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## THE ANTIOXIDANT EFFECT OF AQUEOUS EXTRACT OF *Monodora myristica* L. ON CYANIDE INDUCED HEPATIC AND RENAL TOXICITY IN RATS

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### Abstract

Cyanide generates free radicals in man and animals by altering the enzymes in the metabolic pathways of carbohydrate synthesis and hence induce stress on the organism. This study was aimed at determining the antioxidant effect of *Monodora myristica* (Mn) on cyanide (CN) induced hepatic and renal toxicity. A total of 20 male rats were used for this study. They were divided into 5 groups each with 4 rats. Group 1 control: rats received distilled water daily throughout the experiment. Group 2, 4 and 5; rats in this group were given 8.0mg CN /kg.b.w in form of KCN orally. Groups 3 and 4: received 50mg/kg /0.1mlM by gavage three times a week. Group 5: 400mg Sodium thiosulphate /kg b.w by gavage .The total duration of the experiment was for 4 weeks. Hepatic and renal Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP,) Lipid peroxidation (MDA), superoxide dismutase (SOD), catalase and serum urea and creatinine were determined using standard biochemical procedures. A significant increase ( $P < 0.05$ ) in hepatic and renal MDA, creatinine, urea, AST, ALT and ALP, was indicated in rats exposed to cyanide when compared with the control group. Treatment with aqueous extract of Mn however resulted in a significant decrease ( $P > 0.05$ ) in these parameters which was comparable with the standard antidote sodium thiosulphate ( $\text{Na}_2\text{S}_2\text{O}_3$ ). In conclusion, the result indicates that *M. myristica* increases the antioxidant status in cyanide induced rats and is able to ameliorate the toxic effects of cyanide in the liver and kidney.

**Key words:** *Monodora myristica*, cyanide toxicity, antioxidant enzymes, liver, kidney

### Introduction

Medicinal plants are popularly used by traditional herbal medicine practitioners particularly among the rural dwellers all over the continent. These plants have therapeutic uses that dates back to ancient times. Hence a medicinal plants can be defined as a plant whose parts contains substances that can be employed for treatment or medicinal purposes, or as a

substrate for chemo-pharmaceutical synthesis. These parts can therefore be used in the control or treatment of ailments (Newman and Cragg, 2012; WHO, 2011).

The plant *Monodora myristica* (Mn) popularly known as calabash nutmeg belongs to the custard apple family of flowering plants called Annonaceae. It is native to West,

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Central and East Africa extending from Sierra Leone to Uganda, Kenya, Kongo and Angola. (Ekeanyanwu, *et al.*, 2010). It grows well in the ever green forest zone of West Africa and in the Sothern part of Nigeria. Its local names include: Ehuru or Ehiri (Igbo), Ariwo (Yoruba), Jamaica nutmeg, African nutmeg, Calabash nutmeg (Burabai, 2007;Nwozo, 2015). In Ivory Coast, *M. myristica* is used in the treatment of haemorrhoids and stomach pain.

The seeds are aromatic and are used after pulverisation as condiments in food and this gives a flavour resembling that of nutmeg (Ekeanyanwu, *et al.*, 2010). When, the kernel is grinded it is used to prepare pepper soup where it acts as a stimulant to relieve constipation and control passive uterine haemorrhage in women immediately after child birth. *M. myristica* has been shown in past studies to ameliorate cadmium induced toxicity in the liver of male rats. Nwozo, *et al.*, (2015) and Oyinloye, *et al.*, (2016) also showed that this plant has the ability to lower cholesterol in rats. Photochemical studies of *M. myristica* seeds have shown that it contains antioxidant properties (Uheghu, *et al.*, 2011; Ekeanyanwu and Etienajirhevwe, 2012).

