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Biomarkers of Oxidative Stress and Optic Neuropathy in Wistar Albino Rats Fed with High-Cyanide Content Garri-An Experimental Study

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Abstract
Background*: Cassava tuber crop is a staple food in Nigeria andis utilized in various forms such as garri. Cassava root contains linamarin, a cyanogenic glycoside that is easily hydrolyzed to release cyanide which is toxic to most body tissues especially the nervous system sometimes leading to optic neuropathy and visual impairment. Cyanide has been shown to cause oxidative stress and damage in a number of biological systems.*
Aim*: The aim of is this study is to find out the dynamics of the oxidative markers implicated in optic neuropathy induced by high-cyanide garri feedsin Wistar albino rats.*
Methodology*: 27 Wistar Albino Rats were studied between March and June 2022. The rats were divided into 8 experimental and control groups of 3 animals each. The experimental groups were fed with garri with varying cyanide concentrations and durations. Serumglutathione, catalase,superoxide dismutase, malondialdehyde and reactive oxygen specieswere assessed byMisra and Fridovich and Cohen, Dembiec, and Marcus methods.Pre- and post- experiment parameters were compared using Independent-T and Chi Square testsDifferences were considered to be statistically significant at $p < 0.05$.*
Results*: Levels of serum anti-oxidative stress markers in the rats exposed to high level cyanide were reduced significantly and remained within normal limits in the control group ($p < 0.05$).The animals fed with higher concentration of cyanide had more obvious optic neuropathy with decrease in their anti-oxidative stress biomarkers ($p<0.005$) while animals in the control group maintained normal oxidative stress parameters.*
Conclusion: *There is decreasedanti-oxidative stress markers andincreased levels of ROS-oxidative marker in the consumption of garri with high cyanide content. The public should be educated appropriately on the best way to process cassava into garri for human consumption so as to reduce the cyanide content and thereby prevent optic neuropathy.*

Keywords: *Oxidative stress markers, Cyanide in garri, Wistar Albino rats*

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I. Introduction

Cyanide is a potent cytotoxic compound known to humans and animals. Older cultivars of cassava contain much higher cyanide with its attended neuro toxicity on consumption without adequate processing [1]. Currently, improved varieties of cassava with superior genotype, tolerant/disease-resistantand low cyanide content are being grown by many farmers in Nigeria[1]. However, in Rivers State, many high-cyanide content cassava varieties are still been grown. The quantity of cyanide available for human consumption in garri (a staple food in most parts of Nigeria) depends on the cultivar and to a large extent on the method of its processing.Longer period of fermentation reduces the cyanide content [1]. The commonest methods of processing cassava roots into garri for human consumption in Rivers State are 24-hour fermentation, 48-hour fermentation with or without the addition of fresh red palm oil. Whatever the method of preparing cassava into garri for human consumption, the Nigerian Industrial Standard recommendsmaximum cyanide content of 20 mg/kg in garri [2,3].

Besides acute cyanide poisoning, intake of cassava product containinghigh cyanide could result inoptic neuropathy, impaired body growth, various forms of neurological defects, thyroid disorders, as well as pathological effects on different tissues [4-6].

The underlying mechanism by which cyanide acts injuriously on tissues is not clear, however, some researchers have suggested that oxidative stress may be implicated in harmful effects of cyanide poisoning [7,8].

Cyanide has hitherto been shown to cause oxidative stress and damage in a number of biological systems. Cyanide-induced oxidative stress may be due to increased levels of reactive oxygen species (ROS) and nitric oxide [9] as well as suppression of antioxidant systems such as superoxide dismutasecatalase [10] and mitochondrial function [11] with resultant alteration in the dynamics of the biomarkers of oxidative stress (catalase, malondialdehyde(MDA), and superoxide dismutase [12,13].

