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# Effect of *Garcinia kola* on Atorvastatin Dissolution Profile: An Indication for Possible Drug-Drug Interactions After Oral Administration

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

## Abstract

**Background**: Herb-drug interactions are of growing concern due to the widespread use of herbal supplements alongside medications. These interactions can affect therapeutic outcomes. Understanding and identifying specific interactions is crucial for ensuring safe and effective medication use.

**Objective:** This study investigated the impact of *Garcinia kola*, a common food supplement, on the dissolution of atorvastatin tablets.

**Methods:** The dissolution profiles of atorvastatin tablets were investigated alone and in the presence of varying concentrations of *G. Kola* by mixing 1, 2, or 4g of *G. Kola* powder respectively with the dissolution medium. Samplings were performed at predetermined time points (10, 20, 30, 45 and 60 minutes) and the amount of atorvastatin dissolved was measured using a validated HPLC method. Statistical analyses were conducted to assess the significance of the observed differences.

**Results**: The percentages of atorvastatin released in dissolution medium without *G. kola* were 31.38±11.81, 46.02±8.73, 72.23±33.30, 63.55±27.10, 82.54±31.12% across the sampling time points. Whereas the percentage of drug released were 17.01±7.33, 27.02±8.42, 34.70±13.90, 39.74±13.53, 28.47±11.78% in the presence of 1g *G. kola*; 12.44±5.89, 11.87±1.51, 23.33±5.18, 27.33±8.50, 52.49±11.66% in the presence of 2g *G. kola* and 2.28±3.53, 4.94±7.21, 7.26±9.01, 4.68±7.37, 6.86±8.70% in the presence of 4g *G. kola*. There was a statistically significant difference in the amount of drug dissolved in conditions studied.

**Conclusion:** There was a significant change in the dissolution profile of atorvastatin with increasing concentrations of *G. kola*. This suggests a need to establish the impact of *G. kola* on the disposition of atorvastatin in vivo.

**Keywords:** Garcinia kola, Atorvastatin, In-vitro experiment, Dissolution, Drug-drug interactions, Food-drug interactions

## INTRODUCTION

Lipid metabolism encompasses a range of intricate biochemical processes responsible for the breakdown, storage, and utilization of lipids. However, abnormal lipid metabolism can give rise to elevated cholesterol blood levels (hypercholesterolemia) which may result in atherosclerotic cardiovascular disease (ASCVD) and metabolic disorders such as diabetes and obesity (Natesan & Kim, 2021; Ye *et al.*, 2015). Hypercholesterolemia is among the leading causes of disease burden globally. It accounts for approximately

33% of ischemic heart disease and 20% of stroke (WHO, 2016). The prevalence of hypercholesterolemia in Nigeria, the most populous African country, is approximately 38% (Adeloye *et al*., 2020) therefore its control is highly necessary. Treatment approaches for lipid metabolism disorders are contingent on the specific condition. These may involve lifestyle modifications such as dietary adjustments, regular physical activity, and pharmacological interventions aimed at reducing lipid levels (Su *et al*., 2021; Trentman & Ramakrishna, 2016). Among the medications employed in managing or reducing hypercholesterolemia statins which are secondary metabolites from fungi act by selectively inhibiting hydroxymethyl glutaryl-coenzyme A (HMG-CoA) reductase an enzyme needed in the first step of cholesterol biosynthesis. By this mechanism, statins play a prominent role in managing hypercholesterolemia.

*G. kola* is utilized in folklore medicine to treat liver disorders, hepatitis, diarrhea, laryngitis, bronchial diseases, fever, malaria and gonorrhea (Oluwatosin *et al*., 2014; Tauchen *et al*., 2023). Phytochemical analysis of *G. kola* reveals that the nut contains several phytochemical compounds including oleoresin (Onayade *et al*., 1998), tannins, saponins, alkaloids, and cardiac glycosides, bioflavonoids such as kolaflavone and 2-hydroxybiflavonols, garcinianin, kolaviron, kolanone, gakolanone, garcinoic, garcinal, benzophenones, benzofurans, benzopyran, vitamin E derivatives, xanthones, and phytosterols (Akoro *et al*., 2020; Emmanuel *et al*., 2022; Tauchen *et al*., 2023). Bioactivity screenings have positioned the plant as a possible source of pharmaceutically important drugs. For instance, biflavonoid, kolaviron, isolated from the seed of *G. kola* obtained in Nigeria is known to have a protective effect in rats against liver damage induced by carcinogens (Adedara *et al*., 2015).

