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Research article

Protective Effects of Quercetin on Hepatotoxicity Induced by Cyanide in Male Wistar Rats

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ABSTRACT

Increased generation of reactive oxygen species has been reported during cyanide exposure, and quercetin, a flavonoid present in onions, has been proven to protect against it. Following sub-acute cyanide exposure, the protective effect of quercetin was investigated in the livers of rats in this study. Thirty male Wistar rats were grouped into 5 groups (n=6). Group 1 was administered conoil (control). Groups 2, 3, 4, and 5 were administered 7mgKCN/kgbwt/day, 60mg quercetin/kgbwt/day, 60mg Quercetin/kgbwt/day + 7mgKCN/kgbwt/day, and 600mg $Na_2S_2O_3$/kgbwt/day+ 7mgKCN/kg bwt/day respectively for 2 weeks. Groups 4 and 5 were pre-administered with 60 mg Quercetin/kgbwt/day and 600 mg Na2S2O3/kgbwt/day respectively for 2 weeks. Activities of enzymes; Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and Gamma-glutamyltransferase (GGT) in serum were measured as indicators of liver function. Liver malondialdehyde (MDA) and antioxidant parameters were assessed as indices of oxidative stress. When cyanide-treated rats were compared to control rats, serum ALT, AST, GGT, and liver MDA were considerably higher. Antioxidant parameters decreased significantly as a result of this. When quercetin and $Na_2S_2O_3$ were given together, the liver function indices, liver MDA, and antioxidant markers all improved. Finally, the findings imply that quercetin protects the liver against cyanide-induced oxidative stress. These might be linked to an increase in the antioxidant state of the liver in cyanide-exposed rats

Keywords: *Quercetin, Sodium thiosulphate, Cyanide, Malondialdehyde, Hepatic toxicity*

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INTRODUCTION

Cyanides, a broad class of chemicals containing the extremely reactive cyanide anion (CN–), are created anthropogenically and naturally (ATSDR, 2014). Potassium cyanide, sodium cyanide and gaseous hydrogen cyanide are the most frequent cyanide compounds found in the environment, with the latter being the most prevalent type found in the air (Boron, 2006). The cyanide ion or the cyanogen radical (CN) in a chemical is referred to as cyanide. During the course of industrial use, cyanides may be discharged into the environment. The mining sector is an example of such an industry (Bennun, 2013). The most prevalent source of cyanide exposure is from incomplete combustion products of nitrogen-containing organic polymers from Smoke or vehicle exhaust (Gigengack, *et al*., 2020). The Agency for Toxic Substances and Disease Registry (ATSDR), 2014, found that many plant species have cyanogen glycosides (cyanide attached to sugar molecules) that might emit hydrogen cyanide when biodegraded or consumed. A considerable amount of cyanogen glycosides may be found in the cassava root (tapioca), an important dietary staple in tropical areas. As a result, additional processing is required to limit the risk of toxicity (Bolarinwa *et al*., 2016).

Several studies show that cyanide exposure leads to an increase in the generation of oxygen-free radicals. It also causes a considerable drop in the activity of superoxide dismutase and catalase, as well as antioxidant vitamins, in rabbit lenses and retinas (Okolie & Osobase, 2005). In the BHK-21 (baby hamster kidney) cell line, cyanide has also been shown to decrease GSH levels (Bhattacharya *et al*., 1999).

The key detoxifying enzyme rhodanese detoxifies cyanide, like other chemical products of metabolism, mostly in the liver (Tayefi-Nasrabadi & Rahmani, 2012). The major pathway of cyanide excretion is rhodanese detoxification, which leads to the creation of thiocyanate (SCN), that can be expelled in the urine (Ola-Mudathir and Maduagwu., 2014). Compared to cyanide and its metabolic metabolites, cyanate (CNO) and isocyanate, thiocyanate has a lower intrinsic toxicological risk. Sodium thiosulfate is a key component in the treatment of cyanide poisoning. It provides sulphur for the cyanide detoxification enzyme rhodanese. Antidotes

including sodium thiosulfate and hydroxycobalamin have been useful in treating cyanide poisoning (Reade *et al*., 2012; Petrokovics *et al*., 2015).