Ingestion of high cyanide directly or by contaminated feeds significantly increased the lipid peroxidation in all the organs but with the severest effect in the liver and the nerve tissues. Though enhanced production of reactive oxygen species during stress can pose a threat to cells, animals have an in-built mechanism to counteract and scavenge the reactive oxygen species. The scavenging mechanisms include the presence of antioxidant enzymes: superoxide dismutase (SOD) and catalase. Under natural conditions, these internal antioxidant enzymes eliminate reactive oxygen species (ROS), providing protection for the cells.

Damaging or inhibiting just one of these enzymes-antioxidants could significantly affect the defensive mechanisms. When an imbalance between free radicals and antioxidants occurs in favour of free radicals, an oxidative stress will be induced which can lead to chronic permanent cellular damage [14].

Increased generation of ROS has been implicated in the pathogenesis of several diseases and in the toxic effects of a wide variety of compounds [15].Decrease in the activity of SOD also portends reduction in the capacity of the animals to handle reactive oxygen species [16].

Catalase is an important enzyme that protects a living system against oxidative stress, by scavenging hydrogen peroxide produced by superoxide dismutase. This it does by converting it to less-reactive gaseous oxygen and water molecules [17] and a reduction in the activity of this enzyme in the organs may be due to the inhibitory effect of cyanide on the enzyme. The concomitant decrease of SOD and catalase in the tissues of the cyanide-exposed animal confirms that both enzymes are linked functionally and as suggested by other investigators have shown that they work in tandem [14,18].

According to Fulda et al., cells respond histopathologically to toxic insult by degeneration, proliferation, inflammation, and repair [19].

This work will serve as a transitional experimental study in considering the biomarkers of oxidative stress and their implication in optic neuropathy,highlighting the role of the various common processing methods in Rivers State that yields the optimal concentration of cyanide tolerable for human consumption.

Materials and Methods

This was an experimental study on 27male Wistar Albino Ratsthat were fed with differently processed high level cyanide cassava (higher than FAO/WHO recommended level) into garri (of predetermined varying concentrations of cyanide for different frequencies and duration (once and twice daily for 30 days and 60 days). The animals were put into 9 groups consisting of 3 rats each.

Group 1 - treated with 24-hr fermented cassava daily for 30 days, Group 2- treated with 24-hr fermented cassava twice daily for 30 days, Group 3- treated with 24-hr fermented cassava daily for 60 days, Group 4- treated with 24-hr fermented cassava twice daily for 60 days, Group 5- treated with 48-hr fermented cassava daily for 30 days, Group 6- treated with 48-hr fermented cassava twice daily for 30 days, Group 7- treated with 48-hr fermented cassava daily for 60 days, Group 8- treated with 48-hr fermented cassava twice daily for 60 days, Group 9 was the control group- treated with exclusively normal rat-feeds – "Grower Mash" (composed of crude protein -15.5%, fat -3.6%, crude fiber -4.6%, calcium -1.1%, phosphorus -0.4%, methionine -0.37%, lysine 0.75%, metabolizable energy -2550kcal/g) for the same number of days. Ingredients in the grower mash- cereals/grains, vegetable protein, premix (vitamin/minerals), essential amino acids, galt, antioxidants, prebiotics andanti-toxins.

The weight of fried garri for 30 and 60 days either once daily or twice daily was determined. The individual animal in each group was marked with permanent ink: on the head (HM), at the back (BK), and unmarked (UM) for identification and subsequent follow up.

Collection and processing fresh cassava roots

Fresh tubers of cassava from known heavy cassava producing and consuming communities in Rivers State, Nigeria: Etche, Omuma, Khana, Gokhana, Ikwerre, Emohua, Eleme, Tai, Oyigbo, Ahoada-East, Ahoada-West, Ogba/ Egbema/ Ndoni, Port Harcourt and Obio-AkporLocal Government Areas of Rivers state were purchased from the open markets and analyzed for their cyanide contents.

