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Adverse hematological profiles associated with chlorpromazine antipsychotic treatment in male rats: Preventive and reversal mechanisms of taurine and coenzyme-Q10

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ABSTRACT

Chlorpromazine (CPZ) is one of the most effective antipsychotic drugs used for managing psychotic related disorders owing to its dopamine receptor blocking action. However, pharmacological investigations against CPZ's cytotoxic effect have remained scarce. Hence, this study investigated the preventive and reversal effects of taurine and coenzyme-Q10 (COQ-10), which are compounds with proven natural antioxidant properties, against CPZ-induced hematological impairments in male rats. In the preventive study, rats received oral saline (10 ml/kg), taurine (150 mg/kg/day), COQ-10 (10 mg/kg/day) or in combination for 56 days, alongside CPZ (30 mg/kg, p.o.) between days 29–56. In the reversal protocol, rats had CPZ repeatedly for 56 days before taurine and COQ-10 treatments or their combination from days 29–56. Rats were also given taurine (150 mg/kg/day), and COQ-10 (10 mg/kg/day) alone for 56 days. Serums were extracted and assayed for hematological, with oxidative and inflammatory markers. CPZ induced decreased red/white blood cells, erythropoietin, platelet count, packed cell volume and hemoglobin, neutrophil, and lymphocyte, which were prevented and reversed by taurine and COQ-10, or their combination. Taurine and COQ-10 improved mean corpuscular volume, hemoglobin concentration, with increased erythropoietin levels relative to CPZ groups. CPZ-induced increased malondialdehyde, tumor necrosis factor-alpha and interleukin-6 levels with decreased interleukin-10, glutathione, and superoxide-dismutase were prevented and reversed by taurine and COQ-10 in comparison with CPZ groups. Taurine and COQ-10 alone notably improved the antioxidant/anti-inflammatory status relative to controls. Among other mechanisms, taurine and COQ-10 abated CPZ-induced hematological deficiencies, via decreased serum levels of oxidative stress, and pro-inflammatory cytokines release, with increased antioxidants and anti-inflammation function.

1. Introduction

The use of drugs in the management of various medical conditions owing to the alarming disease burden, has increased tremendously in the last three decades [61]. Consequently, pharmaceutical companies have doubled their technological strategies in search of new drugs, based on pressing needs (Harman et al., 2023). Of note, the prevalence of hematological disorders, such as impairments in platelet, white blood cell functions, hemoglobin levels, and coagulation/fibrinolytic activity, has progressively increased due to the toxic effects of existing drugs developed from obsolete animal models [26,38]. Accordingly, some first- and second-generation antipsychotic medications such as chlorpromazine (CPZ) and clozapine respectively, used in the treatment of different psychotic disorders such as schizophrenia and bipolar disorder, have been associated with several adverse effects, notably promoting hematological disorders [37,43,49,50]. Hematological perturbations

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including any changes in the normal functioning of blood cells, including alterations in their numbers, size, or function, have been linked to chemical exposure and long-term use of some drugs [14,22,31]. Consequently, these perturbations were moreover related to the emergence of serious hematological disorders such as anemia, eosinophilia, eosinopenia, thrombocytopenia, leukocytosis, neutropenia, agranulocytosis, thrombocytopenia, and leukopenia, all of which have been adjudged as contributors to low quality of life of vulnerable patients ([22,26,38,48]; Gover et al., 2020). More so, a study on different antipsychotic drugs notably of the second generation such as CPZ, promazine thioridazine, flufenazine and prochlorperazine, proved that hematological derangements were significantly associated with these drugs after chronic usage (Flanagan et al., 2007). Although the frequency of hematological disorders induced by these medications is relatively low, the majority of the cases are reported in patients with co-morbidity underlying conditions [40,50]. According to a review of case reports, the frequency of hematological disorders induced by these medications is estimated to be approximately 1% [25,31]. However, the severity of these hematological disorders can vary greatly, ranging from mild abnormalities in blood counts to life-threatening conditions such as agranulocytosis and thrombocytopenia [31]. Agranulocytosis is a condition where the body produces an abnormally low number of white blood cells, leaving the patient at risk for severe opportunistic infections has been repeatedly reported [47,50,77]. Thrombocytopenia is a disorder where the body produces an abnormally low number of platelets, leading to excessive bleeding. The direct causality of these medications in inducing hematological disorders is not fully understood. It is believed that these medications may affect the production and function of blood cells in the bone marrow, leading to hematological abnormalities [31,47]. In some cases, these medications may also cause an immune-mediated reaction, where the body's immune system attacks its blood cells [77,81].

Although the mechanisms involved in drug and chemical-induced blood dysfunctions remain completely unknown, notable mechanisms involving increased production of free radicals and inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [16,2], as well as hormonal imbalance [68] have been identified with the use of CPZ. Studies have shown that oxidative stress and inflammation play important roles in damaging blood cell membranes, notably, impairing RBC deformability, which is the ability of RBCs to squeeze through tiny capillaries to eliminate damaged or old RBCs from the circulation, thereby derangements of blood cells [58]. Pivotal mechanistic nexus to this, include depletion of RBC antioxidants such as catalase, glutathione peroxidase and peroxiredoxin-2 [58], decrease glucose-6 phosphate dehydrogenase (G6PD) [65], prostanglandin-E2 (PGE_2)-mediated activation of Ca^{2+} permeable nonselective cation channels in cell membranes [52], and protein kinase C-induced increased phosphatidylserine exposure at erythrocyte surface (de Jong et al., 2002), evidently promoting suicidal death or eryptosis of blood cells, commonly seen in anemic conditions [15,51]. Of note, CPZ-induced red blood cell swelling, evidenced by mean cell volume and water content, was linked to increased RBC monovalent cation and Cl^- content [23]. Moreover, CPZ-induced cytotoxicity mediated by oxidative stress and inflammation, was also connected with alteration of mitochondrial membrane potential, pericanalicular distribution of F-actin, excessive expression of oxidative stress genes, increased IL-1β and IL-6 release, and reduced Na^+-taurocholate-co-expression polypeptide (NTCP), an important transporter that plays key role in the regulation of bile homeostasis [10]. Therefore, inhibition of oxidative stress and inflammatory pathways serves as important targets to protect against or reverse the hematological perturbations induced by drug toxicity such as CPZ-related hematological changes.

Taurine and coenzyme-Q10 (COQ-10) are two naturally occurring compounds reported to have protective and reversal effects on antipsychotic therapeutic-associated side effects [69,67,66]. Taurine is a protein-containing amino acid abundantly present in mammalian tissues, particularly in the brain, heart, and blood cells [13,36,66,73,79]. COQ-10, on the other hand, is a fat-soluble vitamin-like compound found in all human cells. It plays a crucial role in the production of energy and acts as a potent antioxidant [8,74]. Both taurine and COQ-10 have been extensively studied for their beneficial effects against various diseases, including psychiatric disorders and reproductive impairment [13,69,67,79] and inhibits leukocyte toxicity [19]. Although every drug is expected to have side effects whether mild or not, numerous proofs have shown the beneficial effects of taurine and co-enzyme Q10 and their beneficial interactions with different medications, notably by improving the function of distribution, CYP45-induced metabolism and excretion induced by some xenobiotics ([55]; Mochizuki et al., 2023). However, these alterations can be prevented and reversed by the supplementation of taurine and coenzyme-Q10. However, given the evident cases associated with CPZ-induced hematological derangements, we hypothesized that CPZ-induced hematological alterations would be prevented and reversed by the supplementation of taurine and coenzyme-Q10. Hence, this was designed to evaluate the protective effects of COQ-10 and taurine as well as its possible mechanism against CPZ-induced hematological perturbations in rats. Specifically, we investigated the preventive and reversal effects of COQ-10 and taurine on RBC and WBC changes, the role of oxidative stress and inflammation, and erythropoietin alteration in drug naïve and CPZ-treated rats.

2. Materials and Methods

2.1. Animals

The approved experimental protocol for the animal handling [male rats: 200–250 g; 12:12 hr light/dark cycle] agreed with that of the National Institute of Health (NIH) policies for animal use and care, as well as the Delta State University (DELSU) Ethics Committee on Animal Care (REC/FBMS/DELSU/18/04). The number of rats (n=6) approved for this study was based on the 3Rs principle, the analysis of the results obtained from our formal investigations with the same sample size, and the power analysis formula: sample size/(1 [percent attrition/100]) that is dependent on the effect size and standard deviation of previous findings of similar studies.

2.2. Drugs and chemicals

The study utilized CPZ, COQ-10, and taurine (Sigma-Aldrich, St. Louis, USA). As a vehicle, propylene glycol - PG (Mistral industrial chemicals, UK) was used. The doses of CPZ (30 mg/kg.bw/day), COQ-10 (10 mg/kg.bw/day) [75], and taurine (150 mg/kg.bw/day) (Oyewole et al., 2021) followed previous effect sizes from previous studies. The vehicle, 20% PG at 0.5 ml body weight/day, was administered based on the study by [75]. CPZ and taurine were dissolved in sterile distilled water, while COQ-10 was dissolved in 20% propylene glycol (0.5 ml) in the COQ-10 group [28]. All treatments were administered orally using an orogastric canula. However, for standardization of drug administration of animals throughout 56 days treatments, the dosages were adjusted weekly based on body weight. All administrations were given once daily between 8.00 am and 9.00 am through oral route for 56 consecutive days (8 weeks).

2.3. Experimental Procedures

The study utilized three distinct experimental phases:

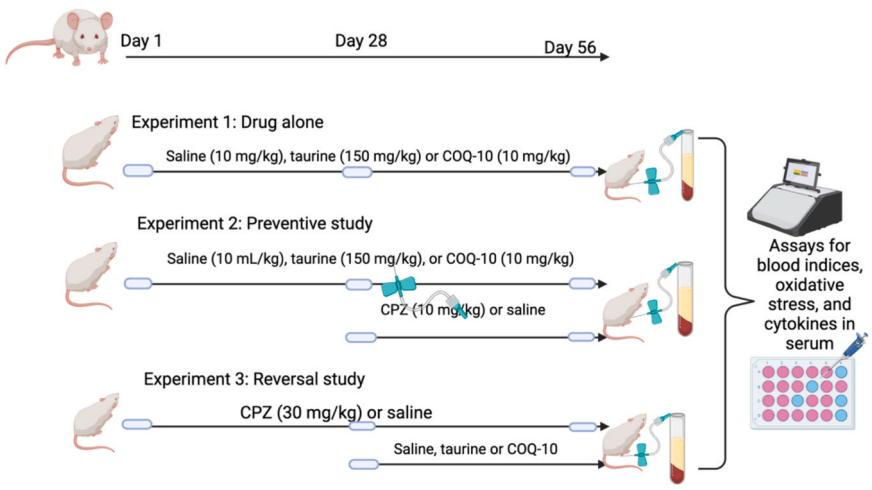
Phase 1-(Drug alone)

A total of 30 Wistar rats were randomly divided into five (5) groups with six animals allocated in each group (Scheme 1):

Group 1: Received normal saline (0.5 ml/kg) and served as a negative control

Group 2: Received PG (0.5 ml of 20%) and served as a vehicle control

Group 3: Received taurine (150 mg/kg)



Scheme 1. Experimental approach.

Group 4: Received COQ-10 (10 mg/kg)
Group 5: Received taurine (150 mg/kg) + COQ-10 (10 mg/kg)
Phase 2-(Reversal study)

To avoid duplication of the same groups 1 and 2 across phases 1–3 experiments based on the rule of R3 (reduce, reuse, and recycle) [41], the control rats in groups 1 and 2 of phase 1 experiment served as the same controls (normal and vehicle controls) for phase 2 experiment. Accordingly, 24 male Wistar rats were randomly divided across groups 3–6 (n=6). Rats in group Groups 3–6 had CPZ (30 mg/kg, p.o./day) continuously for 56 days. From days 29–56, rats in group 4 were additionally treated with taurine (150 mg/kg, p.o./day), group 5 was given COQ-10 (10 mg/kg, p.o./day), while group 6 had the combination of taurine (150 mg/kg, p.o./day) + COQ-10 (10 mg/kg, p.o./day) (Scheme 1). Administrations were made 30 min between each treatment.

Group 1: Received normal saline (0.5 ml/kg) and served as a normal control
Group 2: Received PG (0.5 ml of 20%) and served as a vehicle control
Group 3: Received CPZ (30 mg/kg) + normal saline (10 ml/kg)
Group 4: Received CPZ (30 mg/kg) + taurine (150 mg/kg)
Group 5: Received CPZ (30 mg/kg) + CoQ-10 (10 mg/kg)
Group 6: Received CPZ (30 mg/kg) + taurine (150 mg/kg) + CoQ-10 (10 mg/kg)
Phase 3-(Preventive study)

As regards phase 3, control rats in groups 1 and 2 from phase 1 experiment also served as the same controls (normal and vehicle controls) for the phase 2 experiment. Here also, a total of 24 male Wistar rats were distributed between groups 3–6 (n=6). Rats in group 3 had received normal saline (10 ml/kg ml/kg, p.o.), group 4 was pre-treated with taurine (150 mg/kg, p.o./day), group 5 received COQ-10 (10 mg/kg, p.o./day)), while group 6 was pre-treated the combination of taurine (150 mg/kg, p.o./day) + COQ-10 (10 mg/kg, p.o./day) for 56 days. However, from days 29–56, rats in groups 3–6 additionally received chlorpromazine (30 mg/kg, p.o./day) once daily (Scheme 1). All treatments were made 30 min between each treatment.

Group 1: Received normal saline (0.5 ml) and served as a negative control
Group 2: Received PG (0.5 ml of 20%) and served as a vehicle control
Group 3: Received normal saline (0.5 ml/kg) + CPZ (30 mg/kg)
Group 4: Received taurine (150 mg/kg) + CPZ (30 mg/kg)
Group 5: Received COQ-10 (10 mg/kg) + CPZ (30 mg/kg)
Group 6: Received taurine (150 mg/kg) + COQ-10 (10 mg/kg) + CPZ (30 mg/kg).

2.4. Body Weight measurement

Rats' body weight was recorded just prior to the start of the experiment with insignificant differences between all groups. On the 56th day of the experiment, every rat was weighed, euthanized under mild thiopentone sodium anesthesia to prevent major biochemical effects, and dissected.