*G. kola* nut is a commonly used social masticatory agent in Africa and previous reports have revealed that this nut possesses antimicrobial, antidiabetic, antihypertensive, anti-analgesic, anti-inflammatory (Dogara *et al*., 2022), antimalarial (Oluwatosin *et al*., 2014). lower intraocular pressure effects (Ilechie *et al*., 2020), boost sexual desire, pleasure, and performance activities (Sewani-Rusike *et al*., 2016). It has also been reported to regulate lipid profile (Adejor *et.al*., 2016). . Due to the acclaimed health benefits, many individuals consume *G. kola* as a dietary supplement or herbal remedy,and this is often without the knowledge of healthcare professionals . Also, a number of studies earlier reported an interaction between *G. kola* and drugs such as ofloxacin, quinine, rifampicin and ofloxacin (Esimone *et al*., 2007 , Igbinoba *et al*, 2015 and 2016; Ayogu *et al*., 2020,) This present study is premised on the assumption that since *G. kola* could offer some beneficiary effects, particularly in the regulation of lipid profile, there is a high possibility of its coadministration with other drugs such as statins, raising a potential for an interaction that may alter the disposition of the statins when administered. . It is a common knowledge that for a drug to be bioavailable, it must first be released from its dosage form and dissolution experiment evaluates the release of drug from a dosage form. Against this background, understanding potential interactions with commonly prescribed drugs, such as atorvastatin, via dissolution model is crucial as the preliminary data may predict the influence of *G. kola* on the bioavailability of atorvastatin. This study aimed to determine how the absence or presence of *G. kola* affects the dissolution profiles of atorvastatin.

## METHODOLOGY

### Materials and Equipment

Acetonitrile was purchased from Honeywell® (Riedel-de Haen, Seelze, Germany). A brand of atorvastatin 20 mg tablets was purchased from a retail pharmacy in Ilesa, Osun State, while *G. kola* nuts were bought from Atakumosa market, Ilesa and Whatman® filter paper from Cytiva (Massachusetts, United States). Equipment included adjustable micropipettes (Inviotro Biotech Limited, Hyderabad, India), D510 ultrasonic sonicator (MrC, Cambridge, England), weighing balance Mettler Toledo (Columbus, United States), hot air oven, Eurosonic ES-242 electric blender (Manchester, United Kingdom) and BK-RC8 dissolution tester (Biobase, Jinan city, China).

### Collection of *G. kola* nut and authentication

The *G. kola* nuts collected from Atakumosa market in Ilesa, Osun State were identified and authenticated at the Herbarium Unit, Department of Pharmacognosy, Obafemi Awolowo University and a Voucher Number was obtained for the nuts. A voucher specimen was deposited at the Herbarium for reference.

### Preparation of *G. kola* powder

About 60 nuts of *G. kola* were confirmed to be unblemished and without any signs of mold or insect damage. The nuts were washed thoroughly under running water to remove any dirt or debris, minced into small pieces and spread over an aluminum tray to air-dry. Sorting was carefully done to remove those

that had been affected by mold. After drying, the nuts were further pulverized into a coarse powder using mortar and pestle. The granules obtained were finally powdered into fine particles using an electric blender. The powder obtained was stored in a cool, dry and airtight container and stored at room temperature.

**Chromatographic conditions**

High-performance liquid chromatography was carried out on an Agilent 1200 system (Palo, CA. LISA), with an isocratic pump, injector, a 100mm x 4.6mm 3 um Fortis $C_{18}$ column, variable wavelength detector (VWD) and HP ChemStation software. The mobile phase (acetonitrile 60% with 40% of 0.1% formic acid) ran at a flow rate of 1 mL/min at a wavelength of 247 nm was used to elute the sample within 6 minutes run time. 100 µ*g*/mL of atorvastatin solution was prepared from the stock of 1000 *µ*g/mL. Other calibration standards were prepared as 60, 20, 10, 5, 2.5, 1 and 0.5 µg/mL. 20 µL of each calibration standard was chromatographed in triplicate and the peak areas were plotted against the concentrations to obtain the calibration curve.