Tubers of cassava with high content of cyanide (> 400mg HCN/kg as recommended by FAO) were processed using the usual most popular methods in Southern Nigeria and fed the rats for 30 and 60 days in their various groups. The popular durations of fermentation and processing methods used in the various communities in Rivers State were: 24-hour, 48 hours, fermentation; with and without- red palm oil additive. The commonest frequencies of garri consumption (once and twice daily were also employed to treat the animals).

Determination of cyanogenic glycoside content in the various varieties of cassava samples

The Cyanogenic glycoside of the purchased cassava roots was determined using alkaline picrate method of Onwuka (2005). Ground sample (5.0 g) was weighed and dissolved in 50 cm3 distilled water. The cyanide extraction was allowed to stay overnight and then filtered.

Preparation of cyanide standard curve: Different concentrations of KCN solution containing 0.1 to 1.0 mg/mL cyanide were prepared. To 1 mL of the sample filtrate and standard cyanide solution in test tubes, 4 mL of alkaline picrate solution (1 g of picrate and 5 g of Na_2CO3 in 200 cm3 distilled water) was added and incubated in water bath for 15 min. After colour development, the absorbance was read at 490 nm against a blank containing only 1 mL distilled water and 4 cm3 alkaline picrate solution. The cyanide content was extrapolated from the cyanide standard curve**.**

Table 1: Results of the cyanide contents of the various raw cassava cultivars

Samples	mg CN^-/kg dry weight of cassava	FAO/WHO recommended level (mg CN^-/kg dry weight of cassava)	Percentage Increase (%)
1	1286.00	15 - 1000	28.6
2	2486.39		148.6
3	1791.80		79.2
4	1204.07		20.4
5	1734.81		73.4
6	1417.79		41.8
7	2386.0		133.0

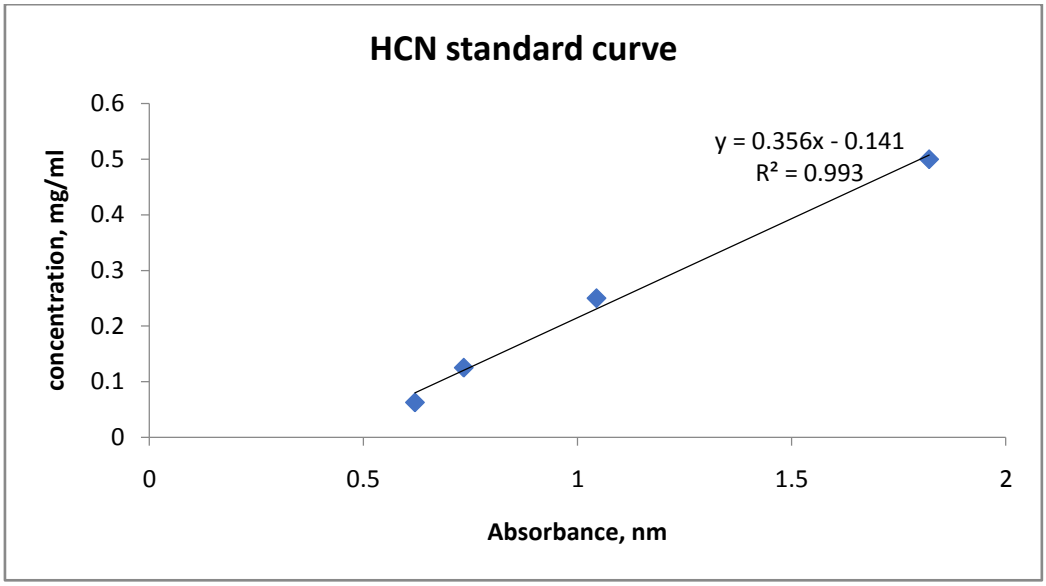

Figure 1: Determination of cyanide contents of various cassava processing methods

Cassava species (Sample 7 above) having the highest cyanide content (2336.79mg CN^-/kg dry weight of cassava) were processed using different durations of fermentation and processing methods that are popularly used in the various communities in Rivers State, viz: 24-hour, 48 hours, fermentation; with and without- red palm oil additive.