2.5. Blood Sample Collection

The hematological and biochemical parameters were obtained from blood samples of every animal through cardiac puncture. Samples for hematological parameters were collected in EDTA bottles, while samples for biochemical parameters were received in plain bottles. The plain bottles containing blood samples were left to clot for 45 min at room temperature before being centrifuged at 600 x g for 15 min. The resulting serum was then used to analyze the various biochemical parameters.

2.6. Hematological Parameters

2.6.1. Blood Cell Count

Red blood cell count (RBC count), total leukocyte count (TLC), and platelet count were manually performed using a hemocytometer with phosphate-buffered saline, turks fluid, and 1% ammonium oxalate, respectively. The resulting counts were recorded as the number of cells per μL of blood, in accordance with the method described by Lewis and Aitken [53]. The individual responsible for conducting the count was blinded to the experimental group of the animals.

2.6.2. Estimation of hemoglobin content

The hemoglobin test kit (Diagnova, Ranbaxy India) was utilized to determine the hemoglobin content, following the cyanmethemoglobin method. The resulting Hb content was expressed in g%.

2.6.3. Hematocrit [Packed cell volume (PCV)]

To determine the hematocrit level, the microhaematocrit method was utilized. This involved filling a plain capillary tube with blood and securing it with a plastic seal. The tube was then subjected to centrifugation at a force of 12000 g for 5 min. Following centrifugation, the ratio of cells to the entire column was assessed and the resulting value was expressed as a percentage, as stated by Lewis and Aitken [53].

2.6.4. Blood Indices

The calculation of Mean Corpuscular Volume (MCV), Mean

Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC) followed the formulae outlined by Dacie and Lewis and were presented in units of μm3, pg, and percentage, respectively [53].

2.6.5. Differential Count

Leishman's stain was used to stain blood smears, and a differential count was carried out. The resulting count was presented as a percentage for each type, as stated by Lewis and colleagues in 2006. The individual conducting the count was not informed of the sample's experimental group.

2.7. Biochemical Assay

2.7.1. Assessment of oxidative status

As previously reported [12,11], spectrophotometry was used to perform assays for malondialdehyde (MDA) (Vancouver, WA, USA), superoxide dismutase (SOD) and catalase (CAT) (Cayman Chemicals Company in Ann Arbor, MI, USA), and glutathione (GSH) (Sigma-Aldrich Chemie GmbH in Stein Dorf, Germany) using different commercial kits.

2.7.2. Measurement of inflammatory indicators

The indicators for inflammation such as TNF-α, IL-6, and IL-10 were analyzed using a rat ELISA kits from Shanghai YL Biotech Co. Ltd., China. The tests were carried out following the instructions provided by the manufacturer.

2.8. Measurement of Erythropoietin

Erythropoietin concentration was measured using rat ELISA kits from Shanghai YL Biotech Co. Ltd., China. The tests were carried out following the instructions provided by the manufacturer.

2.9. Statistical Analysis

Outliers were identified by the interquartile range method followed by normality examination with Shapiro–Wilk test. Thereafter, mean, and standard error of mean (SEM), was performed. The analysis was carried out with the aid of GraphPad Prism (Version 8), and statistical significance was determined through One-way ANOVA (Analysis of Variance). When necessary, a Turkey post-hoc test was utilized for multiple comparisons. Any disparities in the mean values were deemed significant at a level of $p<0.05$.

3. Results

3.1. Effects of taurine, CoQ-10 or their combination on the body weight of naïve and chlorpromazine-induced changes in male Wistar rats

As shown in Fig. 1a-c, treatment with these substances did not significantly affect initial or final body weights (Fig. 1a-c). In rats treated with CPZ (Figs. 2b-c and 3b-c), there was a decrease in final body weight and weight loss. However, taurine, COQ-10, and their combination reversed this effect, notably leading to weight gain, with the combination being the most effective. Pre-treatment with taurine and COQ-10 also prevented the decrease in body weight caused by CPZ.

3.2. Effect of taurine, CoQ-10 or their combination on naïve and chlorpromazine-induced changes in hematological indices in rats

Taurine and CoQ-10, either alone or in combination, had no significant effect on RBC, PCV, and platelet counts compared to normal control rats. However, the combination of taurine and COQ-10 improved RBC, WBC, and PCV counts in rats compared to the normal control (Table 1a). Treatment with CPZ caused a significant decrease in various blood parameters, but these effects were reversed with the use of taurine and COQ-10 alone or in combination (Table 1b). The combination of taurine and COQ-10 showed better results compared to individual use in reversing the adverse effects of CPZ. However, there was no

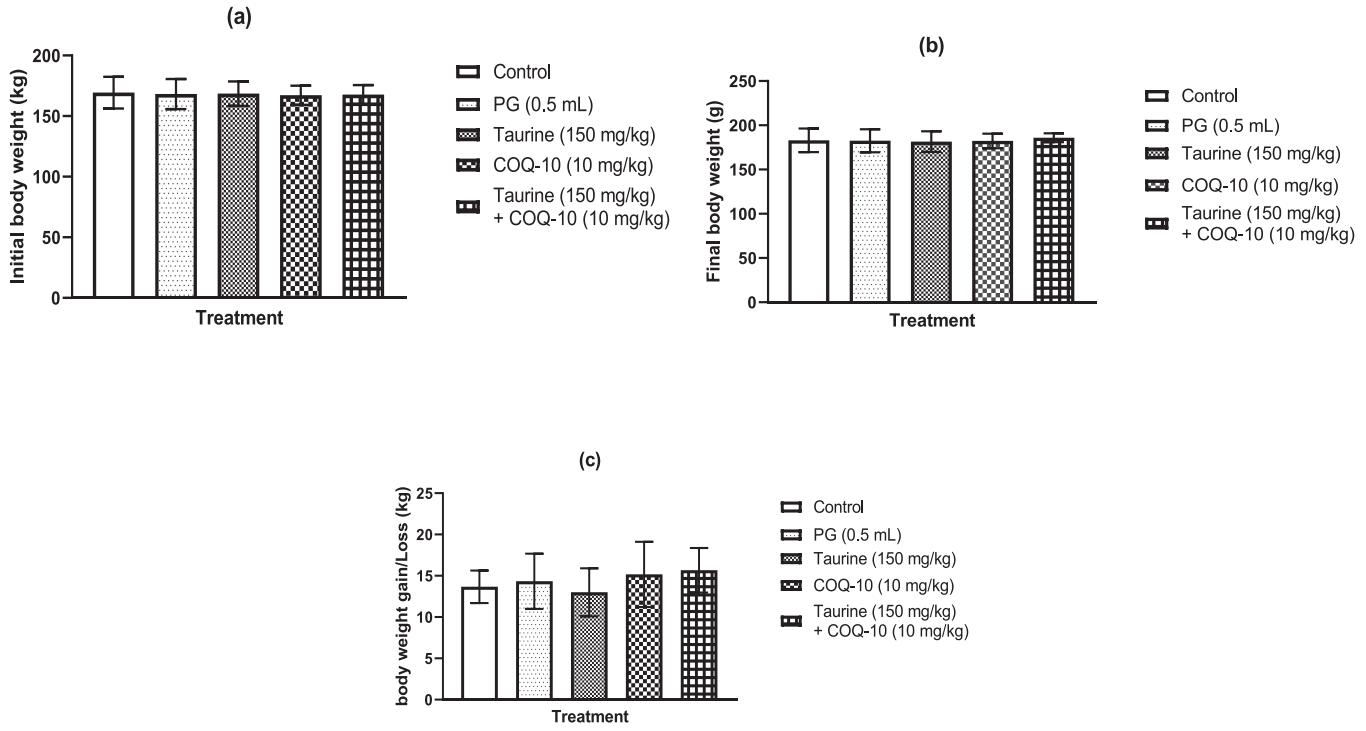


Fig. 1. Effects of taurine, COQ-10 or their combination on the body weights of naïve male Wistar rats: (a) initial body weight, (b) final body weight and (c) body weight gain/loss. Data are expressed as mean ± S.E.M. (n = 6). PG: Propylene glycol; COQ-10: Coenzyme Q10.

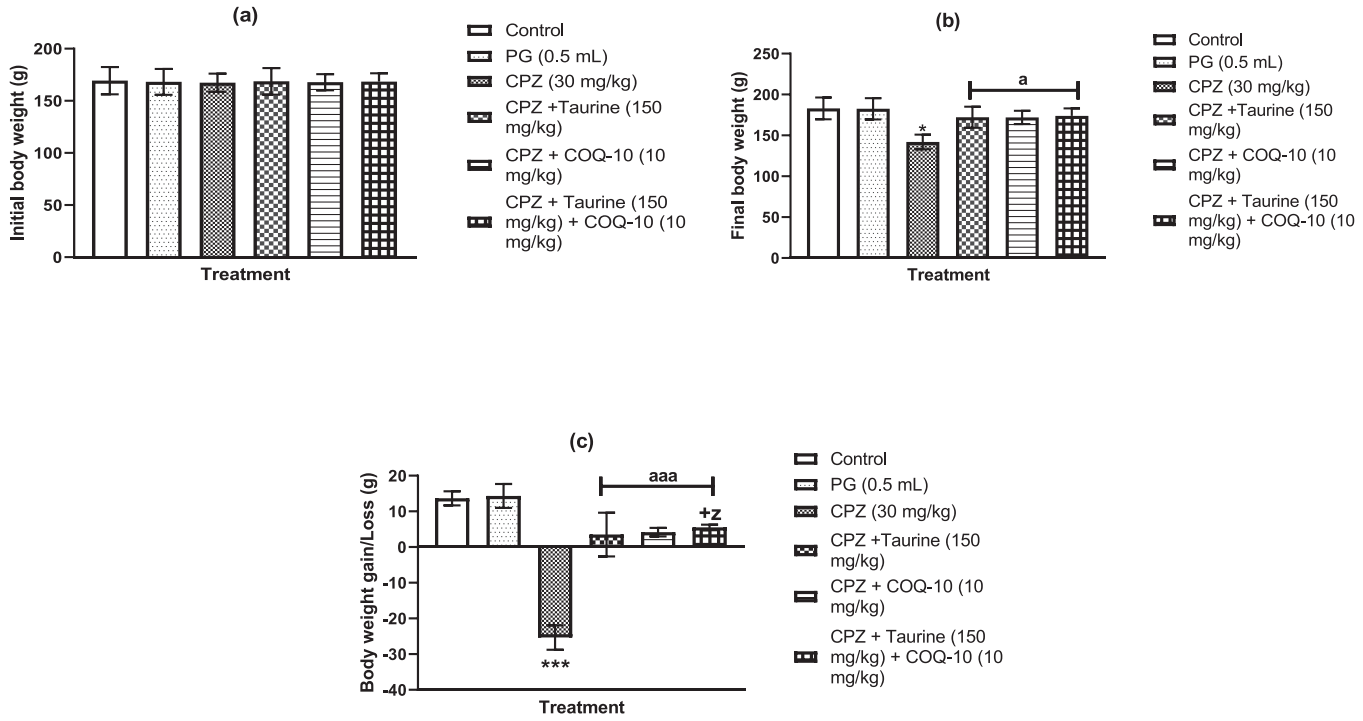


Fig. 2. Reversal effects of taurine, COQ-10 or their combination on CPZ-induced changes in body weight in male Wistar rats: (a) initial body weight, (b) final body weight and (c) body weight gain/loss. Data are expressed as mean ± S.E.M. (n = 6). $^{*}p<0.001$ and $^{***}p<0.001$ when compared with normal controls; $^{a}p<0.05$ and $^{aaa}p<0.001$ when compared with CPZ; $^{+}p<0.05$ when compared with CPZ + taurine group; $^{z}p<0.05$ when compared with CPZ + CoQ-10 group. PG: Propylene glycol; COQ-10: Coenzyme Q10; CPZ; Chlorpromazine.

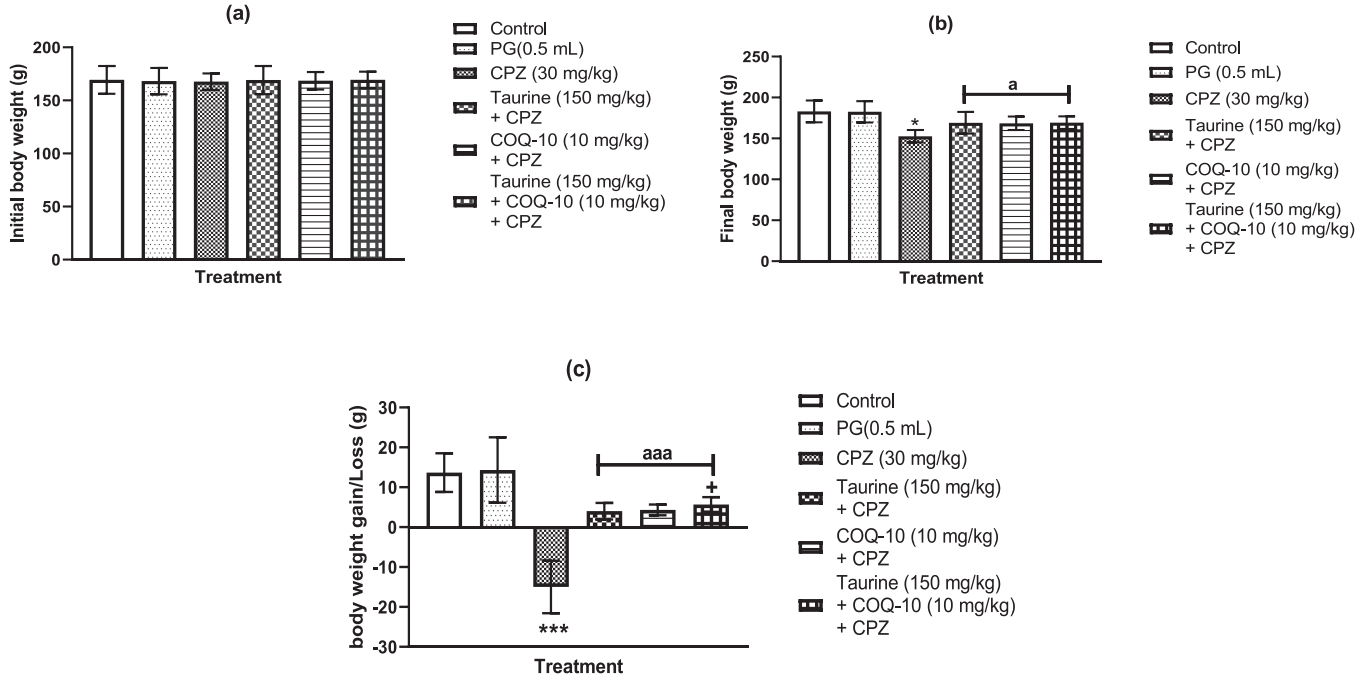


Fig. 3. Preventive effects of taurine, CoQ-10 or their combination on CPZ-induced changes in body weight in male Wistar rats: (a) initial body weight, (b) final body weight and (c) body weight gain/loss. Data are expressed as mean ± S.E.M. (n = 6). $^{*}p<0.001$ and $^{***}p<0.001$ when compared with normal controls; $^{a}p<0.05$ and $^{aaa}p<0.001$ when compared with CPZ; $^{+}p<0.05$ when compared with taurine + CPZ; $^{z}p<0.05$ when compared with COQ-10 + CPZ. PG: Propylene glycol; COQ-10: Coenzyme Q10; CPZ; Chlorpromazine.

significant change in platelet count when the two compounds were used together. Similarly, the preventive treatment with taurine and COQ-10 significantly prevents the negative effects of CPZ on RBC count, Hb concentration, PCV, platelet and WBC counts. Pre-treatment with COQ-10 alone also increased RBC count levels compared to the taurine alone. The combination of taurine and COQ-10 showed the most significant increase in RBC count, PCV, platelet count, and WBC count compared to either alone (Table 1c).

