

Tridax procumbens Leaf Extract Mitigated Vincristine-Induced Organ Pathology and Oxidative Imbalances in Wistar Rats

Ekundayo Samuel^{1*} , Emmanuel Ajisope¹ , Olabode Olabintan² , Theophilus Jarikre³ , Omowumi Adewale⁴ , Ademola Oyagbemi¹ , Oluwatoyin Ajala⁵ , Olufunke Ola-Davies¹ , Oyeronke Odunola² 

¹Oncology Research Unit, Department of Veterinary Physiology and Biochemistry, University of Ibadan, Ibadan, Nigeria; sekundayo90@yahoo.com (E.S.); emmanuel.ajisope@gmail.com (E.A.); ademola.oyagbemi778@gmail.com (A.O.); ooladavies@yahoo.com (O.O.-D.)

²Cancer Research and Molecular Biology Laboratories, Department of Biochemistry, University of Ibadan, Ibadan, Nigeria; bintanola3@gmail.com (O.OL.); ronodunola@yahoo.com (O.OD.)

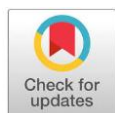
³Department of Veterinary Pathology, University of Ibadan, Ibadan, Nigeria; get2theo@yahoo.com (T.J.)

⁴Department of Biochemistry, Osun State University, Osogbo, Nigeria; adewaleomowumi13@gmail.com (O.AD.)

⁵Department of Theriogenology, University of Ibadan, Ibadan, Nigeria; oluwatoyinajala63@yahoo.com (O.AJ.)

*Corresponding Author: sekundayo90@yahoo.com (E.S.)

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ABSTRACT

Objective: This study investigated the effect of *Tridax procumbens* (TP), a medicinal plant, on Vincristine sulphate (VC)-induced oxidant-antioxidant imbalances in the liver and pancreas of male Wistar rats.

Methods: Thirty rats (80-100 g) were randomly allocated into six groups (Groups 1–6) and treated as follows: Group 1 (control) received 1 mL/kg body weight distilled water orally (p.o.), Group 2 received 0.1 mg/kg body weight VC intraperitoneally (i.p.), Groups 3 and 4 received 50 and 100 mg/kg body weight TP extract orally (p.o.), respectively. Group 5 received VC (0.1 mg/kg body weight, i.p.) plus TP (50 mg/kg body weight, p.o.) while Group 6 received VC (0.1 mg/kg body weight, i.p.) plus TP (100 mg/kg body weight, p.o.). The rats were treated for 10 consecutive days. Oxidant-antioxidant biomarkers and histology of the liver and pancreas of the rats were assessed.

Results: Vincristine sulphate reduced the activities of Glutathione S-Transferase (GST), Glutathione Peroxidase (GPx) ($p < 0.05$), Superoxide Dismutase (SOD) ($p < 0.05$), and reduced glutathione (GSH) ($p < 0.05$) levels in the liver compared to the control group, while TP administration enhanced the activities and concentrations of these antioxidant parameters. In the pancreas, VC reduced the concentration of GSH ($p < 0.05$) and the activities of GPx and SOD compared to the control group, while TP produced opposite effects in groups exposed to TP. VC increased the contents of Malondialdehyde (MDA) ($p < 0.05$) and hydrogen peroxide (H_2O_2) ($p < 0.05$) generation and decreased total protein concentration in the liver and pancreas compared to the control group, with a counteracting effect by TP. Lastly, histological analysis of the liver exposed to VC showed moderate portal infiltration of inflammatory cells and random centrilobular degeneration, while there was more representation of islets of Langerhans and secretory acini cells in TP alone-treated rats.

Conclusion: The *Tridax procumbens* ethanol leaf extract mitigated vincristine sulphate-induced oxidant-antioxidant imbalances in the liver and pancreas of experimental rats, thus reflecting its comparative advantage.

Keywords: *Tridax procumbens*, vincristine sulphate, oxidant-antioxidant, liver, pancreas

1. INTRODUCTION

Cancer has been described as a disease characterised by excessive proliferation of cells leading to tumour formation with a tendency to spread to other body parts through metastasis [1]. It was reported as the second most common reason for death globally in 2022 [2]. The increasing incidence and prevalence of cancer are exacerbated by an ageing population and some unhealthy lifestyle choices, such as smoking [3]. In Nigeria, about 127,000 new cancer cases were recorded in 2022, with about 79,000 cancer-related deaths, while globally, in the same year, there were 20 million new cases of cancer and 9.7 million deaths from the disease. [4,5]. The conventional cancer treatment approaches include radiation therapy, immunotherapy, surgery, and chemotherapy, which have all been adopted to enhance health outcomes among patients over the past decades [6].

Specifically, chemotherapy includes the use of cytotoxic drugs, such as vincristine sulphate, against excessively proliferating cells [7]. Anticancer drugs can be used alone or with other treatment modalities, such as radiation and surgery. However, it has been reported that chemotherapeutic agents demonstrate unintended and severe side effects that result in unwanted health consequences [8]. For instance, studies have associated the use of Vincristine sulphate, a common anticancer drug, with organ toxicity and impaired physiological functions [9,10].

Vincristine sulphate, a vinca alkaloid derived from *Catharanthus roseus*, [11] and approved in July 1963 by the US Food and Drug Administration (FDA), was reported to demonstrate anti-leukemic activity in children and mice [12]. Vincristine use, experimentally, was associated with neurotoxicity, myelosuppression, cell cycle arrest, and apoptosis [9,13]. This was linked with the disruption of the oxidant-antioxidant system of different organs, causing oxidative stress through the build-up of reactive oxygen species (ROS) [8]. ROS have the potential to attack macromolecules, including lipids, proteins, and DNA, resulting in further damage [7]. As a result of this limitation, there has been an ongoing effort to explore the identification of therapeutic agents from medicinal plant sources, which have been proven to possess little to no side effects, compared to the conventional chemotherapeutic agents [14].