Experiment on rats

A total of 27 rats (3 rats pergroup of 8)and a control group of 3 rats were fed with the determined cyanide content for 30-days and 60-days. The control group was fed on normal rat-feeds – "Grower Mash"

The quantity of cyanide in cassava-product consumed by an average adult weighing approximately 70kg was determined and the equivalent in weight for the rats determined. For instance, if an average 70Kg adult consumes an average of 5 cups of garri/day (45units of cyanide) then 2kg rat was administered with 1.3 units of cyanide contained in the processed cassava (garri) in three divided doses/day. We ensured that the rat consumed all the measured-out quantity of garri before it was given any other meal for the day. At the end of specified period, the rats were sacrificed and examined for changes in the optic nerve.

Assessment of optic neuropathy in experimental rat subjects

Pre- and post- experimental optic nerve status of the rats were assessed clinically- fundoscopy of the optic disc, optical coherence tomography (OCT) analysis of the optic disc head and the histopathological analyses of the optic nerve head.

All the analyses were carried out in the analytical chemistry laboratory of the University of Port Harcourt. Histopathological sections were analyzed at the Histopathology laboratory of the University of Port Harcourt Teaching Hospital, while the clinical assessment was done at the ophthalmology department of the University of Port Harcourt Teaching Hospital.

Statistical Analysis:

The data obtained were entered into Microsoft Excel sheet, cleansed and later exported to IBM Statistical Package for Social Sciences (SPSS) version 25 software (SPSS) Inc; Chicago, IL, USA was employed for descriptive and Inferential statistical analyses Relevant data were presented in tables and charts. Statistical significance was performed using Chi-square and independent T-test. Statistical significance was set at $p \leq 0.05$.

II. Results:

The individual weight and mean group weight are presented in table 2. The mean weight of all the animals in the experimental group at the beginning of the experiment was 68.5gm and at the end of the experiment was 74.5 grams while the mean weight of the rats in the control group at the beginning of the experiment was 48.8 gm and at the end of the experiment was 120.2 grams [table 2].The difference in the mean weight of the rats in the various groups was statistically significant (p=0.000)

Table 2: Weight Dynamics of the 27Wistar Albino Rats in the Experimental Study

Group 1	Baseline (WK 0)	WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7	WK 8	Mean Weight (Grams)
Sub-group 1										
HD	71	76	73	82	85					79.0
BK	64	70	68	77	77					73.0
UM	50	48	47	53	58					51.5
Mean Grp Wt	61.6	64.6	62.6	72.3	73.3					67.8
Group 2										
HD	71	68	72	75	83					74.5
BK	65	64	66	71	81					70.5
UM	65	64	63	72	74					68.2
Mean Grp Wt	67.0	65.3	67.0	72.6	79.3					71.1
Group 3										
HD	60	60	61	67	73	79	86	91	106	77.9
BK	74	79	94	105	120	131	141	148	152	121.2
UM	73	99	81	99	106	111	119	122	131	108.5
Mean Grp Wt	69.0	79.3	78.6	90.3	99.6	107.0	115.3	120.3	129.6	102.5
Group 4										
HD	79	74	88	92	107	116	122	127	131	107.1
BK	70	71	79	82	98	104	113	115	130	99.0
UM	63	60	74	74	81	88	91	93	102	82.9
Mean Grp Wt	70.6	68.3	80.3	82.6	95.3	102.6	108.6	111.6	121.0	96.3
Group 5										
HD	74	79	77	79	88	98	102	109	112	93.0
BK	60	61	59	64	78	81	84	91	102	77.5