Cyanide (CN<sup>-</sup>) is a very toxic substance that is dangerous to all forms of life. Its consumption either in a short term or over a long period of time has been implicated in many diseases such as goiter, neurological diseases and death. (Ghodsi and Baghshani, 2013). It is found in food such as cassava as cyanogenic glycosides and is also produced by manufacturers during production process such as during electroplating, steel and plastic production (Oyinloye, *et al.*, 2016). Studies have shown that Cyanide generates free radicals in man and animals by altering the enzymes in the metabolic pathways of carbohydrate synthesis and

hence induce stress on the organism. (Okolie and Iroanya, 2003; Okolie and Asonye, 2004) This study is therefore carried out to investigate the antioxidant potentials of *M. myristica* on hepatic and renal induced toxicity in male rats.

## MATERIALS AND METHODS

### Extract preparation

*Monodora myristica* G. (Mn) was purchased from Abraka main market, Delta State and was identified by Prof (Mrs) Edema, N.E a Professor in the department of Botany, Delta State University Abraka The spices were cracked opened to remove the seeds and sun-dried for three days. This was followed by grinding to powder using an electric blender, 100g was weigh using an electrical weighing balance and soaked in 400ml of distilled water for 24hours and then filtered using whatman filter paper pore size 11µm. The extract was then concentrated using rotary evaporator at 40°C-50°C under reduced pressure. The dried sample was dissolved in 1g of 10% Tween 8 and kept in deep freezer until required for use.

### Experimental animals

Rats were procured from Delaw medical laboratory Abraka, Delta State, Nigeria. The animals were housed in a standard animal cage and maintained under controlled condition. The animals were fed with their normal food diet (grower mashed) and water for two weeks before the commencement of the study which lasted for twenty- eight (28) days. All the animals were handled in accordance with the principles of laboratory animal care as documented in National Institute of Health (NIH) for laboratory animal welfare (National research council, 1996)

**Experimental design** Twenty male Wister rats weighing between 150-180g were used for this study. Rats were divided into five groups containing four rats:

**Group 1**(1<sup>st</sup> control): rats received distilled water daily throughout the experiment.

**Group 2** rats were given 8.0mg CN /kgb.w in form of KCN orally, three times a week throughout the experiment.

**Groups 3** (2<sup>nd</sup> Control) received 50mg/kg /0.1ml Mn by gavage three times a week throughout the experiment without exposure to cyanide.

**Group 4** were given 8.0mg CN /kgb.w in form of KCN orally three times a week and was also treated with 50mg/kg /0.1ml Mn three times a week by gavage throughout the experiment.

**Group 5** (3<sup>rd</sup> control): were given 8.0mg CN /kgb.w in form of KCN orally three times a week and was treated with 400mg Sodium thiosulphate (Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>) /kg b.w by gavage. Three times a week throughout the experiment. At the end of the experiment which lasted for 28 days the animals were sacrificed by cervical decapitation and the blood, liver and kidney were collected for further biochemical analysis.

### Biochemical analysis

Assay for AST and ALT activity was by use of randox kits using the method of Reitman and Frankel (1957). AST and ALT activity is expressed in Unit/ L. Assay for alkaline phosphatase (ALP) activity was by the method of Annino and Giese (1976). It's activity is expressed in micromoles p-nitrophenol/min/mg /protein Urea activity was assayed using the randox kit according to the method of Tietz (1990). Creatinine assay for using the randox kits according to the method of Bartels and Bohmer (1952). For assay of Catalase, the method of Cohen et al method was adopted. Superoxide dismutase (SOD) activity was determined using the method

Misra and Fridovich (1972) were 1 unit of the enzyme is equal to the amount the enzyme needed for 50 % inhibition of epinephrine. The level of Lipid peroxidation was determined by the method of Gutteridge and Wilkins (1982) and  $1.56 \times 10^5 \text{M/cm}$  was the value used as molar extinction coefficient. This was expressed in terms of MDA units /g tissue with a unit representing 1 umol of MDA.

