



Ameliorative effect of a multi-nutrient-rich product against cyanide induced hepatorenotoxicity

Ilesanmi O. Babatunde[✉], Asaba Abigail

Department of Biochemistry, Faculty of Science, Federal University, Otuoke, Bayelsa State, Nigeria

[✉]**Corresponding author:**

Department of Biochemistry,
Faculty of Science, Federal University, Otuoke,
Bayelsa State, Nigeria;
Email: ilesanmiob@fuotuoke.edu.ng

Citation

Ilesanmi O. Babatunde, Asaba Abigail. Ameliorative effect of a multi-nutrient-rich product against cyanide induced hepatorenotoxicity. *Drug Discovery*, 2021, 15(35), 51-59

ABSTRACT

The present study was designed to investigate the protective effects of trevo, on potassium cyanide-induced hepato- and nephrotoxicity in male Wistar rats. Rats received Trévo (2 ml) after cyanide (0.5 mg/kg) exposure. Twenty-four hours after last administration rats were sacrificed and blood, liver and kidney tissues collected for haematological (neutrophils, lymphocytes, monocytes, eosinophils, basophils, white blood cells (WBC) and packed cell volume (PCV)), biochemical and histological assays. Our results shows that trevo significantly reverse the increased activity of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) induced by cyanide while it had no significant effect on aspartate aminotransferase (AST) induced increased ($P < 0.05$) at the various time of trevo administration. Trevo also significantly decrease the concentration of urea as compared to cyanide group while it caused an insignificant effect in creatinine concentration in comparison to cyanide only group. The alteration in all the hematological parameters analysed caused by cyanide was significantly reversed by treatment with trevo ($P < 0.05$) at the various time of administration. Histology showed that cyanide caused pathological lesion in the hepatocyte as observed with increased bile deposition and fatty droplets and reduction in hepatocyte density which was reversed by treatment with trevo. In the nephrocyte, cyanide caused no pathological lesion in the kidney tissue, neither did administration of trevo had any pathological effect. The reversal of cyanide-induced hepato- and nephrotoxicity by trevo, shows that it can be administered as an antidote against cyanide exposure, especially when administered immediately after cyanide poison.

Keywords: cyanide; phyto-nutrient; hepatoprotective; nephroprotective; histology

1. INTRODUCTION

The uses of cyanide in industries, presence in some foods and environmental contaminants makes it one of the chemicals human are often exposed to [1]. Some of its industrial uses include - mining of gold, synthesis of organic compounds, electroplating and buffing [2]. Cyanide is a highly toxic compound, and its toxicity is often initiated via alteration in oxygen metabolism through cytochrome C oxidase inhibition. There are several approved drugs for treating cyanide poison, however, their availability and side effects are some of the limitation [3,4]. These have led to continuous search for drugs that are effective, low or zero toxicity and readily available for the treatment of cyanide poison. The liver is one of the biggest organs in the human and it is involved in various metabolic processes. It is involved in the catabolism and anabolism of important nutrients for physiological processes, drugs and other chemicals are metabolized and processed for excretion in the liver, prevents the accumulation of toxic chemicals in the body through detoxification and elimination from the body [5,6]. The role of kidney in filtering and excretion of drug and toxic compounds makes it one of the organs prone to injury from chemical exposure [7]. Apart from the above functions, the kidney also plays important role in homeostasis processes, such as electrolyte balance, blood pressure, water and metabolite concentration [8]. The role of kidney in excretion, filtering and excretion of drug and toxic compounds, makes it a potential target for drug and chemical toxicity [9]. Nature has provided human and animals with plethora of plants that can be used to treat various infections and poison. Investigations have shown that more than 80% of human population depends on these plants for survival [10]. With studies confirming the therapeutic effects of some of these plants in the management and treatment of several ailments, scientists were able to identify the active phytochemicals present in the plants and developed them into various nutraceutical and pharmaceutical products [11]. These group of phytochemicals are generally safe and work by acting as antioxidant, anti-inflammatory and improving the host-defense system and they include, polyphenols and flavonoids. Trévo is an America product that contains several bioactive phytochemicals, vitamins and minerals that are uniformly mixed to give a standard phytonutrient-rich product [12]. [13] reported that some of the health benefits of trevo includes improving cardiovascular, immune and digestive systems as well as regulating cholesterol, blood sugar, pH level. Some investigations has reported to possess hepatoprotective and cardioprotective properties which can be linked to the presence of various phytochemicals such as phenolic acid, coumarin, flavonoids, stilbenes, alkaloids, tannins and lignans (trevo, 2020). The toxicity of cyanide via alteration in oxygen metabolism makes it a chemical that can damage most of the organs in the body [14] as they all requires oxygen for efficient performance.

2. MATERIALS AND METHODS

Chemicals and Reagents

All reagent kits were purchased from Sigma-Aldrich, Germany. Trévo was a product of Trévo™ LLC, Oklahoma City, USA. Other chemicals were of analytical grade.

