Iranian Journal of Toxicology
ARAK UNIVERSITY OF MEDICAL SCIENCES
April 2023, Volume 17, Number 2

Research Paper

Vitamin C Protects Against Blood and Thyroid Toxicities Induced by the Chronic Use of Carbamazepine in Rats

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How to cite this paper Akorede GJ, Ambali SF, Olatunji AO, Aremu A , Ahmed AO, & Basiru A, et al. Vitamin C Protects Against Blood and Thyroid Toxicities Induced by the Chronic Use of Carbamazepine in Rats. Iranian Journal of Toxicology. 2023; 17(2):147-156. http://dx.doi.org/10.32598/IJT.17.2.1080.1

http://dx.doi.org/10.32598/IJT.17.2.1080.1

Article info:
Received: 13 Jan 2023
Accepted: 20 Jan 2023
Online Published: 01 Apr 2023

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ABSTRACT

Background: Drugs are the mainstay of the clinical management of epilepsy. Carbamazepine (CBZ) is commonly used for treating epilepsy and neuropathic pain. This drug has been reported to have toxic effects on the hematological system due to its induction of oxidative stress. This study aimed to investigate the protective effects of vitamin C against hematological and thyroid toxicities caused by the chronic use of carbamazepine in male Wistar rats.

Methods: Thirty-two adult Wistar rats were categorized randomly into four groups of eight rats each and treated as follows: Group 1 received distilled water (2 mL/kg); group 2 was treated with vitamin C (100 mg/kg); group 3 received carbamazepine (20 mg/kg), and group 4 was pre-treated with vitamin C (100 mg/kg) and given carbamazepine (20 mg/kg) 30 min later. All treatments were administered via gavage once per day over fifteen consecutive weeks. The rats' blood samples were tested for changes in hematological parameters while the sera were evaluated for liver biochemical enzymes and thyroid hormone levels.

Results: The results revealed that pre-treatment with vitamin C protected against alterations in parameters associated with hematological and thyroid toxicities.

Conclusion: Based on the study results, it was concluded that: a) The chronic use of CBZ caused hematological and thyroid toxicities, and b) Vitamin C protected against these toxicities. Therefore, it is highly likely that vitamin C has the potential to protect experimental animals against injuries induced by CBZ to the liver, blood cells, and hypothalamic-pituitary-thyroid axis in a Wistar rat model.

Keywords: Blood biochemical changes, Carbamazepine, Chronic exposure, Thyrotoxicity, Vitamin C

Introduction

Drugs are the mainstay in the management of epilepsy, a neurological disorder, characterised by spontaneous recurring seizures originating from the central nervous system [1]. Carbamazepine (CBZ), an iminostilbene, is a derivative of dibenzepine, and primarily used for treating epilepsy, trigeminal neuralgia and bipolar disorder [2]. This drug exerts its effect via reduction of sustained repetitive firing in neurons by blocking voltage-gated sodium channels, thus inhibiting repetitious brain neu-

[DOI: 10.32598/IJT.17.2.1080.1]

ronal activities [3]. The metabolism of CBZ primarily occurs in the liver by the increased formation of cytochrome P_{450}, subunit $3A_4$ [3]. This drug and its active metabolite, carbamazepine-10,11-epoxide, evoke oxidative stress, which may be central to its toxic manifestations [4]. Numerous studies have shown that CBZ causes oxidative damage by increasing free radicals, such as reactive oxygen species (ROS) in the blood and tissues [5-7].

The primary means of transporting oxygen and carbon dioxide among tissues are erythrocytes [7]. These red blood cells are susceptible to oxidative stress secondary to exposure to increased oxygen radicals, causing high concentrations of membrane polyunsaturated fatty acids, and increased binding of iron to haemoglobin [8]. Prolonged exposure to CBZ can lead to aplastic anaemia and lymphocytosis, apparently due to epoxide formation by raising the activity of cytochrome P_{450} [9, 10]. The liver is the main organ where CBZ is metabolized, resulting in elevated hepatic enzymes or perhaps hepatic toxicity or failure [11, 12]. Carbamazepine has also been reported to affect the hypothalamic-pituitary-thyroid axis [13]. It tends to alter the concentrations of thyroid hormones, likely induced by the hepatic P_{450} enzyme and thereby increasing thyroid hormone metabolism [13].

