Effect of *Garcinia Kola* (Heckel) on Pharmacokinetic Parameters of Rifampicin

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ABSTRACT

Most herbal products are used with prescription drugs and have been found to affect the pharmacokinetics of these prescription drugs. The effect of concurrent administration of *Garcinia kola* on the pharmacokinetic parameters and penetration profile of rifampicin into the lung tissues were investigated using animal model. Albino rats in group A received rifampicin 10 mg/kg alone orally; Group B and C received 100 mg/kg and 200 mg/kg of *Garcinia kola* extract respectively for 10 days and on day 11, rifampicin 10 mg/kg was given. Blood samples were withdrawn from each group at 0.5, 1, 2, 4, 8, 12 and 24 h time intervals respectively. Blood samples were also withdrawn from the lungs in each group after 24 h and assayed to determine the concentration of rifampicin in the lungs. Both 100 and 200 mg/kg of *Garcinia kola* showed reduction in the maximum concentration ($C_{\text{max}}$), area under concentration (AUC), clearance (Clr), and time for plasma concentration to decrease by half (t1/2) of rifampicin. *Garcinia kola* significantly ($P = 0.01$) decreased concentration of rifampicin in the lungs by 32% and 39% respectively. Our results show that the co-administration of *Garcinia kola* and rifampicin impairs the bioavailability of rifampicin and its penetration into the lungs.

Keywords: *Garcinia Kola*, Pharmacokinetics, Rifampicin

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INTRODUCTION

Plants naturally produce large number of diverse bioactive compounds used for management of ailments (Altemimi et al., 2017; Dranca and Oroian, 2016). Thus the use of herbs in disease management has historical and traditional background with a belief that they are safe (Mohammad and Mohammad, 2009). Traditional knowledge of the values of these plants were earlier downplayed by pressures of modern lifestyle, orthodox medicine and effects of rampant deforestation (Onyekwelu et al., 2015); However current researches has fanned into flame the indispensable use of plants in disease management. Recently, the rate of self-medication with herbs and food supplement is on the increase and this has led to greater potentials for interaction between these agents when administered concurrently with prescription drugs (Ulbricht et al., 2008). Though people believe that natural plants are safe, they contain active constituents in varying proportions which make them potential drugs as well as poisons. Of great concern is the fact that as herbal drugs and food supplement becomes more popular, the more the consumers, health professionals and manufacturers tend to overlook the issue of safety concerning them. It is on this ground that most of the commonly used herbs are under researched by researcher Clinical Pharmacokinetics is the use of principles derived from pharmacokinetics in the management of patient drug therapy. Basic parameters that influence these principles are Peak Plasma Concentration ($C_{\text{max}}$) and the time it takes to reach this peak ($T_{\text{max}}$). These two parameters are influenced by rate of absorption. Other factors include elimination half-life which is very useful in the calculation of drug dosage regimen; Volume of distribution which is simply a proportionality constant whose sole purpose is to relate the plasma concentration (Cp) and the mass of drug (X) in the body at a time. It is not a physiological volume”. [4].Volume of distribution is very vital in determining how readily an administered drug is distributed between the body tissues and blood; Clearance which is an inevitable parameter in the calculation of loading dose and dose needed to maintain steady state concentration.

In Africa, *Garcinia Kola* (Clusiaceae), known as bitter kola is a treasured multipurpose tree indigenous to West and Central Africa. Garcinia Kola tree is often referred to as “wonder plant” because all of its part is medicinal (Manourová et al., 2019; Onasaniwo et al., 2016). Its seed has been used in several ways in the management of a good number of health problems (Ezeigbo et al., 2016) which include liver disease, cold, cough aphrodisiac, voice coarseness (Farombi, 2011; Alabi et al., 2017), and neurodegenerative diseases such multiple sclerosis (Omotosho et al., 2018).Other studies shows it has antibacterial activities against multi-drug-resistant *A. baumannii* (Badger-Emeaka et al., 2018), anti-inflammatory and pain relieving effects (Bironke et al., 2015; Tchimene et al., 2016). Some of the phytochemicals compounds in *G. kola* include: oleoresin, tannin, saponin, alkaloids, cardiac glycoside,
flavonoids and metallic ions like aluminium, magnesium, calcium, copper. Its flavonoid extract - kolaviron possess anti-malarial, wound healing properties (Nwaehujor, et al., 2015; Tshibangu, et al., 2016), is effective in treatment of benign prostatic hyperplasia (Kalu, et al., 2016) and can be clinically active against ischemia/reperfusion injuries (Akinmoladun et al., 2015)