Experimental Animals

All the animals used for the experiment were in accordance with the protocol provided by Basic and Clinical Pharmacology and Toxicology policy for experimental and clinical studies [15] and approved (APN:0418062019) by the departmental committee on animal ethics (Department of Biochemistry, Faculty of Science, Federal University Otuoke, Bayelsa state, Nigeria). Animals with average weight of 200 g were used for the experiment. They were placed in a well-regulated room that is alternated between 12 light and dark cycle. They were fed on rat pellets and water ad libitum.

Experimental Protocol

Twenty-four animals divided into four groups of six rats each as follows: [I] Normal control (administered distilled water); [II] negative control (administered a single dose of KCN); [III] treatment group (administered KCN and Trévo (5 min later)) and [IV] treatment group 2 (administered KCN and trévo (60 min later)). Animals were sacrificed 24 h after administration of trévo via mild anaesthetic using chloral hydrate. KCN was administered at 5 mg/kg per body weight (bwt), which according to [16] induced moderate to severe toxicity with little lethality. The effective dose of trévo (2 mL/kg bwt) was based on an unpublished pilot study. Administration of trévo was based on method described by [16]. Prior to sacrifice, the rats were denied food overnight. Unconsciousness was induced by exposing them to chloral hydrate and the blood collected through cardiac puncture into serum bottles for biochemical and hematological assays.

Hematological Analysis

White blood cell (WBC) count and differential count (Eosinophil, monocyte, lymphocyte, neutrophil and PCV) were assayed by an electronic automate Coulter MAXM (Beckman Coulter, Inc., Fullerton, CA).

Serum Biochemistry

Serum Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), urea and creatinine kit were assayed spectrophotometrically using commercial kits purchased from Bio Diagnostic Co., according to the manufacturer's protocol.

Histology

Histopathological assay: Histopathological examination of the kidney and liver isolated from experiment rats were carried out by fixing them in 10% formalin solution, prior to preparation for staining and assessing under a microscope with x100 magnification. Slides were captured with a camera attached to the microscope and then analyzed for histopathology according to the method described by [17].

Statistical Analysis

Data were organized, tabulated, and statistically analyzed using the SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. (SPSS Inc., Chicago, USA). For quantitative data, the mean and SD were calculated and were expressed as mean \pm standard deviation and were analyzed using Analysis of Variance (ANOVA). For comparison of means of more than two groups, the F-test was used. Statistical significance was taken at a P value of less than 0.05.

3. RESULTS AND DISCUSSION

The effect of trevo and cyanide on hematological parameters is presented in table 1. The results showed that cyanide caused a significant increase in neutrophil, lymphocyte, monocyte, eosinophil, basophil and white blood cell (WBC) count as compared to the unexposed rats ($P < 0.05$). While there was a decrease in PCV count, though not significant at $P < 0.05$. The table shows that early administration of trevo caused a significant reversal of the effect of KCN on the hematological parameters. Hematology test is done to determine the health status of the host. There is a strong correlation between cyanide increase in the blood with respect to high WBC and anemic condition [18]. A decrease in RBC is an indication of anemic and inability of the host to utilize oxygen efficiently, while an increase in WBC reflects infection and the host response to combat it [19] in the work of [20]. Our results supported the reported toxicity of cyanide through its binding to hemoglobin, thereby causing low concentration of RBC [21, 22]. Phytochemical rich plant and products have been shown to be effective in combating the damaging effect of toxicants including cyanide [23], which are often measured by the level of different blood parameters (This test has been shown to be a good determinant of homeostatic status as a reflection of healthy state of human). They have been shown to improve and boost the immune system and increase RBC [24]. As observed in our result, trevo was able to increase WBC volume as well as decrease WBC and other hematology parameters measured. The protective effect of trevo might be as a result of trevo reacting with cyanide, thereby preventing or limiting their destruction of RBC and stressing the host immune system. Another possibility is the potential of trevo to increase RBC production and aid the body in attacking radicals that can cause oxidative stress in the body.

Table 1. Effect of trevo on hematology following cyanide poisoning

Group	Neutrophils ($\times 10^3/\text{mm}^3$)	Lymphocytes ($\times 10^3/\text{mm}^3$)	Monocytes ($\times 10^3/\text{mm}^3$)	Eosinophils ($\times 10^3/\text{mm}^3$)	Basophils ($\times 10^3/\text{mm}^3$)	WBC ($\times 10^3/\text{mm}^3$)	PCV (%)
Control	4.93 \pm 0.23	3.74 \pm 0.45	0.33 \pm 0.014	0.22 \pm 0.017	0.00 \pm 0.00	9.00 \pm 1.58	32 \pm 1.22
KCN	5.98 \pm 0.35*	5.89 \pm 0.58*	0.83 \pm 0.52*	0.42 \pm 0.05*	0.9 \pm 0.1*	10.8 \pm 1.33*	29.50 \pm 1.05
KCN+trevo (5 min)	5.2 \pm 0.34 [#]	3.83 \pm 0.31 [#]	0.60 \pm 0.07 [#]	0.33 \pm 0.03 [#]	0.4 \pm 0.02 [#]	9.64 \pm 0.78 [#]	32.2 \pm 1.92
KCN+ trevo (60 min)	5.37 \pm 0.50 [#]	3.91 \pm 0.41 [#]	0.84 \pm 0.04	0.36 \pm 0.05 [#]	0.7 \pm 0.10	9.5 \pm 0.88 [#]	29.5 \pm 2.58