UM	68	72	74	77	87	98	101	107	121	92.1
Mean Grp Wt	67.3	70.6	70.0	73.3	84.3	92.3	95.6	102.3	111.6	85.0
Group 6										
HD	68	98	106	108	116					107.0
BK	72	74	77	79	89					79.7
UM	67	77	82	86	93					84.5
Mean Grp Wt	69.0	83.0	88.3	91.0	99.3					90.4
Group 7										
HD	63	76	74	81	87					79.5
BK	75	89	90	94	101					93.5
UM	77	75	63	80	88					76.5
Mean Grp Wt	71.6	80.0	75.6	75.0	92.0					83.2
Group 8										
HD	63	84	86	90	100	97	102	108	112	97.4
BK	73	78	82	83	98	91	93	100	115	92.5
UM	80	83	82	88	99	92	95	102	118	94.8
Mean Grp Wt	72.0	81.6	83.3	87.0	99.0	93.3	96.6	103.3	115.0	94.9
Mean weight at the start of Experiment =					Mean weight at the end of experiment =					
Group 9 (Control Group)										
HD	51	68	83	98	118	132	147	153	167	120.7
BK	49	74	92	96	116	118	124	126	130	109.5
UM	46	74	113	128	138	140	146	150	155	130.5
Mean Grp Wt	48.6	72.0	96.0	107.3	124.0	130.0	139.0	143.0	150.6	120.2
Mean weight at the beginning of Experiment = 48.6					Mean weight at the end of experiment =120.2					

Changes in the weights of Wistar Albino Rats in the Experimental and Control Groups

The individual weights as well as the mean weight of the 27 rats in this study, increased gradually from the first week to the 9th week of the experiment [Figure 2]. However, a slight reduction of weight in most of the animals were observed on the third and fourth weeks except the weight of animals in the control group. This observed difference was not statistically significant (p=0.092).

There was a steady increase in the weights of the animals in the control group throughout the 9 weeks of the study [Figure 3].

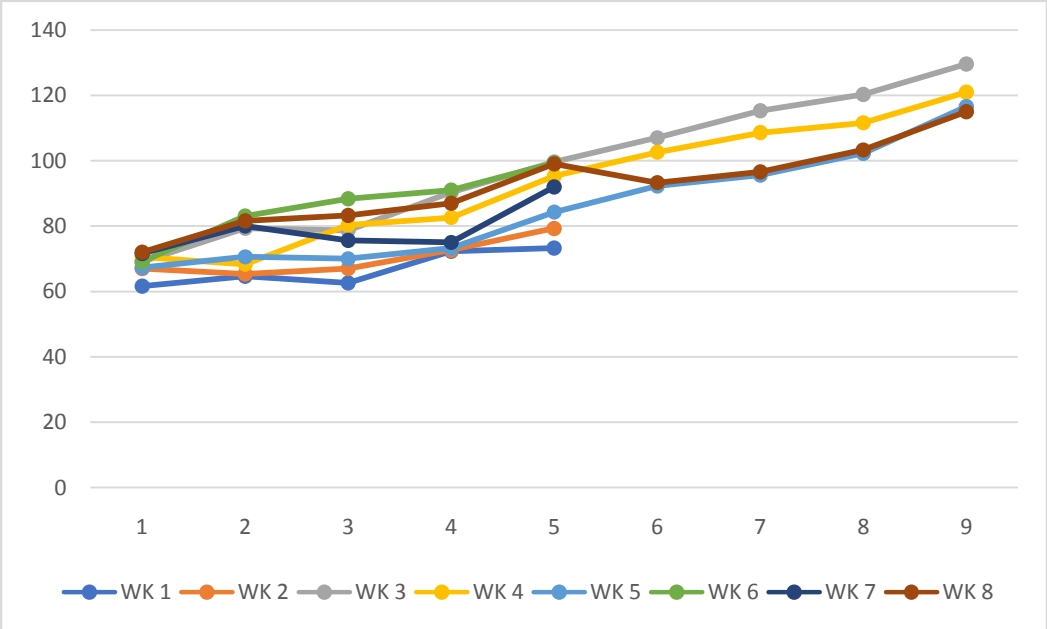

Figure 2: Changes in the Mean Weight of the Rats in the Experimental Groups during the period of the study