Studies have shown that flavonoids and metallic ions form various intermolecular complexes with a variety of compounds (Terashima et al., 2002, Esimone, 2002a). Earlier studies have shown that ethanol extract of Garcinia kola has activities against the antimicrobial properties of some commonly used antibiotics such as tetracycline, gentamycin, penicillin G, ofloxacin, co-trimoxazole and amoxicillin-clavulanic acid, when administered concurrently (Esimone et al., 2007; Esimone et al., 2002a; Esimone et al., 2003).

Rifampin is a semisynthetic antibiotic produced from Streptomyces mediterranei. It has a broad antibacterial spectrum, including activity against several forms of Mycobacterium. In susceptible organisms it inhibits DNA-dependent RNA polymerase activity by forming a stable complex with the enzyme. It thus suppresses the initiation of RNA synthesis. Rifampin is bactericidal, and acts on both intracellular and extracellular organisms. (William, 2001) Rifampicin is an antitubercular medicine which helps to treat tuberculosis and meningococcal meningitis. A common side effect of rifampicin includes reddish colouration of the urine, sweat, sputum and tears. WHO has recommended that tuberculosis (TB) should be treated with a combination of anti-TB drugs, preferably in fixed dose combinations (FDC) to enhance compliance. Rifampin is one of the first-line and most important anti-TB drugs approved for use in combination with other anti-TB drugs for the treatment of TB. Earlier researchers have shown that rifampicin exhibits variable bioavailability upon administration, being less soluble and highly permeable. (Ashokraj et al., 2008). Hence worldwide, the recommended administration of rifampicin is before breakfast. Therefore, challenges such as suboptimal or failed treatment resulting from interaction with another drug, food or herb could occur (NerraI and Glassroth, 2003).

The most valued part of the tree is the seed, which is commonly eaten to prevent or cure gastric disorders and for their typical astrangent taste (Manourová et al., 2019). This is worked by the support of Oluwatosin et al., who reported that some people consume Garcinia kola seeds instead of cola nuts coming from Cola spp (Oluwatosin et al., 2014). There are no reports of harmful effects resulting from overdosing with G. kola. (Konziase, 2015) hence it is safe for consumption. Esimone et al., 2003 has shown that in Nigeria, most patients on antibiotics therapy also consume G. kola habitually or as a result of the general belief that it has anti-infective properties. Therefore, this study was designed to investigate the effect of co-administration of G. kola extracts on the pharmacokinetic parameters and penetration profile of rifampicin into the lung tissue.

**MATERIALS AND METHODS**

**Drug and Plant Material:** Rifampicin (Sanofi-aventis Ltd, Lagos Nigeria) and Garcinia kola were used. Garcinia kola seeds used in this study were obtained locally in Nsukka (Southeast Nigeria), authenticated at the Department of Pharmacognosy, University of Nigeria, Nsukka and stored in their herbarium.

**Animals:** Albino rats (190-300g) of both sexes were obtained from the Faculty of Veterinary Medicine, University of Nigeria, Nsukka. The animals were monitored under light and dark cycle in metabolic well-ventilated rodent cubicle before commencement of the experiment for the purpose of acclimatization. Measures like separate housing by sex was taken to avoid conception. Food and water were allowed them within the period of monitoring but was withdrawn 12 h before the commencement of the experiment. The animals were handled according to internationally and locally approved protocols for experimental animals.