**Dissolution Studies**

Simulated Intestinal Fluid (SIF) without enzyme, consisting of 0.2 M monobasic potassium phosphate ($KH_2PO_4$), was prepared according to the USP dissolution test 3 and the pH was adjusted to 6.8 ± 0.1 with 1 M NaOH. The USP basket method was used to set up the dissolution rate studies at the GIT condition. A stirring rate of 75 rpm and a medial temperature of 37 ± 0.5 ℃ were maintained while each run was completed in 60 minutes. Seven (7) containers were used with one containing only the SIF buffer which represents the blank, 3 containing a mixture of the SIF buffer and *G. kola*, and the remaining 3 containing only the SIF buffer. The containers with only the SIF buffer and those with 1.0, 2.0 or 4.0 g of *G. kola* powder were placed in alternating positions. One tablet of atorvastatin was placed in each dry basket with a total of 6 tablets per run. A total of six runs were conducted per treatment and during each run, sampling was conducted at 10, 20, 30, 45 and 60 minutes. An aliquot of 1 ml was taken from the dissolution medium using a 1 mL micro-pipette. Samples were taken from a zone midway between the top of the basket and the surface of the dissolution medium. Each sample taken was replaced with 1 ml of the buffer pre-warmed to 37 °C. For each aliquot taken, a 1 in 10 dilution was carried out where 1 mL of the sample was added to 9 ml of the mobile phase, and the mixture was vortexed. 20 µL of the final dilution of each sample was injected into the column and atorvastatin released at each sampling point was estimated.

**RESULTS AND DISCUSSION**

**HPLC assay of atorvastatin**

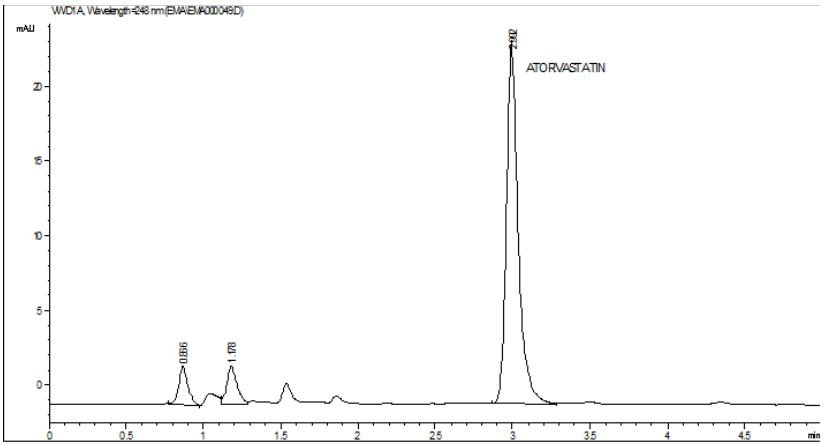
The HPLC chromatogram (**Figure 1A**) showed atorvastatin with a retention time of 3 minutes with separation achieved on a C18 column and isocratic mobile phase of 60% acetonitrile and 40% formic acid. The calibration curve (**Figure 1B**) with a linear equation, y = 60.121x + 12.416 and coefficient of determination (R-squared) value of 0.999 indicating 99.9% of the variation in the average peak area is explainable by the linear relationship with the concentration. A high R-squared value close to 1 suggests that the linear regression model provides a good representation of the relationship between the concentration and the peak area.