Because the liver is implicated in cyanide poisoning, oxidative stress caused by cyanide may have a greater impact on this organ. Previous research has demonstrated that onion can be utilized as an antidote to cyanide poisoning, by boosting antioxidant enzymes thereby lowering oxidative stress in the kidneys of cyanide-exposed rats.

The most prevalent flavonoid in onion is quercetin, a flavonol type of flavonoid found in plants. It's well-known for its antioxidant properties (Maroon, 2009). Quercetin can protect PC-12 neurons from oxidative stress caused by toxins and peroxides in vitro at concentrations of 25-100 M. (Sasaki, 2003). At concentrations as low as 0.5uM of quercetin-3-glucuronide, quercetin has been shown to protect against some ROS (Shirai, 2006).

The goal of this study is to investigate the antioxidant impact of quercetin on cyanide-induced toxicity in rats' livers, as well as compare quercetin's protective effect to that of sodium thiosulphate.

MATERIALS AND METHODS

Chemicals: Sodium Carbonate (Na_2CO_3), Sodium hydroxide (NaOH), Copper Sulphate ($CuSO_4$), Potassium Sodium tatartrate$C_4H_{12}KNaO_{10}$), Folin-Ciocalteau reagent, Epinephrine, Sodium hydrogen Carbonate decahydrate ($Na_2CO_3.10H_2O$), Sodium carbonate (anhydrous), 1-Chloro-2,4-dinitrobenzene (CDNB), Ethanol (C_2H_5OH), Reduced Glutathione (GSH), Dipotassium hydrogen phosphate (K_2HPO_4), Potassium dihydrogen phosphate (KH_2PO_4) Disodium hydrogen phosphate Dodecahydrate ($Na_2HPO_4.12H_2O$), Sodium dihydrogen phosphate dihydrate ($NaH_2PO_4.2H_2O$), Ellman's Reagent (5,5 –Dithiobis- (2-nitrobenzoate) DTNB), Sulphursalicyclic acid ($C_7H_6S.2H_2O$), Potassium heptaoxodichromate ($K_2Cr_2O_7$), Hydrogen Peroxide (H_2O_2), Glacial acetic acid, Hydrochloric acid (HCl) Trichloroacetic acid (TCA) and 2-thiobarbituric acid (TBA) were purchased from Sigma-Aldrich Chemical, United Kingdom. ALT, AST, and GGT kits from Randox Laboratory, United Kingdom.

Animals: For this experiment, researchers employed a colony of 30 male rats from the University of Ibadan's Central Animal House. Water and food pellets were available to all the animals, who were kept at a comfortable temperature. Before the experiments began, the animals were given two weeks to become used to their new surroundings. The NIH publication/85-23, amended in 1985, contains the International Ethical Standards for the Care and Use of Laboratory Animals and was used to guide the conduct of all animal research.

Experimental Design: Thirty Wistar rats (weighing between 180-200g) were divided into five groups of six rats per group. Group 1 served as control and received 0.4ml/day conoil. Group 2 was treated orally with 0.4ml of potassium cyanide (7mg/kg bwt). Group 3 was treated orally with 0.4ml of quercetin (60 mg/kg bwt/day). Group 4 was treated orally with 0.4 ml quercetin (60 mg/kg bwt/day) and 0.4 ml potassium cyanide (7mg/kg bwt/day). Group 5 was treated orally with 0.4ml of $Na_2S_2O_3$ (600 mg/kg bwt/day) + 0.4ml of potassium cyanide (7mg/kg bwt/day). Groups 4 and 5 were pre-administered with 0.4ml of 60 mg quercetin/kg bwt/day, 0.4ml of $Na_2S_2O_3$ (600 mg/kg bwt/day) respectively for 2 weeks. The animals were observed daily and weighed at intervals of 2 days for two weeks. At the end of the experiments, the animals were fasted overnight and sacrificed by cervical dislocation. Blood samples were collected into plain tubes and centrifuged at 3000g for 10 minutes to obtain serum for biochemical analysis. The livers were removed immediately and rinsed in 1.15% ice-cold KCl. The dry weight of the liver was taken using diagital weighing balance (OHAUS electronic weighing balance, Model 031-02-00.0D34). They were then homogenized in phosphate buffer (pH 7.4) and centrifuged in a cold centrifuge (4^0C) at 10,000g for 10 minutes to obtain the post-mitochondrial fraction for evaluation of oxidative stress and antioxidant enzymes. The tissue sample for histology was fixed in 10% saline formalin.

