

Short Communication

***Garcinia kola* extract reduced cisplatin-induced kidney dysfunction in rats**

Okoko Tebekeme¹ and Awhin Ejiro Prosper²

¹Biochemistry Division, Department of Chemical Sciences, Niger Delta University. P. M. B. 71, Yenagoa, Bayelsa State, Nigeria.

²Department of Medical Biochemistry, Delta State University, Abraka, Delta State, Nigeria

Accepted 22 October, 2007

The effect of *Garcinia kola* extract on cisplatin-induced renal insufficiency in rats was studied. A total of fifteen rats were used for the study and were split into three groups of five rats per group. Rats in group I were normal controls. Renal insufficiency was induced in rats of groups II and III by a single intraperitoneal administration of cisplatin (5 mg/kg b.w.). After three days, rats in group III received a daily dose of 10 mg/kg b.w. of the extract orally for another seven days. Renal insufficiency was later assessed by serum urea, serum creatinine and urine protein levels. The results showed that the levels of the measured parameters which were elevated as a result of the cisplatin administration were brought to near normal levels by the *G. kola* seed extract. This indicates that *G. kola* possessed significant potentials of ameliorating mild kidney insufficiency induced by the anticancer drug, cisplatin.

Key words: *Garcinia kola*, cisplatin, renal insufficiency, urea, creatinine.

INTRODUCTION

Garcinia kola Heckel (family Guttifera) is a dicotyledonous plant found in moist forest and grows as a medium sized tree up to about 12 m high. The seeds have a bitter taste hence the plant is commonly called bitter kola in Nigeria. As a result of this bitter taste, the seeds have been consumed as a stimulant (Atawodi et al., 1995). The seeds have been used in the treatment of liver disorders, and diarrhoea (Iwu et al., 1990; Braide, 1991). It has also been used in the treatment of diabetes, bronchitis and throat infections (Tita et al., 2001; Orié and Ekon, 1993). The plant has been used traditionally as a natural antimicrobial (Ositelu et al., 2004). *G. kola* has been reported to possess some hepatoprotective and aphrodisiac properties (Akintowa and Essien, 1990; Adaramoye and Adeyemi, 2006; Ajibola and Satake, 1992). Other notable bioactivities are its bronchodilatory effect (Orié and Okon, 1993) and its proposed effectiveness in the treatment of dermatological disorders associated with melanin pigmentation (Okunji et al., 2007). *G. kola* is now known to contain a high content of biflavonoid compounds (Iwu, 1986) and its remarkable bioactivities have been ascribed principally to the possession of these flav-

onoids due to their enormous antioxidant activities (Adaramoye et al., 2005; Emerole et al., 2005).

Based on these findings and others, this work investigates the effect of a methanolic extract of *G. kola* in cisplatin-induced renal insufficiency in rats. Cisplatin (also called cisplatinum, carboplatin) is an anticancer drug and dose dependent nephrotoxicity is a major limiting effect in its chemotherapy (Stein et al., 1978).

MATERIALS AND METHOD

Animals

Fifteen adult rats of the Wister strain were purchased from the Nigerian Institute of Medical Research, Yaba Lagos. After purchase, they were acclimatised to laboratory conditions for one week in the animal housing facility owned by the Biological Sciences Department of the Niger Delta University. The rats were placed in specially designed laboratory cages and fed with growers' mash and water *ad libitum*.

Chemicals and reagents

All chemicals were standard laboratory reagents and solvents of Analar grade and were obtained from registered distributors hence were used without further purification.

*Corresponding author. E-mail: tebebuddy@yahoo.com

Table 1. Effect of *Garcinia kola* seed extract on the levels of serum creatinine, urea, and urine protein.

Groups	Creatinine (mg/dl)	Urea (mg/dl)	Urine protein(mg/dl)
I (normal controls)	1.7 ± 0.11	15.6 ± 0.12	0.43 ± 0.21
II (cisplatin alone)	2.8 ± 0.88*	28.4 ± 0.43*	3.54 ± 0.07*
III (cisplatin+extract)	1.8 ± 0.18*	18.4 ± 0.15*†	0.72 ± 0.15*†

Table 1. Values presented as the means ± S.E.M of readings from 5 individual rat sera and urine. (*significantly different from group I; † significantly different from group II).

Preparation of extract

G. kola seeds were purchased from a local market. It could not be guaranteed whether all the seeds were from the same source. The seeds were chopped to smaller pieces after the outer coats were removed. They were air-dried and finally ground to fine powder using a blender. The resulting powder was transferred to an 80% methanol solution in a round-bottomed flask, and kept airtight for three days. It was filtered and the filtrate was concentrated by means of a rotary evaporator at 40°C. The resulting residue was further air-dried. The percentage yield was 18.6% of the dried sample. A 0.05 g/ml of the extract was prepared in distilled water.