**Dissolution profile of Atorvastatin with and without G. kola.**

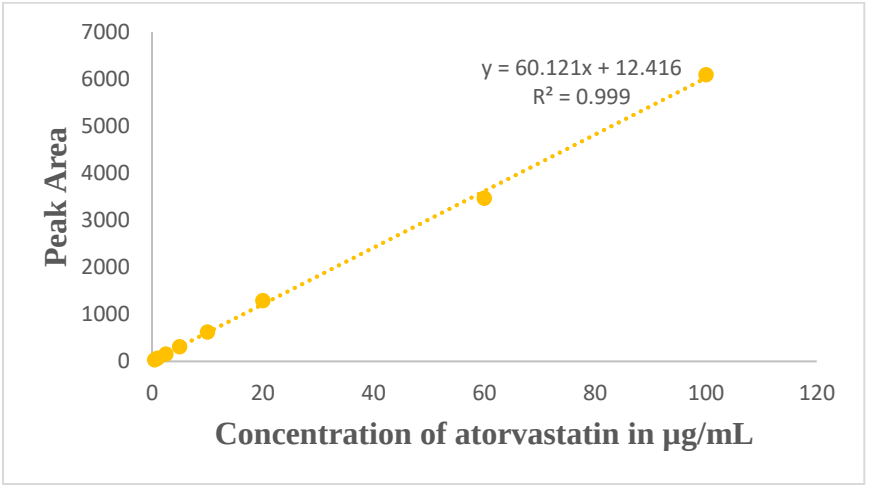
The findings in this study revealed that the presence of G. kola in the dissolution medium brought about a decrease in the release of atorvastatin. The average percentage of atorvastatin dissolved at each sampling time was 31.38±11.81, 46.02±8.73, 72.23±33.30, 63.55±27.10, 82.54±31.12 at 10, 20, 30, 45 and 60 minutes, respectively. However, when the dissolution medium was saturated with 1g of G. kola, the percentage dissolved became 17.01±7.33, 27.02±8.42, 34.70±13.90, 39.74±13.53, 28.47±11.78 respectively (Figure 2A). The paired t-test analysis showed that the observed difference between the two treatments was statistically significant (P-value of 0.0145). The mean difference of the two conditions was calculated as -29.76%, indicating that, on average, there is a reduction of 29.76 % in atorvastatin dissolution when 1g of G. Kola is present.

When the dissolution medium was saturated with 2g *G. kola*, the percentage amount dissolved at times 10, 20, 30, 45, 60 minutes were 12.44±5.89, 11.87±1.51, 23.33±5.18, 27.33±8.50, 52.49±11.66% respectively (**Figure 2B**) and the difference between the two treatments was also statistically significant (P = 0.0107). The mean difference with and without 2g of *G. kola*, was 40.36%. In addition, the incorporation of 4g of *G. Kola* into the dissolution medium also diminished the percentage of atorvastatin released at each sampling point. At each sampling time, the percentage amount dissolved in the presence of 4g of

*G. kola* was lower than that without it (**Figure 2C**). The paired t-test result provides insights into the statistical significance of the difference between the percentage amount of Atorvastatin dissolved with and without 4g of *Garcinia Kola*. (P = 0.0036). The mean difference was calculated to be -37.35, suggesting that, on average, there is a reduction of 37.35 percentage points in atorvastatin dissolution when 4g of *Garcinia kola* was present compared to without its presence.
Besides, two sampling points, 30 and 45 minutes, were chosen for comparison of the amount of the drug dissolved with or without *G. kola.* By examining dissolution at 30 and 45 minutes, it was possible to capture the initial dissolution kinetics and evaluate the impact of *G. kola* on the early release of atorvastatin from the tablets. These time points for immediate release oral tablet correspond to the period when at least 75% of the active drug is released and their choice for comparing the dissolution serves as a targeted approach to assess the immediate impact of *G. kola* on atorvastatin release and potential implications for its therapeutic effectiveness (EMA, 2017).