Biochemical analysis: Following treatments, the markers of liver function - ALT and AST - were assayed according to the method of Reitman and Frankel (1957), while GGT was assayed according to the method described by Tietz and Bsaunders (1987), using commercially available Randox® (Randox Laboratory, United Kingdom) ALT, AST, and GGT kits respectively according to manufacturer manual. Oxidative stress parameters were assessed using established methods as follows.

Determination of Oxidative Stress (Lipid Peroxidation Assessment): The thiobarbituric acid reactive compounds (TBARS) generated during lipid peroxidation were measured to assess lipid peroxidation. This was done in accordance with Buege and Aust's techniques (1978).

Determination of Catalase Activity: The activity of catalase was measured using Sinha's technique (1971). This approach is based on the fact that when dichromate in acetic acid is heated in the presence of H_2O_2, it is reduced to chromic acetate, with perchromic acid as an unstable intermediate. Colorimetrically, the chromate acetate generated is detected at 570-610 nm. The presence of dichromate in the test mixture does not affect the colorimetric measurement of chromic acetate since it has no absorbance in this area. For various durations of time, the catalase preparation is allowed to split H_2O_2. The reaction is halted at a certain time by the addition of dicromate acetic acid mixture, and the residual H_2O_2 is estimated by colorimetrically measuring chromic acetate after the reaction mixture has been heated.

Determination of Superoxide Dismutase (SOD) Activity: Misra and Fridovich's technique were used to assess SOD activity (1972). The SOD test is based on the capacity of superoxide dismutase to limit the autooxidation of adrenaline at pH 10.2. The oxidation of adrenaline to adrenochrome is known to be caused by superoxide anion (O_2) produced by the xanthine oxidase process. With rising pH and likewise with increasing adrenaline content, the quantity of adrenochrome

synthesized per superoxide anion increased. These findings led to the hypothesis that adrenaline auto-oxidation occurs via at least two mechanisms, one of which is a free radical chain reaction involving superoxide radicals that might be blocked by SOD.

GST: The activity of glutathione-S-transferase in serum was measured using the Habig *et al*. technique (1974). With 1-chloro-2, 4-dinitrobenzene as the second substrate, glutathione-S-transferase activity is quite high; as a result, the traditional test for glutathione-S-transferase activity uses 1-chloro-2, 4-dinitrobenzene as the substrate. When this substrate was conjugated with reduced glutathione, its maximum absorption wavelength shifted to a longer wavelength. The increase in absorption at the new wavelength of 340 nm allows for direct enzymatic reaction measurement.

GSH: To calculate the amount of reduced glutathione (GSH), the technique of Beutler *et al*., (1963) was used. In most cases, the reduced form of glutathione contains the majority of cellular non-protein sulfhydryl groups. This approach is based on the production of a rather stable yellow colour when sulfhydryl substances are treated with 5,5 – dithiobis – (2-nitrobenzoic acid) (Ellman's reagent). Ellman's reagent reacts with reduced glutathione to produce 2 – nitro-5-thiobenzoic acid, a chromophoric compound having a molar absorbance of 412 nm. The absorbance at 412 nm is proportional to the reduced GSH concentration.

