrin and deltamethrin significantly ( $p < 0.05$ ) increased the TLC, MCH and MCHC values as compared to combined treatment of cypermethrin and deltamethrin in both 14 and 28 days study. *Withania somnifera* treatment alone and resveratrol treatment alone did not have any effect on TLC, MCH and MCHC values as compared to naive group in both 14 and 28 days study.

**Table 3:** Effect of combined treatment of cypermethrin and deltamethrin on TLC, HCH and HCHC and their amelioration by *Withania somnifera* and resveratrol in adult male Wistar rats in 14 days study

Treatment	TLC ( $\times 10^3/\mu\text{L}$ )	MCH (pg)	MCHC (g/dL)
Naïve	5.25 $\pm$ 0.14	18.35 $\pm$ 1.13	32.87 $\pm$ 0.22
C + D	2.54 <sup>a</sup> $\pm$ 0.24	13.10 <sup>a</sup> $\pm$ 0.70	28.72 <sup>a</sup> $\pm$ 0.64
C + D + W	4.30 <sup>ab</sup> $\pm$ 0.06	16.84 <sup>b</sup> $\pm$ 0.40	31.78 <sup>b</sup> $\pm$ 0.19
C + D + R	4.15 <sup>ab</sup> $\pm$ 0.05	17.20 <sup>b</sup> $\pm$ 0.45	31.97 <sup>b</sup> $\pm$ 0.45
W	5.48 <sup>bcd</sup> $\pm$ 0.23	18.55 <sup>b</sup> $\pm$ 0.77	33.14 <sup>b</sup> $\pm$ 0.63
R	5.32 <sup>bcd</sup> $\pm$ 0.07	18.17 <sup>b</sup> $\pm$ 0.99	32.78 <sup>b</sup> $\pm$ 0.59

Values are expressed as Mean  $\pm$  SE of seven animals in each group.  
a, b, c, d, e, f ( $p \leq 0.05$ ) vs. control, C + D, C + D + W, C + D + R, W and R respectively.

C + D mean 10% of MTD of cypermethrin and deltamethrin individually used in combination.

**Table 4:** Effect of combined treatment of cypermethrin and deltamethrin on TLC, HCH and HCHC and their amelioration by *Withania somnifera* and resveratrol in adult male Wistar rats in 28 days study

Treatment	TLC ( $\times 10^3/\mu\text{L}$ )	MCH (pg)	MCHC (g/dL)
Naïve	5.71 $\pm$ 0.14	20.12 $\pm$ 0.37	36.10 $\pm$ 0.45
C + D	2.62 <sup>a</sup> $\pm$ 0.20	12.77 <sup>a</sup> $\pm$ 0.45	31.58 <sup>a</sup> $\pm$ 0.41
C + D + W	5.05 <sup>ab</sup> $\pm$ 0.07	18.51 <sup>b</sup> $\pm$ 0.26	35.17 <sup>b</sup> $\pm$ 0.56
C + D + R	4.94 <sup>ab</sup> $\pm$ 0.04	18.78 <sup>b</sup> $\pm$ 0.21	35.78 <sup>b</sup> $\pm$ 0.58
W	5.94 <sup>bcd</sup> $\pm$ 0.15	20.17 <sup>b</sup> $\pm$ 0.37	36.65 <sup>b</sup> $\pm$ 0.29
R	5.75 <sup>bcd</sup> $\pm$ 0.04	20.21 <sup>b</sup> $\pm$ 0.57	36.28 <sup>b</sup> $\pm$ 0.56

Values are expressed as Mean  $\pm$  SE of seven animals in each group.

a, b, c, d, e, f ( $p \leq 0.05$ ) vs. control, C + D, C + D + W, C + D + R, W and R respectively.

C + D mean 10% of MTD of cypermethrin and deltamethrin individually used in combination.