Treatment of animals

All experimental procedures were approved by the ethical committee of the Niger Delta University. The rats were split into three experimental groups of five rats per group. Rats in groups II and III were intraperitoneally-treated with cisplatin (5 mg/kg body weight) in order to induce mild renal insufficiency. Three days after the cisplatin administration, rats in group III were given the *G. kola* extract (10 mg/kg body weight) once for seven days via the oral route. Rats in group II were not given any extract while rats in group I were not treated with cisplatin hence were normal controls. They were all allowed unlimited access to water and growers' mash *ad libitum* throughout the duration of the experiment.

Collection of sera and urine

The cages had special provisions for urine collection, thus urine was collected by means of special canisters that were attached to the cages for the last night before the end of the experiment and analysed. Thereafter, each rat was given light anaesthesia in a chloroform saturated chamber and dissected. Under this condition, blood was drawn through cardiac punctures immediately by means of hypodermic syringes and delivered into sterile sample canisters which had no anticoagulant. Blood was allowed to clot and centrifuged at 3500 rpm for 10 min using a bench centrifuge. Each supernatant (serum) was decanted into sterile tubes and immediately analysed for kidney function.

Assessment for kidney function

Serum creatinine and urea were determined at 37°C colorimetrically by the modified Jaffe method, and the modified Berthelot-Searcy enzymatic method respectively. They were assayed using reagents obtained from assay kits (Quimica Clinica Aplicada, Spain).

Urinary protein was quantified by the Biuret method using bovine serum albumin as the standard.

Statistical analysis

Results of representative measures were expressed as mean ± S.E.M. The data were analysed using a two-tailed student's t-test

were appropriate. A confidence level exhibited at $p < 0.05$ was considered statistically significant.

RESULTS

The serum urea, creatinine, and urine protein levels in the rats are shown in Table 1.

A significant increase ($P < 0.05$) in the serum creatinine, urea and urine protein was observed in rats in group II when compared with rats in group I. Cisplatin induced almost a two-fold increase in the creatinine and urea levels, and an eight-fold increase in the urine protein levels over the controls rats. All the indices were reduced to near control levels when the *G. kola* extract was administered to the rats treated with cisplatin (group III).

DISCUSSION

Dose related nephrotoxicity which predisposes to renal dysfunction is a side effect of cisplatin chemotherapy. Early studies on cisplatin suggested that it was cell cycle phase non-specific being an alkylating agent, however extensive research has it that it has complex and variable effects on the cell cycle (Haskel, 1990; Chabner and Myers, 1989; Raefsky and Wasserman, 1992).

Chemotherapeutic levels known to induce relatively mild acute kidney failure in rats is thought to be a single dose of 5 mg/kg body weight which peaks about 3 – 5 days (Stein et al., 1978; Singh, 1989) thus the choice of a single dose of 5 mg/kg body weight, and the three days exposure before the administration of the extract for the present study.

During the period of study, no mortality was recorded and no physical signs of weakness were noticed. Since the cisplatin induced alterations were obvious in the parameters assessed, it was taken that only a mild renal insufficiency was induced.

The near-control-levels of the measured indices of the rats in group III clearly show that the extract ameliorated the toxicant induced nephrotoxicity.

Lipid peroxidation has been implicated in various kidney disorders especially chemically induced disorders thus the amelioration of the renal insufficiency may be due to the inhibition of lipid peroxidation. In *G. kola*, the active component responsible for the inhibition of lipid peroxidation is tentatively identified as isoflavones- a group

of flavonoids (Adegoke et al., 1998) and biflavonoids (Iwu, 1986) and the reported remarkable bioactivities have been credited principally to the possession of these flavonoids due to their enormous reported antioxidant activities (Adaramoye et al., 2005; Emerole et al., 2005) but it has also been reported that flavonoids also possess some pro-oxidant effects (Awad et al., 2001; Galati and O'Brein, 2004). Some remarkable bioactivities have been ascribed to terpenes (Zhou et al., 2006) which are important phytochemicals and may be present in *G. kola*. Thus the use of *G. kola* as part of the formulations for diets of kidney failure patients is recommended but fractionation of the various components is necessary so that each fraction could be exposed to tests. Progress in this area will also extend the frontiers of cisplatin chemotherapy.