**Experimental protocol**

**Extraction of Garcinia kola:** The seeds of G. kola were washed, peeled, dried and pulverized in a milling machine into powder (gunning form). About 2 kg powder of the G. kola was placed into 10 L maceration bottle with 5 L of ethanol and was macerated for 72 h, after maceration, the solvent was sieved out with porcelain cloth and later with 22 cm filter paper. The extract was evaporated to dryness using rotary evaporator. The sample was collected and stored in refrigerator at 4 °C.

**Beer-lambert’s Plot:** The standard solutions of Rifampicin was prepared in the concentration of 1 to 8 μg/ml and dissolved in 3 ml plasma. The plasma solutions were further diluted with 10 % v/v of methanol and determine the absorbance of the samples using UV spectrophotometer (Sp-6-450 UV/Vis Pye unicam). In the method, protein free samples were prepared by mixing each sample of 5ml plasma with equal volume of 10 %v/v of methanol; the samples were centrifuged and filtered (Onyishi et al., 2014). The absorbances of the filtrates collected were determined at 375nm using spectrophotometer.

**Administration of Garcinia kola/Rifampicin and determination of plasma drug concentrations in rats:** Fifteen albino rats were divided into three groups: A, B and C. The experiment was carried out in 3 Phases. In Phase 1, Group A received 10 mg/kg of rifampicin alone orally. In Phases 2 and 3, Groups B and C received 100 mg/kg and 200 mg/kg of G. kola extract respectively for 10 days and on day 11, rifampicin 10 mg/kg was given as in group A. Blood samples were collected from each group at 0.5, 1, 2, 4, 8, 12 and 24 h time intervals respectively (Onyishi et al., 2014) for the determination of plasma drug concentration in the rats.

**Determination of the effects of Garcinia kola on rifampicin penetration into the lungs:** At the 24th h, following the oral administration of rifampicin and G. kola in each group, all the animals were sacrificed with chloroform and their lungs collected. Blood was also withdrawn from the lung area with their plasma collected after centrifugation. For the purpose of removing contaminated blood, non-bacteriostatic saline was used to rinse the lungs. Each lung was homogenized individually and centrifuged to collect fluid and stored in a refrigerator for preservation before assay.

**Determination of pharmacokinetic parameters:** Following a single oral administration of rifampicin, different pharmacokinetic parameters were determined using non-compartmental method as implemented in WinNonLin pharmacokinetic programs (version 5.0). (Pharsight Corporation, Mountain View California). Pharmacokinetic properties of rifampicin were determined for each animal.

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Statistical Analysis
In analyzing this result, it was assumed that after administration, rifampicin followed first order kinetics. Results were expressed as mean ± standard deviation (SD) and statistical comparisons for differences among the treatment groups were made using the students’ paired t-test and one way analysis of variance (ANOVA). Data were analyzed at 95% confidence interval with statistical significance set at P < 0.05.

RESULTS
Effect of Garcinia kola (100 mg/kg) on rifampicin (10 mg/kg) plasma concentration in rats following a single oral administration of rifampicin: When rifampicin was administered alone, it attained its maximum concentration of 18.24 ± 1.38 μg/ml at 1 h, while co-administration with G. kola at 100 mg/kg achieved a maximum concentration of 16.58 ± 1.07 μg/ml at the same 1 h. The difference in the concentration of rifampicin alone and that of rifampicin and 100 mg/kg G. kola was statistically significant (P = 0.03). The concentrations 18.00 ± 0.80, 16.57 ± 0.45, 16.29 ± 0.33 and 11.30 ± 1.29 μg/ml were obtained at 2, 4, 8, 12 and 24 h respectively for rifampicin alone while concentrations 15.92 ± 0.90, 15.05 ± 1.38, 13.92 ± 0.86, 9.80 ± 1.51 and 7.25 ± 1.81 μg/ml were obtained at 2, 4, 8, 12 and 24 h for rifampicin plus 200 mg/kg G. kola. A graphical representation of rifampicin concentration (μg/ml) at different time intervals following oral administration of rifampicin alone (10 mg/kg) and in the presence of 100 mg/kg Garcinia kola is shown in Fig. 1.