### 3.3 Effect of combined treatment of cypermethrin and deltamethrin on absolute differential leukocyte count and their amelioration by *Withania somnifera* and resveratrol in adult male Wistar rats in 14 and 28 days study

Effect of combined treatment of cypermethrin and deltamethrin on absolute differential leukocyte count and their amelioration by *Withania somnifera* and resveratrol in adult male Wistar rats in 14 and 28 days study is presented in Table 5 and 6 respectively. Combined treatment of cypermethrin and deltamethrin significantly ( $p < 0.05$ ) increased the neutrophils level and decreased the lymphocytes level as compared to naive group in both 14 and 28 days study. *Withania somnifera* co-treatment along with combined treatment of cypermethrin and deltamethrin significantly ( $p < 0.05$ ) reduced the

neutrophils level and increased the lymphocytes level as compared to combined treatment of cypermethrin and deltamethrin in both 14 and 28 days study. Resveratrol co-treatment along with combined treatment of cypermethrin and deltamethrin significantly ( $p < 0.05$ ) reduced the neutrophils level and increased the lymphocytes level as compared to combined treatment of cypermethrin and deltamethrin in both 14 and 28 days study. *Withania somnifera* treatment alone and resveratrol treatment alone did not have any effect on neutrophils and lymphocytes level as compared to naive group in both 14 and 28 days study. No significant changes were observed in monocytes, eosinophils, and basophils values in between various treatment groups of animals in both 14 and 28 days study.

**Table 5:** Effect of combined treatment of cypermethrin and deltamethrin on absolute differential leukocyte count and their amelioration by *Withania somnifera* and resveratrol in adult male Wistar rats in 14 days study

Treatment	Cells/100 leucocytes are expressed as Mean ± SEM				
	Neutrophil (% cell)	Lymphocyte (% cell)	Monocyte (% cell)	Eosinophil (%cell)	Basophil (%cell)
Naive	21.35 ± 0.17	74.64 ± 0.15	1.94 ± 0.11	1.80 ± 0.11	0.25 ± 0.05
C + D	35.41 <sup>a</sup> ± 0.61	59.75 <sup>a</sup> ± 0.61	2.21 ± 0.06	2.11 ± 0.04	0.37 ± 0.05
C + D + W	28.75 <sup>ab</sup> ± 0.17	65.70 <sup>ab</sup> ± 0.14	2.17 ± 0.04	1.98 ± 0.24	0.28 ± 0.05
C + D + R	28.81 <sup>ab</sup> ± 0.08	66.84 <sup>ab</sup> ± 0.20	2.17 ± 0.06	1.95 ± 0.05	0.28 ± 0.02
W	22.57 <sup>bcd</sup> ± 0.12	73.95 <sup>bcd</sup> ± 0.38	1.95 ± 0.04	1.75 ± 0.11	0.27 ± 0.03
R	22.11 <sup>bcd</sup> ± 0.18	73.65 <sup>bcd</sup> ± 0.40	1.92 ± 0.05	1.80 ± 0.04	0.25 ± 0.03

Values are expressed as Mean ± SE of seven animals in each group.

a, b, c, d, e ( $p \leq 0.05$ ) vs. control, C + D, C + D + W, C + D + R, W and R respectively.

C + D mean 10% of MTD of cypermethrin and deltamethrin individually used in combination.

**Table 6:** Effect of combined treatment of cypermethrin and deltamethrin on absolute differential leukocyte count and their amelioration by *Withania somnifera* and resveratrol in adult male Wistar rats in 28 days study

Treatment	Cells/100 leucocytes are expressed as Mean ± SEM				
	Neutrophil (% cell)	Lymphocyte (% cell)	Monocyte (% cell)	Eosinophil (% cell)	Basophil (%cell)
Naive	23.57 ± 0.79	70.54 ± 0.75	3.02 ± 0.14	2.21 ± 0.05	0.44 ± 0.06
C + D	40.34 <sup>a</sup> ± 0.94	51.37 <sup>a</sup> ± 0.41	3.38 ± 0.08	2.55 ± 0.04	0.57 ± 0.05
C + D + W	26.68 <sup>ab</sup> ± 0.05	65.12 <sup>ab</sup> ± 0.32	3.21 ± 0.08	2.44 ± 0.04	0.48 ± 0.10
C + D + R	27.51 <sup>ab</sup> ± 0.11	66.25 <sup>ab</sup> ± 0.45	3.15 ± 0.04	2.38 ± 0.18	0.47 ± 0.06
W	24.35 <sup>bcd</sup> ± 0.08	69.82 <sup>bcd</sup> ± 0.41	3.04 ± 0.05	2.20 ± 0.04	0.45 ± 0.06
R	24.22 <sup>bcd</sup> ± 0.07	70.01 <sup>bcd</sup> ± 0.26	3.01 ± 0.05	2.21 ± 0.04	0.44 ± 0.05

Values are expressed as Mean ± SE of seven animals in each group.

a, b, c, d, e ( $p \leq 0.05$ ) vs. control, C + D, C + D + W, C + D + R, W and R respectively.