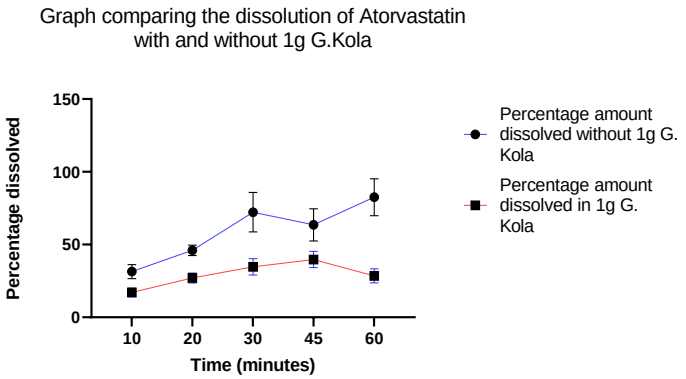



**A**

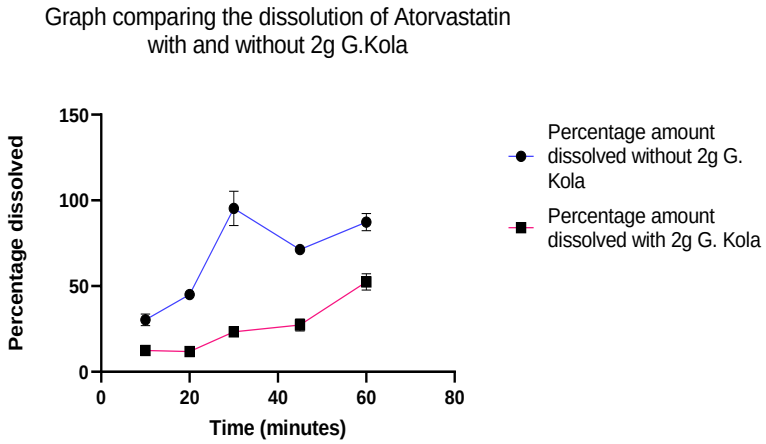



**B**

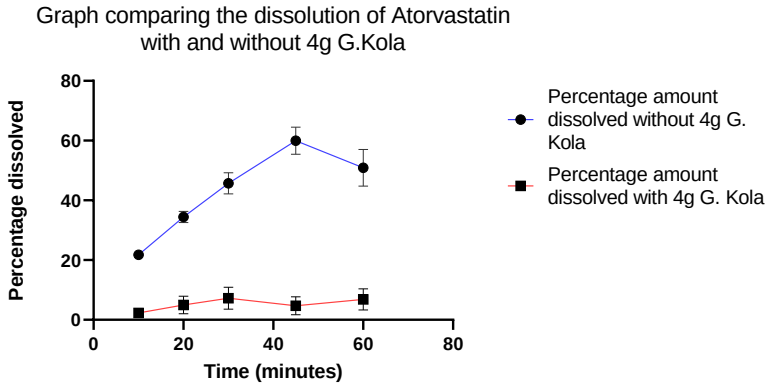
Figure 1: HPLC Chromatogram and calibration curve of atorvastatin




**A**




**B**




**C**

Figure 2: Dissolution profile of Atorvastatin with or without 1g, 2g or 4g of *G. kola*.

