Effect of *Garcinia kola* upon alcohol induced Hyperuricemia

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https://doi.org/10.21816/ijfmi.v4i2

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ABSTRACT

Introduction: Garcinia kola has been hypothesized to enhance alcohol clearance or oxidation, however, its influence on alcohol-induced hyperuricemia is yet to be documented. Therefore, this study investigated the hyperuricemia effect of Garcinia kola on ethanol-induction.

Materials and Methods: 20 male adult albino rabbits were adopted and categorized into five experimental groups of A- E. Rabbits in group "A" (control) was treated with normal diet and distilled water only, while group "B" was given Garcinia kola plus fed in a ratio of 1:4 and later orally received 0.125g (20%) ethanol /kg body weight (small dose). Group "C" and D animals received Garcinia kola plus fed in a ratio of 1:4 in addition; administered 0.550g and 1.100g (20%) ethanol per kg body weight (as moderate and large doses) respectively. Group "E" was given 1.100g ethanol/ kg body weight only. The different regimens adopted for all animals were conducted for 12 weeks and the ethanol delivered as a single daily dose. Institution Ethical approval was obtained with ref No: DELSU/CHS/MBC/70/144.

Result: Changes in serum urate induced by the different treatment procedures and statistical analysis demonstrated that the toxicant caused 43.4% increase from the basal value (0 Week) and 33.7% when compared with the control, meanwhile in the presence of G. kola, groups B, C, and D generated a change of 6.9%, 8.3%, and 11.7% respectively when compared the normal group. At the 12th week, the % change from basal values for G. kola treated groups are 15.7, 17.3, 18.1 with increasing ethanol dosage.

Conclusion: From this study, G. kola demonstrated potential of attenuating ethanol-induced hyperuricemia, albeit human studies are required to corroborate animal model for predicting potential human consequences.

Keyword: *Ethanol, Garcinia kola, Hyperuricemia, Serum Urate*

INTRODUCTION

In these contemporary times, alcohol (ethanolic form) is rated amongst the highly misused pharmacological substance. [1] Alcohol toxicosis with associated health complications have emanated from ingesting ethanol and allied products.[2] Consequentially, health anomalies, complications and challenges from alcohol consumption are being attributed to its (-OH) group attached to the hydrocarbon chain with high propensity of readjusting and altering NAD^+/NADH ratios of both mitochondria and cytosolic origin. [3, 4] These NAD^+/NADH alterations generates acetaldehyde metabolites which are toxic to hepatocytes and other tissues associated with its biotransformation. [5] However, the extent of alcohol toxicosis is chiefly conjoins the length of exposure of cellular systems to alcoholic products. [6]

In humans, uric acid is dissipated as end product of purine degradation and can be generated via the activity of xanthine oxidase. [7] Since uric acid is a weak diprotic acid with low solubility index, an imbalance between the generation (endogenous or exogenous sources) and the elimination of uric acid, is consequential in its retention in blood (hyperuricemia) and its deposition in tissues. [8]

Documentations have expounded alcohol consumption to escalate serum urate, eventually culminating into hyperuricemia. [9, 10, 11, 12] Hyperuricemia when unchecked or monitored can degenerate into kidney diseases, cardiovascular complications and most significantly gouty attack in susceptible individuals. [13] Depict below (Fig 1) are some metabolic consequences of ethanol on intermediary metabolism of other substrates.

The dependence of mankind on plant products directly or indirectly cannot be over flogged, however such dependence has been translated into both pharmacological and therapeutic purposes in a wide variety of illnesses. [14] *G. k.* is commonly identified as bitter kola and contributes immensely to the socio-cultural development of some local communities in Western and Central African as it relates to their application in ceremonies, entertainments and ethnomedicinal practices. [15] Although all parts of this "*Wonder*" plant (as nick named) are useful, the most valuable part of *G. k* are the seeds which is masticated for its astringent taste and medicinal assertions.

Garcinia kola species have gained so much recognition in the Sub-Sahara regions because of its medical usefulness. [16, 17] The kernel contains myriads of bioactive and phytochemical agents such as tannins and flavonoids. Other constituents of *G. k* kernel include the biflavonoid - kolaviron complex. This complex scientifically possesses antimicrobial, antioxidant, neuroprotective, aphrodisiac properties, anti-inflammatory, and other health beneficial ingredients. [18, 19] In addition, laboratory trials reveal the seed extract of *G. kola* to inhibit the growth of Ebola virus [20]

However, of all the medicinal implications and applications documented and accruable to *G. kola*, little or no information has been attributed to this plant in the management and treatment of hyperuricemia. Sequel to this, alcohol abuse and addiction is escalating daily, portraying serious health and economic challenges to numerous societies globally. Hence, the search for efficacious plant-base substances in ameliorating or reverting the affiliated metabolic disturbances of ethanol with respect to hyperuricemia would be of global interest particularly in Africa were alcohol intake has outrageously risen due to social attachments. In addition, diseases like atrial fibrillation (AF)[21] which is associated with high serum uric acid would be effectively managed if this research portrays uric acid attenuating properties.