Vitamin C is an important water-soluble antioxidant in the blood, lymph, CSF and other biological fluids [14]. It is a potent intracellular antioxidant that inhibits lipo-peroxidation, reduces endothelial disorder, and replenishes lipoprotein and cell membrane's vitamin E [14]. This vitamin protects against free radical production evoked via lipoproteins and lipid damages in various cells and tissues [14]. It prevents different tissues including red blood cells from encountering oxidative injury, protects against biochemical and hematological changes induced by drugs in animals and humans [15]. It is also required for collagen synthesis, production of neurotransmitters and specific hormones, metabolism of vitamins and amino acids, removal of systemic toxins, and adequate functioning of the immune system [15]. The regular use of ascorbic acid, i.e. vitamin C, has been reported to increase thyroid hormone levels due to its antioxidant properties [15].

Aim of the study: In light of the above reviews [1-15], this research aimed to assess the protective effects of vitamin C on hematological and biochemical changes, and toxic effects against thyroid gland caused by the prolonged use of carbamazepine in male Wistar rats.

Materials and Methods

Drug and chemical acquisitions and preparations: Carbamazepine, 200 mg (Tegretol®, Novartis Farma, Italy) and vitamin C, 100 mg (Biopharma, Nigeria) were obtained from a reliable pharmaceutical supplier in Ilorin, Nigeria. They were dissolved in distilled water to prepare a workable solution before their use. All chemicals used in this study were of analytical grades.

Experimental animals: The thirty-two male Wistar rats, weighing150-250 g used in the study, were acquired from the Department of Veterinary Pharmacology and Toxicology's vivarium section. They were held in plastic cages and offered grower's feed (Chikun®, Nigeria) with free access to rat feed and water. The animals were acclimatized to the laboratory environment for two weeks before initiating the study.

Treatment protocol: The animals were categorized randomly into four groups of eight rats each, and treated as follows:

Group 1 received distilled water at 2 mL/kg,

Group 2 was treated with vitamin C at 100 mg/kg [16],

Group 3 received carbamazepine at 20 mg/kg [17], and

Group 4 was pre-treated with vitamin C (100 mg/kg) plus carbamazepine at 20 mg/kg, 30 minutes later [18].

The treatments were given via gavage once daily for fifteen consecutive weeks. The rats were then sacrificed via jugular venesection after a mild anaesthesia with ether. Blood samples were subsequently collected into sterile test tubes, containing anticoagulant and EDTA, and stored in a refrigerator for the next hematological and serum biochemical evaluations.

Evaluation of blood parameters: For this purpose, blood parameters were analyzed, such as packed cell volume (PCV), haemoglobin (Hb), red blood cell (RBC) count, absolute and total differential leukocytes. Also, platelets, erythrocyte indices, such as mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and neutrophil-lymphocyte ratio (NLR) were evaluated. The analyses were performed on an auto-analyzer unit (Perlong HA6000 Auto Haematology Analyzer; China).

