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ANTIOXIDATIVE ROLE OF AQUEOUS LEAF EXTRACT OF *CYMBOPOGON CITRATUS* (LEMON GRASS) ON PARACETAMOL- INDUCED HEPATOTICITY IN ALBINO RATS

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Abstract

The aqueous leaf extract of *Cymbopogon citratus* (lemongrass) was investigated for its anti-oxidative role in paracetamol-induced hepatotoxicity using these biochemical markers: Superoxide dismutase (SOD), Catalase (CAT), and total Glutathione (GSH). A total of forty eight adult albino rats (male/female) weighing between 150g to 200g were used for the study. The animals were randomly divided into six groups of eight animals each. Group I served as healthy control and was fed with normal animal feed and water throughout the experiment. Animals in groups II to VI were administered with paracetamol (lg/ kg) in distilled water solution per oral. After three days of this challenge, animals in groups III, IV, V and VI were treated with 100mg/kg, 200mg/kg, 300mg/kg and 400mg/kg body weight of aqueous lemongrass leaf extract respectively daily for 14 days. Animals in group II (disease control) however did not receive any treatment with lemongrass extract and were instead given sterile water. AH the animals were allowed unlimited access to tap water and grower's mash. There were significant decreases ($p<0.05$) in final body weight (161.3 ±11.3g), liver weight (3.3 ± 0.2g), catalase (13.50 + 2.88 nmol/min/ml), SOD (0.03 ± 0.01 U/ml), and total glutathione (6.51 ± 0.90 uM) ± 0. 18 mg/dl) of group II when compared with those of group 1: final body weight (182. 5 ± 15.8g), liver weight (5.9 ± 0.6g), catalase (25. 25 ± 1.91 nmol/min/ml), SOD (0.20 ± 0.02 U/ml), and total glutathione (12.26 ± 1.27 uM) (0.53±0,16mg/dl). However, post-treatment of the diseased animals of groups III to VI with different concentrations of aqueous leaf extract of *Cymbopogon citratus* alleviated most of those changes though not strictly in a dose dependent manner. The results of this study indicate that aqueous leaf extract of *Cymbopogon citratus* possesses anti-hepatotoxic action against paracetamol-induced hepatotoxicity in rats.

Keywords: *Cymbopogon citratus,* Antioxidative role, Paracetamol, Hepatotoxicity.

Introduction

Acetaminophen (paracetamol) is a widely used over- the-counter analgesic and antipyretic. It is commonly used for the relief of headaches and other minor aches and pain. Acetaminophen is usually well tolerated in prescribed dose but overdose is the most common cause of drug induced liver disease and acute liver failure worldwide (Keeffe and Freidman, 2004). Damage to the liver is not due to the drug itself but to a toxic metabolite (N - acetyl - p -benzoquinone imine (NAPQI) which is produced by cytochrome P450 enzyme in the liver (Wallace, 2004).

There are several mechanisms that have been postulated to be important in the development of acetaminophen toxicity. One of such mechanisms is oxidative stress. Thus, increased formation of superoxide would lead to hydrogen peroxide and peroxidation reactions by Fenton-type mechanisms (Laura *et al.,* 2003). Consequently, it has been shown that NAPQI reacts very rapidly with glutathione (GSH) (Coles *et al.,* 1988), and there are a number of potential mechanisms that have been suggested to play a role. Interestingly, evidence has shown that administration of encapsulated superoxide dismutase decreased the toxicity of acetaminophen in the rat (Nakae *et al.,*1990).