### Statistical analysis

The value obtained from the experiment were represented as mean  $\pm$  SD. The data for various biochemical parameters were analyzed using analysis of variance (ANOVA) and the group means were compared lest significant difference (LSD).

## RESULTS

**Table 1:** The effect of *M. myristica* on AST and ALT activities in the kidney and liver of wistar albino rats exposed to cyanide toxicity.

GROUPS	Liver	Kidney	Liver	Kidney
	AST (U/L)	AST (U/L)	ALT (U/L)	ALT U/L
1: Control	72.13 $\pm$ 11.66 <sup>a</sup>	61.13 $\pm$ 8.81 <sup>a</sup>	50.25 $\pm$ 3.47 <sup>a</sup>	43.08 $\pm$ 2.45 <sup>a</sup>
2: Cyanide	89.17 $\pm$ 3.68 <sup>a</sup>	83.42 $\pm$ 8.53 <sup>b</sup>	72.00 $\pm$ 12.75 <sup>b</sup>	61.80 $\pm$ 4.45 <sup>b</sup>
3: Mn	68.00 $\pm$ 9.93 <sup>b</sup>	55.00 $\pm$ 3.37 <sup>a</sup>	46.00 $\pm$ 5.58 <sup>a</sup>	39.13 $\pm$ 3.27 <sup>c</sup>
4. CN + Mn	81.75 $\pm$ 6.34 <sup>c</sup>	73.25 $\pm$ 3.18 <sup>c</sup>	63.13 $\pm$ 3.17 <sup>c</sup>	53.17 $\pm$ 2.36 <sup>d</sup>
5: CN+ Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>	78.12 $\pm$ 3.64 <sup>c</sup>	67.13 $\pm$ 8.84 <sup>ac</sup>	58.00 $\pm$ 3.32 <sup>c</sup>	48.80 $\pm$ 4.32 <sup>d</sup>

Values are given as mean  $\pm$  S.D, n=4. Values not having a common superscript on the same column differ significantly at (p< 0.05). Mn=*Monodora myristica* seed extract. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>= sodium thiosulphate. CN=Cyanide.

**Table 2:** The effects of *M. myristica* on ALP (U/L) activities in the kidney and liver of wister albino rats induced with cyanide toxicity.

Groups	Liver (U/L)	Kidney (U/L)
1: Control	192.82±30.89 <sup>a</sup>	180.13±16.26 <sup>a</sup>
2: Cyanide	250.36±7.00 <sup>b</sup>	221.9±22.57 <sup>b</sup>
3: Mn	193.80±3.88 <sup>a</sup>	177.43±9.06 <sup>a</sup>
4: Cyanide+Mn	218.59±14.55 <sup>c</sup>	205.35±14.37 <sup>c</sup>
5: CN + Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>	203.26±30.37 <sup>c</sup>	193.26±22.37 <sup>c</sup>

Values are given as mean ±S.D, n=4. Values not having a common superscript letter on the same column differ significantly at (p< 0.05). Mn=*M. myristica* seed extract. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>= sodiumthio-sulphate. CN=Cyanide.

**Table 3:** The effects of *M. myristica* on serum Urea and Creatinine in wister albino rats induced with cyanide toxicity.

GROUPS	UREA	CREATININE
1: Control	24.44±3.28 <sup>a</sup>	3.49±0.26 <sup>a</sup>
2: Cyanide	31.28±7.00 <sup>b</sup>	8.49±1.46 <sup>b</sup>
3: Mn	22.52±6.67 <sup>a</sup>	2.30±1.16 <sup>a</sup>
4: CN + Mn	27.36±0.71 <sup>c</sup>	6.38±2.06 <sup>c</sup>
5: CN + Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>	25.36±6.71 <sup>ac</sup>	5.36±1.71 <sup>c</sup>

Values given as mean ±S.D, n= 4. Values not having a common superscript on the same column differ significantly at (p< 0.05). Mn = *M. myristica* seed extract Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>= sodium thiosulphate CN=Cyanide.

