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Research Article
Bersama engleriana (Melianthaceae) Extracts Alleviate Cypermethrin-induced Alteration of Haemato-biochemical Parameters in Male Guinea Pigs

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Abstract

Background and Objective: Previous studies demonstrated the toxicity of cypermethrin, a commonly used insecticide in vector control and agriculture in Cameroon. Medicinal plants such as *Bersama engleriana* (*B. engleriana*) are considered as potential source remedy in local medicine. This study aimed at evaluating the protective effects of *B. engleriana* extracts on cypermethrin toxicity on haematological and biochemical parameters in male guinea pigs. **Materials and Methods:** Eighty animals were divided into 8 groups, which received daily distilled water (2 mL kg^{-1}), cypermethrin alone (137.5 mg kg^{-1}) or co-administered cypermethrin and *B. engleriana* aqueous/ethanol extract at the doses 50, 100 and 200 mg kg^{-1}. The products were administered orally for 13 weeks and the animal body weight recorded weekly. At the end of the treatment, blood was collected for determination of haematological and biochemical parameters and differences between groups were determined using one way ANOVA followed by the Duncan's test. **Results:** Cypermethrin increased ($p<0.05$) the total white blood cells and lymphocytes number and moderately decreased red blood cells. The cypermethrin-induced changes on blood cells count were prevented when the pesticide was co-administered to the animals with either aqueous or ethanol extract of *B. engleriana*. Moreover, impairment of liver and kidney parameters observed in the animals exposed to the pesticide was alleviated with *B. engleriana* treatment. **Conclusion:** This study concluded the beneficial effects of *B. engleriana* in alleviating alteration of haemato-biochemical parameters induced by cypermethrin. The *B. engleriana* extract can be considered as a valuable remedy in prevention of pesticide induced toxicity.

Key words: *Bersama engleriana*, biochemical parameters, cypermethrin, haematological parameters, antitoxic effect

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The global population is rapidly increasing. It was estimated 7.35 billion in 2015 and will reach 8.5 billion in 2030[1]. In addition to the increase of population, food production capacity faces falling ratio of arable land available to population. Therefore, to provide adequate food supply to such population remains a challenge for many countries and institutions[2]. Sustained and intensive agricultural production then uses pesticides to prevent, control or destroy pests in order to increase crop production and maximize yield. Besides this role, pesticides are also useful in elimination of vector-borne diseases[2,3]. Pesticides are classified into organochlorines, organophosphorus, carbamates, pyrethrin and pyrethroids. Pyrethroids are among the latest developed pesticide groups because of the ban of long lasting organochlorine pesticides[4].

Cypermethrin is one of the highly common synthetic pyrethroids with high insecticidal activity. It is used to control many pests including moth pests of cotton, fruit and vegetable crops and it is available as an emulsifiable concentrate or wettable powder[5]. Cypermethrin is also used for environmental and hygienic purposes such as control of insect pests in stores, industrial buildings, houses, laboratories and means of transports[6]. Because of such large utilization, this pesticide may get into the human system or non-intended animal through direct or indirect exposure. Interestingly, cypermethrin residues have been found in many food commodities including fresh vegetables, water sources and aquatic animals[7-9].

In vertebrates and invertebrates, cypermethrin acts mainly on the nervous system. Cypermethrin is a stomach poison and a contact insecticide[6]. Mechanistically it can induce damage to the voltage-dependent sodium channel, causing sodium channels to stay open much longer than normal and inhibits ATPase enzymes involved in movement of ions against a concentration gradient which are regulated by active transport[10]. These molecular disturbances may prompt certain toxicity of cypermethrin at the macroscopic level in living organism. Cypermethrin has also been shown to negatively affect various blood parameters in mammals including red blood cells (RBCs), total white blood cells (WBCs), haemoglobin, lymphocytes, neutrophiles, eosinophils, monocytes and platelets[11-14].