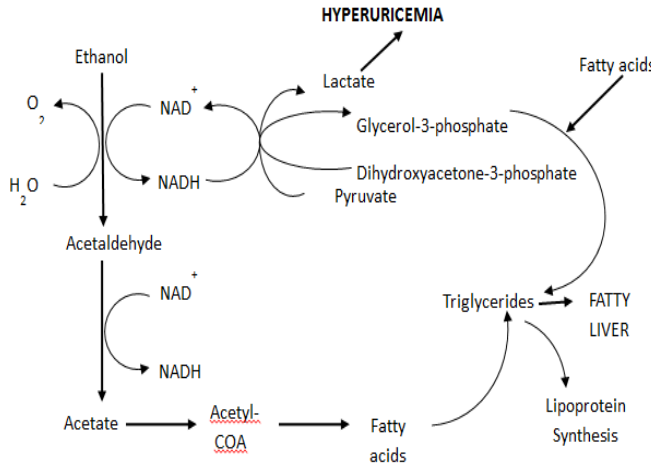


Fig. 1: Metabolic consequences of ethanol on intermediary metabolites. [9]

MATERIALS AND METHODS

Experimental animal

Under controlled standard room temperature of 25–28 ºC and illumination of 12 hours dark:12 hours light cycle, 20 male English rabbits (*Sylvilagus nuttallii* spp - mean weight 1.50kg) inbred at the animal Unit of Medical Biochemistry Department, Delta State University, Abraka were utilized. The animals were fed *ad libitum* to commercially available growers' pellets (Top feed, Sapele-batch No: BB/2018/2277) and distilled water. Placed in improvised metal hutches, the animals were subdivided into five groups with four members per grouping.

Ethical Authentication

Ethical regulations were adopted in accordance to PHS[22] guidelines for animal protection and welfare with experimental protocol consented by the Institutions Ethical Committee (IEC) (ref No: DELSU/CHS/MBC/70/144).

Extract Preparation

The method of Akpantah *et al*, [23] was adopted but with slight modification as not to digress from the original and natural state of consumption by humans. Having purchased the *G. kola* seeds from Obiaruku local market in Ukwuani, Delta State, Nigeria, the outer flaky brownish covering was peeled off and the seeds chopped in bits before air-dried until completely water free and a constant weight obtained. The dried seeds were ground into fine powder with the aid of a Binatone blender (Model BLG 452). The yield obtain was weighed and then preserved in the dried and solid form until required for use.

Animal treatment

Rabbits in group "A" (control) were treated with normal diet and distilled water only. Animals in group "B" were given *Garcinia kola* and fed in a ratio of 1:4 (20g *G.K*/100g) and later orally received 0.125g (20%) ethanol / kg body weight (representing small dose) as a single daily dose, while group "C" animals received *Garcinia kola* and fed in a ratio of 1:4 alongside 0.550g (20%) ethanol per kg body weight (representing moderate dose). In the same manner, rabbits in group "D" were given *Garcinia kola* and fed in a ratio of 1:4 with 1.100g (20%) ethanol /kg body weight (indicating large dose). Group "E" was given 1.100g ethanol/ kg body weight only. The different regimens adopted for all animals were conducted for 12 weeks of which body weight, mortality, behavioural and food consumption were monitored. Dose equivalence of ethanol introduced to each rabbit was adopted from Onyesom and Oriero. [24] Note that the *G.k* was mixed in a ratio of 1:4 which is 20g *G.K*/100g fed (%w/w).

Homogenization/Sample collection

Within the 12 weeks of feeding and treatment, whole blood was collected via the ear vein by means of a 2ml hypodermic syringe. The collection was performed after the 4th, 8th, and 12th week into plain bottles, allowed clotting and then, centrifuged (Model ALC4217MKII) at 1,200 x g for 5 minutes at 28ºC (room temperature). The obtained serum was transferred into plain bottles for urate assay.

Biochemical Assay

The uricase method of Caraway, [25] was adopted for serum urate and was estimated using commercial test kit supplied by Randox Laboratories Ltd. Crumlin UK.

Data Analysis

The results were presented as the mean standard values (mean ± SD) of three replicates. Students t-test was applied to compare results of each of the test groups with control group at 95% probability level.