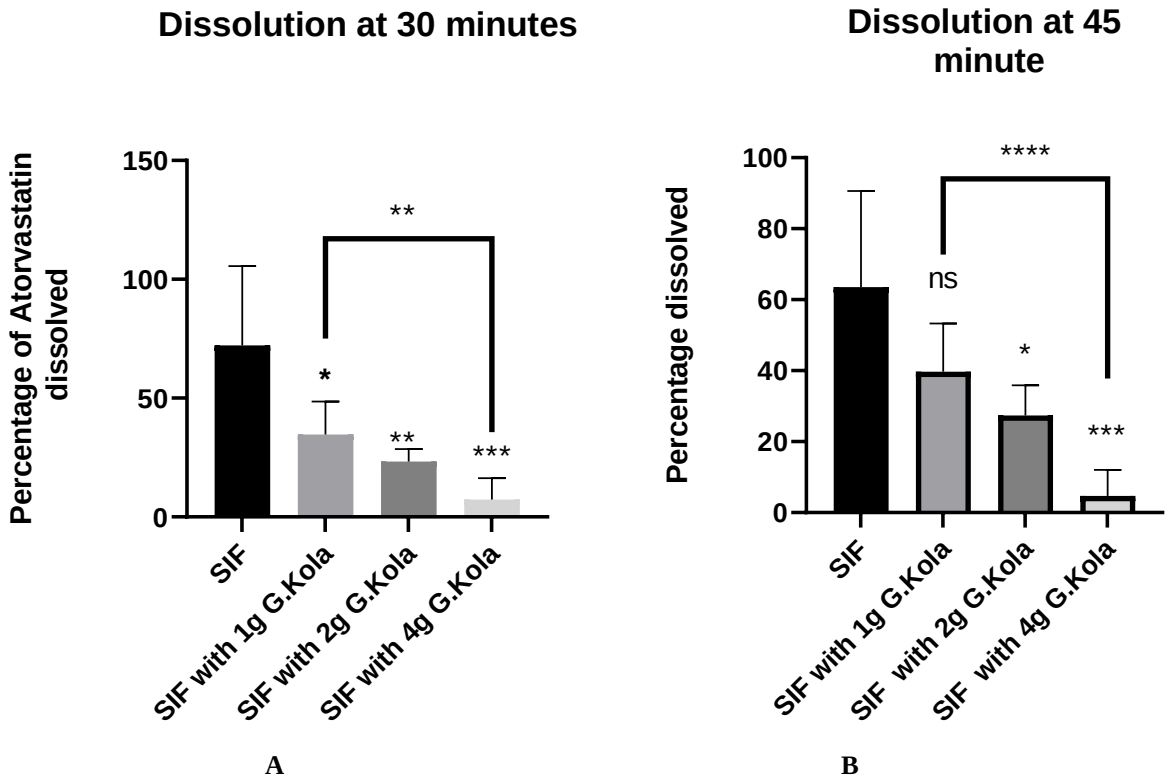
Figure 3A represents the effect of *Garcinia kola* 1g, 2g and 4g on dissolution of Atorvastatin dissolved in 30 minutes. The amount dissolved was significantly (F = 12.71, P=0.0084) reduced compared to treatment with simulated intestinal fluid (SIF) only and ANOVA analysis revealed the significant effect with the administration of an increased amount of *G. kola*. The mean (SD) without or with 1g, 2g, and 4g of *G. kola* at 30 minutes were 72.23±33.30, 34.70±13.89, 23.34±5.178, 7.26±9.01 respectively. Figure 3B represents the effect of *G. kola* 1g, 2g and 4g on dissolution of atorvastatin dissolved in 45 minutes with or without 1g, 2g and 4g of *G. kola*. The percentage dissolved was significantly (F = 12.90, P=0.0054) reduced compared to treatment with simulated intestinal fluid (SIF) only and ANOVA analysis revealed the significant effect with the administration of an increased amount of *G. kola*. The mean (SD) without or with 1g, 2g, and 4g of *G. kola* at 45 minutes were 63.55±27.10, 39.74±13.53, 27.33±8.50, 4.68±7.37 respectively.

The repeated measures ANOVA analysis indicates that there is a statistically significant difference in the amount of atorvastatin dissolved among the different treatments (without *G. kola*, with 1g, 2g and 4g of *G. kola*) at the specified time point of 30 minutes. The F-value of 12.71 and the associated P-value of 0.0084 suggest that the observed differences are unlikely to be due to random chance. The relatively high R-squared value of 0.7176 indicates that the treatments explain a substantial proportion of the variance in the data. The ANOVA test confirms that the different treatments have a significant effect on the amount of atorvastatin dissolved at 30 minutes.

Similarly, the presence of *G. kola* caused a significant change in the amount of atorvastatin dissolved at 45 minutes. The repeated measures of ANOVA analysis indicate that there is a statistically significant difference in the amount of Atorvastatin dissolved among the different treatments (without or with 1g, 2g and 4g of *G. kola*) at the specified time point of 45 minutes. The F-value of 12.90 and the associated P-value of 0.0054 suggest that the observed differences are unlikely to be due to random chance. The relatively high R-squared value of 0.7207 indicates that the treatments explain a substantial proportion of the variance in the data.