REFERENCES

- Adaramoye OA, Nwaneri VO, Anyanwu KC, Farombi EO, Emerole GO (2005). Possible anti-atherogenic effect of kolaviron (a *Garcinia kola* seed extract) in hypercholesterolaemic rats. *Clin. Exp. Pharm. Physiol.* 32: 40–46.
- Adefule Ositelu AO, Adefule AK, Oosa BO, Onyenefa PC (2004). Antifungal activity of *Garcinia kola* nut extract as an ocular bacterial isolates in Lagos. *Nig. Qt. J. Hosp. Med.* 14: 112-114. (not cited in the text. Please provide).
- Adegoke GO, Kumar MV, Sambaiha K, Lokesh BR (1998). Inhibitory effect of *Garcinia kola* on lipid peroxidation in rat liver homogenate. *Indi. J. Exp. Bio.* 36: 907-910.
- Ajibola AO, Satake M (1992). Contributions to the phytochemistry of medicinal plants growing in Nigeria as reported in the 1979-1990 literature – A preview. *Afr. J. Pharm. Pharm. Sci.* 22: 172-201.
- Akintonwa A, Essien AR (1990). Protective effects of *Garcinia kola* seed against paracetamol – induced hepatotoxicity in rats. *J. Ethnopharmacol.* 29: 207-211. (Not cited in the text. Please provide).
- Atawodi S, Mende P, Pfundstein B, Preussmann R, Spiegelhalder B (1995). Nitrosatable amines and nitrosamide formation in natural stimulants, *Cola acuminata*, *Cola nitida* and *Garcinia kola*. *Food. Chem. Toxicol.* 33: 625-630.
- Awad HM, Boersma MG, Boeren S, Van Bladeren PJ, Vervoort J, Reijtens IM (2001). Structure-activity study of the quinone/quinone methide chemistry of flavonoids. *Chem. Res. Toxicol.* 14: 398-408.
- Braide VD (1991). Pharmacology Effects of Chronic Ingestion of *Garcinia kola* Seeds in the Rats. *Phytother. Res.* 4: 39 – 41.
- Chabner BA, Myers CE (1989). Clinical pharmacology of cancer chemotherapy. In Devita, V. T., Helman, S., and Rosenberg, S. A. eds. *Cancer: Principles and practice of oncology*. 3rd ed. Philadelphia: J. B. Lippincott Co.
- Emerole GO, Farombi EO, Adaramoye OA, Adeyemi EO (2005). Comparative study on the antioxidant properties of flavonoids of *Garcinia kola* seeds. *Pak. J. Med. Sci.* 21:331-339.
- Galati G, O' Brien PJ (2004). Potential toxicity of flavonoids and other dietary phenolics: Significance for their chemoprotective and anticancer properties. *Free Rad. Biol. Med.* 37: 287-303.
- Haskel CM (1990). *Cancer treatment*. 3rd ed. Philadelphia, W. B. Saunders Co. pp. 55-56.
- Iwu M, Igbok OA, Okunji CO, Tempesta MS (1990). Antidiabetic and aldose reductase activities of biflavonones of *Garcinia kola*. *J. Pharm. Pharmacol.* 42: 290-292.
- Iwu M (1986). Biflavonones of *Garcinia*: Pharmacological and biological activities. In *Plant Flavonoids in Biology and Medicine*, V. Cody, E., Middleton and J.B. Harbone eds. Alan R. Liss, New York. pp. 485-488.
- Okunji C, Komarnytsky S, Fears G, Poulev A, Ribnicky DM, Awachie, PI, Ito Y, Raskin I (2007). Preparative isolation and identification of tyrosinase inhibitors from the seeds of *Garcinia kola* by high-speed counter-current chromatography. *J. Chromatogr. A* 1151: 45-50.
- Orie NN, Ekon EU (1993). The Bronchodilator effects of *Garcinia kola*. East. pp55-56 preview. *Afr. J. Pharm. Pharm. Sci.* 22: 172-201.
- Raefsky EL, Wasserman TH (1992). Combined modality therapy. In: Perry, M. C. ed. *The chemotherapy source book*. Baltimore, Williams and Wilkins. pp. 114-116.
- Singh J (1989). A possible mechanism of cisplatin-induced nephrotoxicity. *Toxicology* 58: 71-80.
- Stein J, Lifschitz M, Barnes L (1978). Current concepts on the nephrotoxicity of acute renal failure. *Am. J. Physiol.* 243: F171-F181.
- Tita RK, Odeigah PG, Agomo PU, Bassey E (2001). Some properties of Medicinal Plants used by the Igbos of Nigeria. In: Triats, tracts and traces. (Germany). Edited by Wolfgang Kreis. pp. 209-210.
- Zhou Q, Xie H, Zhang L, Stewart JK, Gu X, Ryan JJ (2006). cis-Terpenones as an effective chemopreventive agent against aflatoxin B1-induced cytotoxicity and TCDD-induced P4501A/B activity in HepG2 cells. *Chem. Res. Toxicol.* 19: 1415-1419.