**Table 4:** The effects of *M. myristica* (Mn) on Superoxide dismutase (SOD) activity, Catalase activity and Lipid peroxidation (MDA) level in the liver of rats induced with cyanide toxicity.

GROUPS	SOD	Catalase	MDA
1 Control	72.41±1.55 <sup>a</sup>	24.44±3.28 <sup>a</sup>	3.49±0.26 <sup>a</sup>
2 Cyanide	52.53±2.24 <sup>b</sup>	11.28±7.00 <sup>b</sup>	8.49±1.46 <sup>b</sup>
3 Mn	60.50 ± 1.73 <sup>a</sup>	20.22±5.90	3.01±0.25 <sup>a</sup>
4 CN+ Mn	63.46±7.61 <sup>b</sup>	26.05±6.24 <sup>a</sup>	5.09±2.24 <sup>c</sup>
5 CN + Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>	61.10±10.7 <sup>a</sup>	26.48±11.21 <sup>a</sup>	4.42± 0.77 <sup>c</sup>

Values are given as mean ± S.D, n=7. Values not sharing a common superscript on the same column differs significantly at (P< 0.05). Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>= sodium thiosulphate CN= Cyanide.

**Table 5:** The effects of *M. myristica* (Mn) on Superoxide dismutase (SOD) activity, Catalase activity and Lipid peroxidation (MDA) level in the kidney of rats induced with cyanide toxicity.

GROUPS	SOD	Catalase	MDA
1 Control	67.32±1.55 <sup>a</sup>	48.43±3.28 <sup>a</sup>	0.71±0.08 <sup>a</sup>
2 Cyanide( +CN)	42.53±2.24 <sup>b</sup>	29.42±7.00 <sup>b</sup>	4.74±1.46 <sup>b</sup>
3 Mn	62.50 ± 1.73 <sup>a</sup>	18.22±5.90 <sup>c</sup>	0.78±0.04 <sup>a</sup>
4 CN+ Mn	56.19±7.61 <sup>b</sup>	40.26±6.24 <sup>a</sup>	1.96±2.24 <sup>c</sup>
5 CN + Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>	58.30±3.79 <sup>b</sup>	50.78±11.17 <sup>a</sup>	1.03±0.31 <sup>a</sup>

Values are given as mean ± S. D, n=7. Values not sharing a common superscript on the same column differs significantly at (P< 0.05). Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>= sodium thiosulphate CN= Cyanide.

## DISCUSSION

AST and ALT are markers of liver and kidney function and are distributed in various organs in the body and are used primarily to diagnose liver disease (Purcell et al., 1979). The result from this present study (Table 1) indicates that there was a significant increase in the liver and kidney AST and ALT all the rats exposed to sublethal dose of cyanide. This increased activity is in agreement with the work of Baghshani and Ghodsi (2016) and Elsaid and Elkomy (2012). However there was a significant decrease in the activities of these enzymes in the rats treated with the *M. myristica* (Mn) extract when compared with the untreated Group 2 this indicates that *M. myristica* was able to ameliorate the effect of cyanide damage on the liver of rats. In addition, there was no significant difference between Group 4 rats treated with Mn and Group 5 rats treated with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. This indicates that *M. myristica* was able to not only able to ameliorate the effects of cyanide damage on the liver of rats but its antidote effect was comparable to the standard antidote for cyanide poisoning, Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>.

Increase in Alkaline Phosphatase (ALP) activity has also been implicated in diseases associated with the liver, bone and kidney and it has also been shown to affect the inflammatory responses particularly in patients with chronic kidney disorders (Sharma et al., 2014; Badve et al., 2015).

