Effect of *Garcinia Kola* in Ivermectin-Induced Toxicity in the Hematology of Treated Rats (*Rattus Novergicus*)

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Garcinia kola (GK) is prized in African herbal medicine for its diverse uses, including social, economic, and medicinal purposes. This study examined the dose-dependent toxicity of ivermectin and the protective effects of *Garcinia kola* extract on the hematological parameters of Wistar rats. A

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total of 32 Wistar Rats (120 – 150g) were randomly chosen from PAMO University of Medical Sciences' Animal House. They were acclimatized for two weeks. Divided into 4 main groups (A, B, C, D), which were further subdivided into 2 subgroups each (A1, A2, B1, B2, C1, C2, D1 and D2) with each subgroup containing 4 rats. Subgroup A: negative control (0 mg/kg BW of ivermectin, no *Garcinia kola*). Subgroup A2: positive control (0 mg/kg BW of ivermectin and 20 mg/kg/ml *Garcinia kola*). Test Subgroups 1 (B1, C1 and D1) received respectively doses of 10 mg/kg/ml, 20 mg/kg/ml, and 40 mg/kg/ml of Ivermectin intraperitoneally, Subgroups 2 (B2, C2 and D2) received respectively the same doses followed by oral administration of *Garcinia kola* at 20 mg/kg BW of rat per ml daily for 7 days, starting 24 hours after toxicity induction. On the eighth day, each rat was anesthetized with chloroform. 5mls of blood was collected via cardiac puncture into EDTA bottle for the analysis of the CBC parameters. ANOVA was used to test the hypotheses at alpha = 0.05. The result showed a significant dose-dependent difference in anaemia indicators in ivermectin induction but there was no significant change in after bitter kola treatment. The study has shown that ivermectin inflicted haematological toxicity particicular in particular in anaemic indicators but bitter kola couldn't ameliorate the effect of the toxicity.

1. INTRODUCTION

With the shifting of attention from synthetic drugs to natural plant products, plants that were once considered of no value are now investigated, evaluated and developed into drugs [1]. One of such plant is *Garcinia kola*. *Garcinia kola* (*G. kola*) is commonly known as bitter kola, male kola or false kola; 'Adu' in Esan, 'Miji-goro' in Hausa, 'Akilu or Ugolo' by the Igbos, 'Orogbo' among the Yoruba tribes of Nigeria. It is a medium-sized tree growing up to 12 m tall and 1.5 m wide and usually found in the Rainforest of Nigeria [2].

Toxicants whether household, environmental, industrial or biological have impacted on both the environment and the living components existing in it [3-11]. Ivermectin (IVM) is a macrolide antibiotic produced from a fungus first isolated from a soil sample in Japan, *Streptomyces avermitili*s. The avermectins are a class of chemicals that have a novel mode of action against nematode and arthropod parasites [12,13-16]. All major gastrointestinal and lung nematodes and certain ectoparasites of cattle, sheep, horses and swine, intestinal nematodes, ear mites and sarcoptic mange of dogs, infective-stage heartworm and microfilariae of dogs, and certain intestinal nematodes of chickens are effectively eliminated by IVM [17], Eight fractions of avermectins contains a-major and b-minor components for the prevention of cellular hyperpolarization [18]. Ivermectin (IVM), doramectin (DME) are the two main types of avermectins [19]. Both drugs are fermentation products of avermectins. IVM is formed from a B1-a, and B1-b (80: 20) mixture of natural avermectin, used in animals and human antiparasitic medication [20]. It is oxidised in the liver primarily and excreted in the faeces and urine causing significant alterations in the liver and kidney tissues [21]. The persistence of avermectins' residues in the tissues and fluids is dose-dependent and produces variable side effects from mild to extremely severe [22,23], up to CNS (central nervous system) depression as a sign of poisoning [24].