Table 1a
Effects of taurine, COQ-10 or their combination on the hematological indices of naïve rats.

Group	RBC ($x10^{12}$/L)	PCV (%)	Hb (g/dL)	WBC ($x10^{9}$/L)	Platelets Count ($x10^{9}$/L)
Control	8.18 ± 0.10	42.17 ± 0.75	14.06 ± 0.25	15.32 ± 0.59	315.8 ±12.53
PG (0.5 ml/kg)	8.18 ± 0.09	42.17 ± 1.17	14.05 ± 0.39	15.33 ± 0.47	317.2 ± 16.42
Taurine (150 mg/kg)	8.22 ± 0.08	43.50 ± 1.05	14.50 ± 0.35	17.00 ± 0.62*	319.7 ± 15.50
COQ-10 (10 mg/kg)	8.26 ± 0.06	43.83 ± 1.84	14.61 ± 0.61	17.11 ± 0.22*	320.5 ± 10.31
Taurine (150 mg/kg) + COQ-10 (10 mg/kg)	8.56 ± 0.24*	45.50 ± 1.52b,c,*	15.17 ± 0.50*	19.55 ± 1.12*	322.2 ± 15.09

Data are expressed as mean ± S.E.M. (n = 6).
* $p<0.05$ when compared with normal controls;
b $p<0.05$ when compared with taurine;
c $p<0.05$ when compared with COQ-10. PCV: Packed Cell volume; RBC; Red blood cell; WBC: White blood cell; Hb: Hemoglobin. PG: Propylene glycol; TAU: Taurine; COQ-10: Coenzyme Q10.

Table 1b
Reversal effect of taurine, CoQ-10 or their combination on chlorpromazine-induced changes in hematological indices in rats.

Group	RBC ($x10^{12}$/L)	PCV (%)	Hb (g/dL)	WBC ($x10^{9}$/L)	Platelets Count ($x10^{9}$/L)
Control	8.18 ± 0.10	42.17 ± 0.75	14.06 ± 0.25	15.32 ± 0.59	315.8 ± 12.53
PG (0.5 ml/kg)	8.18 ± 0.09	42.17 ± 1.17	14.05 ± 0.39	15.33 ± 0.47	317.2 ± 16.42
CPZ (30 mg/kg)	3.06 ± 0.05*	31.33 ± 1.21*	10.45 ± 0.41*	7.030 ± 0.13*	228.2 ± 10.07*
CPZ + Taurine (150 mg/kg)	6.75 ± 0.39a	40.83 ± 0.98a	13.61 ± 0.33a	12.95 ± 0.69a	284.8 ± 5.12a
CPZ + COQ-10 (10 mg/kg)	6.82 ± 0.54a	41.67 ± 1.63a	13.89 ± 0.55a	13.11 ± 0.64a	285.0 ± 7.07a
CPZ + Taurine (150 mg/kg) + COQ-10 (10 mg/kg)	6.97 ± 0.21a,+,z	4.17 ± 0.75a,+,z	14.33 ± 0.47	14.06 ± 0.30a,+,z	287.5 ± 6.22a

Data are expressed as mean ± S.E.M. (n = 6).
PCV: Packed Cell volume; RBC: Red blood cell; WBC: White blood cell; Hb: Hemoglobin. PG: Propylene glycol; COQ-10: Coenzyme Q10; CPZ: Chlorpromazine.
* $p<0.05$ when compared with normal controls;
a $p<0.05$ when compared with CPZ;
+ $p<0.05$ when compared with the group given CPZ + taurine
z $p<0.05$ when compared with CPZ + COQ-10.

3.3. Effect of taurine, CoQ-10 or in combination on naïve and chlorpromazine-induced changes in mean red blood cell indices in rats

Treatment with these substances did not cause any significant effect on RBC indices (Fig. 2a). However, they were able to reverse the effects of CPZ on mean corpuscular volume and mean corpuscular hemoglobin (Fig. 2b). In the preventive treatment, taurine and COQ-10 increased MCV and MCH levels but did not affect MCHC levels (Fig. 2c).

3.4. Effect of taurine, CoQ-10 and in combination on naïve and chlorpromazine-induced changes in mean white blood cell differentials in rats

Taurine and COQ-10, alone or in combination, increased neutrophil and lymphocyte levels in rats (Table 3a). They also reversed the negative effects of CPZ on WBC levels (Table 3b). The combination had a greater effect than the individual treatments. In the preventive treatment (Table 3c), following CPZ treatment from days 29–56, the levels of neutrophil and lymphocyte levels were significantly decreased, but eosinophil levels increased compared to the normal controls. Pre-treatment with taurine and COQ-10, either alone or in combination, increased neutrophil and lymphocyte levels significantly compared to the CPZ treatment alone. The combination of taurine and COQ-10 showed the most significant increase in neutrophil and lymphocyte levels compared to individual treatments. (Table 3c).

Table 1c
Preventive effect of taurine, CoQ-10 or their combination on chlorpromazine-induced changes in hematological indices in rats.

Group	RBC ($x10^{12}$/L)	PCV (%)	Hb (g/dL)	WBC ($x10^{9}$/L)	Platelets Count ($x10^{9}$/L)
Control	8.18 ± 0.10	42.17 ± 0.75	14.06 ± 0.25	15.32 ± 0.59	315.8 ± 12.53
PG (0.5 ml/kg)	8.18 ± 0.09	42.17 ± 1.17	14.05 ± 0.39	15.33 ± 0.47	317.2 ± 16.42
CPZ (30 mg/kg)	2.46 ± 0.31*	34.17 ± 3.60*	11.39 ± 1.20*	8.62 ± 0.73*	252.5 ± 29.98*
Taurine (150 mg/kg) + CPZ	8.24 ± 0.11a	44.17 ± 1.17a	15.06 ± 0.88a	15.16 ± 0.32a	321.7 ± 6.62a
COQ-10 (10 mg/kg) + CPZ	8.407 ± 0.13a,+	45.83 ± 1.47a	15.28 ± 0.49a	15.85 ± 0.48a	336.2 ± 13.09a
Taurine (150 mg/kg) + COQ-10 (10 mg/kg) + CPZ	8.79 ± 0.32a,+,z	48.8 ± 1.94a,+,z	16.28 ± 0.65a	17.22 ± 0.85a,+,z	379.7 ± 18.08a,+,z

Data are expressed as mean ± S.E.M. (n = 6).
PCV: Packed Cell volume; RBC: Red blood cell; WBC: White blood cell; Hb: Hemoglobin. PG: Propylene glycol; COQ-10: Coenzyme Q10; CPZ: Chlorpromazine.
* $p<0.05$ when compared with normal controls;
a $p<0.05$ when compared with CPZ;
+ $p<0.05$ when compared with taurine + CPZ;
z $p<0.05$ when compared with the group given COQ-10 + CPZ.

Table 2a
Effect of taurine, COQ-10 and their combination on mean red blood cell indices in naïve in rats.

Group	MCV (fL)	MCH (pg)	MCHC (g/dL)
Control	51.57 ± 1.42	17.19 ± 0.47	33.33 ± 0.00
PG (0.5 ml/kg)	51.55 ± 1.84	17.18 ± 0.61	33.33 ± 0.00
Taurine (150 mg/kg)	52.68 ± 1.81	17.65 ± 0.52	33.33 ± 0.01
COQ-10 (10 mg/kg)	53.11 ± 2.49	17.57 ± 0.77	33.47 ± 0.33
Taurine (150 mg/kg) + COQ-10 (10 mg/kg)	53.20 ± 2.82	17.73 ± 0.94	33.33 ± 0.01

Data are expressed as mean ± S.E.M. (n = 6). MCV: Mean corpuscular Volume; MCH: Mean corpuscular Hemoglobin; MCHC: Mean corpuscular Hemoglobin concentration. PG: Propylene glycol; COQ-10: Coenzyme Q10.

3.5. Taurine and Coenzyme Q10 abate chlorpromazine-induced oxidative stress in rats serum

The results shown in Fig. 4a-c demonstrate the effects of taurine and COQ-10 on the levels of oxidative stress markers in both naïve and CPZ-

Table 2b
Reversal effect of taurine, CoQ-10 and their combination on chlorpromazine-induced changes in mean red blood cell indices in rats.

Group	MCV (fL)	MCH (pg)	MCHC (g/dL)
Control	51.57 ± 1.42	17.19 ± 0.47	33.33 ± 0.00
PG (0.5 ml/kg)	51.55 ± 1.84	17.18 ± 0.61	33.33 ± 0.00
CPZ (30 mg/kg)	102.4 ± 3.82*	34.14 ± 1.27*	33.33 ± 0.01
CPZ + Taurine (150 mg/kg)	60.60 ± 2.69[a]	20.20 ± 0.89[a]	33.33 ± 0.01
CPZ + COQ-10 (10 mg/kg)	61.36 ± 4.35[a]	20.36 ± 1.52[a]	33.33 ± 0.01
CPZ + Taurine (150 mg/kg) + COQ-10 (10 mg/kg)	61.66 ± 3.51[a]	20.53 ± 1.26[a]	33.47 ± 0.78

Data are expressed as mean ± S.E.M. (n = 6).
* $p<0.05$ when compared with normal controls;
[a] $p<0.05$ when compared with CPZ. MCV: Mean corpuscular Volume; MCH: Mean corpuscular Hemoglobin; MCHC: Mean corpuscular Hemoglobin concentration. PG: Propylene glycol; COQ-10: Coenzyme Q10; CPZ: Chlorpromazine

Table 2c
Preventive effect of taurine, CoQ-10 and their combination on naïve and chlorpromazine-induced changes in mean red blood cell indices in rats.

Group	MCV (fL)	MCH (pg)	MCHC (g/dL)
Control	51.57 ± 1.42	17.19 ± 0.47	33.33 ± 0.00
PG (0.5 ml/kg)	51.55 ± 1.84	17.18 ± 0.61	33.33 ± 0.00
CPZ (30 mg/kg)	142.4 ± 33.43*	47.48 ± 11.14*	33.33 ± 0.01
Taurine (150 mg/kg) + CPZ	53.60 ± 1.95[a]	18.27 ± 1.12[a]	34.09 ± 1.86
COQ-10 (10 mg/kg) + CPZ	54.55 ± 2.44[a]	18.10 ± 0.88[a]	33.33 ± 0.01
Taurine (150 mg/kg) + COQ-10 (10 mg/kg) + CPZ	55.62 ± 2.83[a]	18.54 ± 0.94[a]	33.34 ± 0.01

Data are expressed as mean ± S.E.M. (n = 6).
* $p<0.05$ when compared with normal controls;
[a] $p<0.05$ when compared with CPZ. MCV: Mean corpuscular Volume; MCH: Mean corpuscular Hemoglobin; MCHC: Mean corpuscular Hemoglobin concentration. PG: Propylene glycol; COQ-10: Coenzyme Q10; CPZ: Chlorpromazine

Table 3a
Effect of taurine, CoQ-10 and in combination on mean white blood Cell indices of naïve rats.

Group	Neutrophil (%)	Eosinophil (%)	Lymphocyte (%)
Control	31.17 ± 7.36	1.50 ± 0.55	81.71 ± 2.22
PG (0.5 ml/kg)	31.17 ± 5.08	1.50 ± 0.55	81.70 ± 1.76
Taurine (150 mg/kg)	34.83 ± 2.93*	1.00 ± 0.89	85.23 ± 2.72*
COQ-10 (10 mg/kg)	36.17 ± 3.31[b],*	0.83 ± 0.98	86.46 ± 2.37*
Taurine (150 mg/kg) + COQ-10 (10 mg/kg)	39.17 ± 2.04[b,c],*	0.67 ± 0.52*	88.16 ± 1.42*

Data are expressed as mean ± S.E.M. (n = 6).
* $p<0.05$ when compared with normal controls,
[b] $p<0.05$ as compared to taurine treatment;
[c] $p<0.05$ as compared to COQ-10 treatment. PG: Propylene glycol; COQ-10: Coenzyme Q10

treated rats. Fig. 4 illustrates that the administration of either an individual drug or a combination of both significantly reduced MDA levels ($p < 0.001$) compared to the control group. In both the preventative and reversal treatment groups, CPZ caused an increase in MDA levels, while

Table 3b
Reversal effect of taurine, CoQ-10 and in combination on chlorpromazine-induced changes in mean white blood cell differentials in rats.

Group	Neutrophil (%)	Eosinophil (%)	Lymphocyte (%)
Control	31.17 ± 7.36	1.50 ± 0.55	81.71 ± 2.22
PG(0.5 ml/kg)	31.17 ± 5.08	1.50 ± 0.55	81.70 ± 1.76
CPZ (30 mg/kg)	10.33 ± 1.03*	3.17 ± 0.75*	50.41 ± 1.02*
CPZ (30 mg/kg) + Taurine (150 mg/kg)	24.50 ± 1.05[a]	2.33 ± 0.52[a]	63.12 ± 2.59[a]
CPZ + COQ-10 (10 mg/kg)	26.17 ± 0.75[a,+]	2.17 ± 0.41[a]	63.10 ± 2.66[a]
CPZ + Taurine (150 mg/kg) + COQ-10 (10 mg/kg)	29.17 ± 0.75[a,+,z]	1.67 ± 0.52[a]	67.00 ± 1.59[a,+,z]

Data are expressed as mean ± S.E.M. (n = 6).
PG: Propylene glycol; TAU: Taurine; COQ-10: Coenzyme Q10; CPZ: Chlorpromazine
* $p<0.05$ when compared with normal controls;
[a] $p<0.05$ when compared with CPZ;
[+] $p<0.05$ when compared with CPZ + taurine;
[z] $p<0.05$ when compared with the group given CPZ + COQ-10.