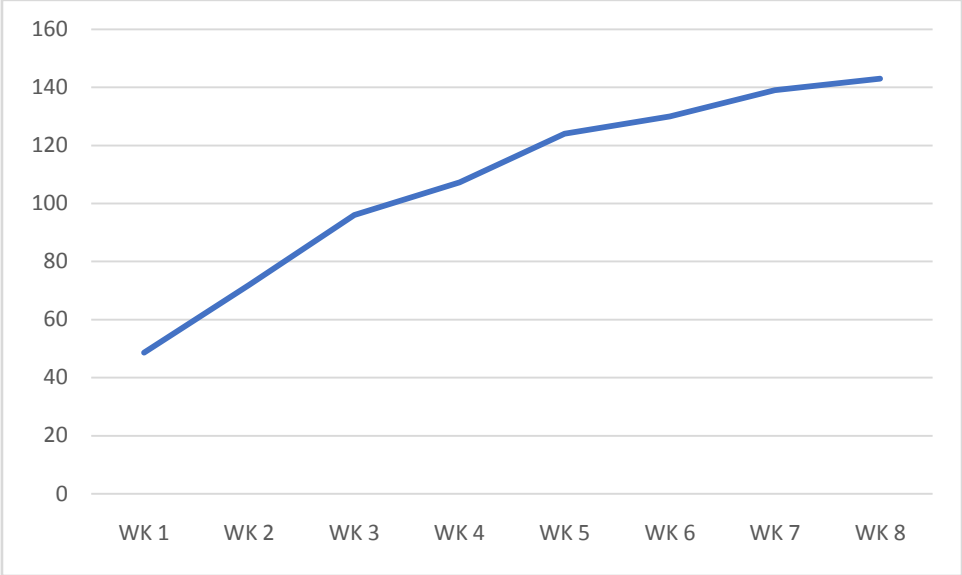

Figure 3: Changes in the Mean Weight of the Rats in the Control Group during the period of the study

Cyanide contents of the processed cassava cultivars using different methods

The results of the cyanide contents of the processed cassava cultivars using different methods are presented in table 3.

The high-cyanide cassava cultivar in this study exceeded the FAO/WHO recommended cyanide in cassava level by over 148%. After undergoing different processing methods, the cyanide contents reduced considerably. The highest reduction was observed with 48-hour fermentation with red palm oil additive (58.4%), 48-hour fermentation without red palm oil (51. 6%), 24-hour fermentation with red palm oil (27.9%) and the least reduction in cyanide content was with 24-hour fermentation without red palm oil additive (4.2%) [Table 3]. This observed difference in the reduction of cyanide content with various processing methods was statistically significant (p=0.000).

Table 3: Results of the cyanide contents of the processed cassava cultivar using different methods

Samples	mg CN^-/kg dry weight of cassava	FAO/WHO recommended level (mg CN^-/kg dry weight of cassava)	Percentage Exceeded FOA/WHO Recommendation (%)	Percentage Reduction After Processing (%)
Raw Cassava	2486.39	15 - 1000	148.6	
24-hour Fermentation without Red Palm Oil	2386.65		138.7	4.2
24-hour Fermentation with Red Palm Oil	1791.8		79.2	27.9
48-hour Fermentation without Red Palm Oil	1204.07		20.4	51.6
48-hour Fermentation with Red Palm Oil	1034.81		3.5	58.4
Pearson Chi-Square value = 200.571 p-value = 0.000				

Serum Oxidative Stress Biomarkerslevels in the Wistar Albino Rats in the Experimental and Control Groups

The levels of serum anti-oxidative stress biomarkers (glutathione, catalase,superoxide dismutase, malondialdehyde)in the rats exposed to high level cyanide in cassava (groups 1 to 8) were reduced whereas the oxidative marker-reactive oxygen species increased significantly when compared with the changes in the control group ($p < 0.05$) [Table4].