Historically, plants have provided a source of inspiration for novel drug compound as plant-derived medicines have made large contributions to human health and well-being. *Garcinia kola* (bitter kola a name sometimes also used for G. afzelii) is a specie of flowering plant belonging to the Mangosteen genus Garcinia, of the family Clusiaceae (also known as Guttiferae). It is found in Benin, Cameroon, The Gambia, Democratic Republic of Congo, Ivory Coast, Mali, Gabon, Ghana, Liberia, Nigeria, Senegal and Sierra Leone. Its natural habitat is subtropical or tropical moist lowland forests [25]. The fruit, seeds ("bitter kola nuts") and bark of the plant have been used for centuries in folk medicine to treat ailments from coughs to fever [26]. According to a report from the Center for International Forestry Research, *Garcinia kola* trade is still importhe indigenous communities and villages in Nigeria [27]. *Garcinia kola* is traditionally used by African folk healers who believe that it has purgative, antiparasitic, and antimicrobial properties. The seeds are used for liver disorders, bronchitis, throat infections, colic, head or chest colds, and cough [28].

More than 900 drugs have been implicated in causing liver injury [29], and it is the most

common reason for a drug to be withdrawn from the market, Drug induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures. There is limited knowledge of the mechanism and effects of *Garcinia kola* on the liver due to sparsity of research around that area and the fact that it is an important traditional nut. Not many works have been reported by scholars on the effect of *Garcinia kola* in health and its ability to hepato-repair. The chemical properties of *Garcinia kola* has been claimed to be effective in the treatment of liver disorders, bronchitis, cough in traditional medicine. The liver metabolic activities were significantly reduced in rats by inducing toxicity with the use of Ivermectin and then compared to the control groups and the treatment with *Garcinia kola* [30]. This will prove beneficial in hematology improvement therapy as well as increasing its metabolic activities.

Less priority has been given to some of the native edibles we take in, as it relates to the effect it has on the livers metabolic activity. Therefore *Garcinia kola* which is an accepted well known masticatory in Nigeria especially in the southern part of the country was chosen because studies have been reported by [31] that *Garcinia kola* has protective effect against variety of experimental hepatotoxins. It is on this note that this research work is designed to establish if ethanolic extract of *Garcinia kola* has any effect on hepatotoxicity of ivermectin. Despite the acclaimed myriad of uses of G. kola seeds in the folklore medicine of Nigeria, the effects of the seed extract on the haematological parameters (Hb, PCV, RBC, MCV, MCH, MCHC, WBC, platelets, neutrophils and lymphocytes) of male rats has not been reported in the open scientific literature. It is a well-known knowledge that *Garcinia kola* has antioxidants properties as a result of its large phytochemical ranges of flavonoids, alkaloids and others. These properties if harnessed properly and utilized as medicaments in cases of hematotoxicity, may go a long way in ameliorating the toxicity of most toxicant (e.g Ivermectin). By evaluating the hematological parameters, as indices of toxicity, the oral administration of *Garcinia kola* will

provide a direction to follow during desired repairs of hematotoxicity incidents [23].

This study is focused at investigating the ameliorative effects of *Garcinia kola* on Ivermectin induced hematologicl toxicity in Wistar rats (*Rattus Norvegicus*).

2. MATERIALS AND METHODS

2.1 Study Design

The design for The Singular, Acute intraperitoneal (I.P) dose-dependent administration of Ivermectin and the subsequent co-administration of *Garcinia kola* (GK), per oral, to the Rats (*Rattus Norvegicus*) is as tabulated in the Table 1.

The animals were randomly assigned to different Control and Test groups (8 animals in each group and divided as 4 animals per subgroup). The experimental groups consist of: (A) Control (no Ivermectin); (B) Ivermectin, 10 mg/kg body weight; (C) Ivermectin, 20 mg/kg body weight and (D) Ivermectin, 40 mg/kg body weight. After two weeks of acclimatization, the treatment started by the animals being singularly administered with 1 ml of different equivalent doses of the toxicant, Ivermectin, intraperitoneally (IP). After 24 hours of intoxication, oral administration of 1 ml of equivalent dose of Garcinia (20mg/kg BW) was given to the rats in subgroups (A2, B2, C2 and D2) daily till the end of the experiment. On the eight day, all the animals were sacrificed using anaesthetic chloroform. 5 ml of blood samples were collected by cardiac puncture [32,33] into anticoagulation bottle with ethylenediaminetetraacetic acid disodium (EDTA). The samples were analysed for full blood count.