The therapeutic effects of medicinal plants have been attributed to their phytochemical and bioactive constituents that demonstrate antioxidant, anti-inflammatory, anticancer, and other desirable effects [15]. One of these plants is *T. procumbens*, commonly known as Coat buttons, rich in flavonoids, tannins, and other phytochemicals [16]. It has been reported to demonstrate wound healing, antimicrobial, and hepatoprotective activities [17]. In a study by Ahamad et al. [18], it was reported that *T. procumbens* extract significantly scavenges DPPH and hydroxyl radicals, further emphasising the role of the plant as a potent antioxidant. The potential of *T. procumbens* to modulate antioxidant homeostasis makes it a possible agent in the mitigation of chemotherapy-induced organ toxicity. In addition, since cancer progression has been reported to be enhanced by oxidative stress [19], the antioxidant effects of this plant further establish its possibility to provide a therapeutic advantage. Although several studies have investigated and evaluated the therapeutic effects of these medicinal plants with claims that it scavenges free radicals and modulate enzymatic antioxidant defences [16,17], there is a limited study on the direct comparison of *T. procumbens* with chemotherapeutic agents, such as Vincristine, making this study relevant to chemotherapy research.

Therefore, this study aimed to investigate the comparative effects of Vincristine sulphate and *T. procumbens* leaf extract on the oxidant-antioxidant system in the liver and pancreas of male Wistar rats

2. MATERIALS AND METHODS

2.1. Ethical Statement

The experimental protocol was approved by the University of Ibadan institutional animal ethics committee (UI ACUREC/039-0224/28) on 15th May, 2024, prior to the commencement of the study, and all ethical criteria regarding the use of animals for research purposes were adhered to.

2.2. Chemicals and Reagents

Vincristine sulphate (1 mg/mL, $C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$ by Bruck Pharma Ltd), and other chemicals and reagents purchased from Sigma-Aldrich, St. Louis, MO, USA, including xylenol

orange, trichloroacetic acid (TCA), Tris Base, thiobarbituric acid, sodium hydroxide, 5,5'-dithio-bis-2-nitrobenzoic acid, reduced glutathione, and 1,2-dichloro-4-nitrobenzene, were freshly prepared for every experiment and of analytical grade.

Experimental Animals

Thirty (30) male outbred Wistar rats weighing between 80 and 100 grams, purchased from the University of Ibadan Experimental Animal Unit, were utilised in this study. They were kept in standard laboratory conditions with free access to food and water. The rats were housed in plastic cages with a 12-hour dark/light cycle in an animal house with good ventilation. They were acclimatised for two weeks before the commencement of the experiment. Only male Wistar rats were used in this study to address the issue of hormonal fluctuations in female rats as a result of their oestrous cycle [20], which could negatively affect biochemical findings.

2.3. Experimental Design

For this research, six (6) experimental groups of five (5) rats each were utilised. The animals were weighed and randomly allocated into groups. Treatment was done for 10 days, as provided below.

Group I (Control): Received distilled water (1 mL/kg body weight, p.o.).

Group II (VC): Received vincristine sulfate (VC; 0.1 mg/kg body weight, i.p.).

Group III (TP-50): Received *T. procumbens* extract (TP; 50 mg/kg body weight, p.o.).

Group IV (TP-100): Received TP (100 mg/kg body weight, p.o.).

Group V (VC+TP-50): Received VC (0.1 mg/kg body weight, i.p.) followed by TP (50 mg/kg body weight, p.o.).

Group VI (VC+TP-100): Received VC (0.1 mg/kg body weight, i.p.) followed by TP (100 mg/kg body weight, p.o.).

2.4. Ethanol extraction of *T. procumbens*

Fresh *T. procumbens* leaves (27kg) were collected, rinsed with clean tap water, air-dried, and ground into a fine powder. The 27 kg of fresh leaves yielded 5.5 kg (20.37%) of air-dried leaves, which later yielded 3 kg (54.55%) of dried powdered leaves that were subjected to cold plant extraction as documented by Njar et al. [21]. Cold absolute ethanol (96%) extraction (12 litres) was repeatedly carried out at an ambient temperature, and filtered using Whatman filter paper 1 (Sigma). A rotary evaporator was utilised to concentrate the filtrate under reduced pressure at a stable temperature (40 °C). After concentration, 4.94% (148.258 g) extract yield was obtained and preserved (at 4 °C) till when needed.

The leaves were sourced from the University of Ibadan, Nigeria. Identification and authentication were performed, and a voucher with the number (UIH-22542) was kept in the Department of Botany herbarium.

2.5. Sacrifice of experimental animals

Following the ten days of treatments in compliance with the standard guidelines for laboratory animal care and use, Animal (Scientific Procedures) Act, 1986, the rats were euthanised through cervical dislocation after being anaesthetised by an intraperitoneal injection of ketamine (50 mg/kg) and xylazine (10 mg/kg).

2.6. Sample Collection

Blood Collection

Blood was collected using ocular venipuncture via the retro-orbital sinus. The samples were allowed to clot at room temperature and were then centrifuged at 3,000 rpm for 10 minutes to obtain serum, which was stored until biochemical analysis.

Tissue Samples Collection

The liver and pancreas were excised using dissecting scissors and forceps. The organs were washed in ice-cold normal saline solution, blotted with filter paper, and small portions of the tissues were promptly fixed with 10% neutral buffered formalin. The remaining portions were stored in the refrigerator at -4 °C for biochemical assays.