Free radicals or oxidative injury is widely fecognized to play essential role in the pathogenesis of human neurologic and other disorders (Atawodi, 2005). For instance in diabetes mellitus, increased oxidative stress which coexists with diminution in the antioxidant status has been postulated (Ojo *et al.,*2006).Oxygen free- radical can initiate peroxidation of lipids, which in turn stimulates glycation of protein, inactivation of enzymes and alteration in the structure and function of collagen basement and other membranes, and play a role in the long term complication of diabetes (Sabu and Kuttan, 2002). Oxygen species such as hydroxyl radicals, superoxide anion radicals and singlet oxygen are agents that attack polyunsaturated fatty acids incellmembranes and elicitlipid peroxidation in living systems. However, under normal physiological conditions low concentrations of lipid peroxidation products are found in tissues and cells. In the presence of oxidative stress more lipid peroxidation products are generated and subsequently released into the serum owing to cell damage.

However, living systems are protected from active oxygen species and oxidative stress by cellular antioxidant enzymes and non-antioxidant enzyme systems. The antioxidant enzymes include superoxide dismutase, catalase, and glutathione peroxidase while the non-enzymatic antioxidants include a -tocopherol, p-carotene, uric acid, ascorbic acid etc. There are available data to support the chemo-preventive capacities of ethnobotanicaJs and components of vegetable diets with free-radical scavenging potential on diabetes (Sabu and Kuttan, 2002), memory and cognitive function (Howes *et al.,* 2003; Perry *et al.,* 1998), age-related neurological dysfunction (Youdim and Joseph, 2001; Delanty and Ditcher, 2000) including other human diseases.

Liver diseases remain as one of the serious health problems. However, there seems to be no satisfactory liver protective drugs in allopathic medical practice for serious liver disorders. Herbal drugs play a role in the management of various liver disorders most of which speed up the natural healing processes of the liver (Deepak *et al.,* 2007). Numerous medicinal plants and their formulations are used for liver disorders in ethnomedical practice as well as traditional system of medicine in India. More than fifteen of these plants are evaluated for their hepatoprotective action in light of modern medicine (Subramoniam *et al,,* 1998). According to Ojo *et at.* (2005), recent studies of some tropical African plants used in traditional medical practices have shown that these plants possess antioxidant properties. This study reports the result of the investigation of the antioxidant potentials of aqueous leaf extract *tf Cymbopogon citratus* (lemongrass) in rats challenged with toxic dose of acetaminophen. *Cymbopogon citratus* is a widely used herb in tropical countries, especially in Southeast Asia. The essential oil of the plant is used in aromatherapy (Gagan *et al.,* 2011). *Cymbopogon citratus* of the Poaceae family is a tall aromatic coarse grass of 1.5m high. It is a monocotyledonous hypogeal perennial plant with slender sharp edged leaves with a pointed apex. The entire plant is attached to the soil by fibrous root (Burkill, 1996). Lemongrass stalks are commonly used in the cuisines of Africa, the Middle East and Southeast Asia. It is native to Sri Lanka and South India and is currently widely cultivated in the tropical areas of America and Asia.

Lemongrass is also a folk remedy for coughs, consumption, elephantiasis, flu, gingivitis, headache, leprosy, malaria, ophthalmia, pneumonia and vascular disorders (Ojo *et al.,* 2006). Studies also indicate that *Cymbopogon citratus* possesses various pharmacological activities such as anti-amoebic, antibacterial, antifilarial, antifungal and anti-inflammatory properties. Various other effects like antimalarial, antimutagenicity, antimycobacteria, antioxidants, hypoglycaemic and neurobehavioral have also been studied. These results are very encouraging and indicate that this important herb should be studied more extensively to confirm these results and possibly reveal and explore other potential therapeutic effects.

Materials and Methods

Plant material

Fresh and apparently uninfected leaves *of Cymbopogon citratus* (lemongrass) were collected from plants growing within Ikeduru L. G. A. of Imo state in February, 2013. The botanical identification of the plant was confirmed by Dr. F.N. Mbagwu at the Department of Plant Science and Biotechnology, Imo State University, Owerri, where voucher samples are kept for reference.