Values are expressed as Mean \pm SD (n=6). * $P < 0.05$ (control vs KCN), # $P < 0.05$ (KCN vs trevo)

Hepatoprotective effect of trevo against cyanide toxicity

Figure 1 and 2 shows the effect of trevo on serum level of AST, ALT and ALP respectively following KCN intoxication in male wistar. There was a significant increase in AST concentration of animals administered KCN only as compared to the animals in the control group ($P < 0.05$). The figure also showed that administration of trevo after 5 minutes of exposure to KCN caused a significant decrease in serum level of AST when compared to the group administered only KCN. Administration of trevo after 1hr of KCN intoxication also decrease creatinine concentration, however it was not significant ($P > 0.05$). Figure 1 also showed that cyanide did not have a significant effect on serum level of ALT ($P > 0.05$). With respect to ALP, it was observed that KCN caused a significant

increase in ALP activity in the serum of animals administered KCN only as compared to the animals in the control group ($P < 0.05$). Figure 2 also showed that administration of trèvo after 5 minutes and 1h of exposure to KCN cause a significant decrease in serum activity of ALP, when compared to the group administered only KCN ($P < 0.05$).

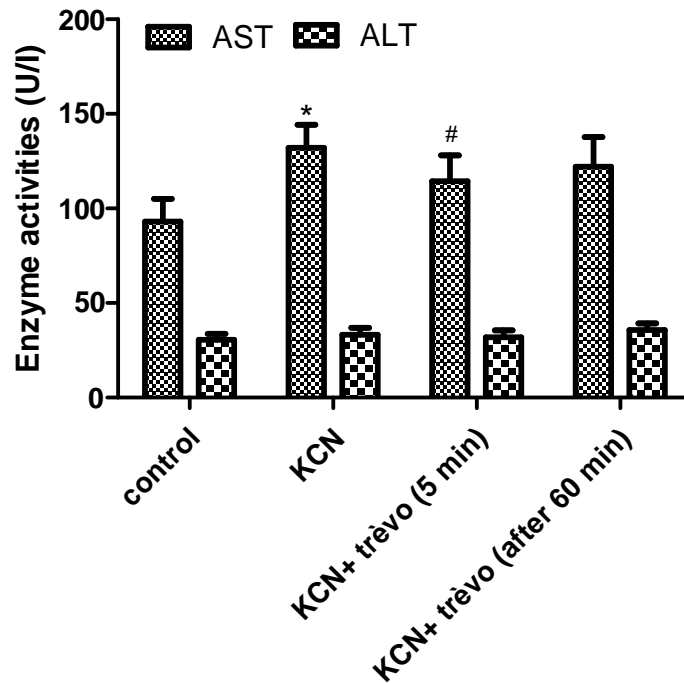


Figure 1. Effect of trèvo on serum activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) following KCN intoxication in male Wistar. Results are expressed as mean \pm SD (n=6). * $P < 0.05$ (control vs KCN), # $P < 0.05$ (KCN vs trèvo)