Determination of tissue protein level: Lowry *et al*'s method of protein estimation was used. Lowry utilized the Folin-Ciocalteau reagent to measure protein concentrations. The reagent identifies tyrosine residues in their most basic form due to their phenolic composition. A protein in solution reacts with the Folin reagent in two stages: Cu^{++} reaction in an alkaline medium and phosphomolybdic-phosphotungstic reagent reduction by the Cu^{++} protein complex. The reduced complex produces a blue solution with absorption in the visible spectrum's red region (600–800 nm).

Histology: Hematoxylin and Eosin (H&E) staining methods were used to perform kidney histology. The tissues were fixed in 10% buffered formalin and processed for paraffin wax embedding as usual. Using standard H and E staining, 5 m thick sections were prepared and histological alterations were assessed. A light microscope was used to examine the sections, and a photomicrograph was taken.

Statistical Analysis: The data was given as Mean ± SEM, with Anova used to compare the findings, and Tukey's posthoc test used to compare the means of the different treatment groups. The significance level was set at $P<0.05$. GraphPad Prism Version 5.0 for Windows was used to do the data analysis. (GraphPad® Software, San Diego, CA, USA)

RESULTS

Relative liver weight and liver protein levels: The relative liver weights and liver protein levels for the cyanide-treated group were not significantly different from the control, and other treated groups (Table1).

Markers of liver damage: Illustrated in Table 1 are the results of serum ALT, AST, and GGT. Treatment with cyanide significantly ($p<0.001$) raised serum ALT and AST when compared to control, however, their level was significantly reduced with the co-administration of quercetin and $Na_2S_2O_3$ ($p<0.001$). Also, treatment with cyanide significantly increased serum GGT ($p<0.01$) relative to the control, and this was reduced significantly with the co-administration of quercetin and $Na_2S_2O_3$; ($p<0.05$) and ($p<0.01$) respectively.

Table 1:
Effects of quercetin on relative organ weight, liver protein, serum ALT, AST and GGT

Groups	Relative organ wt	S_{ALT} (IU/l)	S_{AST} (IU/l)	S_{GGT} (IU/l)	Liver protein (mg/g tissue)
1	3.509±0.210	71.543±0.654	60.55±0.712	3.214±0.260	262.215±13.03
2	3.954±0.4310	3.067± 0.320*	121.117±2.890 *	5.68±0.930*	247.138±24.11
3	3.432± 0.420	79.698±0.450*#	65.88±1.1863.	16±.254	283.400±14.70
4	3.585± 0.280	95.857±0.046*#	73.084±1.600#*	3.590±0.180#	204.108±10.60
5	3.60± 0.320	90.652±0.421*#≠	70.00±1.230*#	3.20±0.162#	242.60±9.20

*1=Control, 2=Cyanide only, 3=Quercetin, 4=Cyanide+ 60mg Quercetin, 5=Cyanide+Sodium thiosulphate, S=Serum *p< 0.05 (compared to control),#p<0.05(compared to cyanide),≠p<0.05(compared to Cyanide+60mg Quercetin)*

Table 2:
Effects of quercetin on liver MDA, GSH, GST, SOD and CATALASE levels

Groups	MDA(µg/g tissue)	GSH (µg/g tissue)	GST(nmol/mg protein)	SOD (U/mg protein)	Catalase (Katf)
1	0.689±0.102	6.80±0.460	0.465±.056	3.452±0.268	0.2014±0.006
2	2.001±0.35*	4.84±0.100*	0.187±0.030*	2.200±0.087*	0.0704±0.008*
3	0.830±0.087	7.20±0.720	0.445±0.046	3.23±0.207	0.176±0.004
4	1.124±0.116#	5.12±0.540	0.404±0.0207	3.213±0.143#	0.129±0.009#*
5	1.100±0.133 #	8.5±0.40 #≠	0.620±0.032#≠	2.80±0.150	0.138±0.006#*

*1=Control, 2=Cyanide only, 3=Quercetin, 4=Cyanide+ 60mg Quercetin, 5=Cyanide+Sodium thiosulphate, S=Serum *p< 0.05 (compared to control), # p<0.05(com*