Table 3c
Preventive effect of taurine, CoQ-10 and in combination on chlorpromazine-induced changes in mean white blood cell differentials in rats.

Group	Neutrophil (%)	Eosinophil (%)	Lymphocyte (%)
Control	31.17 ± 7.36	1.50 ± 0.55	81.71 ± 2.22
PG (0.5 ml/kg)	31.17 ± 5.08	1.50 ± 0.55	81.70 ± 1.76
CPZ (30 mg/kg)	15.83 ± 2.32*	2.667 ± 0.82*	61.51 ± 2.05*
Taurine (150 mg/kg) + CPZ	37.33 ± 1.75[a]	1.00 ± 0.00[a]	80.08 ± 0.63[a]
COQ-10 (10 mg/kg) + CPZ	38.83 ± 1.17[a]	0.83 ± 0.75[a]	80.48 ± 0.57[a]
Taurine (150 mg/kg) + COQ-10 (10 mg/kg) + CPZ	41.00 ± 3.58[a,+,z]	0.67 ± 0.52[a]	83.31 ± 1.24[a,+,z]

Data are expressed as mean ± S.E.M. (n = 6).
PG: Propylene glycol; TAU: Taurine; COQ-10: Coenzyme Q10; CPZ: Chlorpromazine
* $p<0.05$ when compared with normal controls;
[a] $p<0.05$ when compared with CPZ;
[+] $p<0.05$ when compared with taurine + CPZ;
[z] $p<0.05$ when compared with the group given COQ-10 + CPZ.

taurine, COQ-10, or their combination of both drugs effectively prevented and reversed CPZ-induced oxidative stress.

3.6 Taurine and CO-QIO improved chlorpromazine-induced changes in enzymatic antioxidant systems in the preventive and reversal treatments in rats' serum.

Figs. 5 and 6 depict the effects of taurine, COQ-10, or a combination of both drugs on serum enzymatic antioxidant levels in both naïve and CPZ-treated rats. Upon administration of taurine and COQ-10, SOD and GSH were significantly increased ($p > 0.05$) (Figs. 5a and 6a) compared to the control groups. Furthermore, the combined treatment of taurine and COQ-10 significantly ($p < 0.001$) increased the activities of SOD, and GSH levels compared to the control groups (Figs. 5a and 6a). In both experiments, CPZ treatment significantly reduced the activities of SOD ($p < 0.001$) (Fig. 5b-a) and GSH (Fig. 6b-c) compared to the control groups. However, this reduction was counteracted by the administration of taurine, COQ-10, or a combination of both drugs in both studies.

3.7 Taurine and CO-QIO prevent and reverse chlorpromazine-induced alterations in pro-inflammatory and anti-inflammatory cytokines in rats' serum.

The results shown in Figs. 7 and 8 demonstrate the effects of taurine and COQ-10 on inflammatory markers in both naïve and CPZ-treated rats. Figs. 7 and 8 illustrate that administration of either taurine and COQ-10, or their combination of both significantly reduced TNF-α and IL-6 levels ($p < 0.001$), with profound increases in IL-10 (Fig. 9)

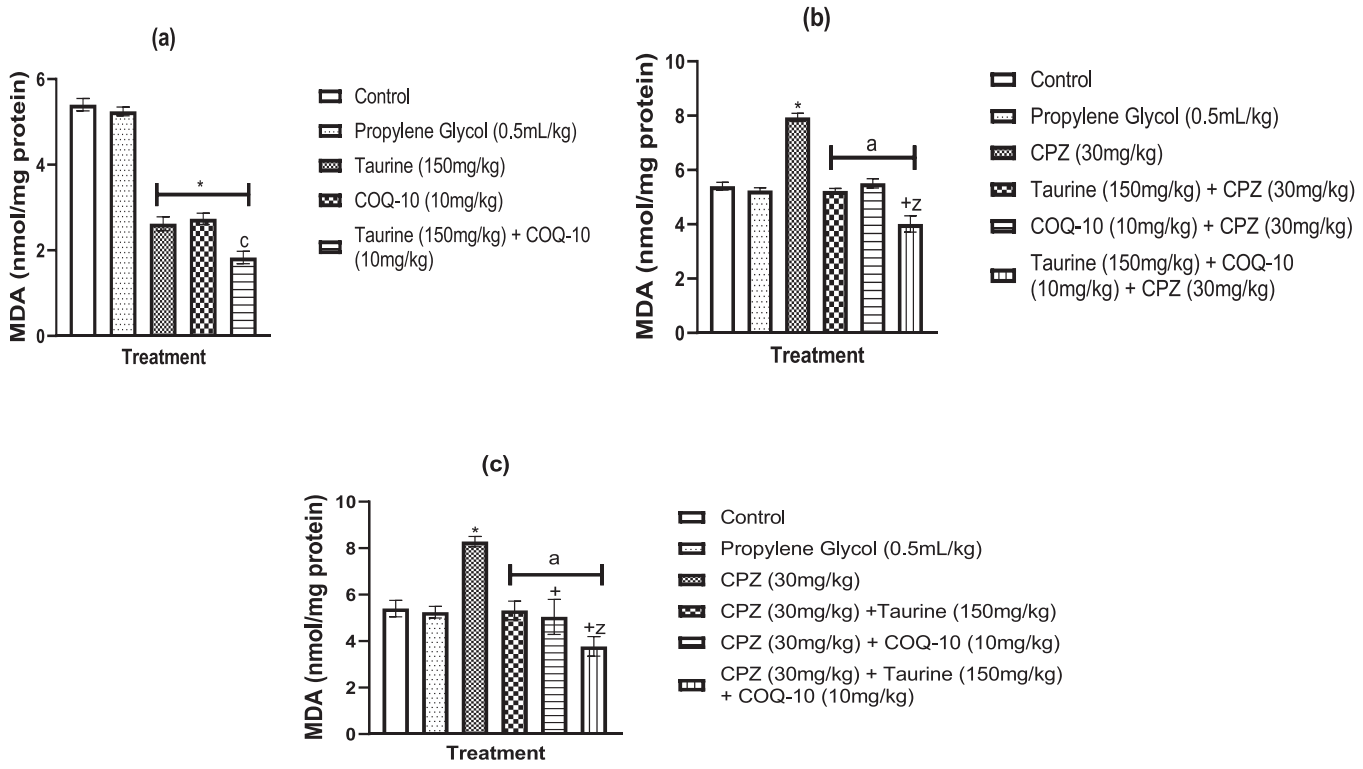


Fig. 4. Effects of taurine and COQ-10 in male Wister rats exposed to chlorpromazine-induced alterations in malondialdehyde (MDA) in naïve (a), preventive (b) and reversal (c) studies. Mean ± S.E.M. (n = 6) are presented in bars. *$p < 0.05$ as compared to normal control; $^{a}p < 0.05$ as compared to CPZ; $^{b}p < 0.05$ as compared to taurine treatment; $^{c}p<0.05$ as compared to COQ-10 treatment; $^{+}p<0.05$ when compared with CPZ + taurine/ taurine + CPZ; $^{z}p<0.05$ when compared with CPZ + COQ-10/ COQ-10 + CPZ. PG = Propylene glycol; COQ-10 = Coenzyme-Q10.

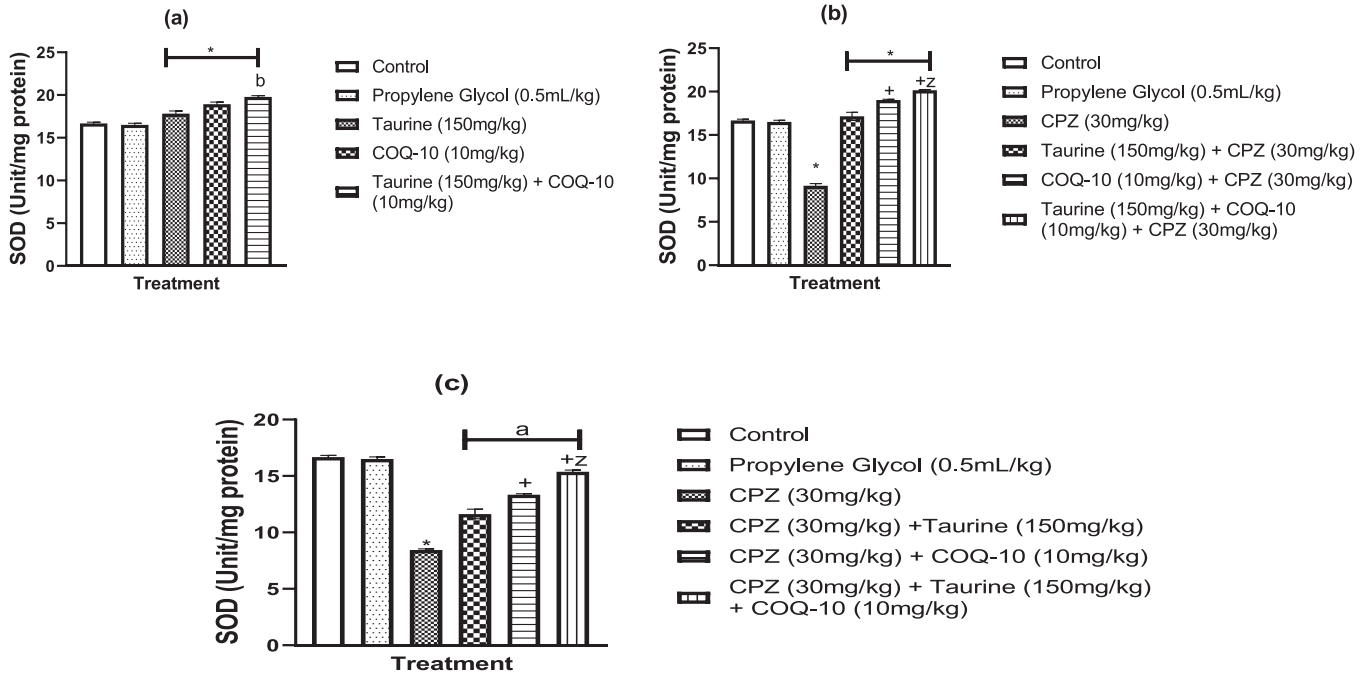


Fig. 5. Effects of taurine and COQ-10 in male Wister rats exposed to chlorpromazine-induced alterations in superoxide dismutase (SOD) in naïve (a), preventive (b), and reversal (c) studies. Mean ± S.E.M. (n = 6) are presented in bars. *$p < 0.05$ as compared to normal control; $^{a}p < 0.05$ as compared to CPZ; $^{b}p < 0.05$ as compared to taurine treatment; $^{c}p<0.05$ as compared to COQ-10 treatment; $^{+}p<0.05$ when compared with CPZ + taurine/ taurine + CPZ; $^{z}p<0.05$ when compared with CPZ + COQ-10/ COQ-10 + CPZ. PG = Propylene glycol; COQ-10 = Coenzyme-Q10.

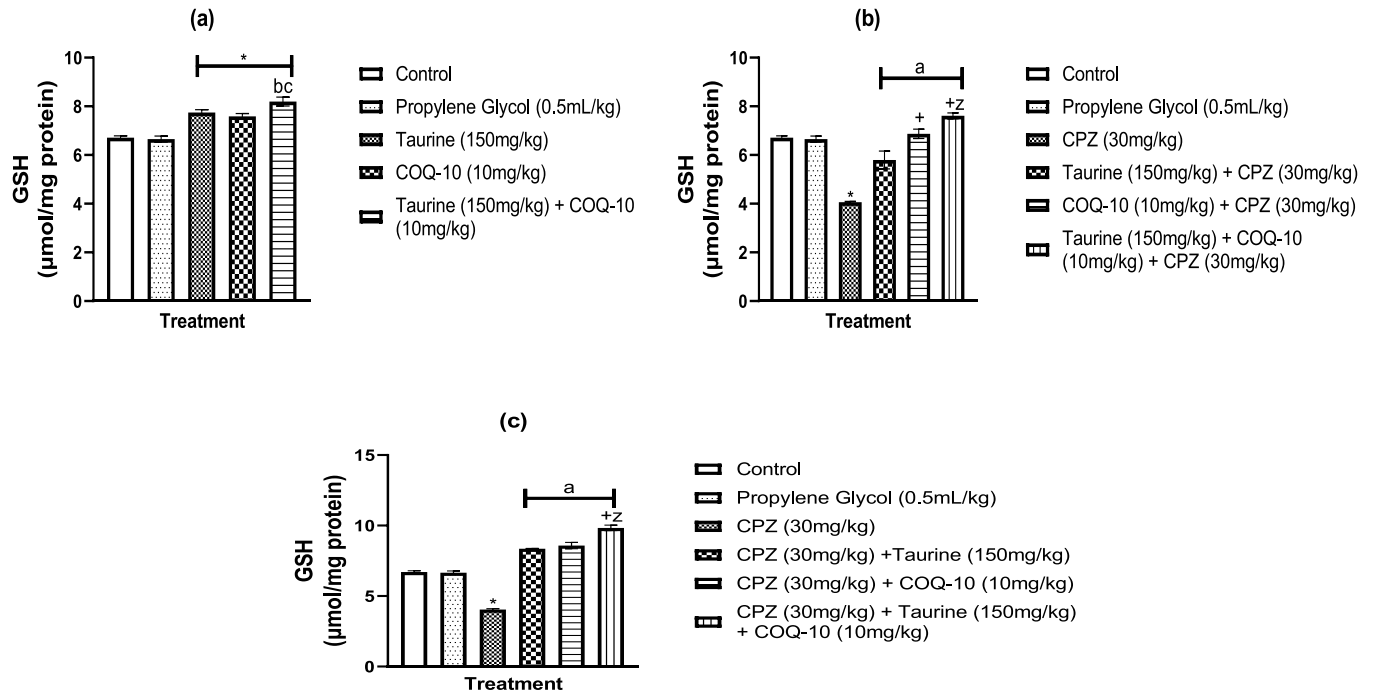


Fig. 6. Effects of taurine and COQ-10 in male Wister rats exposed to chlorpromazine-induced alterations in glutathione (GSH) in naïve (a), preventive (b), and reversal (c) studies. Mean ± S.E.M. (n = 6) are presented in bars. *$p<0.05$ as compared to normal control; $^{a}p<0.05$ as compared to CPZ; $^{b}p<0.05$ as compared to taurine treatment; $^{c}p<0.05$ as compared to COQ-10 treatment; $^{+}p<0.05$ when compared with CPZ + taurine/ taurine + CPZ; $^{z}p<0.05$ when compared with CPZ + COQ-10/ COQ-10 + CPZ. PG = Propylene glycol; COQ-10 = Coenzyme-Q10.