2.2 Study Area

The study was conducted in the Animal house of PAMO University of Medical Sciences, Port Harcourt, Rivers State. Nigeria with feeding environment: temperature is 20–26°C, relative humidity is 40 – 70% and animals were under a 12 h light-dark circle.

Table 1. Treatment design

Treatment	Groups:		A	B	C	D		
Subgroups	A1	A2	B1	B2	C1	C2	D1	D2
IVM mg/kg (IP)	0	0	10	10	20	20	40	40
GK mg/kg Per oral(daily)	0	20	0	20	0	20	0	20
Duration(days)	8	8	8	8	8	8	8	8

2.3 Study Population

A total of 32 healthy Male Wistar Rats (Rattus Norvegicus) weighing between 120 – 150g, was purchased from the Experimental Animal House of PAMO University of Medical Sciences, Port Harcourt, Rivers State. Nigeria. Rats obtained after two weeks of acclimatization was used.

2.4 Sample Collection

The doses of Ivermectin (IVM) selected were 0, 10, 20, and 40 mg/kg body weight (BW). The highest dose was close to 3/4 the LD50 (50 – 55 mg/kg B.W.) intraperitoneal dose for rats [32,33]. Suspension of the equivalent dose per weight of rats of Ivermectin in saline was administered by intraperitoneal (I.P) route as a single dose. Biochemical Procedures: Complete Blood Count (CBC); was determined using the Automation method Mindray BC 5300 by [34].

2.5 Quality Assurance

For accuracy of laboratory results obtained, known controls were used to assay every functional parameter

2.6 Statistical Analysis

The data were expressed as mean ± standard deviation, and the significance of the data between groups was tested by SPSS 26.0 software. The different studies undertaken were statistically analyzed by One way Analysis of Variance and Post hoc Tukey- Kramer multiple comparison test [35]. The level significance was set at alpha 0.05.

3. RESULTS

Table 2 compares hematological parameters among subgroups treated with ivermectin only. Significant differences were found in Hb, HCT, RBC, and MCHC levels between some subgroups. However, TWBC, MCV, MCH, and PLT levels showed no significant differences.

Table 3 compares hematological parameters among *Garcinia kola* treatment subgroups (A2, B2, C2, and D2). No significant differences were found in Hb, HCT, TWBC, RBC, MCV, MCH, MCHC, and PLT levels between the subgroups. Post hoc analysis confirmed the absence of significant differences in all comparisons (p > 0.05).

Table 4 compares hematological parameters within subgroups (A1 vs A2, B1 vs B2, C1 vs C2, and D1 vs D2). No significant differences were observed in Hb, HCT, TWBC, RBC, MCV, MCH, MCHC, and PLT levels between corresponding subgroups. All comparisons yielded p-values greater than 0.05, indicating no significant variations within each subgroup pair.

Table 2. Comparison of Haematological Parameters among Ivermectin Only Treated Subgroups

Groups	HB(g/dl)	HCT (%)	TWBC $(X10^9/L)$	RBC $(X10^6/L)$	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT $(X10^3/l)$
A1	12.9±0.4	44.4±2.7	7.5±2.1	7.0±0.2	63.3±6.3	18.4±1.2	29.1±1.1	873.5±54.6
B1	13.1±0.4	43.8±1.3	7.6±1.3	7.0±0.2	62.3±1.6	18.7±0.5	30.1±0.3	895±187.6
C1	13.7±1.1	47.3±3.6	7.7±4.4	7.4±0.8	63.7±3.8	18.5±0.5	29.0±1.1	829.8±148.8
D1	15.2±0.9	54.2±3.3	10.9±4.8	8.5±0.4	64.0±2.9	18.0±0.6	28.1±1.0	881.8±146.6
F-value	7.48	7.62	0.90	8.66	0.14	0.70	3.05	0.16
P-value	0.004	0.003	0.46	0.002	0.94	0.57	0.07	0.92
Remark	SS	SS	NS	SS	NS	NS	NS	NS
Post-hoc								
A1 vs B1	NS	NS	NS	NS	NS	NS	NS	NS
A1 vs C1	NS	NS	NS	NS	NS	NS	NS	NS
A1 vs D1	SS	SS	NS	SS	NS	NS	NS	NS
B1 vs C1	NS	NS	NS	NS	NS	NS	NS	NS
B1 vs D1	SS	SS	NS	SS	NS	NS	NS	NS
C1 vs D1	NS	NS	NS	NS	NS	NS	NS	NS