2.7. Homogenization

After removing the pancreas and liver from the refrigerator, they were left to thaw for half an hour. They were chopped into pieces and homogenised using a Teflon homogeniser in a homogenising solution (0.1M phosphate buffer, pH 7.4) while keeping a cold chain. The post-mitochondrial fraction was obtained by centrifuging the resultant homogenates at 10,000 g for ten minutes at 4 °C in a cold centrifuge [22]. Biochemical tests were conducted using the obtained supernatant.

2.8. Biochemical assays

Pancreatic biomarkers

To obtain serum samples, blood was collected into plain tubes, allowed to coagulate, then centrifuged for ten minutes at 3,000 rpm. The Randox laboratory kits (UK) were used to monitor the activity of amylase and lipase as described by the manufacturer (Randox Laboratories Ltd, Crumlin, UK).

Oxidant-antioxidant system biomarkers

The following biochemical assays were conducted on the homogenate of the harvested organs (liver and pancreas): superoxide dismutase activity (SOD) [23], glutathione S-transferase (GST) activity [24], glutathione peroxidase (GPx) activity [25], reduced glutathione (GSH) [26], malondialdehyde (MDA) [27], hydrogen peroxide (H₂O₂) and total protein concentrations [28].

2.9. Histological examination

The liver and pancreas were excised after euthanasia, fixed in 4% neutral buffered formalin, embedded in wax, and then microsectioned into 5 µm thick sections for staining with haematoxylin and eosin (H&E). A bright-field light microscope (Olympus Corporation, Tokyo) was then used to assess the stained slides.

2.10. Statistical Analysis

Using Graphpad Prism version 10.0, Tukey's post-hoc test and One-Way Analysis of Variance (ANOVA) were used to estimate the test of significance among groups. All results were reported as mean ± standard error of mean (SEM). Statistical significance was defined as $p < 0.05$.

3. RESULTS

Figure 1 shows the effect of TP and VC on the antioxidant system in the liver of experimental rats. The activity of GST was reduced in the group exposed to VC compared to the control group, while TP dose-dependently increased GST activity significantly ($p < 0.05$) when compared to the VC group. There was also a significant ($p < 0.05$) decrease in GSH concentration in the VC group compared to the control, with an increased concentration in groups exposed to TP, compared to the VC group. GPx activity was significantly reduced in the VC and TP (50 mg/kg) groups when compared to the control, while it was significantly higher in the TP (100 mg/kg) group when compared to the VC and control groups (Figure 1). In a similar manner, TP dose-dependently and substantially ($p < 0.05$) enhanced SOD activity in comparison to the VC group, whereas VC treatment significantly ($p < 0.05$) decreased SOD activity in comparison to the control group (Figure 1).