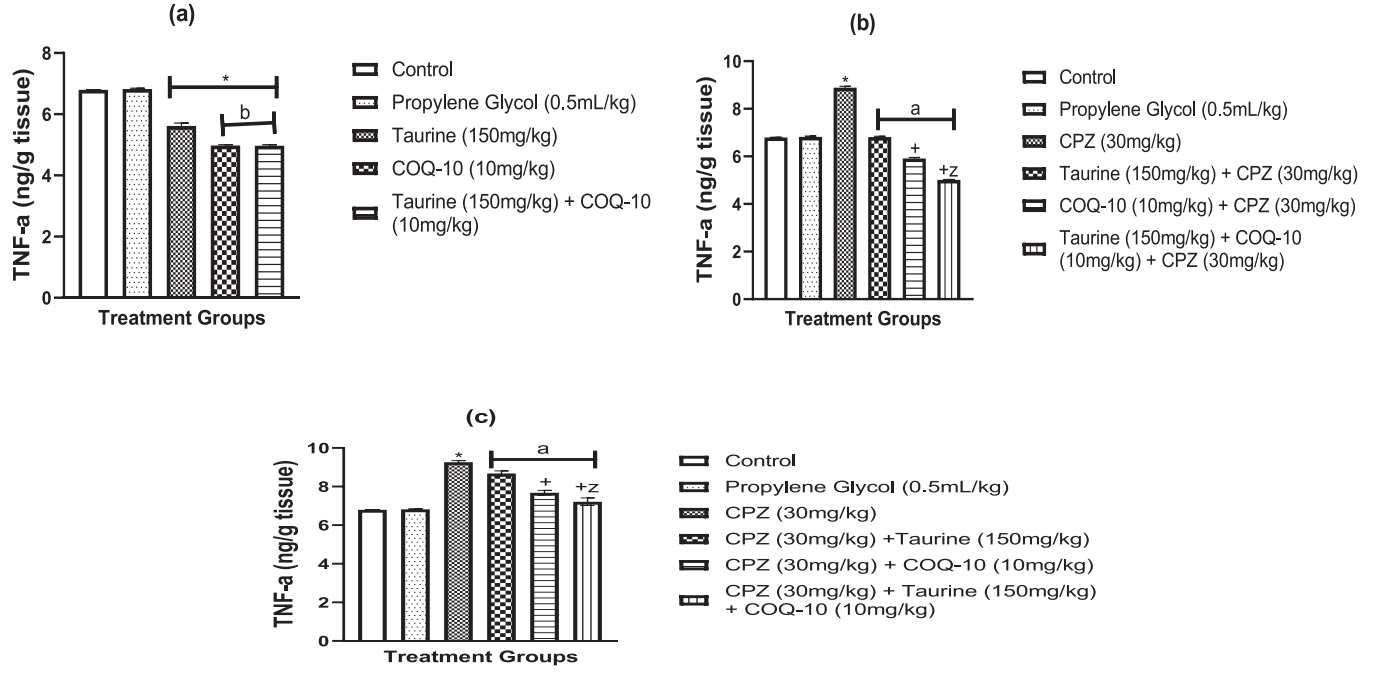


Fig. 7. Effects of taurine and COQ-10 in male Wister rats exposed to chlorpromazine-induced alterations in necrosis factor-alpha (TNF-α) in naïve (a), preventive (b), and reversal (c) studies. Mean ± S.E.M. (n = 6) is represented by bars. *$p<0.05$ as compared to normal control; $^{a}p<0.05$ as compared to CPZ; $^{b}p<0.05$ as compared to taurine treatment; $^{c}p<0.05$ as compared to COQ-10 treatment; $^{+}p<0.05$ when compared with CPZ + taurine/ taurine + CPZ; $^{z}p<0.05$ when compared with CPZ + COQ-10/ COQ-10 + CPZ. PG = Propylene glycol; COQ-10 = Coenzyme-Q10.

compared to the control groups. In both the preventative and reversal treatment groups, CPZ caused a marked increase in TNF-α and IL-6 levels accompanied by decreased IL-10 levels (Fig. 9), which were prevented and reversed by taurine, COQ-10, or their combination (Figs. 7–9).

3.8 Taurine and CO-QIO abate against chlorpromazine-mediated changes in erythropoietin levels in the preventive and reversal protocol in rats' serum.

Fig. 10 depicts the effects of taurine, COQ-10 or a combination of both drugs on serum erythropoietin levels in both naïve and CPZ-treated rats. Upon administration of taurine and COQ-10, erythropoietin

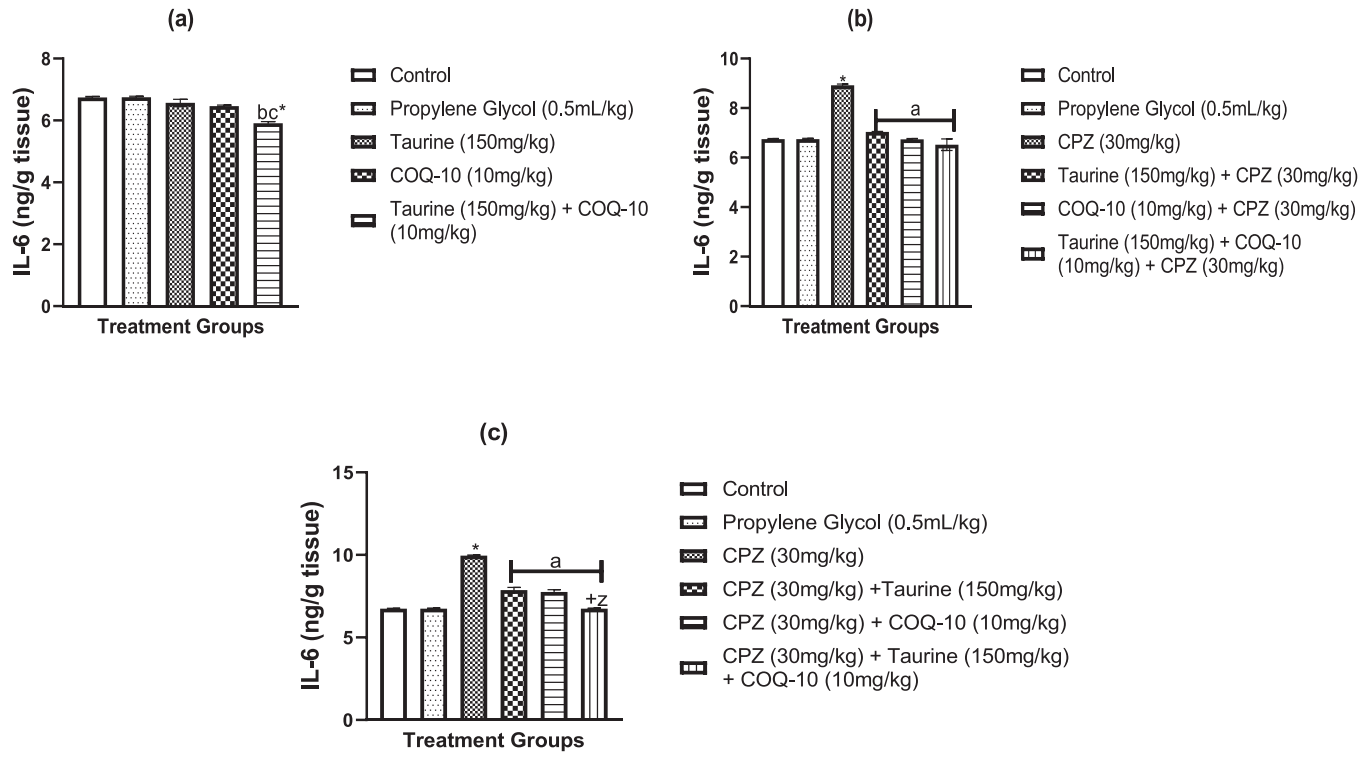


Fig. 8. Effects of taurine and COQ-10 in male Wister rats exposed to chlorpromazine-induced alterations in interleukin-6 (IL-6) (a-c) in naïve (a), preventive (b), and reversal (c) studies. Mean ± S.E.M. (n = 6) is represented by bars. *$p < 0.05$ as compared to normal control; $^{a}p < 0.05$ as compared to CPZ; $^{b}p < 0.05$ as compared to taurine treatment; $^{c}p < 0.05$ as compared to COQ-10 treatment; $^{+}p < 0.05$ when compared with CPZ + taurine/ taurine + CPZ; $^{z}p < 0.05$ when compared with CPZ + COQ-10/ COQ-10 + CPZ. PG = Propylene glycol; COQ-10 = Coenzyme-Q10.

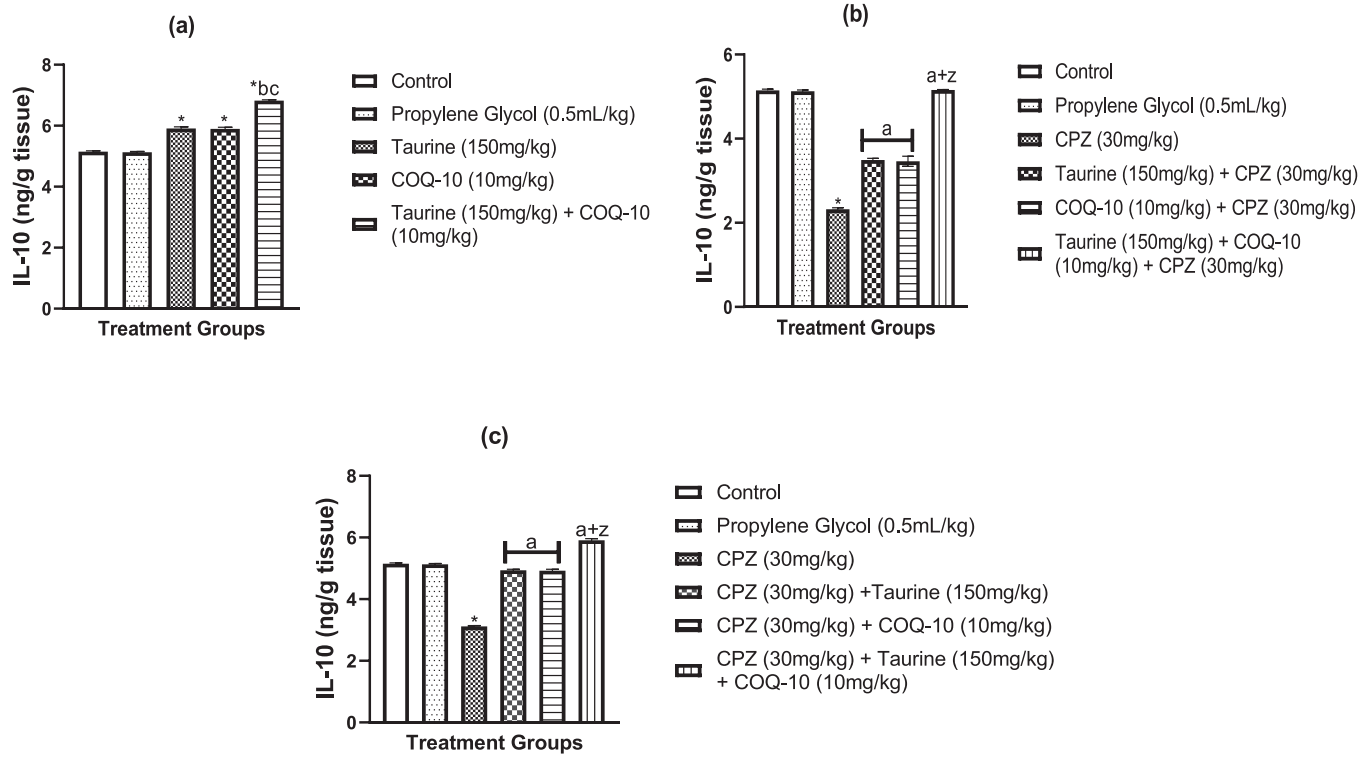


Fig. 9. Effects of taurine and COQ-10 in male Wister rats exposed to chlorpromazine-induced alterations in interleukin-10 (IL-10) (a-c) in naïve (a), preventive (b), and reversal (c) studies. Mean ± S.E.M. (n = 6) are depicted by bars. *$p < 0.05$ as compared to normal control; $^{a}p < 0.05$ as compared to CPZ; $^{b}p < 0.05$ as compared to taurine treatment; $^{c}p < 0.05$ as compared to COQ-10 treatment; $^{+}p < 0.05$ when compared with CPZ + taurine/ taurine + CPZ; $^{z}p < 0.05$ when compared with CPZ + COQ-10/ COQ-10 + CPZ. PG = Propylene glycol; COQ-10 = Coenzyme-Q10.

