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Research Article

The effect of consumption of *Mangifera indica* (*Linn*) fruit on the plasma concentration profile of zidovudine, lamivudine and nevirapine

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Abstract

The concurrent intake of herbal products (of similar phytochemical components as fruits and vegetables) is one of the several factors that can cause inter-patient variability in ARV drugs concentrations and pharmacokinetics which may not be clinically favourable. This study employed a cross-over design to investigate the effect of concurrent consumption of mango fruit with Anti-retroviral drugs (zidovudine, lamivudine and nevirapine). Sixteen (16) human subjects (8 Males, 8 Females) participated in the study, and following a single dose administration per day of a fixed-dose tablet for one week, blood samples were collected at 1hr, 4hr and 12hr for the estimation of each drug using an HPLC analysis. Drug plasma concentrations at baseline, after one week of concurrent Mango fruit consumption and after another one week without Mango were estimated for each subject. Statistical significance was evaluated using p-values generated from a Student's t-test at a C I of 95% with a p-value of less or equal to 0.05. At 1 h, there was a significant decrease in the mean plasma concentration of Lamivudine, dropping from 10.92 ± 2.91 to 7.91 ± 2.35 (Mean ± SD) under the influence of Mango fruit. However, this and other differences in zidovudine and nevirapine mean plasma concentrations demonstrated across the groups are not statistically significant. Hence, the concurrent consumption of Mango fruit and the administration of Anti-retroviral drugs studied are not likely to produce any clinically significant negative outcomes.

1. Introduction

It is a common sight to see people consume varieties of fruits in considerable quantities especially at the peak of their seasons, and people taking medications such as anti-retrovirals are not an exception to this trend. The discovery that grape fruit juice inhibits Cytochrome P450 (CYP3A4) in the wall of the small intestine [1, 2], raises concerns about other possible interactions involving complex phytonutrients (in fruits,vegetables, herbs, spices and teas) that might be of clinical importance. Complex phytonutrients are known to have the greatest potential to induce or inhibit the activity of drug metabolising enzymes which are thought to be highly expressed in the wall of the small intestine [3]. The effect of grape fruit juice, apple, pomegranate, guava and that of mango (*Mangifera indica*) on commonly used medications such as statins, antihypertensives, central nervous system modulators, immune suppressants, anti-histamines and others have been described extensively [4].

Recent evidence has also documented the interaction between St. John's wort and certain antiretroviral drugs. St. John's wort was found to reduce plasma level of indinavir and that of preparation of lopinavir/ritonavir [5, 6]. Food/fruit–drug interactions can result in two main clinical effects; decreased bioavailability of a drug which predisposes to treatment failure or an increased bioavailability which increases the risk of adverse events which may sometimes be life threatening [4]. Such interactions are considered clinically significant if they alter the expected therapeutic response. A lot of research has been done on drug-drug interactions. However, only limited studies have reported food/nutrient–drug interaction with a number of these studies highlighting the effect of different fruits and vegetables on intestinal absorption through interaction with drug transporters as well as drug metabolising enzyme systems [4]. Studies investigating nutrient-ARV interaction are not numerous but it has been widely established that non–nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) are substrates of the CYP450 enzyme system [7, 8].

Current reports indicated that the present failure rate among patients receiving ARVs may be as high as 50% thereby requiring the development of more tools such as therapeutic drug monitoring (TDM) to ensure treatment efficacy [9]. Patients rarely report their concomitant use of herbal products alongside their HAART medications much less see any important correlation between their ARV medications and concurrent intake of fruit or vegetable [10]. In fact, many physicians need more knowledge on this subject matter to enable them to counsel their patients appropriately on possible food/nutrient–ARV interaction which may not be clinically favourable [10]. The aim of this study is to investigate the effect of consumption of Mango fruit on the concentration profile of anti-retroviral drugs i.e. zidovudine, lamivudine and nevirapine.