In general, toxicity due to chemical exposure is difficult to clearly assess and devised treatments are not always effective. An accent is therefore, laid on different measures that may help to reduce and prevent the toxicity[15]. Different plants and herbal products are locally used not only as remedy but also for prophylaxis purposes for different ailments[16-18]. *Bersama engleriana* is a tree used in many areas including the West region of Cameroon in the management of various health problems such as gastrointestinal disorders, malaria, yellow fever, rheumatism, sexual weakness, diabetes, anorexia, epilepsy, haemorrhoids and cancers[19,20]. Such local uses hypothesize a certain pharmacological potential of *B. engleriana*. In fact, previous studies reported the anti-haemorrhoid, hypoglycaemic, aphrodisiac and ejaculatory benefits, anti-malarial, anti-tumoral, antimicrobial and antioxidant properties of *B. engleriana*[19-22]. Though humans population is largely exposed to agrochemicals such as cypermethrin[23-25], which may likely affect the haematological parameters, no or very few studies have been directed towards finding proper therapeutic or preventive options for such toxicity. This study then aimed to evaluate potentials of *B. engleriana* extracts to prevent cypermethrin-induced toxicity on haematological and biochemical parameters of male Guinea pigs.

MATERIALS AND METHODS

Experimental animals: Guinea pigs (*Cavia porcellus)* weighing 357.91±15.18 g were accommodated in the animal house of the Laboratory of Animal Health and Physiology of the University of Dschang (Cameroon), where the study was carried out from March-August, 2016. Animals were identified at the ear and housed in identical cages of dimensions 100 cm×80 cm×60 cm (length, width and height) under standard conditions with 12 h photoperiod and had free access to water and food. Pigs were handled according to ethical guidelines of the Cameroonian National Veterinary Laboratory as reference by the certificate of approval and health control No. 001/17 CCS/MINEPIA/DR-O/DD-ME/SSV.

Plant material and extracts: *Bersama engleriana* (Melianthaceae) leaves were collected in Bagang locality (Bamboutos division, West region of Cameroon) in March, 2016 and identified at the National Herbarium of Cameroon under the voucher number of 32427/HNC. The leaves were dried at room temperature and grinded into fine powder. A portion (250 g) of the plant powder was macerated in 1 L of distilled water for 48 h, the mixture filtered using Whatman filter paper No. 3 and the filtrate evaporated at 50°C to yield a solid paste which constitutes the aqueous extract. Another portion (200 g) of the powder was macerated in 1 L of 70% ethanol for 72 h, filtered and the extraction solvent evaporated at 60°C to yield the ethanol extract.

Chemicals: Cypermethrin on the common name Cigogne manufactured by Louis Dreyfus Commodities (Bonaberi, Cameroon) was obtained from the local market. Kits for biochemical analyses were purchased from Chronolab (Barcelona, Spain).

Experimental design: Eighty adult male Guinea pigs were distributed into 8 groups of 10 animals each, comparable in body weight. One group received the vehicle (distilled water, 2 mL kg^{-1}) while 7 groups were administered 137.5 mg kg^{-1} of cypermethrin. The dose 137.5 mg kg^{-1} of the toxicant was chosen based on the effects observed in authors previous study. The latter dose induced liver and kidney toxicity and altered blood cells count[26]. Six of the 7 groups exposed to the pesticide were divided in 2 sets, which also received either the aqueous or ethanol extracts of *B. engleriana* at the doses of 50, 100 and 200 mg kg^{-1}. Animals were administered the products by gastric intubation and every day for 13 weeks. The animal body weight was recorded weekly and the doses of products to administer adjusted accordingly. Twenty four hours after the last gavage, animals were anesthetized using ether vapours and blood collected by cardiac puncture for analysis of haematological and biochemical parameters.

Measurement of haematological parameters: Blood samples were collected by cardiac puncture in capillary tubes coated with Ethylenediaminetetraacetic acid (EDTA). The blood parameters were analyzed immediately in different samples using automated hematimeter Sysmex apparatus of the type 8999. The analyzed parameters included: WBCs, lymphocytes (LYM), monocytes (MON), granulocytes (GRAN), RBCs, haemoglobin (Hb), hematocrit (Hct), mean cell volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell distribution width (RDW), platelets (PLT), mean platelet volume (MPV) and platelets distribution width (PDW). MCV and MCHC values were calculated from RBCs count, Hb and Hct.

Determination of biochemical parameters of toxicity: The parameters of cellular toxicity including creatinine, alanine transaminase (ALT), aspartate transaminase (AST), urea, proteins, direct bilirubin and total bilirubin, were determined in the serum using kits from Diagnostic Omega (Barcelona, Spain) according to supplier instructions.