[DOI: 10.32598/IJT.17.2.1080.1]

Table 1. Effect of vitamin C on the hematological parameters of adult male Wistar rats subjected to prolonged exposure to carbamazepine

Parameters	Group 1	Group 2	Group 3	Group 4
PCV (%)	40.33±0.88	39.33±1.33	30.67±2.41[a]	43.00±0.58
RBC (mL/mm^3)	7.00±0.23	6.31±0.49	4.79±0.41[b]	6.583±0.34
Hb (g/dL)	12.13±0.24	11.43±0.56	9.85±0.44	12.00±0.56
MCV (fl)	59.67±0.88	61.00±1.53	64.00±0.58	60.33±0.89
MCH (g/dL)	17.43±0.30	19.3±0.31	20.7±0.93[c]	17.67±0.29
MCHC (g/dL)	29.37±0.41	29.47±0.18	32.27±1.12[a]	28.93±0.37
Total leukocytes (×10^9/L))	9.07±0.12	7.1±0.67	13.03±0.64[a]	8.83±0.19
Neutrophils (×10^9/L)	4.1±0.44	3.60±0.44	7.64±0.73[a]	5.01±0.40
Lymphocytes (×10^9/L)	4.93±0.27	3.44±0.43	5.61±0.64	3.29±0.37
Monocytes (×10^9/L)	0.16±0.03	0.11±0.02	0.26±0.01[d]	0.18±0.06
Neutrophil-lymphocyte ratio	0.72±0.13[e]	0.86±0.04	1.81±0.48[b]	1.37±0.16
Platelets (×10^9/L)	183.7±57.95	211±2.89	358.7±8.82[a]	132.3±20.63

Values are presented as Mean±SEM

[a]Compared to groups 1, 2 and 4 (P<0.05), [b]Compared to group 1 (P<0.05), [c]Compared to groups 1 and 4 (P<0.05), [d]Compared to group 2 (P<0.05), [e]Compared to group 4 (P<0.05).

Serum biochemical parameters evaluation: Blood samples (5 mL) were collected from the rats into test tubes and held on the shelf for 60 minutes. These were subsequently centrifuged at 1000 g for 10 minutes to obtain the sera for the later biochemical analyses. The activity of alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, and total serum proteins concentration were determined based on the validated commercial test kits (Agappe Diagnostic, Switzerland), using an auto-analyzer (Rayto RT-9200, Germany). The levels of serum globulin were determined by deducting the albumin concentration from that of the total serum proteins.

Serum thyroid hormones concentrations: Triiodothyronine (T_3), thyroxine (T_4) and thyroid-stimulating hormone (TSH) were determined in the collected sera, using ELISA kits (TS227T, T3225T and T4224T; Calbiotech Inc, USA) as instructed by the suppliers.

Statistical data analyses: The data were analysed as Means±SE of the means (SEM) and then subjected to one-way analysis of variance (ANOVA) followed by a Tukey's post-hoc test. GraphPad Prism software, version 5.03 (California, USA) was used for these analyses. The minimum statistical significance level was set at P<0.05.

Results

Effects on hematological parameters

Effect on packed cell volume: A substantial reduction in PCV was observed in group 3 relative to the other three groups (P<0.05). Also, there was no major change in PCV level of group 1 compared to those of groups 2, 3 and 4 (Table 1).

Effect on hemoglobin concentration: Group 3 that received only CBZ revealed no substantial change in the concentration of Hb compared to other groups (P<0.05). The Hb concentration in group 3 declined relative to the groups 1, 2 and 4 by 25%, 19%, and 13%, respectively (Table 1).

Effect on red blood cells count: The total RBC count in group 3 (CBZ) showed a significant reduction compared to that of group 1. However, the decline (37%) in this parameter was not significant compared to that of group 4 (Table 1).

Effect on erythrocyte indices: No noticeable differences in MCV were observed among the four groups. A relative but insignificant increase (11%) in MCV was

[DOI: 10.32598/IJT.17.2.1080.1]

Table 2. Effect of vitamin C on hepatic enzymes' activities and serum protein concentration of adult male Wistar rats subjected to prolonged exposure to carbamazepine

Parameters	Group 1	Group 2	Group 3	Group 4
AST (U/L)	25.9±0.00	27.7±1.00	30.75±2.25	22.15±0.75
ALT (U/L)	16.2±2.80	21.7±1.70	24.23±2.75	17.2±0.91
ALP (U/L)	29.33±1.43	28.63±0.68	38.60±0.70[a]	32.60±0.92
Total proteins (g/dL)	68.00±1.53	69.33±3.53	79.33±4.06	64.67±4.37
Albumin (g/dL)	24.33±1.20	29.00±0.00	32.33±3.38	27.67±1.86
Globulin (g/dL)	43.00±1.13	32.67±1.86	51.00±3.22	34.00±4.36