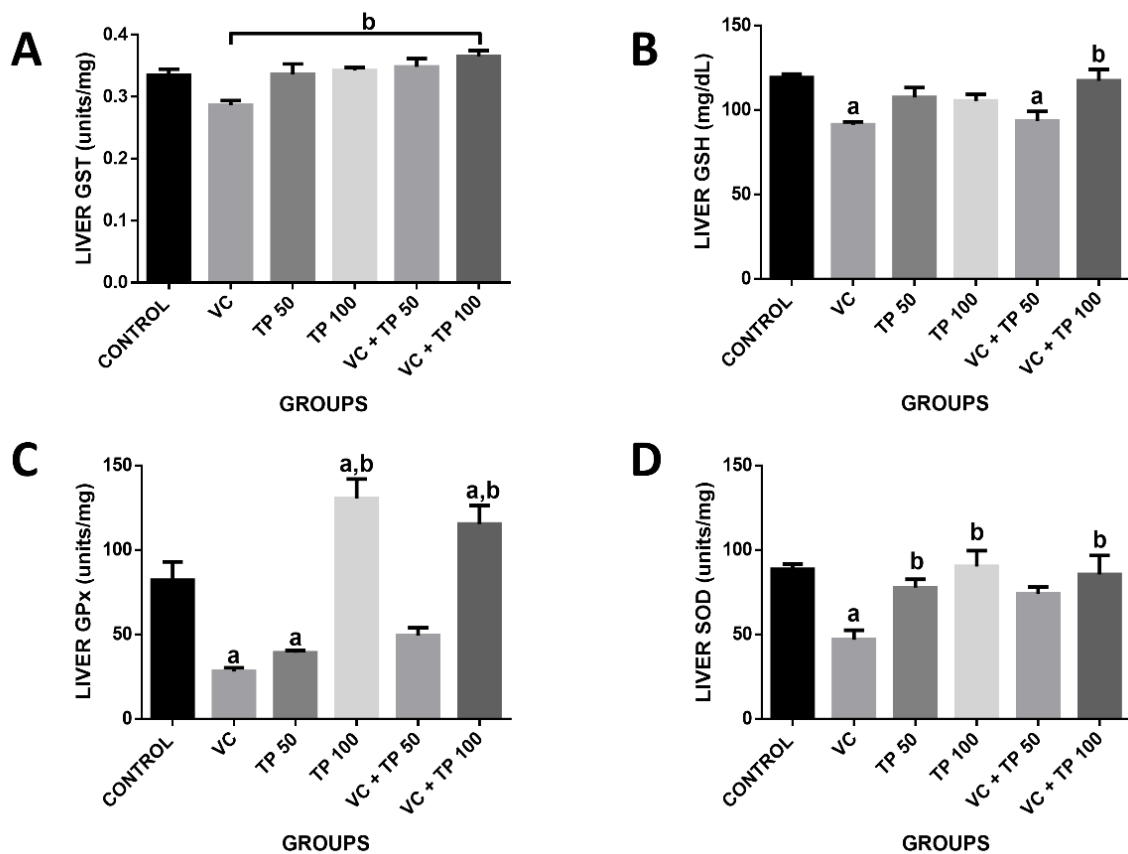


Figure 1. Effect of Vincristine and *T. procumbens* extract on the antioxidant system in the liver of the experimental rats. ^a Significantly ($p < 0.05$) different from the control group, ^b Significantly ($p < 0.05$) different from the Vincristine sulphate (VC) group. Treatment groups: A: 1 mL/kg b.wt distilled water (control); B: 0.1 mg/kg b.wt VC, C: 50 mg/kg b.wt *T. procumbens* (TP), D: 100 mg/kg b.wt TP, E: VC (0.1 mg/kg b.wt) + TP (50 mg/kg b.wt), F: VC (0.1 mg/kg b.wt) + TP (100 mg/kg b.wt). N = 5.

In the pancreas, VC increased the activity of GST, decreased the concentration of GSH ($p < 0.05$) and the activities of GPx and SOD, compared to the control group (Figure 2). In contrast, there was a dose-dependent increase in the concentration and activities of these biomarkers in groups exposed to TP (Figure 2). The increase in GSH concentration observed in the group exposed to 50 mg/kg b.wt and 100 mg/kg b.wt TP was significant ($p < 0.05$) compared to the control and VC group, respectively (Figure 2). Furthermore, the increased activity of GPx in the group exposed to 50 mg/kg b.wt was significant ($p < 0.05$) compared to the VC group, while 100 mg/kg b.wt was significant ($p < 0.05$) compared to the control and VC groups (Figure 2).

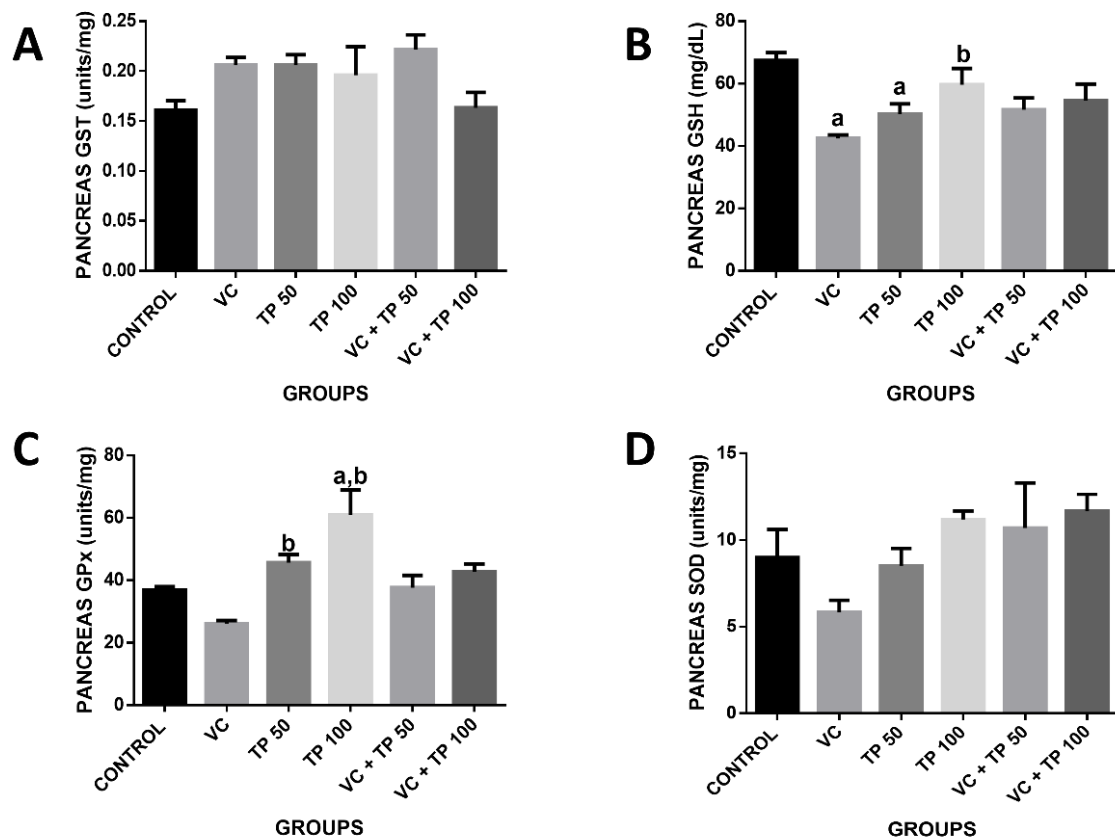


Figure 2. Effect of Vincristine sulphate and *T. procumbens* extract on the antioxidant systems of the pancreas of the experimental rats. ^aSignificantly ($p < 0.05$) different from the control group, ^bSignificantly ($p < 0.05$) different from the Vincristine sulphate (VC) group. Treatment groups: A: 1 mL/kg b.wt distilled water (control); B: 0.1 mg/kg b.wt VC, C: 50 mg/kg b.wt *T. procumbens* (TP), D: 100 mg/kg b.wt TP, E: VC (0.1 mg/kg b.wt) + TP (50 mg/kg b.wt), F: VC (0.1mg/kg b.wt) + TP (100 mg/kg b.wt). N = 5.