Statistical analysis: Results were expressed as mean±standard deviation. Differences between groups were assessed using one way ANOVA followed by the Duncan's test at 5% significance. All analyses were performed using the SPSS 20.0 software.

RESULTS

Animal body weights: In general, the relative body weights of all experimental animals increased continuously during the 13 weeks follow-up period. However, comparison between groups did not revealed any significant difference related to cypermethrin and/or *B. engleriana* extracts (Fig. 1).

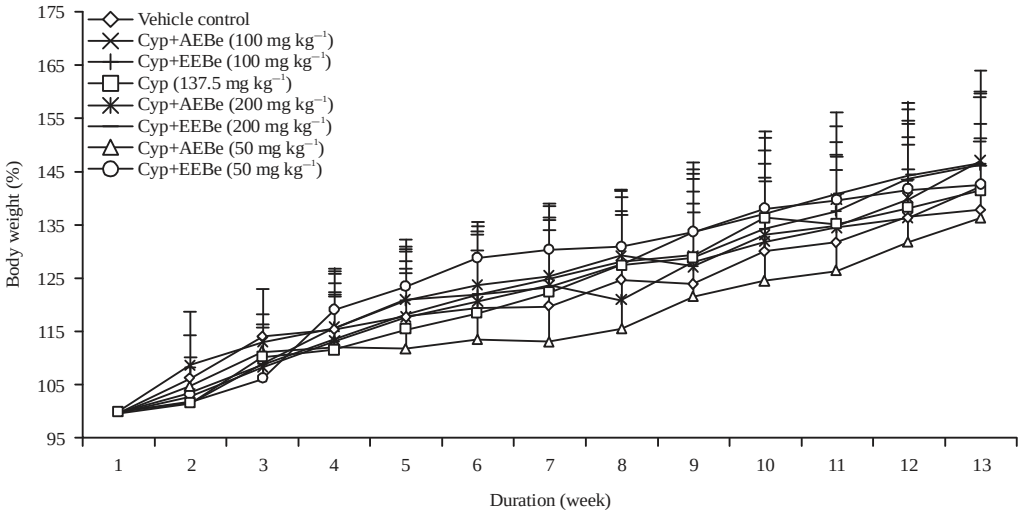

Fig. 1: Variation in body weight of Guinea pigs throughout the treatment period
AEBe: Aqueous extract of *B. engleriana*, EEBe: Ethanol extract of *B. engleriana,* Cyp: Cypermethrin

Table 1: Haematological parameters of male Guinea pigs exposed to cypermethrin and/or *B. engleriana* extracts

Haematological parameters	Control	Cyp (137.5 mg kg^{-1})	AEBe (mg kg^{-1}) 50	AEBe (mg kg^{-1}) 100	AEBe (mg kg^{-1}) 200	EEBe (mg kg^{-1}) 50	EEBe (mg kg^{-1}) 100	EEBe (mg kg^{-1}) 200
WBCs (10^3 µL^{-1})	8.70±2.79^{ab}	12.07±2.45^{a}	7.10±2.14^{b}	10.30±4.24^{ab}	11.53±2.01^{ab}	8.90±2.10^{ab}	8.72±3.44^{ab}	9.15±1.61^{ab}
Lymph (10^3 µL^{-1})	4.05±1.14^{b}	7.62±2.39^{a}	4.20±0.94^{b}	5.97±1.68^{ab}	7.13±1.25^{ab}	4.86±1.24^{ab}	5.10±1.54^{ab}	5.35±1.35^{ab}
Mono (10^3 µL^{-1})	0.95±0.45	1.15±0.31	0.72±0.35	1.06±0.15	1.06±0.23	0.94±0.21	0.82±0.33	1.00±1.63
Granul (10^3 µL^{-1})	3.70±0.98	3.30±1.65	2.17±0.91	3.26±1.58	3.33±0.81	3.10±1.61	2.80±0.87	2.80±0.29
RBCs (10^6 µL^{-1})	4.82±0.81^{ab}	4.20±1.14^{b}	4.59±0.43^{ab}	4.83±0.44^{ab}	5.73±1.22^{a}	5.09±0.40^{ab}	4.94±0.47^{ab}	4.80±0.08^{ab}
Hgb (g dL^{-1})	14.45±1.98	16.40±0.43	14.15±1.63	16.00±1.60	14.57±2.23	15.74±0.80	15.30±1.15	15.17±0.47
HCT (%)	33.35±10.69	36.32±10.57	33.40±6.48	34.00±12.26	46.73±11.49	42.36±5.05	38.47±3.01	37.35±0.96
MCV (fl)	82.77±9.98	77.92±3.72	77.00±3.12	81.23±2.62	81.20±3.64	83.14±5.37	78.77±3.59	77.82±2.02
MCH (PG)	37.37±4.75	37.10±4.34	32.95±3.15	41.77±7.05	26.73±2.67	31.68±1.48	31.22±0.54	31.55±1.03
MCHC (g dL^{-1})	45.20±8.00	47.45±11.10	42.87±4.75	52.03±11.98	33.00±8.30	38.38±4.49	39.72±1.60	40.60±1.83
RDW (%)	14.30±0.90	16.22±1.70	15.57±1.70	16.00±0.87	16.46±1.61	13.98±1.52	15.10±2.04	15.32±1.04
Plat (10^3 µL^{-1})	134.00±44.24	139.75±40.18	121.25±37.50	115.67±27.53	136.00±36.94	133.40±22.04	124.25±36.00	145.00±38.99
MPV (fl)	12.22±1.60	12.20±0.34	13.32±2.46	12.26±1.10	12.53±0.47	11.16±1.81	12.80±1.04	12.02±1.44
PDW (fl)	8.52±0.45	7.60±0.74	7.07±0.34	7.26±1.17	7.97±1.84	8.02±1.16	7.22±0.79	7.17±1.03