Values are presented as Mean±SEM, [a]Compared to groups 1 and 2 (P<0.05).

detected in group 3 that received CBZ compared to that of group 4 that was treated with both vitamin C and CBZ (Table 1). However, a significantly higher MCH value was recorded in group 3 compared to those of groups 1 and 4 (P<0.05). Further, there was no significant change in the MCH values in group 1 compared to those of groups 2 and 4 (Table 1). However, an insignificant reduction (11%) in MCH was observed in group 2 compared to those in other groups (Table 1).

There was a significant increase in MCHC in group 3 (CBZ) relative to those found for other groups (P<0.05). There was an insignificant decrease in MCHC in group 1 compared to those of groups 2 and 4 (Table 1).

Effect on total leukocytes count: The total leukocyte counts in group 3 increased substantially relative to other groups (P<0.05). A relatively insignificant increase in the leukocyte count (22%) was recorded in group 1 compared to that of group 2 (Table 1).

Effect on neutrophils count: The neutrophils count in group 3 increased significantly relative to those for other groups (P<0.05) (Table 1).

Effect on lymphocytes count: There was no noticeable change in the lymphocytes count in group 3 compared to those noted for other groups. A relative increase in lymphocytes count in group 3 was observed compared to those of group 1 (12%), group 2 (39%) and group 4 (44%), respectively (Table 1).

Effect on monocytes count: As shown in Table 1, a significant increase was found in monocytes count in group 3 compared to that in group 2 (P<0.05). However, an insignificant rise in this variable was found in group 2 compared to those for groups 1 (40%) and 4 (31%). No significant change was observed in monocytes count in group 1 compared to those recorded for groups 2, 3 and 4.

Effect on neutrophils vs lymphocytes ratio: A substantially increased neutrophil-lymphocyte ratio was noted in group 3 relative to group 1 (P<0.05), while a relative but insignificant change was noticed in this group compared to groups 4 (24%) and 2 (52%). The neutrophil-lymphocyte ratio declined substantially in group 1 relative to group 4 (P<0.05). However, the ratio in group 1 declined insignificantly compared to that of group 2 (19%) (Table 1).

Effect on platelets count: The platelets count in group 3 increased significantly relative to those in other groups. No major change in the platelets count was observed in group 1 as compared to those in groups 2 and 4 (Table 1).

Effects of treatment on hepatic enzymes activities

Aspartate aminotransferase activity: No significant changes were observed in the serum AST levels among the groups. In this context, a relative increase in AST activity was recorded in group 3 compared to those of groups 1 (16%), 2 (10%) and 4 (28%) (Table 2).

Alanine aminotransferase activity: No significant changes were observed in the serum ALT levels among the four groups. The ALT activity increased relatively in group 3 compared to groups 1 (33%), 2 (10%) and 4 (29%) (Table 2).

Alkaline phosphatase activity: The ALP activity increased significantly in group 3 relative to groups 1 and 2 (P<0.05), but insignificantly versus group 4 by 16% (Table 2).

[DOI: 10.32598/IJT.17.2.1080.1]

Table 3. Effect of vitamin C on thyroid hormone concentration of adult male Wistar rats subjected to prolonged exposure to carbamazepine

Parameters	Group 1	Group 2	Group 3	Group 4
T_3 (ng/mL)	0.41±0.07	0.31±0.02	0.32±0.08	0.36±0.08
T_4 (µg/dL)	2.67±0.02	2.25±0.07	1.99±0.19	2.22±0.09
TSH (µlU/mL)	0.23±0.01	0.24±0.01	0.21±0.01	0.26±0.04

Values are presented as Means±SEM

Effects of treatment on serum proteins

Serum total proteins: No significant changes were documented in the concentrations of total proteins among the four groups. A relative but insignificant increase was found in the concentration of total proteins in group 3 compared to those of groups 1 (14%), 2 (13%) and 4 (18%) (Table 2).