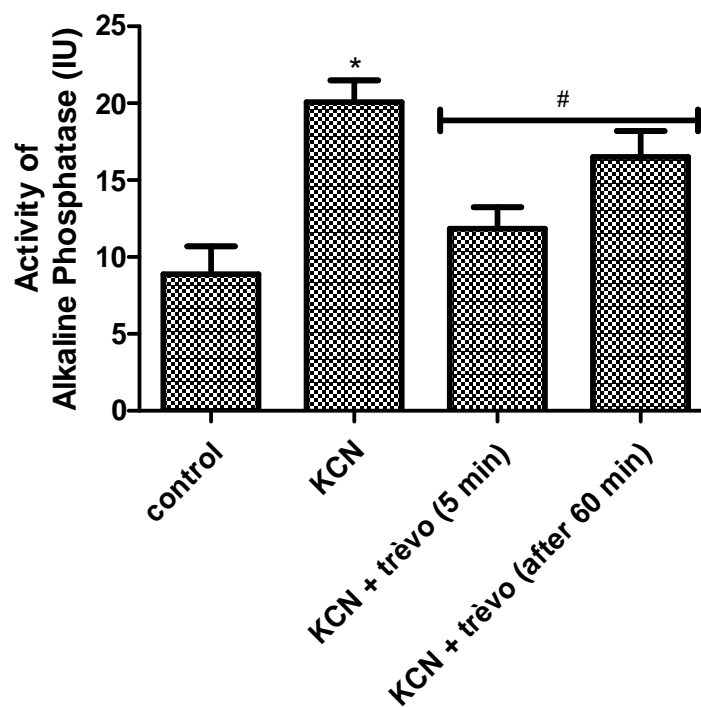


Figure 2. Effect of trèvo on serum activity of alkaline phosphatase following KCN intoxication in male Wistar. Results are expressed as mean \pm SD (n=6). * $P < 0.05$ (control vs KCN), # $P < 0.05$ (KCN vs trèvo).

Administration of trevo significantly reverse the serum markers of renal toxicity induced by KCN. Figure 3 shows the effect of trevo on serum level of creatinine and urea following KCN intoxication in male wistar. There was a significant increase in creatinine concentration of animals administered KCN only as compared to the animals in the control group ($P < 0.05$). The figure also showed that administration of trevo after 5 minutes of exposure to KCN caused a significant decrease in serum level of creatinine when compared to the group administered only KCN. Administration of trevo after 1hr of KCN intoxication also decrease creatinine concentration, however it was not significant ($P > 0.05$). With respect to urea, it was observed that KCN caused a significant increase in urea concentration of animals administered KCN only as compared to the animals in the control group ($P < 0.05$). The figure also showed that administration of trevo after 5 minutes and 1h of exposure to KCN cause a significant decrease in serum level of urea, when compared to the group administered only KCN ($P < 0.05$). However, comparing the time of administration, early administration of trevo significantly decrease urea concentration as compared to late administration of trevo ($P < 0.05$).

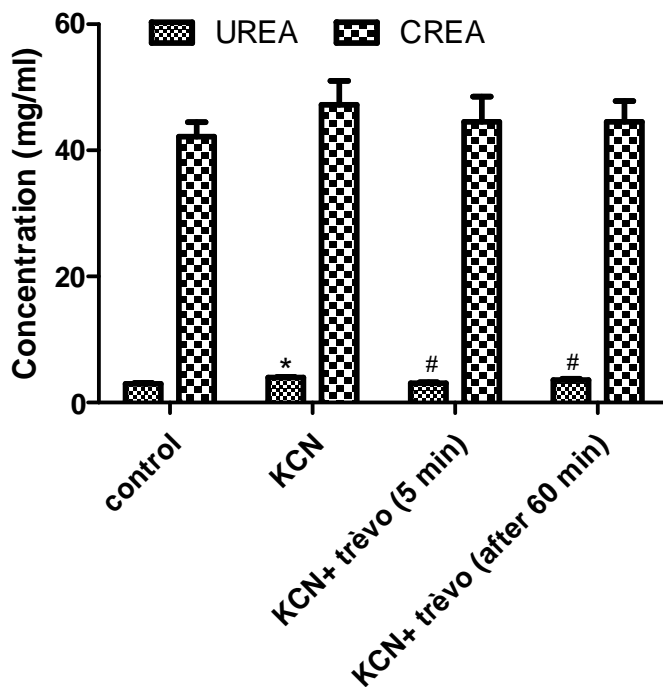


Figure 3. Effect of trevo on serum level of urea and creatinine following KCN intoxication in male Wistar. Results are expressed as mean \pm SD ($n=6$). * $P < 0.05$ (control vs KCN), # $P < 0.05$ (KCN vs trevo).

As observed in various publications, liver damage are often marked by an increase in the AST, ALT and ALP levels in the serum [25, 26]. In most cases, the liver injury is often signified by increase in at least two of the marker enzymes. In our experiments, cyanide caused a significant increase in AST and ALP while it has no significant effect on ALT level. [2] showed that cyanide increase the level of ALT and ALP, which was contrary to our results, while [21] reported a significant increase in all the enzymes. The different in the results might as a result of several factors, such as dosage, route and duration of administration [27, 28, 29]. Kidney is another organ that is also susceptible to cyanide toxicity [30]. An elevated level of urea and creatinine are the major indicators of renal damage [31, 32]. In our result, cyanide induced significant increase in urea and creatinine, in tandem with other report on nephrotoxicity of cyanide [33, 2]. In rats with normal renal function, urea and creatinine are filtered from the blood and excreted from the body, thus the observed increase in blood urea and creatinine are prove of renal damage as a result of cyanide exposure [34]. Kidney and liver related disorders have being linked to anemic condition [35, 36]. This is linked to low or deficiency of erythropoietin and iron required for the production of RBC. Phytochemical rich supplements have been shown to be effective in the management of kidney related disorders [31]. Report also shows that phytochemical rich supplements are also effective in combating toxic effects of chemicals on the kidney [25, 37, 38, 39, 40]. Trevo showed its hepatoprotective and nephroprotective effect against elevated markers of liver and kidney-induced cyanide toxicity. The therapeutic effect might not be unconnected to the presence of bioactive phytochemicals such as ellagic acid, lycopene, ascorbic acid, tocopherol, carotene which were extracted from green tea, grape seed, aloe vera, bacopa and turmeric [41]. All these phytochemicals have both hepatoprotective and nephroprotective properties [42-47].