Different letters for the same parameter mean significant difference (p<0.05). AEBe: Aqueous extract of *B. engleriana*, Cyp: Cypermethrin, EEBe: Ethanol extract of *B. engleriana*, Granul: Granulocytes, HCT: Hematocrit, Hgb: Haemoglobin, Lymp: Lymphocytes, MCH: Mean corpuscular haemoglobin, MCHC: Mean corpuscular haemoglobin concentration, MCV: Mean corpuscular volume, MPV: Mean platelets volume, Mono: Monocytes, Plat: Platelets, PDW: Platelets distribution width, RBCs: Red blood cells, RDW: Red cells distribution width, WBCs: White blood cells

Table 2: Biochemical parameters of toxicity in male Guinea pigs exposed to cypermethrin and/or *B. engleriana* extracts

Biochemical parameters	Control	Cyp (137.5 mg kg^{-1})	AEBe (mg kg^{-1}) 50	AEBe (mg kg^{-1}) 100	AEBe (mg kg^{-1}) 200	EEBe (mg kg^{-1}) 50	EEBe (mg kg^{-1}) 100	EEBe (mg kg^{-1}) 200
Creatinine (mg dL^{-1})	0.24±0.03^{a}	0.61±0.10^{b}	0.19±0.08^{a}	0.51±0.11^{cb}	0.40±0.10^{cd}	0.22±0.09^{a}	0.48±0.05^{cd}	0.34±0.08^{ac}
Urea (mg dL^{-1})	70.00±11.25^{a}	114.29±21.70^{b}	107.86±10.47^{b}	88.57±28.19^{ab}	101.79±23.60^{ab}	113.57±15.41^{b}	98.21±21.14^{ab}	89.29±24.70^{ab}
Direct bilirubin (mg dL^{-1})	0.59±0.06^{a}	0.86±0.09^{b}	0.90±0.19^{b}	0.74±0.09^{ab}	0.75±0.10^{ab}	0.91±0.12^{b}	0.63±0.09^{ab}	0.74±0.08^{ab}
Total bilirubin (mg dL^{-1})	1.96±0.15^{a}	2.44±0.28^{b}	2.41±0.28^{b}	1.51±0.25^{a}	1.54±0.36^{a}	1.89±0.43^{ab}	1.84±0.11^{a}	2.04±0.21^{ab}
ALT (IU L^{-1})	13.80±1.40^{a}	23.10±3.15^{b}	30.66±4.44^{b}	16.19±3.53^{ab}	18.38±2.82^{ab}	19.03±2.40^{b}	17.94±1.91^{ab}	13.91±1.09^{a}
AST (IU L^{-1})	16.72±3.12^{a}	30.43±4.04^{b}	23.80±5.11^{ab}	16.15±3.58^{a}	20.56±2.61^{a}	17.88±4.31^{ac}	19.28±4.21^{ac}	18.73±3.41^{ac}
Serum proteins (mg dL^{-1})	3.43±0.91^{a}	2.42±0.71^{b}	3.46±0.68^{ab}	3.28±0.65^{ab}	3.23±0.82^{ab}	2.57±0.95^{b}	4.05±0.34^{a}	3.15±0.84^{ab}