Table 4: Pre- and Post-Experimental Oxidative Stress Biomarkers

Groups / Biomarkers	1	2	3	4	5	6	7	8	9	Paired T-Test p-value
Baseline Glutathione (1.1-10 mmolL)	8	7.8	7.6	6.8	9.0	8.1	6.7	6.4	7.4	
Post-Exp Glutathione	4	2.5	1.6	0.8	3.2	3.8	2.5	2.2	7.4	
Difference	4	5.3	6.0	5.0	5.8	4.3	4.2	4.2	0	0.001
Baseline Catalase (24-28ng/ug)	23	25	24	25	26	27	25	26	24	
Post-Exp Catalase	17	18	15	8	10	12	14	13	24	
Difference	6	7	9	7	16	15	11	13	0	0.000
Baseline SOD (11-15 units/ml)	12	10	13	13	12	14	16	15	14	
Post-Exp SOD	10	8	7	5	6	8	7	10	13	
Difference	2	2	6	8	6	6	9	5	1.0	0.001
Baseline MDA (106.65-326.6ng/ml)	108	167	156	180	146	159	201	252	220	
Post-Exp MDA	106	160	156	181	146	160	200	252	220	
Difference	2	7	0	1	0	1	1	0	0	0.046
Baseline ROS (115.5±32.6 U)	116	182	166	190	164	135	124	117	122	
Post-Exp ROS	234	239	341	370	380	265	247	259	133	
Difference	118	57	175	180	216	130	123	142	11	0.000

Processing Methods, Cyanide contents, Oxidative Stress Markers and Fundoscopic Findings in the Experimental Wistar Albino Rats

Wistar albino rats in the control group (fed with "Grower Mash" for 60 days) and the rats in sub-groups 5,6,7 & 8 (fed with 48-hour fermented cassava had normal optic disc findings on fundoscopy pre-, intra- and post- experimental duration.However, there was statistically significant decrease in their oxidative stress biomarkers ($p<0.005$).Rats treated with 24-hour fermented cassava (sub-groups 1,2,3 & 4) had varying degrees of papillitis, worse with the rats that had 24-hour fermented cassava twice daily for 60 days. The animals fed with higher concentration of cyanide had more obvious optic neuropathy with severely decreased in their anti-oxidative stress biomarkers ($p<0.005$) post-experiment.The animals in the control group maintained normal oxidative stress parameters throughout the period of the experiment.The intra and inter group differences in the optic disc changes was statistically significant ($p=0.000$)[Table 5].

Table 5: Processing Methods, Cyanide contents, Oxidative Stress Markers and Fundoscopic Findings in the Experimental Wistar Albino Rats

Samples	mg CN^-/kg dry weight of cassava	FAO/WHO recommended level (mg CN^-/kg dry weight of cassava)	Percentage Exceeded FOA/WHO Recommendation (%)	Dynamics in Oxidative Stress Biomarkers	Mean Significant Fundoscopic Findings in the Optic Nerve Head of each grp (Pre-Experiment)	Mean Significant Fundoscopic Findings in the Optic Nerve Head of each grp (post-Experiment)
Raw Cassava	2486.39	15 - 1000	148.6			
24-hour Fermentation without Red Palm Oil	2386.65		138.7	Glutathione** Catalase** SOD** MDA** ROS^^^	Normal Disc	-Swollen Disc -Temporal Disc Pallor -Peripapillary haemorrhages
24-hour Fermentation with Red Palm Oil	1791.8		79.2	Glutathione** Catalase** SOD** MDA** ROS^^	Normal Disc	Mild papilledema
48-hour Fermentation without Red Palm Oil	1204.07		20.4	Glutathione* Catalase* SOD* MDA* ROS^	Normal Disc	-Mild papilledema -Temporal Disc Pallor
48-hour Fermentation with Red Palm Oil	1034.81		3.5	Glutathione* Catalase* SOD*	Normal Disc	Normal Disc findings