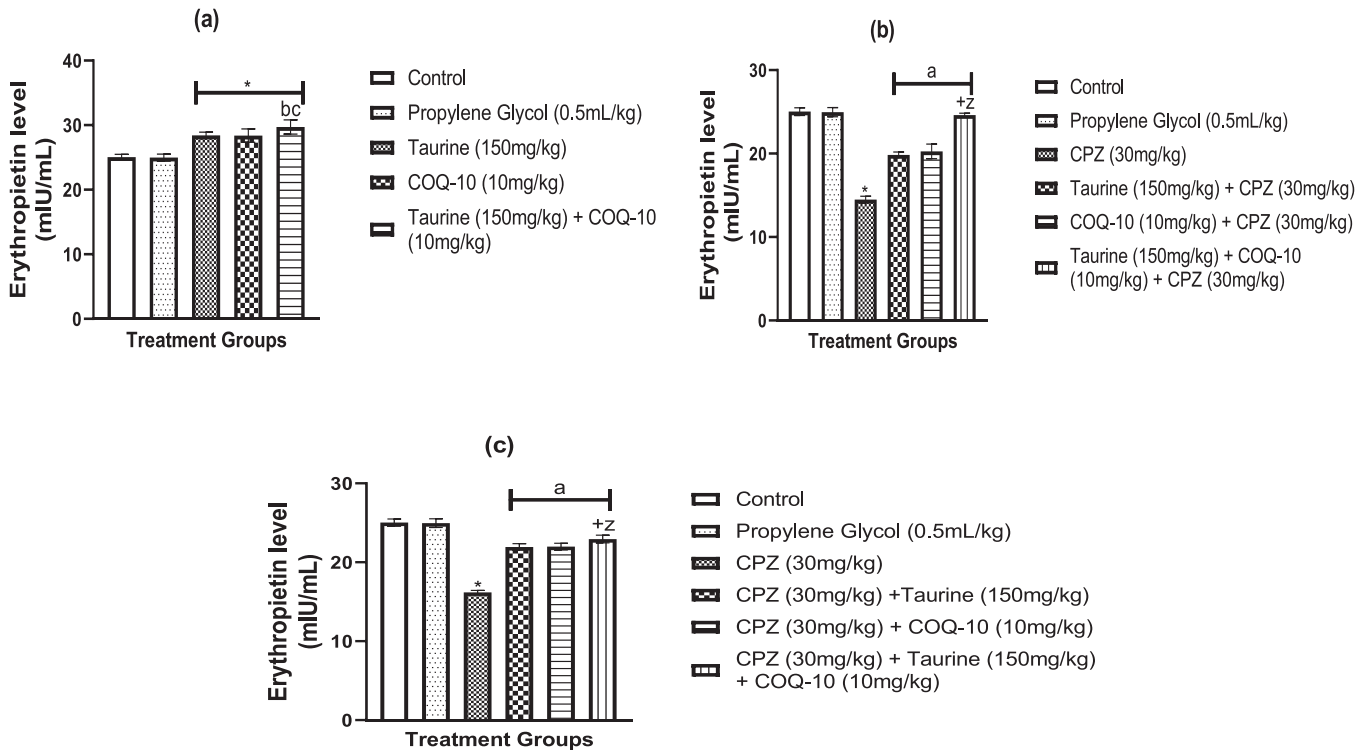


Fig. 10. Effects of taurine and COQ-10 in male Wister rats exposed to chlorpromazine-induced alterations in erythropoietin (EPO) in naïve (a), preventive (b), and reversal (c) studies. Mean ± S.E.M. (n = 6) were shown as bars. $^{*}p<0.05$ as compared to normal control; $^{a}p<0.05$ as compared to CPZ; $^{b}p<0.05$ as compared to taurine treatment; $^{c}p<0.05$ as compared to COQ-10 treatment; $^{+}p<0.05$ when compared with CPZ + taurine/ taurine + CPZ; $^{z}p<0.05$ when compared with CPZ + COQ-10/ COQ-10 + CPZ. PG = Propylene glycol; COQ-10 = Coenzyme-Q10.

significantly increased compared to the control group. Furthermore, the combined treatment of taurine and COQ-10 significantly ($p < 0.001$) increased the activities of erythropoietin compared to the control groups. In both experiments, CPZ treatment significantly reduced erythropoietin compared to the control groups. However, this reduction was counteracted by the administration of taurine, COQ-10, or a combination of both drugs in both studies.

4. Discussion

Despite being a widely utilized antipsychotic drug and for several other uses such as hiccup, CPZ remains a subject of debate due to its adverse effects [26,48,69,67]. While its efficacy has been established since its introduction, concerns about its side effects on blood cells have been ongoing and only a very few pharmacological studies have attempted to investigate agents that can efficiently reverse its hematological derangements. In its early stages, the focus was on its cytotoxicity, but recent studies have shifted to its potentially fatal hematological effects ([22,26,38,48]; Gover et al., 2020).

The regulation of blood within a normal range is crucial for maintaining homeostasis and carrying out its vital functions. In this study, rats treated with CPZ (30 mg/kg/d) for 56 days showed signs of anemia and changes in their blood composition, which are in line with previous studies [32,35,50]. These changes included alterations in RBC, erythropoietin, WBC, platelet count, PCV, Hb, neutrophil, lymphocyte, and a significant increase in MCV, MCH, and Eos levels. Alterations in certain protective blood agents serve as important indicators of the harmful impact of substances such as drugs, chemicals, and diseases [20]. Accordingly, the hematotoxic effects of CPZ were further evidenced by elevated levels of MDA, TNF-α, and IL-6 in the rats' serum relative to controls. The decrease in SOD and GSH levels in the serum is believed to also serve as an important marker for cell damage, especially during monitoring of drug-induced hematological changes. Indeed, previous studies have elucidated the role of oxidative stress and inflammation in the pathogenesis of cytotoxicity and blood impairments. Important mechanisms are interconnected with depletion of RBC antioxidants [58], PGE_2-induced permeability of nonselective cation in cell membranes [52], and protein kinase C and C-reactive protein-induced increased phosphatidylserine exposure at erythrocyte surface (de Jong et al., 2002), evidently promoting blood eryptosis [15,51].

In our analysis, administration of CPZ significantly up-regulates generation of ROS and release of inflammatory cytokines, which have been linked to hematological changes in both clinical and preclinical studies [20,50]. The alterations in MCV and MCH, both of which measure the average size of RBCs and the amount of hemoglobin known to transport oxygen in the RBCs respectively, observed in hematological research indicate that CPZ-induced a hemolytic anemic condition linked to RBC disorders [29], and is in line with previous clinical findings [40]. Chronic life-threatening hematological RBC disorders such as agranulocytosis, have been largely reported in psychotic patients treated with antipsychotic drugs, notably CPZ [32,35,50]. Although the specific management of anemic-like conditions includes the use of blood transfusion and iron-based supplements, application of naturally occurring compounds with antioxidant functions has increased in recent years owing to the role of oxidative stress in the pathogenesis of hemolytic blood disorders [30,72]. In line with this, our intervention with taurine and COQ-10 was shown to profoundly reverse and prevent CPZ-induced anemic-like condition, evidenced by increased RBC, erythropoietin, PCV, Hb, neutrophil, with significant increase in MCV and MCH levels. Erythrocytes have limited antioxidant defenses, making them vulnerable to changes in the balance between antioxidants and pro-oxidants [5]. While decreased GSH levels and increased lipoperoxidation were reported to induce cell lysis [59], in line with a recent finding, our intervention with taurine and COQ-10 suggests as increase in RBC count, possibly mediated through their antioxidant properties, particularly protecting RBCs from oxidative stress. Evidence from previous reports

has shown that taurine and COQ-10 improve xenobiotic-induced down-regulation of nuclear factor erythroid 2-related factor 2 (nfr2) activity, with decreased inflammatory cytokine genes such as *Cox-2, TNF-α, IL-1α,* and *IL-6β*, which were related to inhibition of *NF-κβ* expression [4,54]. Furthermore, previous investigations have determined that PCVs in the blood was closely linked to the size and quantity of RBCs [76]. Therefore, the decrease in Hb and PCV observed in this study may be attributed to the cytotoxic impacts of CPZ, as previously demonstrated (Kumar et al., 1990; [10]). Additionally, it has been consistently reported that the accumulation of RBCs and WBCs in the spleen could lead to a reduction in PCV and Hb levels [26,63]. Previous studies have also shown that exposure to reactive oxygen species (ROS) causes mechanical stress on hematological precursors, thus leading to anemia [71]. However, treatment with taurine and COQ-10, both as a preventative and a reversal measure, resulted in significant increases in RBC counts, Hb levels, and PCV concentrations in the CPZ-exposed rats. The observed effects of taurine and COQ-10 on red blood cells may be attributed to their antioxidant properties, as they can scavenge ROS and prevent membrane lipid peroxidation and hemolysis. This stabilizes the membrane, leading to increased levels of RBCs and associated machinery such as Hb and PCV. This could also be linked to the protection of bone marrow and liver, as well as the inhibition of hematological metabolism. Interestingly, these findings are in line with previous studies by Anand et al. [6] and Akande et al. [3], remarkably showing that taurine and COQ-10 mitigate restraint stress-induced anemic response in rats by improving RBC count, PCV and hemoglobin concentration. Although this is the first study combining the effect of taurine and COQ-10 against CPZ-induced hematological impairments, these findings notably suggest that their ability to improve the integrity of erythrocyte membrane could be associated with reduction of oxidative damage. Additionally, taurine and COQ-10 have been shown to stimulate the production of erythropoietin, a hormone that promotes the production of RBCs, thus reversing the anemia induced by CPZ [62].

Reduced WBCs and other related armouries have also been reported to be reduced in the serum after during treatment with antipsychotic drugs such as CPZ [17,35,50], suggesting altered immune functions during treatment with these drugs. In line with this, we showed that chronic administration of CPZ to rats causes reduced levels of WBCs relative to control, which is in line with previous studies [35,50]. This agrees with the findings of Patrick-Iwuanyanwu et al. (2007), who reported that the introduction of an antigen into an organism triggers the production of antibodies in response. The use of CPZ has been linked to a severe reduction in WBCs and abnormally low platelet count, suggesting the possibility of agranulocytosis, which is a popular life-threatening side effect frequently reported in psychotic patients with schizophrenia [35,50]. This is consistent with the results of Muhammad and Oloyede (2009), who observed a decrease in platelet count in animals treated with CPZ as well as the findings of Kumar et al., [46], as well as Nelson and Cox [64]. However, treatment with taurine and COQ-10 significantly abated CPZ-induced depletion of WBCs and related indices relative to CPZ groups. However, reports by Anand et al. [6] and Paunović et al., [70], demonstrated no noteworthy changes in WBC counts, RBC, Eos, PCV, MCV, Hb, and a decrease in platelet count in taurine-treated albino Wistar rats. Although the reason for this disparity remains unknown, one major explainable reason could be associated with the absence of a disease state. The increase in neutrophil and lymphocyte count mediated by taurine and COQ-10 in CPZ-treated groups indicate that these substances provided protection against destruction of these cells. The ability of taurine to prevent and reverse CPZ-induced depletion of WBCs including eosinophil, lymphocytes and neutrophil, might be linked to their presence in cell membranes where they act as scavengers of lipid peroxide radicals, thereby maintaining the viability of human neutrophils and lymphocytes. This is achieved through mechanisms that involve preserving membrane stability, as demonstrated by studies conducted by Kim et al. [45], Frick et al. [33], and Halliwell and Gutteridge [39].

Although the specific mechanisms underlying CPZ-induced changes in blood cells are not fully understood, previous evidence following CPZ-induced cytotoxicity and genotoxicity suggest the role of inflammation and oxidative stress [7]; Bachour-EL et al., 2014; [69]). Thus, our current findings complement previous reports showing that molecular processes involving the release of pro-inflammatory cytokines, and increased generation of free radicals notably induce oxidative damage-mediated blood cell destruction, and important components [23,60]. Moreover, there is evidence of concentration-dependent effect of CPZ, notably involving red blood cell swelling and shape change [23], increased release of cytokines, loss of membrane integrity and tight junction, increased activity of xenobiotic transporter and membrane phospholipids in HepaRG hepatic cells [60]. CPZ has been shown to alter the release of TNF-a and other interleukins *in vivo* [44] and oxidative markers [30]. In this study, our findings also revealed that CPZ-induced changes in blood cells were associated with an increase in the serum lipid peroxidation product, MDA with decreased antioxidant system (GSH, and SOD) relative to controls, suggesting the role of oxidative damage in CPZ-induced blood cell dysfunction. Furthermore, our study demonstrated that co-administration of taurine and COQ-10 with CPZ significantly reduced the impacts of CPZ on markers of oxidative stress and lipid peroxidation. These findings interestingly support the antioxidant functions of taurine and COQ-10, notably supported by previous studies related to neurotoxic and hematoxic experiments [1,24,42,54, 65,70].

Furthermore, CPZ was also shown to increase the levels of TNF-a and IL-6 levels with reduced levels of IL-10. While TNF-a and IL-6 are popular pro-inflammatory with diverse roles in disease states, IL-10 is a pleiotropic anti-inflammatory cytokine known to regulate inappropriate immune programs and autoimmune dysfunctions, by inhibiting inordinate inflammatory activities in matured hematopoietic cells involving erythropoiesis [21]. Previous evidence established that IL-10 stimulates the differentiation and proliferation of erythroid cells synergistically with erythropoietin, a natural stimulant of pluripotent hematopoietic stem cell growth [78,83], and there is evidence both may play a prominent role in erythropoiesis [80]. More specifically, IL-10 receptor knockout mice were shown to demonstrate decreased hemopoietic stem cells with reduced peripheral blood relative to wide type, suggesting that IL-10 acts on multiple stem and progenitor populations responsible for blood hemostasis. Previous studies have shown that up-regulation of IL-10 inhibits inflammatory cytokines such as TNF-a and IL-6 levels and causes suppression of interferon gamma-dependent emergency myelopoiesis in all T-cells [18,21]. It was therefore proposed that the relative capacity of antioxidant elements such as taurine and COQ-10 to improve IL-10 functions and reduce the levels of TNF-a and IL-6, would indicate improved hematopoietic function. In this study, we showed that CPZ-induced blood derangement was accompanied by reduced the level of IL-10 and increased TNF-a and IL-6 concentrations when compared with normal control. However, we intriguingly showed that up-regulation of IL-10 levels with decreased TNF-a and IL-6 concentration were observed in the prevention and reversal of CPZ-induced hematological dysfunction comparative to CPZ groups. Interestingly, the combination taurine and COQ-10 in this study was also shown to increase IL-10 levels with a complimentary reduction of TNF-a and IL-6 concentrations relative to normal control. These effects are most likely achieved through the direct impact of taurine and COQ-10 on cytokine release, as well as indirectly through their antioxidant properties [69]. These findings with taurine and COQ-10 supplementation are consistent with existing reports [65,70], which demonstrated that treatment with taurine and COQ-10 could protect against cytotoxicity and genotoxicity related erythrocyte damage and anemia involving oxido-inflammatory responses in rats by increasing G6PD, a cytoplasmic housekeeping enzyme found in all cells that protect RBCs from damage and premature destruction from ROS [9]. More so, the hemato-protective effects of taurine and COQ-10 also revealed increased serum levels of erythropoietin in CPZ-treated rats or without CPZ. The ability of taurine and

COQ-10 to increase erythropoietin levels suggest the relative capacity to stimulate erythropoiesis hematologically compromised patients.