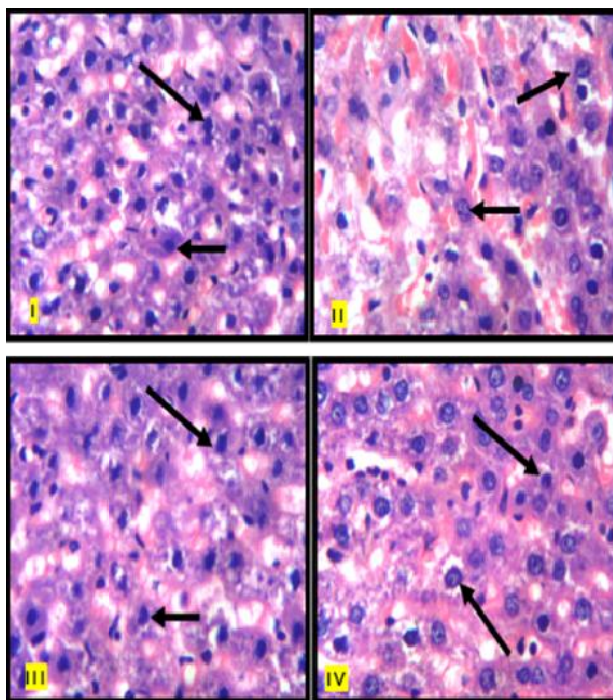


Figure 4. I: The histology of liver sample in the control group, it showed no histomorphology alteration. II: The histology of liver sample in rats intoxicated with potassium cyanide alone, it showed the hepatocyte with increased bile deposition and fatty droplets. Hepatocyte density is reduced. These suggest pathological alterations. III; The histology of liver sample in the group of animals intoxicated with potassium cyanide, followed by trevo administration after 5minutes. It showed normal histomorphology of liver tissue presenting with typical cellular density and cellular distribution. The Nuclei of hepatocytes are distinctively stained and properly disposed within their respective cytoplasm. There are no histopathological alterations in the histological presentation of these tissues. IV: The histology showed that that the hepatocyte appears characteristically normal with typical cellular density and staining intensity.

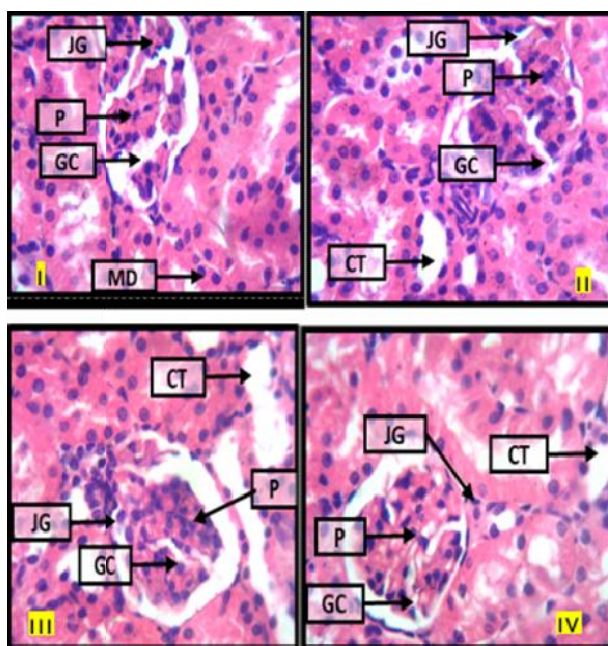


Figure 5. I: The histology showed normal renal corpuscle with typical cellular delineation, distribution, density and staining intensity. The urinary space appears characteristically normally with no vacuolations or cellular erosion. No apparent histopathological alteration. II: The histology showed normal renal corpuscle with typical cellular delineation, distribution, density and staining intensity. The urinary space appears characteristically normally with no vacuolations or cellular erosion. No apparent histopathological alteration. III: The histology showed normal renal corpuscle with typical cellular delineation, distribution, density

and staining intensity. The urinary space appears characteristically normally with no vacuolations or cellular erosion. No apparent histopathological alteration. IV: The histology showed normal renal corpuscle with typical cellular delineation, distribution, density and staining intensity. The urinary space appears characteristically normally with no vacuolations or cellular erosion. No apparent histopathological alteration. I (Control); II (KCN); III (KCN+ Trevo [after 5 min]); IV (KCN+ Trevo [after 60 min]); JG (Juxta-glomerular Cell); P (Podocyte); GC (Glomerular capillary); MD (Macula dense cell); CT (Convolutated tubules).