2. Materials and methods

2.1 Study design

2.1.1 Study participants

Sixteen (16) human subjects comprising of 8 males and 8 females (age 17-50 years and weighing 42-76 kg) were enrolled for the study according to the United States Food and Drug Administration document for conducting bioavailability and FED-bioequivalence studies [11]. Computer-based randomisation was used to allocate the subjects into two (2) groups of eight persons per group, 4 males and 4 females (Decision Analyst STATS™ 2.0). Twelve (12) subjects were recommended but 16 subjects were recruited for this study (Fig 1). A randomised, single dose, one treatment, two periods cross-over design was used [12].

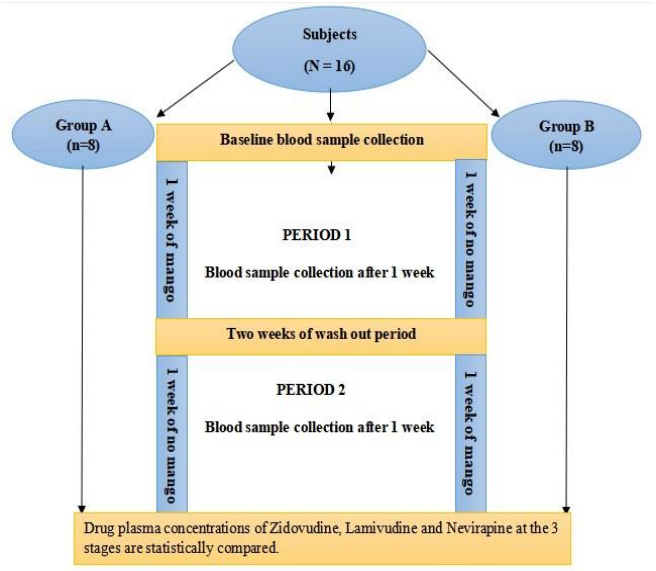

Figure 1: Diagrammatic Representation of the Study Design

2.1.2 Inclusion and exclusion criteria

Any clinically stable patient with CD4 count of 200 cells/mm^3 or above, whose haemoglobin level was at least 10.0 g/dl and who is comfortable with the dosage regimen to be observed during the study was included. They were those who usually take Mango fruit and would be able to tolerate the intended quantity for the duration of the study (relying on their experience with mango consumption). Patients currently taking any prescription or OTC medicine, pregnant women and those who smoke or drink alcohol were excluded.

2.2 Reagents and chemical

Pure samples (Sigma-Aldrich, Germany); Zidovudine pure sample (1 GM); Lamivudine pure sample (1 GM); Nevirapine Pure sample (10 MG), Acetonitrile (HPLC grade); A Fixed dose combination tablet containing zidovudine, lamivudine and nevirapine (300 mg, 150 mg, 200 mg) donated by the Pharmacy Department of the Antiretroviral Clinic of Specialist Hospital Sokoto; A TDL-4 Centrifuge operated at 2000 rpm for 20 minutes was utilized and 0.45 micron Syringe filters were used for the study.

2.3 Ethical approval

Approval was obtained from the Hospital Ethical Committee to carry out this study. Informed consent was obtained from subjects, and the clinical research was conducted in accordance with the hospital ethical committee's guidelines for human experimentation. The study participants were selected based on the earlier stated inclusion and exclusion criteria and the subjects were educated on their involvement in the study. A survey was conducted to determine the species of mango fruit to use, this helped ensure uniformity throughout the study, and species with the local name "Paparanda" was selected. This species was selected because of its constant availability in the market at the quantity that could support the study from start to finish. It is also the species with the widest acceptability by the consumers. Each of the unknown samples was run and from the peak and the lowest area (height) of the chromatogram, the appropriate concentrations for the calibration curves were determined. The calibration curves for the HPLC quantification were obtained by preparing serial concentrations (40,000 ng/ml, 4000 ng/ml, and 400 ng/ml) for lamivudine and zidovudine, and (8,000 ng/ml, 800 ng/ml, and 80 ng/ml) for Nevirapine. Each concentration was run in triplicates.