In terms of safety profile, taurine and COQ-10 have been studied in different preclinical and clinical studies and were shown to be generally safe when administered at different doses. *In vivo* and *in vitro* studies have shown that taurine and COQ-10 are non-toxic in animal studies [34]. Studies have also demonstrated the high safety profile of taurine and COQ-10, with no adverse effects related to genotoxicity and teratogenicity in humans and rodents after ingestion of high doses [56,73,79], notably demonstrating the safe transnationality of these agents to the human setting for future therapeutic strategies. In terms of fertility, there was also no observable effect on sperm quality when rats were fed with taurine and COQ-10 [69,67,66]. Based on the available evidence, the safety profile of taurine and COQ-10 was considered good, as studies have shown that it is generally well tolerated and safe for application [27,82]. When co-administered with other medications, it improves the function of distribution, CYP45-induced metabolism and excretion induced by some xenobiotics (Matsuda et al., 2002; [82]). As regards cytotoxicity, taurine and COQ-10 are naturally distributed in many cells and membranes, both acting as essential co-factor for ATP production, cellular metabolism, and DNA repair enzymes ([57]; Matsuda et al., 2002).

In summary, taurine and CoQ-10 exert their effects through various biological pathways, by improved RBC membrane integrity through improved antioxidant system, modulation of inflammatory response, and enhancement of immune function as evidenced by increased IL-10. These mechanisms work together to protect the hematological system from the adverse effects of CPZ treatment and may also help to reverse possible hematological alterations. While these findings suggest potential benefits of taurine and COQ-10 in mitigating the hematological effects of CPZ in rats, their translation to humans is limited by the differences in species-specific mechanisms of action, lack of human clinical trials, concomitant medications, and different health conditions. Hence, Further studies are needed to clarify their effectiveness and safety in human subjects and to identify the optimal dosages and treatment regimens. Specifically future research is suggested to focus on: i) comparative studies to investigate species-specific differences in CPZ metabolism and hematological effects. ii) clinical trials in humans to evaluate the preventive and reversal effects of taurine and coenzyme-Q10 during CPZ-induced hematological alterations in patients with active psychotic-like disorders. iii) explore the mechanisms of action of taurine and COQ-10 in both rats and humans in different states such as comorbidities, concomitant medications, and environmental factors, to further identify potential targets for therapeutic interventions.

5. Conclusion

The combined findings indicate that taurine and COQ-10 CPZ-induced hematological changes in rats. Our study demonstrated that the hemato-protective properties of taurine and COQ-10 were accompanied by significant prevention and reversal of CPZ-induced oxidative blood cell membrane lipid peroxidation, with increased antioxidant defenses, and anti-inflammatory cytokine (IL-10) levels, as well as a decrease in proinflammatory cytokines. Additionally, taurine and COQ-10 also abated CPZ-induced hematological deficiency by stimulating increased levels of erythropoietin. These findings suggest that taurine and COQ-10 may be beneficial treatment options for patients with psychiatric disorders who are at risk for CPZ-induced hematological side effects.

Compliance with ethical standards

The experimental procedures were approved by the Delta State University Animal Care and Use Research Ethics Committee (REC/FBMS/DELSU/18/04) and performed in accordance with the care and use of Laboratory Animals of the NIH Guidelines by careful handling, treatments and euthanization throughout the period of 8 weeks.

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The study did not receive any sponsor from any agency. The study was carried with author's contributions.

Author contribution statement

MOO, JCI, BAB and EKN conceived the study and designed the experimental protocol. MOO, BBA and EKN carried out the experiment. MOO, BAB, OPE contributed new reagents and analytical tool. MOO and BAB analyzed the data. MOO, BAB, AAE and OPE wrote the manuscript. All authors read and approved the manuscript. All data were generated in-house and no paper mill was used.

CRediT authorship contribution statement

Ohwin Peggy Ejiro: Writing – review & editing, Supervision, Funding acquisition, Formal analysis, Conceptualization. **Nwangwa Eze Kingsley:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Benneth Ben-Azu:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Oyovwi Mega Obukohwo:** Writing – review & editing, Writing – original draft, Resources, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Adeogun Adetomiwa Ezekiel:** Writing – review & editing, Resources, Funding acquisition. **John C. Igweh:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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References

[1] A. Abdel-Rahman Mohamed, A.N. Abdel Rahman, G.A. Salem, M.M.E. Deib, M. A. Nassan, N.R. Rhouma, S.I. Khater, The antioxidant role of a taurine-enriched diet in combating the immunotoxic and inflammatory effects of pyrethroids and/or carbamates in Oreochromis niloticus, Animals *11* (5) (2021) 1318.

[2] Adamson J.W. (2008). The anemia of inflammation/malignancy: mechanisms and management. Hematology. American Society of Hematology. Education Program, 159–165. https://doi.org/10.1182/asheducation-2008.1.159.

[3] M.G. Akande, Y.O. Aliu, S.F. Ambali, J.O. Ayo, Protective effect of taurine in chlorpyrifos and lead-induced haematological alterations in Wistar rats. Toxicol. Environ. Chem. *96* (*1*) (2014) *171–182*.

[4] Al-Johani, N.S., Al-Zharani, M., Aljarba, N.H., Alhoshani, N.M., Alkeraishan, N., & Alkahtani, S. (2022). Antioxidant and Anti-Inflammatory Activities of Coenzyme-Q10 and Piperine against Cyclophosphamide-Induced Cytotoxicity in HuH-7 Cells. BioMed research international, 2022, 8495159. https://doi.org/10.1155/2022/8495159 (Retraction published Biomed Res Int. 2024 Jan 9;2024:9852678).

[5] Al-Naama, L.M., Hassan, M.K., & Mehdi, J.K. (2016). Association of erythrocytes antioxidant enzymes and their cofactors with markers of oxidative stress in patients with sickle cell anemia. Qatar medical journal, 2015(2), 14. https://doi.org/10.5339/qmj.2015.14.

[6] P. Anand, D. Rajakumar, A.J.W. Felix, T. Balasubramanian, Effects of oral administration of antioxidant taurine on haematological parameters in Wistar rats, Pak. J. Biol. Sci. *13* (*16*) (2010) *785–793*.

[7] S. Anthérieu, P.B.E. Azzi, J. Dumont, Z. Abdel-Razzak, C. Guguen-Guillouzo, B. Fromenty, A. Guillouzo, Oxidative stress plays a major role in chlorpromazine-induced cholestasis in human HepaRG cells, Hepatology *57* (*4*) (2013) 1518–1529.

[8] M. Arenas-Jal, J.M. Suñé-Negre, E. García-Montoya, Coenzyme Q10 supplementation: efficacy, safety, and formulation challenges, Compr. Rev. Food Sci. Food Saf. *19* (2) (2020) 574–594.
[9] Arese, P., Gallo, V., Pantaleo, A., & Turrini, F. (2012). Life and Death of Glucose-6-Phosphate Dehydrogenase (G6PD) Deficient Erythrocytes - Role of Redox Stress and Band 3 Modifications. Transfusion medicine and hemotherapy: offizielles Organ der Deutschen Gesellschaft fur Transfusionsmedizin und Immunhamatologie, 39(5), 328–334. https://doi.org/10.1159/000343123.
[10] P. Bachour-El Azzi, A. Sharanek, Z. Abdel-Razzak, S. Antherieu, H. Al-Attrache, C. C. Savary, A. Guillouzo, Impact of inflammation on chlorpromazine-induced cytotoxicity and cholestatic features in HepaRG cells, Drug Metab. Dispos. *42* (9) (2014) 1556–1566.
[11] Ben-Azu, B., Adebayo, O.G., Jarikre, T.A., Oyovwi, M.O., Edje, K.E., Omogbiya, I. A., … & Japhet, K. (2022). Taurine, an essential β-amino acid insulates against ketamine-induced experimental psychosis by enhancement of cholinergic neurotransmission, inhibition of oxidative/nitrergic imbalances, and suppression of COX-2/iNOS immunoreactions in mice. Metabolic Brain Disease, 37(8), 2807-2826.
[12] B. Ben-Azu, O.G. Adebayo, A.R. Fokoua, B. Oritsemuelebi, E.O. Chidebe, C. B. Nwogueze, L. Kumanwee, G.E. Uyere, M.T. Emuakpeje, Antipsychotic effect of diosgenin in ketamine-induced murine model of schizophrenia: involvement of oxidative stress and cholinergic transmission, IBRO Neurosci. Rep. *16* (2024) 86–97, https://doi.org/10.1016/j.ibneur.2023.12.008.
[13] B. Ben-Azu, E.G. Moke, L.E. Chris-Ozoko, E.J. Jaiyeoba-Ojigho, O.G. Adebayo, A. M. Ajayi, M.O. Oyovwi, G. Odjugo, V.I. Omozojie, G. Ejomafuwe, N. Onike, A. O. Eneni, C.P. Ichipi-Ifukor, I.F. Achuba, Diosgenin alleviates alcohol-mediated escalation of social defeat stress and the neurobiological sequalae, Psychopharmacology *241* (4) (2024) 785–803, https://doi.org/10.1007/s00213-023-06509-1.
[14] V. Bhatt, A. Saleem, Review: drug-induced neutropenia— pathophysiology, clinical features, and management, Ann. Clin. Lab Sci. 34 (2004) 131–137.
[15] R. Bissinger, A.A.M. Bhuyan, S.M. Qadri, F. Lang, Oxidative stress, eryptosis and anemia: a pivotal mechanistic nexus in systemic diseases, FEBS J. *286* (5) (2019) 826–854, https://doi.org/10.1111/febs.14606.
[16] J. Bujok, E. Wajman, N. Trochanowska-Pauk, T. Walski, Evaluation of selected hematological, biochemical and oxidative stress parameters in stored canine CPDA-1 whole blood, BMC Vet. Res. *18* (1) (2022) 255, https://doi.org/10.1186/s12917-022-03353-x.
[17] G.J. Burckart, J. Snidow, W. Bruce, Neutropenia following acute chlorpromazine ingestion, Clin. Toxicol. *18* (7) (1981) 797–801, https://doi.org/10.3109/15563658108990307.
[18] A. Cardoso, A.C. Martins, A.R. Maceiras, W. Liu, I. Castro, A.G. Castro, A. Bandeira, J.P. Di Santo, A. Cumano, Y. Li, P. Vieira, M. Saraiva, Interleukin-10 induces interferon-γ-dependent emergency myelopoiesis, Cell Rep. *37* (4) (2021) 109887, https://doi.org/10.1016/j.celrep.2021.109887.
[19] M. Çetiner, G. Şener, A.Ö. Şehirli, E. Ekşioğlu-Demiralp, F. Ercan, S. Şirvancı, B. Ç. Yeğen,). Taurine protects against methotrexate-induced toxicity and inhibits leukocyte death, Toxicol. Appl. Pharmacol. *209* (1) (2005) 39–50.
[20] Coffey, L.L., Pesavento, P.A., Keesler, R.I., Singapuri, A., Watanabe, J. Watanabe, R., Yee, J., Bliss-Moreau, E., Cruzen, C., Christe, K.L., Reader, J.R., von Morgenland, W., Gibbons, A.M., Allen, A.M., Linnen, J., Gao, K., Delwart, E., Simmons, G., Stone, M., Lanteri, M., Bakkour, S., Busch, M., Morrison, J. and Van Rompay, K.K.A. (2017): Zika virus tissue and blood compartmentalization in acute infection of Rhesus Macaques. PLOS ONE. 12(1): e0171148.
[21] A. Collins, C.A. Mitchell, E. Passegué, Inflammatory signaling regulates hematopoietic stem and progenitor cell development and homeostasis, J. Exp. Med. *218* (7) (2021) e20201545, https://doi.org/10.1084/jem.20201545.
[22] C. Compagni, V. Salvi, M. Corulli, R. Rosso, C. Gramaglia, Clozapine-induced eosinopenia correlates with high drug serum levels: a case report, Asian J. Psychiatr. 43 (2019) 83–84.
[23] A.S. Cornelius, M.P. Reilly, M. Suzuki, T. Asakura, K. Horiuchi, The mechanism of chlorpromazine-induced red blood cell swelling, Gen. Pharmacol. *25* (1) (1994) 205–210, https://doi.org/10.1016/0306-3623(94)90034-5.
[24] S. Dabbaghi Varnousfaderani, V. Musazadeh, F. Ghalichi, Z. Kavyani, S. Razmjouei, A.H. Faghfouri, S.S. Ahrabi, S.M. Seyyed Shoura, P. Dehghan, Alleviating effects of coenzyme Q10 supplements on biomarkers of inflammation and oxidative stress: results from an umbrella meta-analysis, Front. Pharmacol. *14* (2023) 1191290, https://doi.org/10.3389/fphar.2023.1191290.
[25] D.A. Danielson, S. 3 Douglas, P. Herzog, H. Jick, J.B. Porter, Drug-induced blood disorders, Jama *252* (23) (1984) 3257–3260.
[26] Duggal H.S., Singh I. (2005). Psychotropic drug-induced neutropenia. Drugs Today (Barc) 41: 517–526.
[27] EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP, Scientific opinion on the safety and efficacy of taurine as a feed additive for all animal species, EFSA J. *10* (2012) 27–36.
[28] El-Sheikh, A.A., Morsy, M.A., Mahmoud, M.M., Rifaai, R.A., & Abdelrahman, A.M. (2012): Effect of coenzyme-q10 on Doxorubicin-induced nephrotoxicity in rats. Adv Pharmacol Sci, 2012, 981461.
[29] M.A. Emam, S.M. Farouk, A. Aljazzar, A.A. Abdelhameed, A.A. Eldeeb, F.A. Gad, Curcumin and cinnamon mitigates lead acetate-induced oxidative damage in the spleen of rats, Front. Pharmacol. *13* (2023) 1072760, https://doi.org/10.3389/fphar.2022.1072760.
[30] S. Ficarra, A. Russo, D. Barreca, E. Giunta, A. Galtieri, E. Tellone, Short-term effects of chlorpromazine on oxidative stress in erythrocyte functionality: activation of metabolism and membrane perturbation, Oxid. Med. Cell. Longev. *2016* (2016) 2394130, https://doi.org/10.1155/2016/2394130.
[31] Flanagan, R.J., & Dunk, L. (2008). Haematological toxicity of drugs used in psychiatry. Human Psychopharmacology: Clinical and Experimental, 23(S1), S27-S41.
[32] A.R. Freeman, M.A. Spirtes, Effects of chlorpromazine on biological membranes-II. Chlorpromazine-induced changes in human erythrocytes, Biochem. Pharmacol. *12* (1963) 47–53, https://doi.org/10.1016/0006-2952(63)90008-x.
[33] L.R. Frick, A.M.L. Barreiro, M. Rapanelli, M.P. Zappia, M. Brocco, C. Mongini, A. M. Genaro, G.A. Cremasch, Chronic restraint stress impairs T-cell immunity and promotes tumor progression in mice, Stress *12* (2009) *134–143*.
[34] Bank Ginny, Kagan Daniel, Madhavi Doddabele, Coenzyme Q10: clinical update and bioavailability, J. Evid. -Based Complement. Alter. Med *16* (*2*) (2011) *129–137*.
[35] S.M. Gowda, K.G. Vijay Kumar, K. Shilpa, Chlorpromazine-induced drug reaction with eosinophilia and systemic symptoms syndrome, Indian J. Psychol. Med. *42* (1) (2020) 99–101, https://doi.org/10.4103/IJPSYM.IJPSYM_364_19.
[36] Groff, J.L., and Gropper, S.S. (2000). Adv Nutr Hum Metab. Third Edition.
[37] S. Grover, A. Shouan, S. Chakrabarti, A. Avasthi, Haematological side effects associated with clozapine: A retrospective study from India, Asian J. Psychiatry *48* (2020) 101906.
[38] R.L. Hall, A.G. Smith, J.G. Edwards, Haematological safety of antipsychotic drugs, Expert Opin. Drug Saf. 2 (2003) 395–399.
[39] Halliwell, B. and Gutteridge, J. (2007). Free Radic Biol Med, 4th Ed. Oxford University press, New York, Pp. 41-50.
[40] J. How, R.J. Davidson, Chlorpromazine-induced haemolytic anaemia in anorexia nervosa, Postgrad. Med. J. *53* (619) (1977) 278–279, https://doi.org/10.1136/pgmj.53.619.278.
[41] R.C. Hubrecht, E. Carter, The 3Rs and humane experimental technique: implementing change, Anim.: Open Access J. MDPI 9 (10) (2019) 754, https://doi.org/10.3390/ani9100754.
[42] S. Ince, D. Arslan-Acaroz, H.H. Demirel, N. Varol, H.A. Ozyurek, F. Zemheri, I. Kucukkurt, Taurine alleviates malathion induced lipid peroxidation, oxidative stress, and proinflammatory cytokine gene expressions in rats, Biomed. Pharmacother. *96* (2017) 263–268.
[43] Y. Izumi, T. Watanabe, N. Awasaki, K. Hikawa, T. Minagi, F. Chatani, Collaborative work on evaluation of ovarian toxicity. Effects of 2 or 4 weeks repeated dose studies and fertility study of chlorpromazine hydrochloride in rats, J. Toxicol. Sci. *34* (2008) *167–174*.
[44] M.J. Jansen, T. Hendriks, M.F. Knapen, L.C. van Kempen, J.W. van der Meer, R. J. Goris, Chlorpromazine down-regulates tumor necrosis factor-alpha and attenuates experimental multiple organ dysfunction syndrome in mice, Crit. care Med. *26* (7) (1998) 1244–1250, https://doi.org/10.1097/00003246-199807000-00029.
[45] Y.M. Kim, K. Son, S.J. Hong, Inhibition of protein synthesis by nitric oxide correlates with cytostatic activity: nitric oxide induces phosphorylation of initiation factor eIF-2 alpha, Mol. Med. *4* (1998) *179–190*.
[46] Kumar, A., Nigam, J.M. and Sharma, S.K. (1999). Diazepam sedation in yaks. Ind. Vet. J., 76: 211-213.
[47] Lally, J., & Flanagan, R.J. (2016). Severe neutropenia and agranulocytosis. In Life-Threatening Effects of Antipsychotic Drugs (pp. 105-148). Academic Press.
[48] J. Lally, N. O'Connor, S. Fullam, N. Corcoran, A. O'Reilly, J. Jordan, A. Guerandel, Rechallenge following clozapine-associated eosinophilia: a case report and literature review, J. Clin. Psychopharmacol. 39 (2019) 504–506.
[49] D. Lambert, M.E. Nothem, Z. Kobylarz, C. Scholcoff, A medication hiccup: chlorpromazine-induced agranulocytosis in a 72-year-old male, WMJ: Off. Publ. State Med. Soc. Wis. *121* (3) (2022) E60–E62.
[50] D. Lambert, M.E. Nothem, Z. Kobylarz, C. Scholcoff, A medication hiccup: chlorpromazine-induced agranulocytosis in a 72-year-old male, WMJ: Off. Publ. State Med. Soc. Wis. *121* (3) (2022) E60–E62.
[51] E. Lang, F. Lang, Mechanisms and pathophysiological significance of eryptosis, the suicidal erythrocyte death, Semin Cell Dev. Biol. 39 (2015) 35–42.
[52] P.A. Lang, D.S. Kempe, S. Myssina, V. Tanneur, C. Birka, S. Laufer, F. Lang, T. Wieder, S.M. Huber, PGE (2) in the regulation of programmed erythrocyte death, Cell Death Differ. 12 (2005) 415–428.
[53] B. Lewis, R.J. Aitken, A redox-regulated tyrosine phosphorylation cascade in rat spermatozoa, J. Androl. *22* (2001) *611–622*.
[54] V. Maleki, R. Mahdavi, F. Hajizadeh-Sharafabad, M. Alizadeh, The effects of taurine supplementation on oxidative stress indices and inflammation biomarkers in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial, Diabetol. Metab. Syndr. *12* (2020) 9, https://doi.org/10.1186/s13098-020-0518-7.
[55] D. Mantle, G. Lopez-Lluch, I.P. Hargreaves, Coenzyme Q10 metabolism: a review of unresolved issues, Int. J. Mol. Sci. *24* (3) (2023) 2585, https://doi.org/10.3390/ijms24032585.
[56] N.E. Masotta, F. Martinez-Perafan, M.A. Carballo, S.B. Gorzalczany, A.M. Rojas, V. P. Tripodi, Genotoxic risk in humans and acute toxicity in rats of a novel oral high-dose coenzyme Q10 oleogel, Toxicol. Rep. *8* (2021) 1229–1239, https://doi.org/10.1016/j.toxrep.2021.06.012.
[57] H. Mochizuki, J. Takido, H. Oda, H. Yokogoshi, Amplifying effect of dietary taurine on the induction of cytochrome P-450 and on the urinary excretion of ascorbic acid in rats fed on phenobarbital-containing diets, Biosci., Biotechnol., Biochem. *64* (2) (2000) 405–407, https://doi.org/10.1271/bbb.64.405.
[58] J.G. Mohanty, E. Nagababu, J.M. Rifkind, Red blood cell oxidative stress impairs oxygen delivery and induces red blood cell aging, Front. Physiol. 5 (2014) 84, https://doi.org/10.3389/fphys.2014.00084.
[59] M.N. Möller, F. Orrico, S.F. Villar, A.C. López, N. Silva, M. Donzé, L. Thomson, A. Denicola, Oxidants and antioxidants in the redox biochemistry of human red