Effect of Garcinia kola (200mg/kg) on rifampicin (10 mg/kg) plasma concentration in rats following a single oral administration of rifampicin: Administration of rifampicin alone attained the maximum concentration of 18.24 ± 1.38 μg/ml within 1 h, which was significantly difference (P = 0.02) compared to the maximum concentration of 16.28 ± 2.41 μg/ml obtained from rifampicin plus 200 mg/kg of G. kola within the same 1 h. The concentrations 18.00 ± 0.80, 16.57 ± 0.45, 16.29 ± 0.42, 15.26 ± 0.33 and 11.30 ± 1.29 μg/ml were obtained at 2, 4, 8, 12 and 24 h respectively for rifampicin alone while concentrations of 15.00 ± 1.58, 14.84 ± 1.51, 12.03 ± 0.86, 9.80 ± 1.51 and 7.25 ± 1.81 μg/ml were obtained at 2, 4, 8, 12 and 24 h for rifampicin plus 200 mg/kg G. kola. A graphical representation of rifampicin concentration (μg/ml) at different time intervals following oral administration of rifampicin alone (10 mg/kg) and in the presence of 200 mg/kg Garcinia kola is shown in Figure 2. There was no statistical difference (P = 0.10) in the plasma concentration of rifampicin produced by 100 mg/kg of Garcinia kola compared to that of 200 mg/kg.

Table 1: Pharmacokinetic parameters of rifampicin (10mg/kg) administered orally alone and Rifampicin+100 and 200 mg/kg of Garcinia kola in rats. (Mean ± SEM) (n = 5)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>RIF ALONE</th>
<th>RIF +100mg/kg GK (% change in parenthesis)</th>
<th>RIF + 200mg/kg GK (% change in parenthesis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_max (hr)</td>
<td>5.60 ± 4.60</td>
<td>5.4 ± 2.69 (3.57)</td>
<td>5.30 ± 1.09 (5.36)</td>
</tr>
<tr>
<td>C_max (μg/ml)</td>
<td>18.60 ± 0.42</td>
<td>16.01 ± 0.52 (13.92)</td>
<td>15.08 ± 0.64 (2.80)*</td>
</tr>
<tr>
<td>C_last (μg/ml)</td>
<td>17.30 ± 0.51</td>
<td>14.52 ± 0.47 (16.07)</td>
<td>16.76 ± 0.74 (3.12)</td>
</tr>
<tr>
<td>AUC (μg/ml/hr)</td>
<td>377.35 ± 2.77</td>
<td>351.67 ± 4.38 (6.80)</td>
<td>309.76 ± 28.4 (17.92)</td>
</tr>
<tr>
<td>t vs (hr)</td>
<td>9.53 ± 2.80</td>
<td>12.6 ± 1.96 (86.78)</td>
<td>2.45 ± 1.21 (74.29)</td>
</tr>
<tr>
<td>V_d (ml/kg)</td>
<td>0.63 ± 0.04</td>
<td>0.60 ± 0.03 (4.76)</td>
<td>0.54 ± 0.07 (14.28)</td>
</tr>
<tr>
<td>Cl_t (ml/kg/hr)</td>
<td>0.009 ± 0.02</td>
<td>0.007 ± 0.04 (22.22)</td>
<td>0.002 ± 0.04 (77.78)</td>
</tr>
<tr>
<td>AUMC (μg/ml/hr)</td>
<td>4739.05 ± 71.56</td>
<td>4257.50 ± 50.55 (10.16)</td>
<td>2420.70 ± 88.64 (48.92)</td>
</tr>
<tr>
<td>MRT (hr)</td>
<td>12.57 ± 0.12</td>
<td>13.9 ± 0.138 (10.60)</td>
<td>15.8 ± 3.66 (25.69)</td>
</tr>
</tbody>
</table>