Histopathological examinations also confirmed the biochemical and hematological parameters obtained from the experiment. This corroborated the report of [48], who reported the degeneration of liver and kidney tissues as a result of cyanide exposure. However treatment with trevo caused a significant reduction in tissue degeneration.

4. CONCLUSION

In summary, our results showed that cyanide induce significant alteration in hematological parameters as well as biochemical changes in both liver and kidney functions which was supported with histological analysis. Trevo was able to reverse the assault of cyanide on the tissues. These protective effects might be linked to the presence of various bioactive phytochemicals and phytonutrients present in it, which have been reported to possess antioxidant, anti-inflammatory, chelating and restorative activities. Further work can be done to investigate the effect of the supplement on long-term exposure to cyanide poison.

Author contribution:

O.B.I. and A.M.B. conducted the research and prepare the manuscript.

Funding:

This study has not received any external funding.

Conflict of Interest:

The authors declare that there are no conflicts of interests.

Peer-review:

External peer-review was done through double-blind method.

Data and materials availability:

All data associated with this study are present in the paper.

REFERENCES AND NOTES

- Brierley, J.B., Brown, A.W., Calverley, J. (2011). Cyanide intoxication in the rat: physiological and neuropathological aspects. *Journal Neurol Neurosurgery and Psychiatry*. 39(2):129–140.
- Ghods V & Baghshani H. Evaluation of sublethal cyanide exposure on plasma biochemical profile in rats and possible protective effect of garlic. *Human & Veterinary Medicine OPEN ACCESS International Journal of the Bioflux Society*. 5(2): 58-61
- Banerjee, K.K., Bishayee B., Marimuthu P. (2010). Evaluation of cyanide exposure and its effect on thyroid function of workers in a cable industry. *Journal of Occupational Medicine*, 39:255–260.
- Graham, D. J., Laman, D., Theodore, J., and Robin, E. D.(2017-2018). Acute cyanide poisoning complicated by lactic acidosis and pulmonary edema. *Arch. Internationl Medicine* 137.
- Kisaoglu A, Ozogul B, Turan MI, Yilmaz I, Demiryilmaz I, Atamanalp SS, Bakan E, Suleyman H. Damage induced by paracetamol compared with N-acetylcysteine. *J. Chin. Med. Assoc.* 77 (2014) 463–468.
- Ogbonnaya E, Uanseoje S, Ojeaburu S. Effect of Gongronemalatifolium leaves ethanolic extract on paracetamol-induced hepatotoxicity in rats, *J.Physiol. Pharmacol. Adv.* 4 (2014) 337–341.
- Hwang, S.J., Tsai, J.C., Chen, H.C, "Epidemiology, impact and preventive care of chronic kidney disease in Taiwan," *Nephrology*, 2010, 15 (Suppl 2). 3-9.
- Ikanone CEO, Akinloye OA, Augbaja RN, Omotainse SO, Ajayi OL, shopein TM. Effect of sub-acute exposure to bonny light crude oil on plasma biochemistry and liver histopathology of albino rat. *Animal Res Inter.*, 2017, 14(1):2652–2659
- Wen, C.P., Cheng, T.Y.D., Tsai, M. K., Chang, Y.C., Chan, H.T., Tsai, S.P., Wen, S.F. et al. "All-cause mortality attributable to

- chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan," *Lancet*, 2008, 371 (9631). 2173-82.
10. Zhou, XP., Wei, YG., Chen, XZ. Effects of Trevo on serum and hepatic uric acid levels in acetaminophen-induced mice and xanthine dehydrogenase and xanthine oxidase activities in mouse liver, *Journal of Ethnopharmacology*. 103: 357-365.
 11. Kumar. A.J., Costa, L.M., De Souza, T.P. (2012). *International Journal of Pharmaceutical Science*.33
 12. Trèvo. Glossary of TrevoTrèvo Ingredients. Available from: <http://www.trevotrèvocorporate.com/healthfocusingredientglossary>. [Last accessed on 2019 Nov 20].
 13. Stevens, M.A. (2015). Trèvo – The power of wellness. www.trevocorporate.com.
 14. Abuye, C., Kelbessa, U., Wolde-Gebriel, S. (2016-2018). Health effects of cassava consumption in south Ethiopia. *East African Medical Journal*, 75:166-170.
 15. Tveden-Nyborg P, Bergmann TK, Lykkesfeldt J. Basic & clinical pharmacology & toxicology policy for experimental and clinical studies. *Basic ClinPharmacolToxicol*. 2018; 123(3):233-235.
 16. Ilesanmi OB and Ikpesu T. Neuromodulatory activity of trèvo on cyanide-induced neurotoxicity viz neurochemical, antioxidants, cytochrome C oxidase and p53. *AdvTradit Med*. 2020;
 17. Stevens and Wilson, 1996. Stevens A, Wilson IG. The haematoxylin and eosin. In: Bancroft JD, Stevens A, Turner DR, editors. *Theory and practice of histological techniques*. 4th ed. New York: Churchill Livingstone 1996: 99-112.
 18. Babatuyi CY, Boboye BE, Fagbemi TN, Enujiughua VN. Cyanide, haematology and histopathology profiles of albino rats fed with 'Fufu'-based diets produced from mixed starter cultures. *Heliyon* 6 (2020) e04391
 19. Omitoyin, B.O., Ajibade, A.O., 2014. Haematological evaluation of *Clariasgariepinus* (Burchell) juveniles exposed to lethal concentrations of the latex of *Calotropisprocera* (Ait). *J. Org. Agric. Environ*. 2, 141-145
 20. Adeosun, O.1., Adedokun, M.A., Ajibade, A.O., Balogun, J.O., 2019. Paper Utilization and Haematological changes of fish fed African star apple (*Chrysophyllumalbidum*) seed meal. *Afr. J. Food Sci*. 13 (9), 203-209.
 21. Kadiri, H.E, "The Effects of Aqueous *VernoniaAmygdalina* (Bitter Leaf) Extract On The Lipid Profile And Some Hematological Parameters In Rats Ex-posed To Cyanide," 2017.
 22. Ehigie AF, Adeleke GE, Ojieniyi FD, Ehigie OL. Bioefficiency of *Chromolaenaodorata* (Linn.) on hematological and lipid profiles in sublethal cyanide poisoning in male wistar rats. *Journal of Applied and Natural Science*, 2020, 12(1): 13 - 18 (2020)
 23. Musyoka TM, Dorothy NW, Wycliffe AM, Juma KK, Nzioka MD, et al. (2016) In Vivo Antianaemic Effect and Safety of Aqueous Extracts of *Erythrinaabyssinica* and *Zanthoxylumambarensis* in Mice Models. *J HematolThrombo Dis* 4: 242. doi:10.4172/2329-8790.1000 242
 24. Akah PA, Okolo CE, Okoye TC, Offiah NV (2010) Aqueous extract and methanol fractions of the leaves of *Brillantaisianitens*Lindau. Reverses Phenylhydrazine-induced anaemia in rats. *J Med Plants Res* 4: 271-277.
 25. Wali AF, Rashid S, Rashid SM, Ansari MA, Khan MR, Haq N, Alhareth DY, Ahmad A, Rehman MU. Naringenin Regulates Doxorubicin-Induced Liver Dysfunction: Impact on Oxidative Stress and Inflammation. *Plants* 2020, 9, 550; doi:10.3390/plants9040550
 26. Afsar, T.; Razak, S.; Almajwal, A. Effect of *Acacia hydaspicia* R. Parker extract on lipid peroxidation, antioxidant status, liver function test and histopathology in Doxorubicin treated rats. *Lipids Health Dis*. 2019, 18, 126
 27. Okolie, N.P.; Osobase, S.; (2005). Cataractogenic potential of cyanide-induced oxidative stress in rabbits. *Global Journal of Pure and Applied Sciences*; 11(1): 57-62.
 28. Hasan B, Vahide G. Modulatory effects of Garlic Powder on Cyanide-Induced Oxidative Stress in some Tissues of Rat. *Experimental Animal Biology*, 2017, 6(1), 71-79
 29. Okoye NF & Nwowo EC. The amelioration of cyanide induced liver toxicity with benoite using Wistar rats as experimental model. *Journal of Applied Agriculture and Biotechnology*, 2017, 14(1): 1-9
 30. Satpute RM, Bhutia YD, Lomash V, Bhattacharya R. Efficacy assessment of co-treated alpha-ketoglutarate and N-acetyl cysteine against the subchronic toxicity of cyanide in rats. *Toxicology and Industrial Health* 2019, 35(6): 410-423
 31. Wu P, Su C, Chang H, Lan A, Yang S. The Effect of a Nutritional Supplement on Chronic Kidney Disease Patients. *Journal of Food and Nutrition Research*, 2016, Vol. 4, No. 2, 115-120
 32. Sureshkumar, D, Shamshad Begum S, Johannah NM, BaluMaliakel, Krishnakumar IM. Toxicological evaluation of a saponin-rich standardized extract of fenugreek seeds (FenuSMARTTM): Acute, sub-chronic and genotoxicity studies. *Toxicology Reports* (2018), <https://doi.org/10.1016/j.toxrep.2018.10.008>
 33. Ola-Mudathir KF and Maduagwu EN. Antioxidant Effects of Methanol Extract of *Allium cepalinnon* Cyanide-induced Renal Toxicity in Male Wistar Rats. *Niger. J. Physiol. Sci*. 29(2014) 147-151
 34. Jaballi, H. Ben Saad, I. Bkhairia, I. Kammoun, M. Droguet, C. Magné, T. Boudawara, C. Kallel, M. Nasri, A. Hakim, I. Ben Amara. Increasing maneb doses induces reactive oxygen species overproduction and nephrotoxicity in adult mice, *Toxicol. Mech. Methods*. 27 (2017) 382-393