RESULTS

The results generated from this study are indicated in Figures 2 and 3 as well as Table 1. Figure 2 depicts fed consumption (mixed meal with *G. kola*) of the animals within the 12 weeks of administration. The food intake of the negative control declined from the 6th, 7th and 8th weeks of treatment when compared to other groups. Furthermore, the body weight changes within the 12th weeks experimental period was reflected in Figure 3. This indicated a statistically significant ($p<0.05$) reduction in the toxicant group from the 5th to the 12th week of administration. Changes in serum urate induced by the different treatment procedures and statistical analysis demonstrated that the toxicant caused 43.4% increase from the basal value (0 Week) and 33.7% when compared with the negative control, meanwhile in the presence of *G. kola*, groups B, C, and D generated a change of 6.9%, 8.3%, and 11.7% respectively when compared with the normal group. Animal mortality was absent alongside hypersensitivity (which lasted for about 5 minutes) upon ethanol intake.

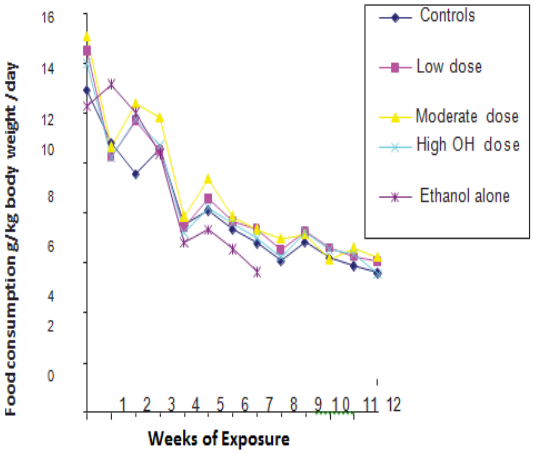
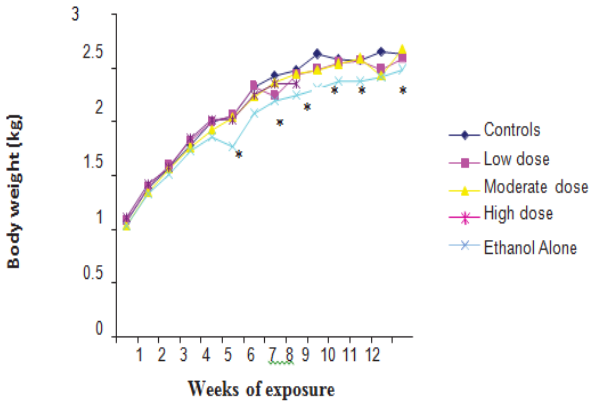


Fig. 2: Food consumption during *G. kola* exposure in male albino rabbits



* $p<0.05$ compared to controls, from 5th week to 12th week of exposure

Fig. 3: Body weights change during *G. kola* exposure in male albino rabbits

Table 1: Serum urate changes induced by ethanol and

Groupings	Treatment concentration (µmol/L)	Serum Urate			
		Week 0	Week 4	Week 8	Week 12
A	Control (Distilled H_2O)	112.06±4.4	123.35±6.6 (10.1%) [a]	127.60±5.1 (13.9%) [a]	119.23±3.9 (6.4%) [a]
B	*G. kola* feed + 0.125g Ethanol/kg bwt	110.10±5.5	123.71±4.5 (12.4%) [a] (0.3%) [b] (14.3%) [c]	129.22±4.7* (17.4%) [a] (1.3%) [b] (17.5%) [c]	127.40±4.4 (15.7%) [a] (6.9%) [b] (25%) [c]
C	*G. kola* feed + 0.550g Ethanol/kg bwt	110.11±3.9	127.05±4.3 (15.4%) [a] (2.9%) [b] (11.3%) [c]	130.07±5.1* (18.1%) [a] (1.9%) [b] (15.7%) [c]	129.17±3.9 * (17.3%) [a] (8.3%) [b] (23.3%) [c]
D	*G. kola* feed + 1.110g Ethanol/kg bwt	112.85±4.1	129.12±3.7 * (14.4%) [a] (4.7%) [b] (9.5%) [c]	135.55±6.8* (20.1%) [a] (6.2%) [b] (10.6%) [c]	133.30±5.1* (18.1%) [a] (11.7%) [b] (19.5%) [c]
E	Ethanol alone	111.09±6.0	141.35±6.3 (27.2%) [a] (14.9%) [b]	149.90±7.5 (34.9%) [a] (17.5%) [b]	159.25±8.6 (43.4%) [a] (33.7%) [b]