The average weight of the powder after the drying and blending processes for the sixty *G. kola* nuts was 58.4131g. This implies that one (1) nut or seed of *G. kola* is approximately equivalent to 1.168g. About two (2) nuts of *G. kola* is recommended to be taken daily (Emmanuel *et al*., 2022). Using this information, it can be assumed that 2.336g of the processed powder is taken daily. This provided the rationale for choosing 1g, 2g and 4g of dried *G. kola* for the study. The findings from the present study revealed that the amount of atorvastatin released decreases in the presence of *G. kola* regardless of the amount of *G. kola* dissolved in the dissolution medium.

In vitro dissolution data may correlate with the in vivo dissolution profiles for some drugs. Atorvastatin belongs to the class II Biopharmaceutical Classification, and dissolution is usually considered a rate-limiting step in its absorption from the small intestine. The data from this in-vitro study suggests that the presence of *G. kola* might influence the in vivo dissolution profile of atorvastatin. Hindrance to the dissolution of drugs may significantly influence the extent and rate of absorption and affect the overall exposure to drugs. Therefore, findings in the present study posit that the disposition of atorvastatin might be affected if *G. kola* is present in the context of GIT contents.




**A** **B**

Figure 3: Amount of atorvastatin dissolved at 30 and 45 minutes without or with *G. kola.* Values are presented as Mean ± SD., (n=6). ns is where, p= 0.051, * P-value <0.05; ** P-value <0.001; *** P-value <0.00001

The observation is in agreement with the findings from a previous in-vitro interaction study between quinine and *G. kola* demonstrated that quinine got adsorbed on *G. kola* (Igbinoba *et al*., 2016). In addition, an in vivo study in rats revealed that the co-administration of *G. kola* and rifampicin impaired the bioavailability of rifampicin (Ayogu *et al*., 2020). The study reported that the presence of *G. kola* resulted in a reduction of maximum concentration and area under the curve for rifampicin in rats (Ayogu *et al*., 2020). This was attributable to a reduced dissolution in the presence of *G. kola*. Similar findings among healthy human volunteers on the salivary pharmacokinetics of ofloxacin showed that both $C_{max}$ and AUC were significantly reduced following the ingestion of *G. kola* nut with the drug (Esimone *et al*., 2007). Igbinoba *et al* (2015) also reported that $C_{max}$ and plasma exposure of quinine and its metabolite, 3-hydroxyquinine, were significantly reduced among healthy volunteers when ingested with 12.5 g of *G. kola* ( Igbinoba *et al*., 2015)

Oral bioavailability is determined by a series of drug characteristics and aqueous environments for dissolution (Jambhekar & Breen, 2013). Dissolution plays a crucial role in the absorption and bioavailability of orally administered drugs. One important factor is the physicochemical properties of the drug itself, such as its solubility and particle size (Jambhekar & Breen, 2013). The formulation characteristics such as the presence of excipients (van der Merwe *et al*., 2020) also play a significant role in drug dissolution. However, adsorption, which refers to the adherence of drug molecules to solid surfaces, can also impact both dissolution and absorption. We suggest a high possibility of adsorption of atorvastatin molecules onto the surface of *G. kola* mass; thus, preventing its release into the dissolution medium. Besides, *G. kola* seed consists of an array of phytochemical compounds that could interact with the atorvastatin molecules and limit its release into the dissolution medium.

## CONCLUSION

The analysis of the dissolution data revealed interesting insights into the impact of *G. kola* on atorvastatin dissolution. The results consistently demonstrated significant differences in the percentage amount of atorvastatin dissolved between the samples with *G. kola*. The present findings suggest a possible herb-drug interaction based on the dissolution of the drug. The significant reduction in atorvastatin dissolution observed in the presence of *G. kol*a suggests that ingestion of *G. kola* nut with atorvastatin may affect the drug's bioavailability and exposure. These implications underscore the importance of considering herb-drug interactions and the need for further in vivo research in healthy volunteers to understand the underlying mechanisms, magnitude of the impact and optimization of the dose of atorvastatin in the context of co-administration with *G. kola*.

The study was conducted using specific concentrations of *G. kola* and it can be difficult to predict the exact quantity of *G. kola* consumed daily. Additional in vivo study may perhaps provide a better explanation of the effect of *G. kola* on the dissolution behavior of atorvastatin.

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