SEM = standard error of mean; n = number of animal per group, * P < 0.05, The negative sign = decrease in parameter measured; RIF = Rifampicin; GK = Garcinia kola; T_max = time taken for drugs to attain maximal plasma concentration; C_max = maximal drug plasma concentration; C_last = measurable drug plasma concentration; AUC = area under concentration time curve from the time of dosing to the time of the last observation; AUMC = area under moment curve from the time of dosing to the time of last measurable concentration; MRT = mean residence time t vs is terminal half-life; V_d = volume of distribution based on the terminal phase; Cl_t = total body clearance.
Effects of 100 and 200 mg/kg Garcinia kola on Pharmacokinetics parameters of Rifampicin: The concurrent administration of both 100 and 200 mg/kg of G. kola showed a non-significant (P = 0.03) decrease in the T_max from 5.60 ± 4.60 to 5.4 ± 2.69 and 5.60 ± 4.60 to 5.30 ± 1.90 respectively. There was a significant (P = 0.02) decrease in the C_max and from 18.60 ± 0.42 to 16.01 ± 0.52 for 100 mg/kg G. kola and 15.08 ± 0.64 for 200 mg/kg G. kola. The t_1/2 was also significantly (P = 0.001) reduced from 9.35 ± 2.80 to 1.26 ± 1.96 for 100 mg/kg G. kola and to 2.45 ± 1.21 for 200 mg/kg G. kola. There was no statistically significant difference (P = 0.20) in the pharmacokinetic parameters of rifampicin produced by 100 mg/kg of Garcinia kola compared to that of 200 mg/kg. The effect of 100 and 200 mg/kg of Garcinia kola on other pharmacokinetic parameters of rifampicin are showed in Table 1.

Effect of Garcinia kola on rifampicin penetration into the lung
Analysis of the result showed that concentration of rifampicin alone in the lung cavity was 14.63 ± 4.06 while that obtained from rifampicin+100 and 200 mg/kg G. kola were 9.81 ± 0.45 and 8.93 ± 0.5 respectively. The reduction in concentration was statistically significant at P = 0.01. A graphical representation of the effect of Garcinia kola on rifampicin penetration into the lung is shown in Figure 3.

![Figure 3](image36x340to291x489)

Figure 3: Effect of 100 and 200 mg/kg Garcinia kola extracts on the rifampicin penetration into the lungs

DISCUSSION
The significance of food-drug interaction as a variable in bioavailability of drugs is now recognized. A major goal of an interaction study is to determine whether there is any increase or decrease in pharmacokinetic properties of a drug in the presence of an interacting substrate, because this has a potential to influence therapeutic outcomes. Hence the results of this work show that there is potential interaction between rifampicin and Garcinia kola when administered concurrently.

Both doses of Garcinia kola reduced the plasma concentration of rifampicin, which resulted in a decrease in maximum concentration (C_max) and AUC of rifampicin compared to the C_max and AUC observed with rifampicin alone. The mechanism by which G. kola elicits this effect was not investigated, but could be attributed to some factors relating to its constituents. Flavonoids and metallic ions are known to form intermolecular complexes with a wide range of compounds. Previous works on phytochemical analysis of G. kola shows that it contains flavonoids (Terashima et al., 2002, Esimone, 2002a) and metallic ions like aluminum, magnesium, calcium, copper (Esimone et al., 2003). The complex formed is usually non-absorbable which results in reduction in the amount of drug absorbed leading to reduced C_max and AUC. Also, food intake has been reported to increase the absorption of some drugs like sulphasdimidine and griseofulvin while decreasing the absorption of others like penicillins and cephalaxins (Iwu and Igboko, 1986).

In this study the presence of G. kola decreased the absorption hence the concentration of rifampicin which is indicative of reduced systemic bioavailability of rifampicin due to actual herb-drug interaction. This decrease in rifampicin C_max and AUC by G. kola is similar to the work by Igbinoba et al., who recorded decreased C_max and AUC of quinine by G. kola (Igbinoba et al., 2014). In the management of any disease, decrease in C_max of antibiotic leads to microorganism being exposed to sub-optimal concentrations with the possibility of drug resistance by the organism and consequent therapeutic failure.