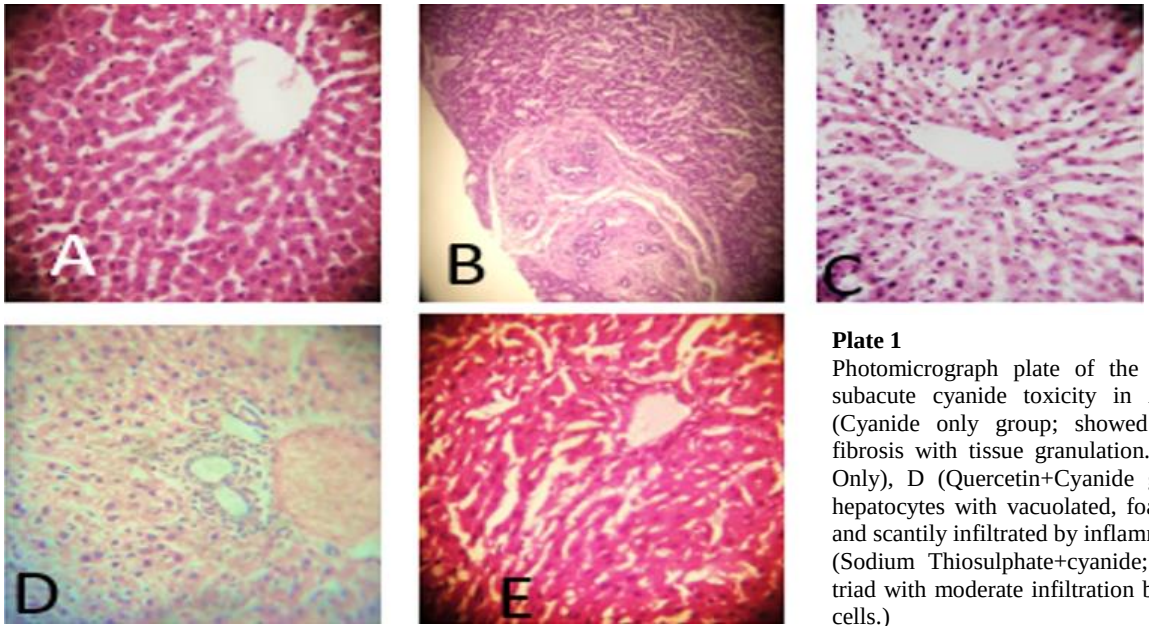

Plate 1
Photomicrograph plate of the liver following subacute cyanide toxicity in A (control), B (Cyanide only group; showed focal area of fibrosis with tissue granulation.), C (Quercetin Only), D (Quercetin+Cyanide group; showing hepatocytes with vacuolated, foamy cytoplasms and scantily infiltrated by inflammatory cells.), E (Sodium Thiosulphate+cyanide; showed portal triad with moderate infiltration by inflammatory cells.)

As shown in Table 2, treatment with cyanide significantly ($p<0.001$) raised the malondialdehyde level when compared to the control, however, the activities of the SOD, GST and catalase were reduced significantly ($p<0.01$). The level of GSH was also significantly reduced by treatment with cyanide ($p<0.01$) when compared to the control. However, co-administration with quercetin and $Na_2S_2O_3$ significantly reduced ($p<0.01$) the MDA level. The activities of GST and catalase were significantly raised by the co-administration of quercetin and $Na_2S_2O_3$ ($p<0.05$). In addition, SOD activities were significantly increased by co-administration of quercetin with cyanide ($p<0.05$). $Na_2S_2O_3$ co-administration also increased the level of GSH ($p<0.001$).

Histopathology

The photomicrograph of the liver of animals given cyanide revealed localized regions of fibrosis and tissue granulation (figure 1b), whereas animals given quercetin had only vacuolated, foamy cytoplasms that were sparsely invaded by inflammatory cells (figure 1d). The portal triads of animals given Na_2S2O_3 were considerably invaded by inflammatory cells (figure1e). Figures 1a and 1c demonstrate normal photomicrographs of liver cells in the control and quercetin-only groups, respectively.