Figure 3 shows the total protein and oxidative stress biomarkers of the liver and pancreas of the experimental rats. The VC significantly ($p < 0.05$) increased the concentration of MDA and H_2O_2 and decreased the concentration of total protein in the liver, compared to the control group, with a counteracting effect by TP. In the pancreas, VC also increased the concentration of H_2O_2 significantly and reduced the concentration of MDA and TP ($p < 0.05$). In contrast, TP functions in a contradictory manner

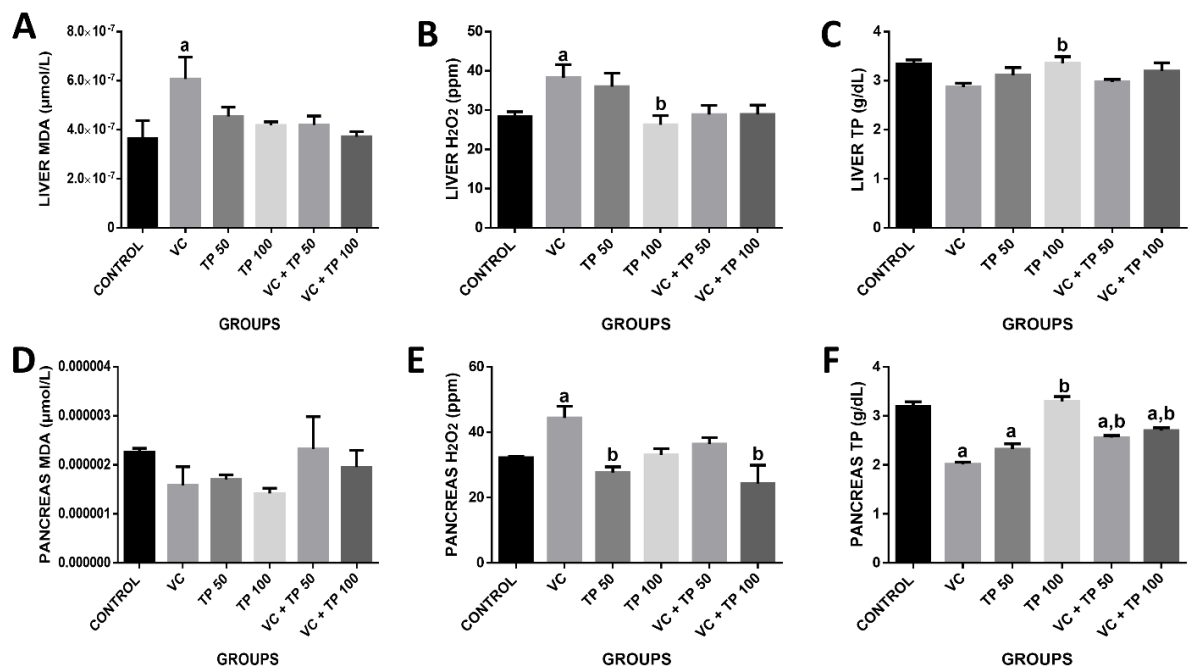


Figure 3. Effect of Vincristine sulphate and *T. procumbens* extract on oxidative stress markers and total protein of experimental rats. ^a Significantly ($p < 0.05$) different from the control group, ^b Significantly ($p < 0.05$) different from the Vincristine sulphate (VC) group. Treatment groups: A: 1 mL/kg b.wt distilled water (control); B: 0.1 mg/kg b.wt VC, C: 50 mg/kg b.wt *T. procumbens* (TP), D: 100 mg/kg b.wt TP, E: VC (0.1 mg/kg b.wt) + TP (50 mg/kg b.wt), F: VC (0.1mg/kg b.wt) + TP (100 mg/kg b.wt). N = 5.

There was a slight increase in the serum activity of amylase and lipase of experimental animals exposed to VC (Figure 4). However, there was a significant ($p < 0.05$) increase in serum amylase activity of experimental animals exposed to TP and the co-exposed groups, compared to the control and VC groups. A similar observation was made for serum lipase activity, although without statistical significance (Figure 4).

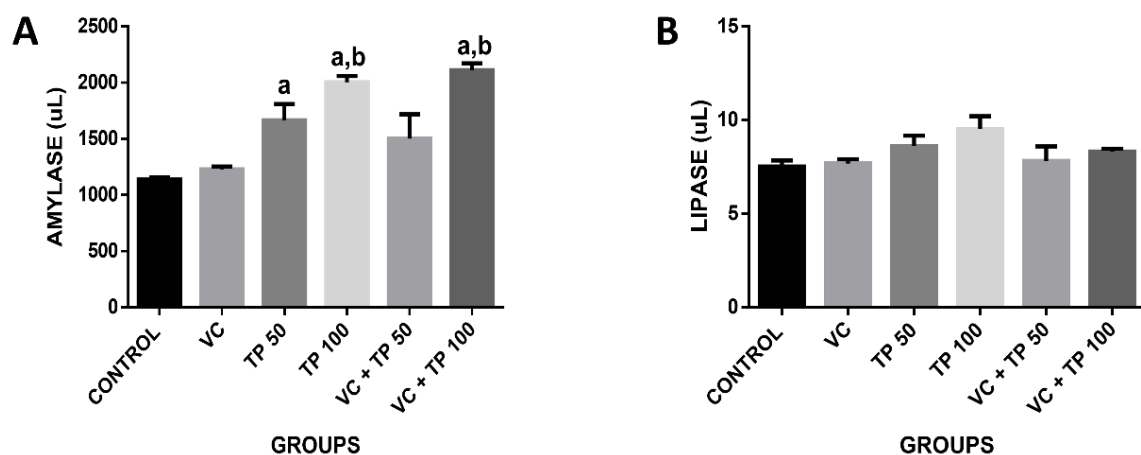


Figure 4. Effect of Vincristine sulphate and *T. procumbens* extract on serum amylase and lipase of experimental rats. ^a Significantly ($p < 0.05$) different from the control group, ^b Significantly ($p < 0.05$) different from the Vincristine sulphate (VC) group. Treatment groups: A: 1 mL/kg b.wt distilled water (control); B: 0.1 mg/kg b.wt VC, C: 50 mg/kg b.wt *T. procumbens* (TP), D: 100 mg/kg b.wt TP, E: VC (0.1 mg/kg b.wt) + TP (50 mg/kg b.wt), F: VC (0.1mg/kg b.wt) + TP (100 mg/kg b.wt). N = 5.