NS: Non-significant
SS: Statistically significant

Table 3. Comparison of Haematological Markers among *Garcinia kola* Treatment Subgroups

Groups	HB(g/dl)	HCT (%)	TWBC $(X10^9/L)$	RBC $(X10^6/L)$	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT $(X10^3/l)$
A2	12.9±1.1	43±4.2	8.5±3.7	6.7±0.2	64.6±6.4	19.4±1.8	30.1±0.8	926.8±176.7
B2	14.1±1.3	49.3±6.2	4.9±1.8	8.3±0.9	58.0±14.9	17.9±1.0	28.7±1.2	1004±65.9
C2	13.5±0.5	45.3±3.1	7.0±2.6	7.3±0.4	62.0±3.1	18.5±0.4	29.8±1.1	896.3±12.3
D2	12.8±2.1	44±7.3	5±1.6	7.1±1.5	62.7±3.7	18.1±1.0	28.9±0.4	856±80.6
F-value	0.78	1.00	1.82	2.21	0.44	1.41	2.15	1.49
P-value	0.53	0.42	0.20	0.14	0.73	0.29	0.15	0.27
Remark	NS	NS	NS	NS	NS	NS	NS	NS

NS: Non-significant
SS: Statistically significant

Table 4. Comparison of haematological parameters between each subgroups

Groups	HB(g/dl)	HCT (%)	TWBC $(X10^9/L)$	RBC $(X10^6/L)$	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT $(X10^3/l)$
A1	12.9±0.4	44.4±2.7	7.5±2.1	7.0±0.2	63.3±6.3	18.4±1.2	29.1±1.1	873.5±54.6
A2	12.9±1.1	43±4.2	8.5±3.7	6.7±0.2	64.6±6.4	19.4±1.8	30.1±0.8	926.8±176.7
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C1	13.7±1.1	47.3±3.6	7.7±4.4	7.4±0.8	63.7±3.8	18.5±0.5	29.0±1.1	829.8±148.8
C2	13.5±0.5	45.3±3.1	7.0±2.6	7.3±0.4	62.0±3.1	18.5±0.4	29.8±1.1	896.3±12.3
D1	15.2±0.9	54.2±3.3	10.9±4.8	8.5±0.4	64.0±2.9	18.0±0.6	28.1±1.0	881.8±146.6
D2	12.8±2.1	44±7.3	5±1.6	7.1±1.5	62.7±3.7	18.1±1.0	28.9±0.4	856±80.6

a: Statistically significant at P < 0.05

4. DISCUSSION

The result of this study in Table 2 explains the comparison of the control and the test subgroups that were administered Ivermectin in different doses. Across the groups, hemoglobin, hematocrit and red blood cell count showed statistical significance ($P < 0.05$) whereas total white blood cell count, mean cell volume, mean cell hemoglobin, mean corpuscular hemoglobin concentration and platelet showed no statistical significance, the parameters that were of statistical significance also showed increasing values, this could imply, that the dose dependent increase in Ivermectin administration across the group could be responsible for the significant increase in the values of hemoglobin, hematocrit and red blood cell count at $P<0.05$. To understand the particular group that had significant differences, Post-hoc analysis was done, when group A1 was compared to D1, a significant increase in D1(HB, HCT and RBC) was seen in their mean levels, significant increase was also seen in D1(HB, HCT and RBC) when compared to B1. This result points to the fact that there was actually a dose dependent toxicity of ivermectin on the rats across the different groups, following significant increase in the blood erythropoietic functions which can

cause hematological fluctuations. Some studies that observed alterations in hematopoietic system parameters may indicate interference with the hematopoietic function of the bone marrow system by exogenous substances [22,36]. Contrarily another study on ivermectin haematotoxicity, reported decrease in hemoglobin levels in ivermectin induced rats, although there was insufficient evidence to prove that the decline in hematological parameters was due to ivermectin suppression of the hematopoietic system [37].