Experimental animals

A total of forty eight (48) adult albino rats of Wister strain (male/ female) weighing between 150g to 200g were purchased from Animal Farm of Michael Okpara University of Agriculture Umudike, Umuahia in Abia State. The animals were housed at the Animal house of College of Medicine, Imo State University Owerri and were acclimatized for two (2) weeks. The animals were allowed free access to normal animal feed and water before the experiment. In addition they were maintained at twelve (12) hour light and dark cycle.

Drug (Paracetamol) / chemical

The paracetamol tablets and sucrose used were purchased from Milan Chemists Douglas road Owerri. Other chemicals were purchased from HI -TECH Diagnostics Ltd, Nigeria and were of analytical grade, AR.

Preparation of the extract.

Fresh leaves of *Cymbopogon citratus* were sun-dried for five days, followed by grinding. Thereafter the ground material was sieved through a 1mm sieve to obtain a fine powder. Exactly 200g of the fine powder was soaked in 1000ml (IL) of distilled water in a conical flask, the mixture allowed to stand on the laboratory bench for 30mins,thereafter shaken and boiled for lhour.lt was then cooled and filtered. The filtrate was evaporated in a hot air oven to yield a dry weight of 60g.The following weights of the residue:lg, 2g, 3g and 4g were prepared in 10ml of distilled water corresponding to 100mg/ml, 200mg/ml, 300mg/ml and 400mg/ml concentrations respectively to be given to the animals per kilogram body weight.

Experimental design

After two weeks of acclimatizing the animals, they were grouped into six groups of eight animals each and their initial body weights taken. Group I served as negative control (control 1) and was fed with normal animal feed and water only until the end of the experiments. Hepatotoxicity was induced in animals in groups II to VI using a relatively high dose of paracetamol (lg/kg body weight) in distilled water solution per oral. Group II served as positive control (control 2), which did not receive treatment with aqueous extract of *Cymbopogon citratus.* Group III, IV, V and VI received treatment with 100mg/kg body weight, 200mg/kg body weight, 300mg/kg body weight, and 400mg/kg body weight of aqueous extract of lemongrass in 1ml volume daily respectively for four weeks through the oral route. During this period however, animals were allowed free access to normal animal feed and water.

Twelve hours after the last treatment and the last meal, the animals were re-weighted and sacrificed. Using a 5ml syringe, about 4ml of blood were collected by cardiac puncture. The blood was collected into EDTA containers.

The EDTA anticoagulated blood was centrifuged at 4,000 rpm for 5mins and plasma removed. The cells after thorough washing with normal saline and constitution of cell lysate using ice-cold distilled water were used for SOD, catalase and total glutathione (GSH) estimations within twelve (12) hours.

Laboratory procedures.

All reagents were commercially purchased and the manufacturer's standard operating procedure (SOP) strictly followed. Cayman's Superoxide Dismutase Assay kit, USA, which is a modification of that used by Malstrom *et al.* (1975) was used for SOD determination. Cayman's catalase Assay kit, USA which is a modification of that used by Johansson and Borg, (1988) was used for the determination of red cell catalase activity. Total glutathione was estimated using the Cayman's Total Glutathione Assay kit, USA which is a modification of that used by Eyer and Podhradsky (1986).

Statistical analysis

All values were expressed as means ±SD. Statistical significance was determined by ANOVA and then the student's t-test using SPSS Version 16 windows 8 and the individual comparisons were obtained by the Least Significant. Difference (LSD) and Turkey method. Differences between groups were considered significant at PO.05 and highly significant at P< 0.01.

Results

The results generated from this study show that there was no significant difference (P> 0.05) in the initial body weight of the animals in all the groups. However, there was a significant decrease (P< 0.05) in the mean final body weight of group II (diseased control) (161.3± 11.3g) when compared with that of group I (healthy control) (182.5± 15.8g). Also the mean value of final body weight of group III (172.5± 7.5g) was significantly (PO.05) lowered compared with that of group I (182.5 ± 15.8g). See table 1.