blood cells, ACS Omega *8* (1) (2022) 147–168, https://doi.org/10.1021/acsomega.2c06768.
[60] K. Morgan, N. Martucci, A. Kozlowska, W. Gamal, F. Brzeszczyński, P. Treskes, K. Samuel, P. Hayes, L. Nelson, P. Bagnaninchi, J. Brzeszczynska, J. Plevris, Chlorpromazine toxicity is associated with disruption of cell membrane integrity and initiation of a pro-inflammatory response in the HepaRG hepatic cell line, Biomed. Pharmacother. = Biomed. Pharmacother. *111* (2019) 1408–1416, https://doi.org/10.1016/j.biopha.2019.01.020.
[61] C.J.L. Murray, The global burden of disease study at 30 years, Nat. Med 28 (2022) 2019–2026, https://doi.org/10.1038/s41591-022-01990-1.
[62] M.W. Musch, E.M. Davis-Amaral, L. Goldstein, Erythropoietin stimulates tyrosine phosphorylation and taurine transport in skate erythrocytes, J. Exp. Zool. *274* (2) (1996) 81–92, https://doi.org/10.1002/(SICI)1097-010X(19960201)274:2<81::AID-JEZ1>3.0.CO;2-9.
[63] Y. Nara, Y. Yamori, W. Lovenberg, Effect of dietary taurine on blood pressure in spontaneously hypertensive rats, Biochem Pharm. *27* (*1978*) (1978) *2689–2692*.
[64] Nelson, D.L. and Cox, M.M., (2000). Oxidative phosphorylation and photophosphorylation. In: Nelson DL, Cox MM, editors. Lehninger principles of biochemistry. 3rd ed. New York: Worth Publishers. p 659–721.
[65] Niknahad, H., Mehrabani, P.S., Arjmand, A., Alidaee, S., Mazloomi, S., Ahmadi, P., … & Heidari, R. (2023). Cirrhosis-induced oxidative stress in erythrocytes: The therapeutic potential of taurine. *Clinical and Experimental Hepatology,* 9(1).
[66] M.O. Oyovwi, Physio-pharmacological potentials of taurine: a review in animal and human studies, Asian J. Biol. Sci. *16* (4) (2023) 452–463.
[67] M.O. Oyovwi, E.K. Nwangwa, B. Ben-Azu, T.P. Edesiri, V. Emojevwe, J.C. Igweh, Taurine and coenzyme Q10 synergistically prevent and reverse chlorpromazine-induced psycho-neuroendocrine changes and cataleptic behavior in rats, Naunyn-Schmiede 'S. Arch. Pharmacol. *394* (2021) 717–734.
[68] M.O. Oyovwi, E.K. Nwangwa, B. Ben-Azu, R.A. Rotue, T.P. Edesiri, V. Emojevwe, C.I. Uruaka, Prevention and reversal of chlorpromazine induced testicular dysfunction in rats by synergistic testicle-active flavonoids, taurine and coenzyme-10, Reprod. Toxicol. *101* (2021) 50–62.
[69] M.O. Oyovwi, B. Ben-Azu, E. Agbonifo-Chijiokwu, E.G. Moke, A.M. Ajayi, J. I. Wilson, J.C. Igweh, Possible mechanisms involved in the prevention and reversal of chlorpromazine-induced testicular damage by taurine and coenzyme-Q10 in rats, Nutrire *47* (2) (2022) 31.
[70] M.G. Paunović, M.M. Matić, B.I. Ognjanović, Z.S. Saičić, Antioxidative and haematoprotective activity of coenzyme Q10 and vitamin E against cadmium-induced oxidative stress in Wistar rats, Toxicol. Ind. Health *33* (10) (2017) 746–756.
[71] Pendav, K.B. and Rizvi, S.I. (2009). Protective effect of resveratol on markers of oxidative stress in human erythrocytes subjected to in vitro oxidative insult. Phytother Res, DOI: 10. 1002/ptr.2853.
[72] Z. Qin, M. Yang, Z. Lu, V.S. Babu, Y. Li, F. Shi, F. Zhan, C. Liu, J. Li, L. Lin, The oxidative injury of extracellular hemoglobin is associated with reactive oxygen species generation of grass carp (*Ctenopharyngodon idella*), Front. Immunol. *13* (2022) 843662, https://doi.org/10.3389/fimmu.2022.843662.
[73] N. Rais, A. Ved, M. Shadab, R. Ahmad, M. Shahid, Taurine, a non-proteinous essential amino acid for human body systems: an overview, Arab Gulf J. Sci. Res. *41* (1) (2023) 48–66.
[74] T.C. Rodick, D.R. Seibels, J.R. Babu, K.W. Huggins, G. Ren, S.T. Mathews, Potential role of coenzyme Q10 in health and disease conditions, Nutr. Diet. Suppl. (2018) 1–11.
[75] S. Samah, Oda1, S. Reham, Waheeb, Kh Zeynab, El-Maddawy, Potential efficacy of Coenzyme Q10 against oxytetracycline-induced hepatorenal and reproductive toxicity in male rats, J. Appl. Pharmac Sci. *Vol. 8* (*01*) (2018) *098–107*.
[76] Schalm, O.W., N.C. Jain and G.H. Carroll, (1975). Veterinary Hematology. 3rd Edn., Lea and Febiger, Philadelphia.
[77] Sernoskie, S.C. (2023). Characterization of the Early Immune Response to Clozapine: Relevance for Idiosyncratic Drug-Induced Agranulocytosis (Doctoral dissertation, University of Toronto (Canada).
[78] A.S. Tsiftsoglou, Erythropoietin (EPO) as a key regulator of erythropoiesis, bone remodeling and endothelial transdifferentiation of multipotent mesenchymal stem cells (MSCs): implications in regenerative medicine, Cells *10* (8) (2021) 2140.
[79] Victor, E., Mega Obukohwo, O., Obidike Alexander, N., Elect Chinaecherem, O., Victoria Obianuju, A., Eze Kingsley, N., … Gregory Uchechukwu, J. (2023). Taurine and N-acetylcysteine reverse reproductive and neuroendocrine dysfunctions in levetiracetam-treated epileptic male rats. *Egyptian Journal of Basic and Applied Sciences*, *10*(1), 733-752.
[80] C.Q. Wang, K.B. Udupa, D.A. Lipschitz, Evidence suggesting a stimulatory role for interleukin-10 in erythropoiesis in vitro, J. Cell. Physiol. *166* (2) (1996) 305–310, https://doi.org/10.1002/(SICI)1097-4652(199602)166:2<305::AID-JCP8>3.0.CO;2-T.
[81] Z. Xu, T. Liu, Y. Jiang, Z. Chen, X. Shi, Y. Xu, S. Guo, Microcrystals of ketal-linked paliperidone prodrugs for long-acting antipsychotics, *Mol. Pharm., 19* (11) (2022) 3846–3857.
[82] P. Yerramilli-Rao, M.F. Beal, D. Watanabe, K. Kieburtz, E.A. Blieck, M. Kitano, K. Hosoe, I. Funahashi, M.E. Cudkowicz, Oral repeated-dose toxicity studies of coenzyme Q10 in beagle dogs, Int. J. Toxicol. *31* (1) (2012) 58–69, https://doi.org/10.1177/1091581811425256.
[83] E.V. Zubareva, S.V. Nadezhdin, Y.E. Burda, N.A. Nadezhdina, A.S. Gashevskaya, Pleiotropic effects of erythropoietin. Influence of erythropoietin on processes of mesenchymal stem cells differentiation, Res. Results Pharmacol. *5* (1) (2019) 53–66.