- ✓ n= 4; values are expressed as mean ± SD *$p<0.05$ Garcinia kola (G. k) treated group compared with ROH group alone
- ✓ a % Change with respect to baseline value for each group
- ✓ b % Change with respect to group A (Control)
- ✓ c % Change with respect to group E (Toxicant)

DISCUSSION

Recently, explosive interest has evolved from studying and scrutinizing the involvement of medicinal plants in disease control and treatment. Such involvements have produced either positive ameliorative potentials or adverse metabolic disturbances.[6]

Evidence unveiled from this study depicts a significant weight reduction in the ethanol alone treated group (Fig. 3). The consequences of the observed weight difference can be attributed to previous postulations that ethanol reduces nutrient intake via appetite inhibition and mucosal degeneration.[26] Although food consumption in ethanol alone group was not significantly different from other groups before the 4th week, a gradual decrease in food consumption was indicated after the 6th week as ethanol dosage were elevated (Fig 2).

This investigative inquisition further demonstrated that ethanol consumption significantly elevated serum urate with increasing ethanol concentrate (Table 1). This increase corroborates previous scientific postulations of the potentiality of ethanol to elevate plasma urate in both man and animals.[10, 11] Relative to mammals, plasma urate is lowered by the transformation of urate into allantoin in the hepatocytes, however, due to the non-functional uricase gene, humans tend to experience fluctuations in serum uric acid level than other mammals. [27, 28] The increased urate (i.e. resultant hyperuricemia) could further compound the incidence of gout and hypertension upon chronic ethanol intake. [29, 30]

Hyperuricemia as a metabolic consequence, is associated with ethanol breakdown. When ethanol is consumed, cytosolic NADH/NAD$^+$ ratio is raised causing increased lactate/pyruvate ratio (Fig 1) mediated via lactate dehydrogenase. The generated hyperlacticaemia enhances decreased P^H (acidosis) thereby lowering the renal capacity to eliminate urate, hence the development of secondary hyperuricemia. [31, 32, 33] The increased NADH/NAD$^+$ ratio in the mitochondria also elevates β-hydroxyl butyrate/acetoacetate ratio with development of ketosis. [34] However, the induced ketosis coupled with enhanced purine breakdown may further compound and escalate hyperuricemia in blood. [35]

Prior to animal treatment, baseline values of serum urate for each group were obtained and depicted as 0week. Upon examination, the negative control group indicated progressive increase in serum urate from the 0week to the period of 12weeks. This however was contrary to groups fed with *Garcinia kola* (*G.k)*, as serum urate declined after 8weeks of exposure with percentage changes as reflected in Table 1

Observation drawn from this investigation suggests the possibility of *Garcinia kola* interfering either with ethanol absorption and its elimination pattern from the GIT or urate metabolism in the kidney. Studies have elucidated that ethanol absorption and elimination patterns can be influenced by meal composition (food) via gastric emptying and elimination by first-pass metabolism.[36,37] Experiments conducted with solid food upon 0.15g/kg dose of ethanol, showed that CHO had the highest effects on ethanol absorption/ elimination followed by fat and protein contents.[38] In addition, the proximate analysis conducted on *G. k* revealed high amount of CHO with minimal quantities of fat and protein.[39] Based on previous researches, it can be deduced that the nutritional contents of *G. k* might influence ethanol absorption/elimination hence the drop in serum urate as seen from this study.

Furthermore, it's been established that ethanol alters NADH/NAD$^+$ ratio with enhanced hyperlacticaemia that competes with urate during tubular excretion. [32, 33] However, a decline in serum urate as indicated in this study might be attributed to the ability of *G. kola* to facilitate urate clearance by the nephrons. Although scientific evidences are scarce or non-existing concerning such relationship, studies have shown protective tendencies of *G. kola* on kidney functions. [40, 41]

Ethanol treatment might have possibly aggravated purine breakdown or impede urate clearance via urine. But the coadministration of *G. kola* as a fed mixture at different ethanol doses seems to attenuate the condition that could generate increased serum urate.

Conclusion:

In this study, *G. kola* consumption mixed in animal fed exhibited urate reducing potential upon various doses of ethanol consumption, however human investigation is advocated to ascertain whether animal-to-human extrapolation would be admissible as anti-intoxicating principle of *G. kola* has already been examined.

Recommendation:

More would have been deciphered or comprehended if an extension of this research correlates the *G.k.* extract constituents and mechanism on renal function. Moreover, since this study reported data generated for short-term treatment with *G.k.*, it is recommended that long-term study be evaluated on kidney biomarkers. This will further enhance our understanding of *G.k.* potentials in ethanol oxidation and elimination.

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