The mean value of the final body weight of groups III, IV, V, and VI (172.5± 7.5g, 173.8±11.9g, I75.6± 14.5g, and 175.0± 13.9g respectively) did not change significantly (P> 0.05) and also did not achieve statistically significant difference except for that of group III (172.5± 7.5g) when compared with group I (healthy control). However that of group II (161.3 ± 11.3g) was significantly (P < 0.05) lowered when compared with those of groups III, IV, V and VI.

The mean value of the liver weight of group II (disease control) (3.3± 0.29) was significantly (P< 0.05) lowered when compared with those of groups I, III, IV, V and VI (5.9± 0.6g, 5.0 ± 0.2g, 5.2 ± 0.2g, 5.4 ± 0.4g, and 5.3 ± 0.3g respectively).

Table 1: Effect of aqueous leaf extract of *Cymbopogon citratus* (lemongrass) on body and liver weights of albino rats in paracetamol-induced hepatotoxicity.

Groups/treatments	Initial body weight(g)	Final body weight(g)	Liver weight(g)
I Healthy control (n=8)	173.8 ± 16.9a	182.5 ±15.8a	5.9±0.6a
II Disease control (n=8)	170.9 ±13.5a	161.3 ±I1.3b	3.3±0.2b
III lOOmg lemongrass/kg" body weight (n=8)	171.9 ±12.5*	172.5 ± 7. 5C	5.0±0.2C
IV 200mg lemongrass/kg b.w. (n=8)	171. 3± 14.1a	173.8±11.9a,c	5.2±0.2C
V 300mg lemongrass/kg b.w. (n^8)	173. l±14.la	175.6 ±14.5a,c	5.4±0.4a'c
VI 400mg lemongrass/kg b.w (n=8)	172.5 ±11. 3*	175.0 ±13.9a,c	5.3±0.3C
ANOVA			
F- Value	0.057	3.348	50.942
P - Value	P>0.05	P < 0.05	P < 0.05

Values are means ± S.D. Means in the same column with different superscript letters) are significantly different, P < 0.05 (One-way ANOVA followed by post-hoc LSD and Turkey).

In addition the mean values of liver weight of groups III, IV, and VI were significantly (P < 0. 05) lowered when compared with group I. That of group V did not change statistically (P > 0.05) when compared with group I (healthy control).

The results generated from this study show that there was no significant difference (P> 0.05) in the initial body weight of the animals in all the groups. However, there was a significant decrease (P< 0.05) in the mean final body weight of group II (diseased control) (161.3± 11.3g) when compared with that of group I (healthy control) (182.5± 15.8g). Also the mean value of final body weight of group III (172.5± 7.5g) was significantly (PO.05) lowered compared with that of group I {182.5 ± 15.8g).

The mean value of the final body weight of groups III, IV, V, and VI (172.5± 7.5g, 173.8±11.9g, I75.6± 14.5g, and 175.0± 13.9g respectively) did not change significantly (P> 0.05) and also did not achieve statistically significant difference except for that of group III (172.5± 7.5g) when compared with group I (healthy control). However that of group II (161.3 ± 11.3g) was significantly (P < 0.05) lowered when compared with those of groups III, IV, V and VI.
The mean value of the liver weight of group II (disease control) (3.3± 0,29) was significantly (P< 0.05) lowered when compared with those of groups I, III, IV, V and VI (5.9± 0.6g, 5.0 ± 0.2g, 5.2±0.2g, 5.4±0.4g, and 5.3 ± 0.3g respectively).

In addition the mean values of liver weight of groups III, IV, and VI were significantly (P < 0. 05 lowered when compared with group I. That of group V did not change statistically (P > 0.05) when compared with group I (healthy control).