C + D mean 10% of MTD of cypermethrin and deltamethrin individually used in combination.

#### 4. Discussion

The effect of combined treatment of cypermethrin and deltamethrin on various haematological parameters and their amelioration by resveratrol and *Withania somnifera* was investigated in adult male Wistar rats in 14 days as well as in 28 days study. The Hb concentration and PCV generally provide an accurate reflection of the extent to which the circulating red cell mass is reduced [21]. Brar *et al.* [3] suggested that if the PCV is decreased, the animal is anemic whereas an elevated PCV indicate polycythemia. The decrease in Hb concentration in our study suggested that combined treatment of cypermethrin and deltamethrin might have interfered with erythropoiesis. The observed results are in agreement to that of Mongi *et al.* [17] who reported similar changes after the administration of deltamethrin in adult male Wistar rats. Sayim *et al.* [20] also reported similar changes following administration of cypermethrin in adult male Wistar rats. Decline in Hb concentration has also been reported by other workers following the exposure to deltamethrin in rats [14] and cypermethrin exposure in rabbits [6] and goats [11]. The fall in Hb concentration on oral exposure of combined cypermethrin and deltamethrin might have occurred because of the interference with heme synthesis. The decrease in leucocyte count was also recorded on giving combined exposure of cypermethrin and deltamethrin in male rats. It may be due to its effect on immune system of body. Decrease in leucocyte count was also recorded on oral administration of cypermethrin in rabbits [6] and fish [22]. Cowell *et al.* [5] stated decreased erythrocyte production and hypoplasia of erythropoietic tissues have also been demonstrated in severe uremia (increased blood urea nitrogen) associated with renal damage [9], as evident in the present study. Decrease in RBCs have also been reported in rats [20], rabbits [6] and fish [22] after the oral administration of cypermethrin. Decrease in MCH and MCHC have also been reported in rats on oral administration of cypermethrin in rats [18, 20].

Our findings showed a significant decrease in TEC, Hb, PCV, MCH and MCHC in both 14 days as well as in 28 days study. Our findings are in agreement with that of Mongi *et al.* [17] who also reported a significant decline in values of PCV, Hb, TEC, MCH and MCHC on administration of deltamethrin in rats. Our findings also showed decrease in TLC. The findings of our study were similar to Khan *et al.* [12] who reported a significant decline in values of TLC on combined administration of deltamethrin and fluoride in treated rats and Rehman *et al.* [19] who also reported a significant decline in values of TLC on combined administration of deltamethrin and cadmium in treated rats.

Our observations are similar to Khan *et al.* [12] who stated that subacute combined intoxication of deltamethrin and fluoride in rats induces a significant decrease in leukocytes due to increase in neutrophils and decrease in lymphocytes.

Resveratrol co-treatment and *Withania somnifera* co-treatment along with combined treatment with cypermethrin and deltamethrin significantly increased the TEC, Hb, PCV, MCH, MCHC and TLC values in both 14 days as well as in 28 days study. These results are in accordance with Davis and Kuttan [7] who reported *Withania somnifera* co-treatment significantly increased the TLC in cyclophosphamide treated rats.

#### 5. Conclusion

In conclusion, Firstly combined treatment of cypermethrin and deltamethrin resulted in significant decrease in TEC, Hb, PCV, MCH, MCH and TLC values, whereas in DLC, lymphocyte decreased and neutrophil values were increased significantly as compared to naive group in both 14 days as well as in 28 days study. Secondly, resveratrol co-treatment and *Withania somnifera* co-treatment significantly ameliorated the toxic effect of combined cypermethrin and deltamethrin exposure in adult male rats in both 14 days as well as in 28 days study.

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