35. Segel GB, Hirsh MG, Feig SA (2002) Managing anemia in pediatric office practice: Part 1. *Pediatr Rev* 23: 75-84.
36. WHO/UNICEF/UNU (2001) Iron deficiency anemia: assessment, prevention, and control. A guide for program managers. Geneva, World Health Organization pp: 1-132.
37. Jacevic, V.; Djordjevic, A.; Srdjenovic, B.; Milic-Tores, V.; Segr, Z.; Dragojevic-Simic, V.; Kuca, K. Fullerene nanoparticles prevents Doxorubicin-induced acute hepatotoxicity in rats. *Exp. Mol. Pathol.* 2017, 102, 360-369.
38. Kocahan, S.; Dogan, Z.; Erdemli, E.; Taskin, E. Protective Effect of Quercetin Against Oxidative Stress-induced Toxicity Associated with Doxorubicin and Cyclophosphamide in Rat Kidney and Liver Tissue. *Iran J. Kidney Dis.* 2017, 11, 124-131.
39. Li, Y.; Yang, D.; Wang, Y.; Li, Z.; Zhu, C. Co-delivery Doxorubicin and silybin for antihepatoma via enhanced oral hepatic-targeted efficiency. *Int. J. Nanomed.* 2019, 14, 301-315.
40. Rehman et al., Rehman, M.U.; Tahir, M.; Khan, A.Q. D-limonene suppresses Doxorubicin-induced oxidative stress and inflammation via repression of COX-2, iNOS, and NF- κ B in kidneys of Wistar rats. *Exp. Biol. Med.* 2014, 239, 465-476.
41. Ilesanmi OB, Atanu OF, Odewale TT, Adeogun E, Nnaemeka CB, Alaneme CU, Ogonye D, Ogbonannya JC. Effect of a Phytonutrient-Rich Product and Administration Time on Cyanide-Induced Cardiotoxicity. *Trop J Nat Prod Res.* 2020; 4(7):304-309.
42. Adikwu E, Ebinyo NC, Benalayefa O. Protective Effect of Lycopene against Tamoxifen-Induced Hepatotoxicity in Albino Rats. *Biomedical and Biotechnology Research Journal* 2020, 4 (1): 69-75
43. Haghhighipour S, Soltan R, Anjomsho A. The protective effect of lycopene supplement against vancomycin-induced nephrotoxicity; a randomized double-blind placebo-controlled clinical trial. *J Renal Inj Prev.* 2020; 9(4): e32.
44. Morikawa T, Imura K, Akagi Y, Muraoka O, Ninomiya K. Ellagic acid glycosides with hepatoprotective activity from traditional Tibetan medicine *Potentilla anserina*. *J Nat Med* 2018; DOI 10.1007/s11418-017-1137-y
45. Khan SI, Begum M, Chowdhury R, Rahman M, Asaduzzaman M. Synergistic Hepatoprotective Interaction between α -Tocopherol and Ascorbic Acid on Paracetamol Induced Liver Damage in Rats. 2020 doi:10.20944/preprints202006.0122.v1
46. Abdel-Daim MM, Abushouk AI, Donia T, Alarifi S, Alkahtani S, Aleya L, Bungau SG. The nephroprotective effects of allicin and ascorbic acid against cisplatin-induced toxicity in rats. *Environmental Science and Pollution Research* <https://doi.org/10.1007/s11356-019-04780-4>
47. Ankara PJ & Sabina EP. Pre-treatment with Beta Carotene Gives Protection against Nephrotoxicity Induced by Bromobenzene via Modulation of Antioxidant System, Pro-inflammatory Cytokines and Pro-apoptotic Factors. *Applied Biochemistry and Biotechnology*, 2019, <https://doi.org/10.1007/s12010-019-03111-0>
48. Avais M, Khan MS, Khan MA, Ashraf K, Hassan Z, Hameed S & Khan JA. Histopathological changes induced in liver, kidney, heart and pancreas of rabbits by prolonged oral cyanide exposure. *Pak. J. Pharm. Sci.*, 2018. 31 (5): 1797-1803

Peer-review

External peer-review was done through double-blind method.

Article History

Received: 12 November 2020

Reviewed & Revised: 13/November/2020 to 20/December/2020

Accepted: 21 December 2020

Prepared: 26 December 2020

Published: January 2021

Publication License



This work is licensed under a Creative Commons Attribution 4.0 International License.

General Note



We recommended authors to print article as color digital version in recycled paper. Discovery Scientific Society will not provide any prints for subscription.