Table 2 shows the mean values of oxidative and anti-oxidative parameters of the experimental groups and control. The MDA value for group II (diseased control) (1.60± 0. 17 nmol/ml) was significantly higher (P< 0.05) when compared with those of groups I, III, IV, V and VI (0.45± 0. 09, 1.45 ± 0. 20, 1.13 ± 0.14, 0.94± 0.07, and 0. 75 ± 0.09nmol/ml respectively).

In addition, the mean values of MDA of groups III, IV, V, VI, were significantly (P< 0.05) higher when compared with that of group I (healthy control). However there were significant decreases (P<0.05) in the MDA mean values down the groups III, to VI.

The mean values of catalase for group II (13.50 ± 2.88nmol/min/ ml) was significantly lower (P< 0.05) when compared with those of groups I, III, IV, V, and VI, (25. 25 ±1. 91, 20. 25 ± 2. 60, 21. 50 ± 2.27, 22.88± 3.31, and 23.00 ± 2. 88nmol/min/ml respectively).

There were no significant differences (P>0.05) in the value of catalase activities among groups III, IV, V, and VI. Also mean values of catalase activities in groups V and VI did not change significantly (P>0.05) when compared with that of group I.

The mean value of SOD of group II (diseased control) (0.03 ± 0.01 U/ml) was significantly low (P< 0.05) when compared with those of groups I, III, IV, V and VI (0.20± 0.02, 0.05 ± 0.01, 0.10 ± 0.01, 0.12 ± O.Oland 0.19 ± 0.01 U/ml respectively). Also the mean values of SOD of groups III, IV, V and VI were significantly (PO.05) lower when compared with that of group I (healthy control). However, the mean values of SOD were significantly (P<0.05) increased down the groups III to VI.

The mean values of total glutathione for groups II and III (6.51 ± 0.90, 7.23 ± 0.58 uM respectively) were significantly lowered (P< 0.05) when compared with that of group I (healthy control) (12.26 ±1.27 uM). Also those of groups III, IV, V, and VI (7.23 ± 0.58, 9.64 ± 0.55, 9.82 ± 0.88, and 9.98 ± 0.54 uM respectively)

were significantly (P< 0.05) lower than that of group I (12. 26 ± 1. 27 uM). There were no significant differences (P> 0.05) in the mean values of glutathione among groups IV, V, and VI. Also there was no significant (P> 0.05) difference between the mean values of glutathione of groups II and III.

Discussion

In recent years, attention has been focused on the role of biotransformation of chemicals to highly reactive metabolites that initiate cellular toxicity. Many compounds, including clinically useful drugs, can cause cellular damage through metabolic activation of the chemical to highly reactive compounds such as free radicals, carbenes and nitrenes (Gupta et al., 2004). Moreover, the hepatotoxicity of acetaminophen has been attributed to the formation of toxic metabolites when a part of paracetamol is activated by hepatic cytochrome p450 to a highly reactive metabolite N-acetyl- P- benzoquinoneimine (NAPQI). NAPQI is initially detoxified by conjugation with reduced glutathione to form mercapturic acid. However, when the rate of generation of NAPQI exceeds the rate of detoxification by reduced glutathione, it oxidizes tissue macromolecules such as lipid or -SH group of proteins and alters the homeostasis of calcium after depleting glutathione (Ojo et al., 2006).

However, there are a number of mechanisms which cells utilize to protect themselvesfrom the toxic effects of free radicals generated by acetaminophen and other toxicants. According to Halliwell et al. (1992), superoxide dismutase SOD eliminates superoxide anion by converting it to hydrogen peroxide H202, which can be rapidly converted to water bycatalase and glutathione peroxidase. The hepatocytes and red blood cells are primereservoirsof reduced glutathione for the detoxification of free radicals and other xenobiotics. This helps to naturally equip the body in eliminating oxidants. However, if the rate of generation ofthese toxicants (oxidants and free radicals) exceeds the cells' capacity to eliminate them, oxidative stress is said to haveensued. This process may cause peroxidative tissue damage in inflammation, cancer, and toxicity of xenobiotics with consequent cell death The results of the present study indicate that there is significant (P<0.05) decrease in the activity of the red cell catalase of the rats exposed to toxic dose of paracetamol who did not receive treatment with aqueous leaf extract of lemongrass (Group II) when compared with the healthy animals (Group 1). Similarly, the activity of red cell SOD and the levels of red cell total glutathione of the animals exposed to toxic dose of paracetamol (Disease control- Group II) were significantly (P<0.05) decreased when compared with those of group I (Healthy animals).