Different letters for the same parameter mean significant difference (p<0.05). AEBe: Aqueous extract of *B. engleriana*, ALT: Alanine transaminase, AST: Aspartate transaminase, Cyp: Cypermethrin, EEBe: Ethanol extract of *B. engleriana*

Hematologic parameters: As shown in Table 1, cypermethrin treatment significantly increased (p<0.05) the total WBC number and lymphocytes while it moderately decreased RBCs when compared to the control pesticide of unexposed animals. Co-administration of cypermethrin with either aqueous or ethanol extracts of *B. engleriana* significantly prevented the increase of total WBCs and lymphocytes as compared to the control group. The other blood parameters were not significantly affected by pesticide alone or in co-administration with the extracts.

Biochemical parameters of toxicity: With the exception of serum protein levels, cypermethrin treatment significantly increased (p<0.05) all investigated biochemical parameters of toxicity as compared to insecticide unexposed animals (Table 2). The lowest dose (50 mg kg^{-1}) of either aqueous or ethanol extracts of *B. engleriana* significantly prevented creatinine increase (p<0.05) with levels comparable to the control group not exposed to pesticide. Co-treatment of the animals with the plant extracts (100 and 200 mg kg^{-1}) significantly prevented fluctuations in the levels of urea, bilirubins (direct and total) and the activity of aminotransaminase (ALT, AST). Indeed, the latter parameters remain close to those of the control group not treated with the pesticide cypermethrin. The aqueous and ethanol extracts of *B. engleriana* normalized animal serum proteins as compared to the vehicle control group.

DISCUSSION

In this study, cypermethrin administration resulted into increased WBCs and lymphocytes in male Guinea pigs. WBCs, help the body to fight infections and external agents. Cypermethrin has been largely used as insecticide in Cameroon for crop protection and yield optimization in agriculture[23-25]. In humans, pesticide exposure has been linked to various health problems including alteration of biochemical and blood parameters[27,28].

Inflammation or affection of the system or other blood diseases can cause changes in the percentage and total numbers of WBCs. In fact the WBC count, also known as immune cells, leukocyte count or differential blood count (DBC), is an indicator of different health problems[29]. The increase of WBC number in the Guinea pigs treated with cypermethrin is therefore, an indication of the affection of the animal system by the pesticide. WBCs comprise granulocytes, monocytes and lymphocytes[30]. In mammals, lymphocytes represent about 20% of total WBC count. An increase in lymphocytes known as lymphocytosis has been associated with exposure to smoking and chemicals[31]. Cypermethrin treatment also resulted into decreased RBCs count in male Guinea pigs. This observation corroborates with previous findings following exposure of rodents (rats and mice) to the pesticide[12,13]. Cypermethrin toxicity on RBCs may cause hypoxia as the RBCs highly serve transport function of blood gas carrying around 98% of oxygen throughout the system[30,32]. The adverse effect of pesticides on WBCs and RBCs in humans has been documented[33]. Through affecting the different blood parameters, cypermethrin could then weaken the immune system of exposed population and therefore, render them sensitive to different affections and infections. Such observations are consistent with the clinical signs such as dizziness and fatigue experienced by farmers in authors localities who have been exposed to pesticides including cypermethrin[25]. Alteration of blood and biochemical parameters in the animals exposed to cypermethrin also corroborates the increased urea, creatinine and total bilirubin, total leukocyte count (TLC) and decreased hemoglobin (Hb), total erythrocytic count (TEC) in rabbits and male rats treated with cypermethrin (24 or 25 mg kg^{-1}) for 12 weeks and 28 days, respectively[34-36]. The decrease in TEC and Hb concentration and increase in TLC and lymphocyte concentration was also observed in adult mice intraperitoneally treated with cypermethrin (0.10-0.25 mL kg^{-1}) every week for 28 consecutive days[12]. Similarly, Shah *et al.*[37] reported elevated TLC, lymphocytes and MCV in female rabbits intraperitoneally exposed to cypermethrin (25-75 mg kg^{-1}) for 17 days. However, the results from this study contrasted with the observation from Faokunla *et al.*[14], who reported increased RBCs, white blood cells (WBC), lymphocytes (LYMP) and decreased the concentrations of the mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and mean corpuscular volume (MCV) in adult male rats following oral administration of cypermethrin in for 28 days. The discrepancy in the effect of cypermethrin on red blood cells or erythrocytes concentration points the fact that the action of this toxicant on the present cell types could vary from an animal species to another.