DISCUSSION

The major function of cyanide is to block the cytochrome c oxidase enzyme, which has hazardous consequences (Kruse *et al*., 2020). This activity affects oxygen absorption and consumption, leading to partial or full oxidative metabolism stoppage over time, a condition known as histotoxic hypoxia (Jaszczak *et al*., 2017). The impact of cyanide on this enzyme causes the production of free radicals such as superoxide anion, which causes lipid peroxidation (Manoj *et al*., 2020). The results of this investigation revealed that animals treated with just cyanide had higher levels of malondialdehyde (a lipid peroxidation product), as well as lower activities of the catalase, SOD, and reduced glutathione (non-enzymatic antioxidant). In the lens and retina of rabbits, cyanide has been demonstrated to cause comparable decreases in SOD, catalase, and antioxidant vitamins, according to Kadiri and Asagba (2019).

Most illness disorders are thought to have an underlying cause of oxidative stress. An increased reactive oxygen species (ROS) or a reduction in the antioxidant defense system is the most common symptom. Tissue damage and cell death result from an autocatalytic chain of metabolic stress which may then amplify and spread the oxidative stress, leading to increased free radicals ($OH^{\cdot}$, $O^{2-\cdot}$, H_2O_2) generation and antioxidant depletion (Tan *et al*., 2018).

Reduced synthesis of this vital biological component as a result of reduced availability of Sulphur-containing amino acids might be one reason for the lower glutathione content in the liver. The use of sulphur-containing amino acids by rhodanese and mercaptopyruvate sulphur transferees (MPST) enzymes for cyanide detoxification is well known (Chaudhary *et al*., 2012). The limiting amino acid in glutathione formation is a sulphur-containing amino acid cysteine, required for the detoxification of cyanide in the liver (Machingura *et al*., 2016). As a result, glutathione synthesis and cyanide detoxification routes may compete for sulphur-containing amino acids.

However, co-administration of quercetin and $Na_2S_2O_3$ resulted in the reduction of malondialdehyde levels and a rise in the antioxidant enzymes SOD, catalase, and GST for quercetin co-administration, and an increase in the antioxidant enzymes GST, catalase, and the non-enzymatic antioxidant GSH for $Na_2S_2O_3$ co-administration, indicating that these treatments reduced oxidative stress. Recent studies have shown that quercetin obtained from the diet improves antioxidant defense via upregulating antioxidant enzymes (Bayliak *et al*., 2016). It has also been reported that the natural dietary antioxidant quercetin may protect rats from cadmium-induced toxicity and oxidative stress (Wang *et al*., 2013); thus, the quercetin therapy may have shielded the rats against the

deadly effects of cyanide in this study, by scavenging reactive oxygen species generated by cyanide according to the researchers.

The sulphane sulphur content of $Na_2S_2O_3$ might explain the large rise in GST and GSH levels seen in animals co-administered with it. Sulphane sulphur compounds have a labile, very reactive sulphur atom in a reduced oxidation state with a covalence of 0 or -1, covalently bonded to another sulphur atom. These chemicals have antioxidant and protective characteristics, as well as being involved in the control of protein functions. They scavenge free radicals and boost antioxidant enzyme activity such as superoxide dismutase, glutathione reductase, and glutathione peroxidase (Mates *et al*., 2012). GSH levels have been demonstrated to be increased by organosulphur compounds containing sulphane sulphur, such as diallyl sulphide (Raza and John, 2015). Since the detoxification system performs extraordinarily well with high GST activity, the protection provided by $Na_2S_2O_3$ on animals exposed to cyanide might be attributable to the antioxidant actions of GST and GSH (Kenan *et al*., 2013). GST conjugates potentially harmful chemicals with GSH to form innocuous metabolites that are quickly removed from the cell.