2.4 Study protocol

Prior to the commencement of the study, all subjects were instructed to stay away from any form of medication (except their HAART medications), fruits or vegetables 72 h, before the commencement of the study and they all volunteered their consent and cooperation. Subjects were received into the site of the study after an overnight fasting lasting at least 10 h, Water intake restriction was observed by all subjects 1 hour before the consumption of the two (2) average sized Mango fruits adopted as the standard meal for this study. The study meal (Mango fruits) was administered 12 h, concurrently with, and in accordance with the usual dosage regimen of the drug combination being studied. The test drug was administered immediately after the consumption of the Mango fruits. Food intake restriction was observed until 4 h, after the administration of the test drug [11].

2.4.1 Baseline

The 16 subjects were randomised into 2 groups of 8 subjects which are denoted as group A and group B. A test dose of a fixed dosed combination tablet containing Zidovudine 300 mg, Lamivudine 150 mg, and nevirapine 200 mg was administered to each subject on empty stomach after an overnight fasting of 10-12 h. Three (3) ml of whole blood was collected at 1hr post dose, at 4hr and a few minutes before (12 h), the evening dose (trough). This marks the baseline data for all the subjects.

2.4.1.1 Period 1

Starting from the following day, subjects in group A immediately commenced 1 week of mango fruit consumption while those in group B took nothing. At the end of the seventh (7) days period, blood samples were collected from both groups as observed during Baseline sampling. The two (2) average sized Mango fruits adopted as the standard meal for this study were consumed by the subjects 12 h, concurrently with, and in accordance with the usual dosage regimen of the drug combination being studied).

2.4.2 Washout period

The two groups were made to proceed on a two weeks wash-out break. During this, they took only their ARV medications with the observance of fruit and vegetable restriction.

2.4.2.1 Period 2

At the end of the two (2) weeks wash-out period, the subjects in group B commenced a one - week of mango fruit consumption, at the end of which the final blood sample collection took place for both groups in a pattern earlier established marking the end of this phase of the study.

2.5 Methodologies

2.5.1 HPLC method development

An already validated method as per USP guideline for the simultaneous determination of lamivudine, zidovudine, and nevirapine was employed [13].

2.5.2 Preparation of mobile phase

A mobile phase consisting of a mixture of 0.015 M of Potassium dihydrogen ortho-phosphate (PH 5.0) and acetonitrile in a ratio of 45:55 % v/v was prepared and degassed by sonication before use.

2.5.3 Chromatographic conditions

A HITACHI HPLC instrument equipped with a Li Chrospher RP 18 (15 cm by 4.6 mm) analytical column, an l-2130, an l- 2200 sample injector with a 20 uL loop and l-2420 UV –Visible detector was employed for this analysis. EZ Chrome Elite software was used for the quantification of peaks. A grant sonicator was used to enhance the dissolution of the standard. A Fisher Scientific AR 10 PH meter was used for PH reading.

2.5.4 Sample pre-treatment and extraction

Drugs were extracted from the plasma sample using a protein precipitation technique [14]. Acetonitrile was selected as the precipitating agent at ratios 1:3 of the plasma sample to the solvent. The mixture was mixed thoroughly, vortexed at room temperature and centrifuged at 2000 rpm for 20 min. The clear supernatant liquid was decanted and filtered through a 0.45 um syringe membrane filter [15].

2.5.5 Preparation of stock standard solution

Stock solution of 1 mg/ml (1,000,000 ng/ml) Lamivudine, Zidovudine and Nevirapine were prepared separately by dissolving 20 mg of each standard drug with a small quantity of methanol in a separate volumetric flask. The content was sonicated for 15 minutes and then made up to volume with methanol. Working standard solutions were prepared from the individual stock solution with the mobile phase as the diluents.