Figure 5 below shows the effect of VC and TP on the liver histology of experimental rats. Control animals (Group A) showed no visible lesions. Group B showed a moderate portal infiltration of inflammatory cells and random centrilobular degeneration (arrow). Group C showed mild hepatocellular swelling. There was portal cellular infiltration in group D rats,

while group E rats showed moderate to severe portal congestion and inflammatory cellular infiltration. Group F showed a mild inflammatory cellular infiltration within the liver parenchyma. Figure 6 shows the effect of VC and TP on the pancreas section of experimental rats. No lesion was found in the treatment groups. However, there were more representations of islets of Langerhans (arrow) and secretory acini cells (arrowhead) in groups C and D.

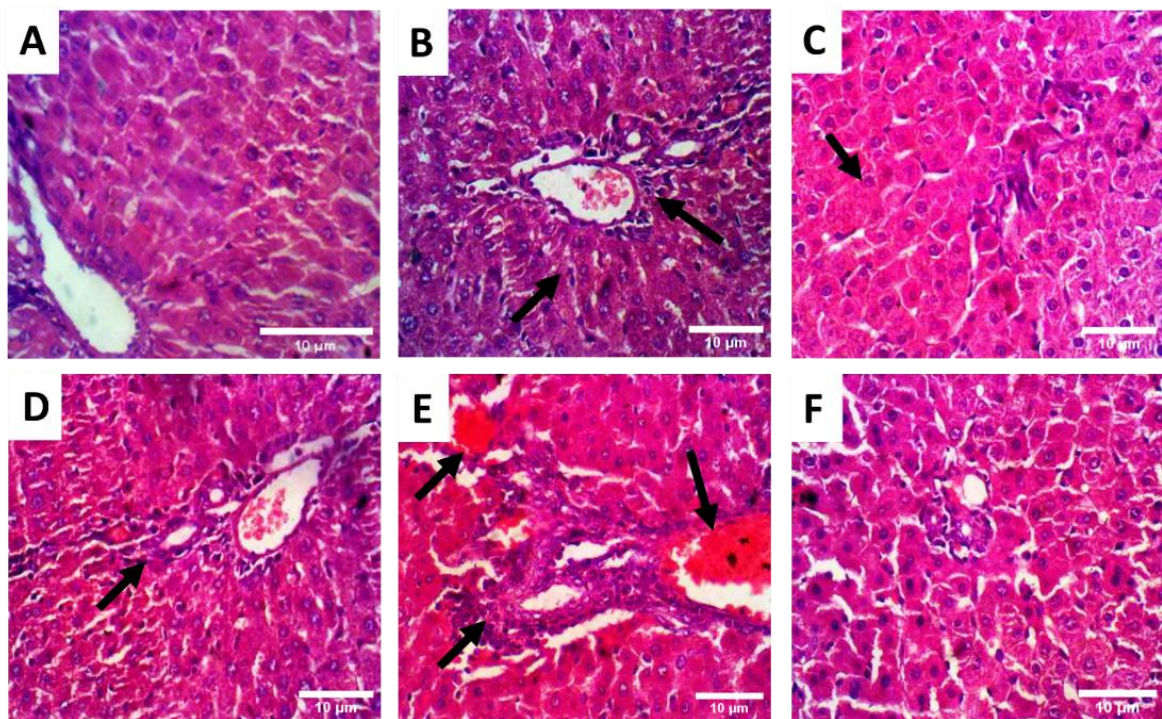


Figure 5. Effect of Vincristine sulphate and *T. procumbens* extract on the rats' liver. Group A showed no observable lesions in the hepatocytes. Group B showed a moderate portal infiltration of inflammatory cells and random centrilobular degeneration (arrow). Group C showed mild hepatocellular swelling. There was portal cellular infiltration in group D rats. There was a moderate to severe portal congestion and cellular infiltration in Group E. Group F showed a mild cellular infiltration of inflammatory cells. Treatment groups: A: 1 mL/kg b.wt distilled water (control); B: 0.1 mg/kg b.wt VC, C: 50 mg/kg b.wt *T. procumbens* (TP), D: 100 mg/kg b.wt TP, E: VC (0.1 mg/kg b.wt) + TP (50 mg/kg b.wt), F: VC (0.1 mg/kg b.wt) + TP (100 mg/kg b.wt). N = 5. H&E stain at x400 magnification. Scale bar = 10µm.