Rhodanese's actions result in the creation of thiocyanate (SCN). Thiocyanate (SCN) has a lower intrinsic toxicological risk than cyanide, cyanate (CNO), or isocyanate, but it is linked to goitre pathogenesis (Dhas *et al*., 2011). The growth of advanced atherosclerotic plaques within coronary arteries is linked to serum SCN, which is favourably connected with lipid peroxidation (Hasuike *et al*., 2004). Quercetin does not detoxify cyanide via the rhodanese route, and hence does not result in the creation of thiocyanate, according to our research. As a result, quercetin supplementation might be a better antidote than $Na_2S_2O_3$.

Following cyanide exposure, the levels of AST, ALT, and GGT were observed to be elevated in the current investigation. Typically, drug-induced hepatotoxicity is measured primarily by detecting GGT and aminotransferase activity in the serum, plasma, or liver. A rise in the values of all three indicators is linked to and affirms liver damage in general (Mohd *et al*., 2013),

The kidneys and liver contain GGT, which is a membrane-bound enzyme. Hepatic GGT has direct access to the bloodstream, whereas renal GGT is eliminated in the urine. As a result, the liver is responsible for the majority of serum GGT activity in the blood. GGT is released into the bloodstream because of cellular damage, cholestasis, or excessive production (Kim, 2018). The increased activity of these enzymes in the cyanide-treated animals might thus be a sign of harm to the liver cells. Oyeyemi *et al*., (2012) showed an increased enzyme activity in the liver of rats fed a cassava diet, which is consistent with these findings. Dhas *et al*., (2011) found that when women were exposed to HCN, their AST enzyme activity increased significantly. The impact of cyanide on these enzymes was greatly diminished when $Na_2S_2O_3$ or quercetin was given together with it. The reduction of liver enzymes in the blood might indicate quercetin and $Na_2S_2O_3$'s hepatoprotective effects. In rats exposed to cyanide, $Na_2S_2O_3$ has been demonstrated to lower ALT and AST activity (Ojeniyi *et al*., 2019). Neha and Ramtej (2012) discovered that quercetin reduces toxicant-induced liver damage by reducing the activity of certain serum enzymes, and they also stated that quercetin functions as a galactosylated liposome against liver damage.

Histopathological examinations were used to further examine the effect of cyanide on organs in this study. The histology of the livers of rats exposed to cyanide revealed only pathomorphological changes, such as cirrohsis and severe fibrosis. Portal triaditis occurs when inflammatory cells invade the portal triad. These findings show that cyanide has a negative impact on liver cells. These findings matched those of Rosly *et al*. (2010), who found tissue necrosis in sheep and other ruminant animals administered 7 mg/kg HCN. The histology of the liver of rats given unprocessed cassava was likewise destroyed, according to Oyeyemi *et al*., (2012). By minimising the morphological alterations caused by cyanide, a combined therapy of 60 mg/kg quercetin and 600 mg/kg $Na_2S_2O_3$ provides modest hepatoprotection. At 60 mg/kg quercetin, the liver revealed sparse infiltration of hepatocytes with vacuolated and foamy cytoplasm, but no portal triaditis, whereas co-administration with $Na_2S_2O_3$ showed considerable inflammatory cells infiltration surrounding the vessel, indicating mild portal inflammation of small intestine, pancreas etc. This shows that periportal hepatocytes may get the highest dosage of toxins, while toxin clearance in the periportal region may protect cells farther down the sinusoid. One of the primary mechanisms of cyanide-induced liver damage is the cyanide free radicals derived lipid peroxides. Thus, quercetin and $Na_2S_2O_3$'s antioxidant action or prevention of free radical formation may give protection against cyanide-induced hepatopathy.

In conclusion, the findings imply that Quercetin's antioxidant effects, which are equal to those of $Na_2S_2O_3$, may protect against cyanide-induced toxicity without the development of thiocyante, a potentially harmful molecule. As a result, employing quercetin or antioxidant-rich plants to guard against cyanide-induced toxicity may be preferable to using $Na_2S_2O_3$.

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