Serum albumin concentration: Insignificant variations were found in the albumin concentrations among the groups. The albumin concentration in group 3 showed a relative increase compared to groups 1 (25%), 2 (10%) and 4 (14%) (Table 2).

Serum globulin concentration: There were no significant changes found in the concentrations of serum globulin among the four groups. In this context, a relative increase was found in the concentration of globulin in group 3 as compared to those of groups 1 (16%), 2 (36%) and 4 (33%) (Table 2).

Effect of treatment on thyroid hormones

Serum tri-iodothyronine (T_3) concentration: There were no significant variations in the concentrations of T_3 observed among the groups. A relative and insignificant decrease was detected in the concentration of T_3 in group 3 compared to those of groups 1 (27%) and 4 (12%) (Table 3).

Serum thyroxine concentration: Based on the data presented in Table 3, no significant variations in the concentrations of T_4 were found among the four groups. In this context, an insignificant decrease was found in the concentration of T_4 in group 3 as compared to those observed in groups 1 (34%), 2 (13%) and 4 (12%).

Thyroid stimulating hormone: There were no significant variations found in the TSH concentrations among the four groups. A relative decline in the concentration of TSH was noted for group 3 compared to those documented for groups 1 (11%), 2 (14%) and 4 (22%) (Table 3).

Discussion

The significant reduction in the PCV found in this study suggests that long-term exposure to CBZ can cause anaemia. This may be attributed to the toxic effects of CBZ on hematopoietic centres in the bones. This adverse effect may also be attributed to the reduction in the tissue iron concentration due to exposure to CBZ, hindering the biosynthesis of Hb and reduced RBC life cycle. These findings disagree with those reported by two earlier studies [19, 20]. We found that pre-treatment of our experimental animals with vitamin C significantly improved the PCV levels in the animals. Besides, vitamin C has proven beneficial effects on anaemia, as supported by our findings [20].

This study provided experimental evidence in support of reduced RBC count and Hb concentration after exposure to CBZ over fifteen consecutive weeks. The observed loss in the Hb level can be due to the decreased iron concentration in the blood induced by CBZ, secondary to a depletion of iron stores in the animals. Reductions in the RBC count are likely to result from discontinued production of RBCs or pure red cell aplasia. This condition can be attributed to the swelling of RBCs and rising oxygen demands in response to CBZ-induced hypoxia. The reported rises in the MCH and MCV levels suggest that RBCs' swelling may be caused by the toxic effect of CBZ. Our findings were also confirmed by an earlier study [19].

Exposure to vitamin C tends to improve the oxygen-carrying capacity of RBCs and hence that of the blood. The improvement in Hb level and RBC count can be indicative of vitamin C's potential to boost RBC survival time via erythrocyte membrane stability and the rise in red blood cells' osmotic resistance [21]. This may also be attributed to the role of vitamin C in the enhancement of iron absorption by the gut through the conversion of oxidized iron to its reduced form [21], thereby increasing the blood iron concentration that is essential for the heme synthesis.

[DOI: 10.32598/IJT.17.2.1080.1]

Conventionally, the MCH, MCV and MCHC levels are used to evaluate the content, size and density of hemoglobin in RBCs, respectively [22]. Higher MCH, MCV and MCHC measures, as recorded in group 3 (CBZ treatment), indicate that prolonged administration of the drug induces macrocytic hyperchromic anemia. This may be due to the toxic effects of CBZ. This finding was in agreement with those reported by earlier findings of Rezaei, et al. [22]. The rise in the levels of MCH and MCV often suggests that RBC swelling can be one of the major adverse effects of CBZ [14]. Further, the increase in MCV can also result from elevated immature RBC numbers, as a result of the regenerative anemia. The restoration of macrocytic hyperchromic anemia in group 2 animals treated vitamin C suggests that this vitamin has beneficial effects on CBZ-induced anemia through enhancing iron absorption and increasing the hemoglobin synthesis [22].