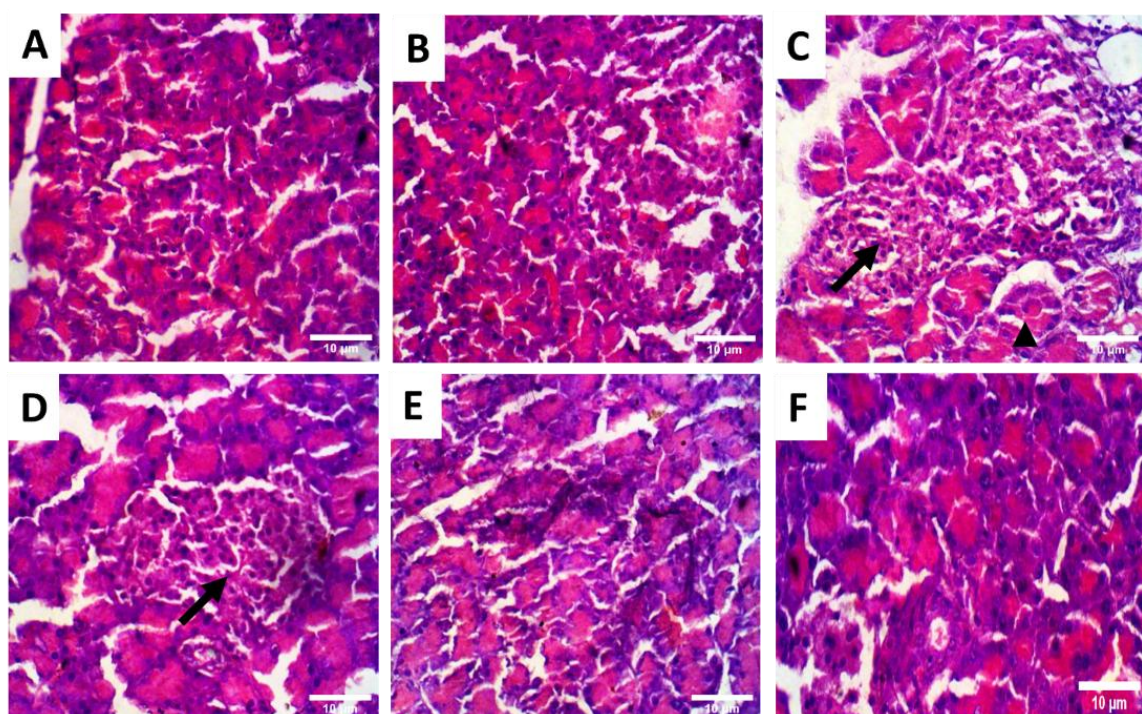


Figure 6. Effect of Vincristine sulphate and *T. procumbens* on the rats' pancreas. No observable lesion was found in the pancreas of the treatment groups. However, there was more representation of islets of Langerhans (arrow) and secretory acini cells (arrowhead) in groups C and D. Treatment: A: 1 mL/kg b.wt distilled water (control); B: 0.1 mg/kg b.wt VC, C: 50 mg/kg b.wt *T. procumbens* (TP), D: 100 mg/kg b.wt TP, E: VC (0.1 mg/kg b.wt) + TP (50 mg/kg b.wt), F: VC (0.1 mg/kg b.wt) + TP (100 mg/kg b.wt). N = 5. H&E stain at x400 magnification. Scale bar = 10µm.

4. DISCUSSION

A balance in the oxidant-antioxidant system of living organisms has a significant implication for cellular function [29]. The disruption in this system results in oxidative stress, which has been associated with various pathological conditions, such as cancer, neurological and cardiovascular diseases [30]. Metabolic reactions, in most cases, generate ROS in the form of free radicals or non-radicals, which may be either oxygen or nitrogen-derived (prooxidants), that cause damage to macromolecules [31]. However, as a defence mechanism, these oxidants are mopped up by another group of compounds known as antioxidants, which can be generated endogenously or obtained from exogenous sources [32].

The liver is a vital organ that has been reported to be susceptible to oxidative stress due to its role in detoxification and metabolism [33]. In the liver and pancreas, the activity of antioxidants, including glutathione S-transferase (GST), reduced glutathione (GSH), glutathione peroxidase (GPx), and superoxide dismutase (SOD) was assessed. The VC-induced reduction in GSH levels, GPx, GST, and SOD activities in the liver could be an indication that these antioxidants were sensitive to Vincristine sulphate-induced oxidative stress [34]. For instance, glutathione peroxidase has a primary role in the neutralisation of hydrogen peroxide (H₂O₂) and lipid peroxides [35], which could accumulate in the tissue due to the cytotoxic mechanisms of vincristine, thereby causing a reduction in GPx activity. This reduction may result in lipid peroxidation and ultimately, impaired hepatocellular function [36]. The findings of this study align with a previous study that reported the potential of Vincristine sulphate to cause oxidative stress through ROS generation and antioxidant depletion [37].

The co-administration of TP extract with VC caused a dose-dependent increase in GST, GPx, and SOD activities, together with GSH level. The ability of TP to demonstrate this effect can be attributed to its constituent phytochemicals, such as flavonoids and polyphenols [17]. These antioxidants serve as an endogenous defence that scavenges free radicals generated through metabolic activities. A possible mechanism was reported by [38], who claimed that many phytochemicals in medicinal plants demonstrate protective effects through the nuclear factor erythroid 2-related factor 2 (Nrf2) signalling, which is associated with the regulation of antioxidant response element (ARE) genes. Therefore, it is probable that the phytochemical constituents of TP have enhanced this signalling pathway. The antioxidative effect of TP has also been established previously by [39,40], who reported a protective role of the medicinal plant through its ability to increase antioxidant activity in streptozotocin-induced diabetic neuropathy in rats, and human and breast cancer cells, respectively.