Co-administration of cypermethrin with either aqueous or ethanol extracts of *B. engleriana* extracts significantly prevented alteration of the different blood cells. This protective effect of *B. engleriana* could be attributed to bioactive compounds such as phenols and flavones that are found in this plant[19]. Similar protective effects against cypermethrin- induced toxicity on haematological parameters have been reported with other plant extracts and derived compounds including alpha-lipoic acid, piperine (a main component of *Piper longum* L. and *Piper nigrum* L.) and leucovorin and the methanolic extract from *Jatropha gossypifolia* in rodents (mice and rats)[14,36,38]. For further understanding of the effect of the plant extracts on cypermethrin toxicity, biochemical markers of liver and kidney functions were evaluated including aminotransferases, bilirubin, urea and creatinine.

Because of the central role it plays in metabolism of xenobiotics, the liver is particularly susceptible to injury following systemic exposure to the xenobiotics[39]. Administration of cypermethrin resulted into significant increase of ALT and AST activities and bilirubin levels. Elevations of these parameters is indicative of hepatocellular injury and impairment of biliary excretion, respectively[40,41]. Similarly, cypermethrin administration to Guinea pigs increased creatinine and urea which are both biochemical markers of the kidney function. The insecticide may alter kidney function, especially the glomerular filtration[42]. Interestingly, co-administration of the toxicant with either aqueous or ethanol extract of *B. engleriana*, enabled normalization of liver and kidney parameters, suggesting a protective effect of the plant extracts. *B. engleriana* is rich in secondary metabolites (flavonoids, phenolics) with antioxidant properties which are well known for their protective effects against liver or kidney damages[19,43,44]. Elevated biochemical toxicity markers such as serum urea and creatinine were shown to be normalized by administration of green tea, vitamin C and cinnamon in adult male rats and female mice[45,46]. In the same line oral administration of a natural alkaloid, piperine along with cypermethrin significantly alleviated cypermethrin-induced changes in transaminase activities, blood urea, creatinine and blood parameters[35,36]. Similar protective effects of plant and derived products such as vitamin C, cinnamon and green tea were observed in rats, Guinea pigs and mice exposed to cypermethrin[45,46]. The hepatoprotective and reno-protective effects observed with

B. engleriana in this study could be attributed to the presence of such bioactive compounds in the plant, which may be identified and studied further for elucidation of their mode of action. The studied extracts, therefore, exert protective and/or preventive effects against cypermethrin-induced toxicity, suggesting the presence of active substances in the plants, which could alleviate pesticide toxicity.

CONCLUSION

Altogether, the results demonstrated the protective effects of *B. engleriana* extracts on haematological, hepatic and renal integrity/function. The findings sustain a certain positive pharmacological effect of *B. engleriana* in prevention of chemical toxicity, especially cypermethrin-induced toxicity on blood, liver and renal parameters. The *B. engleriana* can be considered as a valuable source of remedy, in the development of therapy against pesticide induced toxicity. Further studies would help to better define the bioactive compounds responsible for protective effect of *B. engleriana* extracts.

SIGNIFICANCE STATEMENT

The study evaluates the possible preventing effect of *B. engleriana* on hematological and biochemical parameters in cypermethrin exposed Guinea pigs and discovered that it reduces the toxicity of cypermethrin by alleviating toxicity in liver and by maintaining the kidney function integrity. Thus, this study would help the researchers in evaluating the mechanism of *B. engleriana* as therapeutic medicine against cypermethrin-induced toxicity. But the best theory on it may be arrived at.

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