ALP activity was significantly increased in the liver and kidney of rats induced with cyanide when compared with the control in this present study (Table 2). This is

in agreement with the works of Okolie and Osagie (2000) who reported a rise in ALP activity in the kidney of rabbits after chronic exposure to cyanide. ALP activity however was significantly decreased in the liver and kidney of rats treated with *M. myristica* extract. This indicates that *M. Myristica* is able to protect the cell membrane of the liver and the kidney from damage associated with cyanide toxicity. Again there was no significant difference between Group 4 rats treated with Mn and Group 5 rats treated with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>.

One major function of the kidney is the clearance of metabolites from the blood (Ferguson et al., 2008; Maton et al., 1993). Agents with nephrotoxicity effect, may cause damage to the kidney resulting in increase of urea and creatinine in the serum. (Ferguson et al., 2008; Purcell et al., 2001; Rached et al., 2008). Urea and Creatinine activity was significantly increased in rats exposed to cyanide (Group 2) when compared with control (Group 1; Table 3) in this present study. The increased serum urea and creatinine level may be due kidney damage. The result obtained in this present study is in line with previous studies conducted by Olamudathir and Maduagwu (2014), who reported a rise in serum creatinine level in the kidney of rats induced with cyanide. Okolie and Osagie (2000) also reported degenerative changes in the kidney sections of the cyanide-fed rabbits. However a significant decrease in urea and creatinine activity was indicated in the Group 4 rats treated with Mn extract when compared with those exposed to cyanide without treatment. This again confirms that *M. Myristica* is able to protect the cell

membrane of the liver and the kidney from damage associated with cyanide toxicity. The activity of the two enzymes in the group 4 rats was again comparable to the Group 5 rats treated with a standard antidote to cyanide poisoning. Superoxide dismutase (SOD) is a metallo-proteinase involved in antioxidant defense, while Catalase is a hem protein found in peroxisomes, that protects the cells from oxidative damage.

In this is present study there was a significant decrease in the antioxidant enzymes SOD and Catalase in the liver and kidney (Table 4 and 5) of Groups 2 rats exposed to cyanide when compared with control (Group 1). Several studies has shown that cyanide inhibits these antioxidants (Ola-Mudathir and Maduagwu, 2014; Kanthasamy *et al.*, 1997). However, a significant increase ( $P < 0.05$ ) was indicated in the activity of these enzymes SOD and Catalase in Group 4 rats treated with the Mn extract when compared with the untreated Group 2. Also this increase was comparable with the standard antidote (Group 5).

A significant increase ( $P < 0.05$ ) in MDA levels was also indicated in the liver and kidney of rats exposed cyanide when compared with Group 1 not exposed to cyanide. (Table 4 and 5). This indicates an increase in lipid peroxidation and hence an increase in oxidative stress due to increase in the production of free radicals generated from exposure to cyanide. An increase in lipid peroxidation has been indicated in the kidney of rats induced with cyanide toxicity. (Ola-Mudathir and Maduagwu 2014). However a significant decrease

( $P > 0.05$ ) in MDA level was indicated in Group 4 rats treated with Mn extract when compared with Group 2 not treated. Indicating the protective effect of the Mn extract on the liver and kidney of the rats treated with the extract after cyanide exposure. Again, there was no significant difference between the group 4 rats treated with Mn extract when compared with Group 5 rats treated with sodium thiosulphate a standard antidote.

The ability of this plant extract to protect the rat against any damage to the liver and the kidney can be attributed to the presence of its bioactive components (Oyinloye, *et al.*, 2016). Aqueous extract from this plant has been shown to contain flavonoids, phenols, alkaloids, saponins, tannins and cardiac glycosides (Erukainure *et al.*, 2012; Moukette *et al.*, 2015; Oyinloye *et al.*, 2016). The synergetic effect of all these constituents may have contributed in making this plant a good antioxidant against cyanide poisoning.

## CONCLUSION

*Monodora myristica* been shown to possess antioxidant that is components that is able to ameliorate the effects of sub-lethal cyanide induced toxicity in rats.

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