Unlike in the liver, an increase in GST was observed for groups administered VC in the pancreas. The increase in the activity of GST, a phase II detoxification and drug-metabolising enzyme, may be due to an acute cellular response to ameliorate the oxidative damage caused by Vincristine sulphate [41]. In a study by Seitz et al. [42] on the inhibition of GST as a treatment strategy for multidrug resistance in childhood Rhabdomyosarcoma, it was reported that there was an increase in GST activity after incubation of the cells with cytotoxic agents, such as vincristine, doxorubicin, and topotecan. Contrarily, GSH was decreased in the VC group. Reduced glutathione is an antioxidant that protects against free radicals by a detoxification mechanism, and its depletion might result in unfavourable cellular events, including oxidative stress [43]. This study's finding implies that TP extract might possess a stabilising effect that enables it to preserve intracellular GSH. Previously, Andriana et al. [44] reported similar findings with claims that TP maintains GSH homeostasis. In addition, GPx is an antioxidant enzyme [45], and its activity was decreased in the VC group, which might be due to excessive oxidative stress. However, TP dose-dependently ameliorated this effect and enhanced the activity of GPx. This might be due to its active constituents, including polyphenols and flavonoids [40].

In this study, MDA levels were also used to investigate the oxidant status in the pancreas and liver. Malondialdehyde is a biomarker of lipid peroxidation, which is usually a result of cell membrane oxidative damage [46]. As a product of oxidative stress, MDA is genotoxic and can damage DNA [47]. The concentration of MDA in the liver was increased in the group exposed to VC and decreased in the group exposed to TP, which implies that VC administration might result in lipid peroxidation, while TP provides a protective effect that could prevent genotoxicity, as previously reported [48] due to high concentrations of MDA. However, VC could not induce MDA levels in the pancreas as with the liver, which could indicate organ-specific effect of VC. Hydrogen peroxide is an oxidative stress marker because it can produce metabolites or free radicals, such as hydroxyl radicals ($\text{OH}\cdot$) [49]. H_2O_2 participates in the Fenton reaction, which involves the oxidation of an iron atom (Fe^{2+}) and the generation of reactive free radicals [50]. The VC-induced increase in the concentration of H_2O_2 in the liver and pancreas indicated that this chemotherapeutic agent may be associated with oxidative stress, while TP can reduce the concentration of the oxidative stress biomarker, probably by enhancing the expression of the various antioxidants discussed earlier. Lastly, total protein estimates albumin and globulin levels in specific organs, which can be used to assess organ toxicity [51]. The reduced liver and pancreas total protein levels after VC treatment might be because VC interrupts the protein synthesis pathway, which could impair organ functions [52]. However, the ethanol extract of *T. procumbens* ameliorated this effect.

There was an increase in serum lipase activity in experimental rats exposed to TP extract. Although elevated serum lipase is recognised as a biomarker of pancreatic injury, the increase observed in the present study occurred in the absence of histopathological evidence of pancreatic damage. Histological examination of the pancreas revealed no observable lesions across treatment groups; however, increased representation of the islets of Langerhans and pancreatic secretory acini was observed in rats administered 50 mg/kg and 100 mg/kg body weight of *T. procumbens*. This histological finding suggests a possible enhancement of exocrine pancreatic secretory capacity or functional modulation of acinar cells, which may account for the elevated serum lipase levels. In addition, the absence of acinar degeneration, necrosis, or inflammatory infiltration indicates that the observed enzyme elevation could be explained as an adaptive cellular response rather than an apparent pancreatic toxicity at the administered doses. Nevertheless, serum pancreatic enzyme activity alone cannot definitively distinguish functional stimulation from pancreatic toxicity. Therefore, further studies that integrate inflammatory markers would strengthen this interpretation. This result also aligns with the report that certain plant extracts, including *Mentha piperita* leaf extract, could lower body total cholesterol, low-density lipoprotein cholesterol, and enhance lipoprotein lipase activity [53]. Similarly, the study by Enwa et al. [54] reported that TP extract caused a reduction in the serum levels of total cholesterol, triglycerides, LDL, and VLD, which could be attributed to an increase in the production and activity of lipase.

The increased activity of serum amylase in rats exposed to TP in our study aligns with the report of Samuel [55] that the dichloromethane fraction of TP increases the expression of amylase (acinar cells) by 1.3-fold, in a study that focused on the effects of the different fractions of TP on the differentiation of mouse embryonic pancreas. The histology result of better preservation of secretory acini cells that produce amylase enzymes in this study supports the increased activity of serum amylase in animals exposed to TP [56]. Therefore, it could be suggested that TP could stimulate lipase and amylase activity; essential enzymes that regulate lipid and carbohydrate metabolism in living organisms. These findings align with the results of the histological examination of the liver and pancreas of experimental animals. The moderate portal infiltration and random centrilobular degeneration of the hepatocytes in rats exposed to VC imply a possible accumulation of inflammatory cells (plasma cells and lymphocytes) within the portal tracts [57]. This infiltration of inflammatory cells could result from Vincristine sulphate-induced hepatocellular toxicity [58]. However, the absence of visible lesions in the pancreas of all treatment groups suggests organ-specific VC-induced toxicity.

5. CONCLUSION

This study investigated the effect of Vincristine sulphate and ethanol leaf extract of *T. procumbens* on the oxidant-antioxidant system and histology of the pancreas and liver of experimental rats. It emphasises the induction of oxidative imbalances and promotion of oxidative stress in the liver and pancreas of experimental rats by Vincristine sulphate, including the potential of *T. procumbens* in suppressing this toxicity. The findings highlight a previously underexplored protective role of *T. procumbens* against vincristine-associated organ toxicity, suggesting its potential as an adjunct phytotherapeutic agent during chemotherapy. While

vincristine remains an effective anticancer drug, these results underscore the importance of mitigating its systemic toxicity and support further investigation into *T. procumbens*-derived bioactive compounds as complementary protective agents.

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