The enzymatic antioxidant defense system is the nature protector against lipid peroxidation and oxidative damage. SOD, catalase and glutathione peroxidase enzymes are important scavengers of superoxide ion and hydrogen peroxide. These enzymes prevent generation of hydroxyl radical and thus protect the cellular constituents from oxidative damage. The non- enzymatic antioxidant, glutathione is one of the most abundant tripeptides present in the liver.

Its functions are mainly concerned with the removal of free radical species such as hydrogen peroxide, superoxide radicals, alkoxy radicals and maintenance of membrane protein thiols and as a substrate for gluthathione peroxidase and glutathione -S-transferase (Prakash et al., 2001). In the present study the decreased levels of GSH has been associated with an enhanced lipid peroxidation in paracetamol treated rats. However, administration of aqueous leaf extract of C. citratus significantly (P<0.05) increased the level of total glutathione in a somewhat dose- dependent manner It was observed from the present study that aqueous leaf extract of lemongrass significantly (P<0.05) increased the red cell SOD activity in a dose dependent manner in paracetamol-induced hepatotoxicity in rats. This underscores the fact that Cymbopogon citratus aqueous leaf extract can reduce reactive free radicals that might lessen oxidative damage to the tissues and improve the activities of the hepatic antioxidant enzyme.

Catalase is an enzymatic antioxidant widely distributed in all animal tissues and the highest activity is found in the red cell and in the liver. Catalase decomposes hydrogen peroxide and protects the tissue from highly reactive hydroxyl radicals. Therefore the reduction in the activity of this enzyme as seen in the paracetamol treated animals (group II) of the present study may result in a number of deleterious effects due to the accumulation of superoxide radicals and hydrogen peroxide. However administration of aqueous extract from C. citratus significantly raised the activities of catalase in paracetamol induced liver damage in rats to prevent the accumulation of excessive free radicals and protected the liver from paracetamol intoxication. This finding is consistent with those of Deepak et al.(2007).It is likely that the hepatoprotective role ofjCymbopogon citratus_which stems from its antioxidant properties as reported by Koh et al. (2012) may be traceable to its chemical composition. Several research works have been done aiming at enlarging the knowledge of the chemical composition of the essential oil ofCymbopogon leaves (Chisowa et al., 1998). These studies have been revealing that although the chemical composition of the essential oil of Cymbopogon citratus varies according to the geographical origin, the compounds as hydrocarbon terpenes, alcohols, ketones, esters and mainly aldehydes, have constantly been registered

(Costa,1986;Trease,1996). According to Omotade, (2009) the leaves of Cymbopogon citratus contains saponins, sesquiterpenes, lactones, steroids, flavonoids. Flavonoids are reported to exhibit antioxidant activity (Ramanathan et al., 1989) and are effective scavengers of superoxide anions (Robak and Grygleuski, 1988). The aqueous leaf extract of lemongrass may haveexhibited hepatoprotection due to its possible antioxidant content attributable to flavonoids.

According to Singh et al.(1991) saponins especially terpene glycosides enhance natural resistance and recuperative powers of the body.

Conclusion

The present study indicates that aqueous leaf extract of Cymbopogon citratus exhibits protective role in animals exposed to toxic dose of paracetamol by its ability to enhance free radical scavenging activity which enhanced the levels of the antioxidants measured.

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