The present study was designed to scientifically scrutinize the ethno-medicinal benefit of *G. kola* seed in evaluating its therapeutic effect on the wistar rats. According to the result, Table 3 showed no significant difference in the levels of the haematological parameters studied (HB, HCT, RBC, TWBC, MCH, MCHC, MCV). This could be due to the fact that the concentration of *Garcinia kola* administered was not sufficient enough to effect significant difference as the level of insult was increased across the group. A plausible explanation for this occurrence may be that, the presence of higher amount of *G. kola* would have been used if a proper effect was to be gotten from hematopoietic activities for a short term treatment. In agreement with this study,

another a notable change in erythrocyte values when different concentration of the *Garcinia kola* was administered to fish [38]. The finding on the medicative effect of *Garcinia kola* extract on hematological parameters such as hemoglobin, park cell volume and red blood cells is in disagreement with a different study that reported a reduction in Hb (g/100ml), Hematocrit (%), and erythrocytes (10^6ml) [39]. In addition, another study reported that PCV, Hb, and RBC value increased in response to the administration of *Garcinia kola* [40] but this study reported that *Garcinia kola* had no haematological effect on the rats within the seven days of administration across the groups.

As shown by the levels of hematological parameters in Table 4, the comparison between A1 and A2; B1 and B2; C1 and C2; D1 and D2, indicated that there was no ameliorative effect of *Garcinia kola* in the haematological parameters of the rats, as it relates to the effect of induced toxicity by ivermectin. This finding could be due to the fact that after the toxic insult, the red blood cells that were injured were not properly repaired by the *Garcinia kola* as a result of the short duration of the treatment thus, the red blood cells were eliminated from the circulation. The result of this experiment also showed that *Garcinia kola* caused no significant increase or decrease in total white blood cell, this result is similar to the findings of other authors [41] where they demonstrated that white blood cell count did not show any significant change in values. Some literatures that were in disagreement with the findings of this study were basically long term treatment of *Garcinia kola*, where they reported steady increase in the red blood cell count (RBC), Packed cell volume (PCV), Hemoglobin concentration (Hb), Mean cell Hemoglobin concentration (MCHC) [41,42].

5. CONCLUSION

The findings from the present investigation showed that induction of ivermectin has a toxic effect on hematological parameters, dose dependently, In addition the result obtained from this work is seen to be in agreement with the implication of *Garcinia kola* seed in traditional medicine and most herbal preparations for treatment of blood disorders, which is also contributing to the screening of its natural antioxidant properties. Therefore, providing persuasive scientific support for the traditional use of *Garcinia kola* in the treatment of blood disorders.

6. RECOMMENDATION

The study performed was an acute study which can be provided as a guide for future chronic studies, therefore further investigations is required especially chronic studies to encompass all the effects of *Garcinia kola*. Being an acute study, the duration limitation could not allow the elucidation of both the toxicity effect of ivermectin on the blood and the ameliorative effect of *Garcinia kola* on the hematological toxicity as shown by the parametric findings, therefore it is suggested that further chronic studies should be carried out to completely understand the directions the parameters will follow and also histopathological and histochemical studies should also be carried out to understand how blood cells itself will respond to the toxic insult and also the remediating effect of *Garcinia kola*.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

ETHICAL APPROVAL

This research was approved by the Ethics Committee of the University, PAMO University of Medical Sciences with Approval No: PUMS/REC/07.21/VOL.1/0110, after careful scrutiny of the Research design, mode of sampling and disposal of animal carcase.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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