				MDA* ROS^		
Control Group fed with "Grower Mash" for 60 days	Nil		Nil	Glutathione§ Catalase§ SOD§ MDA§ ROS§	Normal Disc findings	Normal Disc findings

** Remarkable decrease in oxidative stress biomarker (p=0.000) * Mild decrease in oxidative stress biomarker (p=0.046)^^^Remarkable increase in oxidative stress biomarker (p=0.000) ^^ Moderate increase in oxidative biomarker (p=0.001) ^ Mild increase in oxidative biomarker (p=0.046) § No remarkable change in the pre- and post- experimental values of the oxidative biomarker

III. Discussion

This work examines the dynamics of biomarkers of oxidative stress and their impact on optic neuropathy in Wistar albino rats fed with high-cyanide content garri. In this study, the cyanide-content of the various cassava cultivar exceeded the FAO/WHO recommended cyanide in cassava level by over 148% and were used to feed the animals in varying amounts and duration. It was observed that there was an increase in the serum levels of reactive oxygen species proportionately with the quantity of cyanide consumed which was statistically significant (p=0.000).Our observation compares well with the works of Halliwell et al., who noted that the increased generation of ROS in the pathogenesis of several diseases and in the toxic effects of a wide variety of compounds [15].

In our study, we also noticed decreased activities of glutathione, catalase, SOD and MDAin all the animals that were fed with garri with high cyanide content. These observations are in tandem with the findings of Sasaki et al.,Asada, Bartkowiak et al. and Halliwell [14,16-18]. Reductions in oxidative stress indicators portends the reduction in the capacity of the animals to handle reactive oxygen species.

The pathological changes in the optic nerve in this study revealed various degrees of optic neuropathies worse in the animals that took higher quantity of cyanide in their diets. There was no pathological impairment in the optic nerve heads among the animals in the control group. This observed difference was statistically significant (p=0.000). This finding is in agreement with the postulation of Fulda et al., who noted that cells respond histopathologically to toxic insult by degeneration, proliferation, inflammation, and repair [19].

The intra and inter group differences in the optic disc changes was statistically significant (p=0.000). Our findings in this work are in tandem with the study of van Heijst et al., who observed various degrees of optic neuritis and atrophyin 20 West Africans that ingested cassava over an unspecified period [20].

In this study, the individual weight and mean group weight of all the animals in the experimental group at the beginning of the experiment was 68.5gm and at the end of the experiment was 74.5 grams. There was a general decrease in the weight of the animals on the on the third and fourth weeks. This observed difference was not statistically significant (p=0.092). This decline in weight could be as a result of the introduced new diet or as a result of cyanide poisoning or both. However, unlike the weight of the rats in the control group; individual and group mean weight steadily increased from the first week to 9th week of the study. Our observation in this study, is in tandem with the findings ofBlanc et al.,that reported weight loss of 8% due to loss of appetite in about 50% of workers exposed to 15 ppm hydrogen cyanide (for an unspecified duration in a silver-reclaiming facility) and a decreased body weight in rats exposed to 25 ppm cyanogen (12.5 ppm cyanide) 6 hours/day, 5 days/week for 6 months in the work of Lewis et al. [21].

IV. Conclusion

Optic nerve toxicity (Optic neuropathy) following ingestion of garri containing high cyanide levels differs, depending on length of exposure, the amount ingested and the frequency at which the garri is consumed. There is associated decreased in anti-oxidative stress markers:glutathione, catalase, SOD and MDA whereas the levels of ROS-oxidative marker are significantly increased.Policy-makers, food processing industries and the public should therefore, be educated appropriately on the best way to process cassava into garri for human consumption so as to reduce the cyanide content and thereby prevent the adverse impact on the optic nerve with possible visual impairment/loss from nutritional toxic optic neuropathy.

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Conflicts of Interest: There are no conflicts of interest.

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