White blood cells (WBCs) perform important roles in regulating the body's immune defence. The alteration in WBC counts indicates a decline in nonspecific immunity [23]. The leukocytosis observed in group 3 due to CBZ treatment can result from increased neutrophil release (neutrophilia), the stimulatory effects on the immune defence system, and lymphocytosis by lymphoid and myeloid tissues. Our data demonstrated that pre-treatment with vitamin C protected against the CBZ-induced leukocytosis. The observed neutrophilia may be due to the oxidative stress, which triggered the increased production of inflammatory cytokines and caused cellular damages [24]. The lymphocytosis recorded in group 3 (CBZ treated) can be induced via formation of epoxides through cytochrome P_{450} mechanism [25]. It has been shown that epoxide binds covalently to macromolecules and serves as a hapten that induces immunological responses, causing lymphocytosis. The monocytosis, as shown in this study, is likely due to the stress induced by the chronic exposure to CBZ [25]. Our findings further provided evidence that pre-treatment with vitamin C normalized the elevated differential count evoked by prolonged CBZ exposure, and by enhancing chemotaxis and phagocytosis of the leukocytes, hence promoting their removal [19].

The WBC counts and subtypes are commonly used as inflammatory indices. The ratio of neutrophils to lymphocytes (NLR) has recently emerged as a valid marker of the evaluation of systemic inflammatory response [22], which is used as a prognostic factor in the pathology of diseases, and in the case of elevated stress or inflammation [26]. The apparent increase in the NLR in the CBZ-treated group (group 3) suggests the ongoing stress and inflammation reactions in the animals exposed to CBZ. The pre-treatment with vitamin C protected the rats against the altered NLR by CBZ, thereby demonstrating its anti-inflammatory and antioxidant effects.

The current study revealed thrombocytosis, i.e. increased platelet count, in the CBZ group, which contradicted an earlier report [19]. The thrombocytosis could result from oxidative stress induction, causing elevated erythropoietin production and promoting iron-depleted anemia [27]. The thrombocytosis found in our study may be of the reactive type, induced by inflammatory reaction with increased levels of serum interleukin-6. Pre-treatment with vitamin C was shown to normalize the CBZ-induced thrombocytosis due to its protective property on the hematopoietic system.

Liver, as one of the organs that metabolize anti-epilepsy drugs (AEDs), is susceptible to the toxic effects of CBZ, causing disorders from slight and transient elevations of liver enzymes to severe hepatic failure [28]. The increase in AST level, as shown in group 3 rats that were treated with CBZ, suggests hepatic, muscular and intestinal damages, thereby provoking the increased AST release into the peripheral circulation. In this context, our findings agreed with those of two earlier studies [28, 29]. Alterations in the AST activity caused by CBZ has been mitigated by pre-treatment with vitamin C, apparently due to the protection this vitamin offers against CBZ-evoked injury to the liver, muscles and/or intestinal tissues.

The rise in the ALT level seen in the CBZ-treated group 3 is indicative of damages to the liver since this enzyme is more specific to this organ than other non-specific enzymes. The hepatic injuries may be due to strong effects of CBZ on hepatic microsomal enzymes, hence causing hepatocellular damages. In this context, CBZ is known to lead to liver failure, resulting in the release of hepatic enzymes into the blood. This finding by the current study was consistent with that reported by another study [30]. Pre-treatment with vitamin C prevents the hepatic enzymes' levels from rising and provides evidence in support of its protective effect on the liver due to its antioxidant properties.