There was a decrease in the time (T_max) for achieving C_max by rifampicin alone when compared to that of both the 100 and 200 mg/kg G. kola, while there was a significant decrease (P = 0.001) in t_1/2 in the treatment group compared to the group that took rifampicin alone. The decrease in T_max and t_1/2 suggests that G. kola affects both the rate and extent of rifampicin availability for absorption. This implies that the rifampicin dosage regimen needs to be adjusted downwards. Since t_1/2 is a major determinant in the calculation of drug dosage regimen, any drug that affects it will also affect the dosing of such drug.

The clearance of rifampicin was reduced in the treatment group of 100 mg/kg G. kola the reduction became significant (P < 0.01 with 200 mg/kg G. kola. The significant decrease in total clearance (Cl) suggests that G. kola may have induced decreased metabolism of rifampicin. It can be deduced that inhibition of liver metabolic enzymes played important role in the delayed elimination of rifampicin irrespective of the known potent liver enzyme induction by rifampicin. The treatment group also showed increase in the mean resident time (MRT) confirming delayed clearance. MRT is better appreciated when described as the residence time of individual molecules in the body. Each molecule of a drug spends a specific amount of time in the body, some lasting longer than the other, hence the need for calculation of the mean resident time molecules. Increase in MRT suggests that in the presence of G. Kola, some of its molecules still stay longer in the body than when given alone.

Reduced efficacy of tuberculosis therapy (TB) has been shown to be due to but not limited to factors such as high bacterial load and presence of resistant strain resulting to poor therapeutic outcome (Mitchison and Coates, 2004; Sacchettini et al., 2008). Analysis of the concentration of rifampicin in the lung tissue to assess the effect of G. kola on its penetration into the lungs revealed that G. kola caused a significant (P = 0.01) reduction on the concentration of rifampicin in the lung tissue. The plasma concentration of rifampicin for both rifampicin alone and rifampicin plus G. kola was higher than the concentrations obtained from lung tissues. Our result is in agreement with few studies published earlier indicating that in some remote target sites drug concentration can be reduced and the degree of reduction differs from drug to drug. (Din et al., 2017; Rizvi and Saleh, 2017).

The observed decrease in concentration of rifampicin in the lung tissue when taken concurrently with G. kola seed has various therapeutic implications and is of clinical importance especially in the management of Mycobacterium and Staphylococcus species with slightly sensitive strains. This is more likely to lead to therapeutic failure due to initial inadequate
concentration of antibiotic to totally eradicate the microorganism. It could also result to the presence of resistant strains of the organism due to exposure to suboptimal dose since previous studies have shown that the lung is the region where *Mycobacterium* organism inhabits (Kjellsson et al., 2012).

Ascertaining the concentration of administered drug in different cavities like the lungs is of paramount importance because some macrophages and neutrophils needed for the sustenance of *M. tuberculosis* are found growing in such region; hence maximum concentration is inevitable (Kaplan, 2003; Eum, 2010). Furthermore, poor prognosis and development resistance to tuberculosis treatment is associated with the presence and extent of organism growing in these cavities (Chang et al., 2004; Kim, 2008). Hence, any agent that affects the penetration of anti-TB agents into the lung is of great importance as it affects therapeutic goals.

Data analysis showed that there was no significant difference (P = 0.10) in the effect obtained from 100 mg/kg Garcinia kola compared to that of 200 mg/kg, hence the *G. kola* did not show a dose dependent effect.

In conclusion, our results reveal that *Garcinia kola* impairs the pharmacokinetic profile of rifampicin when administered concurrently. It reduced the Cmax, AUC, 1/2 and clearance of rifampicin resulting in decreased bioavailability. It also significantly reduced the concentration of rifampicin in lungs tissue. Hence, patients and health practitioners are advised against concurrent consumption of rifampicin and *G. kola*. If both of them should be taken, a time interval should be observed to avoid interactions.

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