Based on the findings of this study, the increase in the serum ALP level seen in the CBZ-treated group 3 agreed with the findings reported by two earlier studies [27, 31]. Pathological lesions evoked by CBZ in all or some of the organs required for the synthesis and/or secretion of ALP may also result from oxidative damages to the organs. Also, the higher ALP activity following CBZ exposure may be linked to its bone formation effects, probably due

[DOI: 10.32598/IJT.17.2.1080.1]

to enhanced bone turnover [29]. The restoration of the ALP activity as recorded in group 4 further underscores the involvement of oxidative stress in hepatic and muscular injuries induced by the chronic CBZ exposure.

The high level of serum total proteins recorded in the CBZ-treated group suggests disruption in the synthesis of proteins caused by hepatic impairment due to the oxidative stress. The hyperproteinaemia recorded in our study was one of the adverse effects of CBZ, which was in line with the findings of earlier studies [20, 32, 33]. However, the reduction in the serum total proteins, as shown in group 4 that was treated with vitamin C followed by CBZ, suggests that vitamin C ameliorates the drug-induced hepato-toxicity. The elevated albumin concentration, as seen in group 3 (CBZ-treated), can cause over-secretion of cortisol partly due to the hepatocellular injuries [34]. Cortisol production stimulates protein metabolism, thereby causing high serum albumin [33].

Our findings on total proteins corroborate previous reports [19, 33]. The reported decrease in the serum albumin is suggestive of the beneficial role of vitamin C in reversing the hyper-albuminemia by CBZ, due to the vitamin's antioxidant effects. The rise in the serum globulin level following long-term exposure to CBZ may be due to hepatocellular injuries and overproduction of cortisol. It can also be attributed to lymphocytosis, thereby causing increased production of globulin. The increase in the concentration of serum globulin as evident in group 4 (vitamin C+CBZ), further suggests the ameliorative effect of vitamin C against CBZ-induced hepatocellular injuries.

Thyroid hormones are important for the regulation and development of many tissues' metabolic functions. Therefore, disruptions in thyroid functions can hinder their growth and development, and consequently disrupt endocrine haemostasis [35]. The current study revealed a reduction in the serum TSH, T_3 and T_4 concentrations in the rat group treated with CBZ (group 3). The findings are suggestive of CBZ's disruptive effects on the hormones released from hypothalamus and/or anterior pituitary [18]. This drug can evoke direct thyroid injuries, as evident by the thyroid gland impairments. Earlier studies have also shown that CBZ alters thyroid hormone concentrations, apparently induced by the hepatic cytochrome P_{450}. This enzyme promotes the thyroid hormone metabolism [12], or inhibits iodide uptake by the thyroid gland [14]. The significant improvement in the concentrations of T_3, T_4 and TSH in group 4 rats that were treated with both vitamin C and CBZ could be related to the beneficial effects of the vitamin on the hypothalamic-pituitary axis [18]. These effects are likely to enhance the thyroid function, and increase its secretions, secondary to the vitamin C antioxidant capacity.

Conclusions

This study provided experimental evidence, indicating that long-term administration of carbamazepine causes biochemical alterations in the blood, and in the functions of the liver and thyroid gland. Administration of vitamin C protects against blood and thyroid toxicities induced by the chronic use of carbamazepine in rats. It is, therefore, recommended that patients undergoing chronic carbamazepine therapy should be periodically monitored for the systemic hematological and biochemical alterations, and indices of thyroid functions. It is also advised that concomitant use of vitamin C is advocated in patients on long-term carbamazepine treatment to protect them against the toxicity associated with the use of this drug.

Ethical Considerations

Compliance with ethical guidelines

The research was performed consistent with the national and institutional guidelines for the use and care of animals (Code: UERC/FVM/2020/019).

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

The authors appreciate the contributions and the support of the staff of the Department of Veterinary Pharmacology and Toxicology, University of Ilorin in the process of conducting this study.

[DOI: 10.32598/IJT.17.2.1080.1]

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[DOI: 10.32598/IJT.17.2.1080.1]