2.5.5.1 Working standard solution 1

Lamivudine (40,000 ng/ml) = 40,000 x 25/100,000 = (1 ml of stock standard lamivudine in 25 ml volumetric flask and make up to volume with the mobile phase).

Zidovudine (40,000 ng/ml) =40,000 x 25/100,000 = (1 ml of stock standard zidovudine in 25 ml volumetric flask and make up to volume with the mobile phase).

Nevirapine (8,000 ng/ml) = 8,000 x 5/100,000 = (0.2 ml of stock standard nevirapine in 25 ml volumetric flask and make up to volume with the mobile phase.)

Therefore 1 ml each of lamivudine, zidovudine and 0.2 ml of nevirapine stock solution was mixed in a 25 ml volumetric flask and made up to volume with the mobile phase.

2.5.5.2 Working standard solution 2

A volume of 2.5 ml was pipetted from working standard solution 1 into a 25 ml volumetric flask and made up to volume with the mobile phase to give 4,000 ng/ml lamivudine, 4,000ng/ml zidovudine and 800 ng/ml nevirapine standard concentrations.

2.5.5.3 Working standard solution 3

A volume of 2.5 ml was pipetted from working standard solution 2 into a 25 ml volumetric flask and made up to volume with the mobile phase to give 400 ng/ml lamivudine, 400 ng/ml zidovudine and 80 ng/ml nevirapine standard concentrations.

2.6 Statistical analysis

A paired sample student T-test was conducted, using a confidence interval (CI) of 95 % at a P-value of less than 0.05, statistical significance or otherwise was determined between various concentrations from different phases of the study. The null hypothesis states that the concurrent consumption of Mango fruit has no statistically significant effect on the concentration profile of the antiretroviral drugs.

3. Results

3.1 Plasma concentration of lamivudine; baseline (no treatment), period 1 and period 2

Fig.2a-2c Show the Mean Concentration –Standard Deviation Plots for groups A and B at the Baseline, Period 1 and Period 2.

3.1.1 Plasma concentration of lamivudine

3.1.1.1 Baseline (no treatment in the two groups)

At the baseline, group B demonstrates a generally higher mean plasma concentration than subjects in group A (Fig. 2a). At 1 h, group A has a mean concentration of 10.62 ± 1.93 while group B has 10.92 ± 2.30. At 4 h, group A has a mean concentration of 8.77 ± 2.56 while group B has 10.00 ± 2.68. At 12 h, group A has a mean plasma concentration of 8.70 ±

2.41 while group B has 10.18 ± 2.55. However, all the differences in mean plasma concentration observed were not statistically significant (P>0.05).

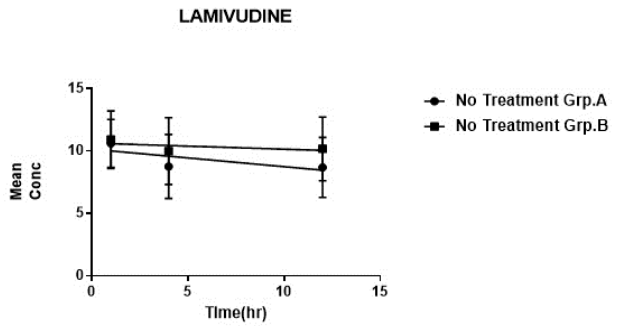

Figure 2a. Mean Concentration-Standard deviation plot of Group A and Group B at Baseline (No Treatment in the Two (2) groups).

3.1.1.1.1 Period 1 (group A 'with Mango' against group 'No Mango')

Across all the three time points, group A subject present higher mean concentration than the subjects in group B with the exception of the 1 h, time point where group A has 7.91 ± 2.35 which is lower compared to 10.92 ± 2.91 presented by group B. But at 4 h, and 12 h, group A presents a mean concentration of 10.18 ± 3.34 and 9.69 ± 1.69 which are higher than 10.06 ± 2.26 and 9.18 ± 1.36 of group B respectively (Fig. 2b).

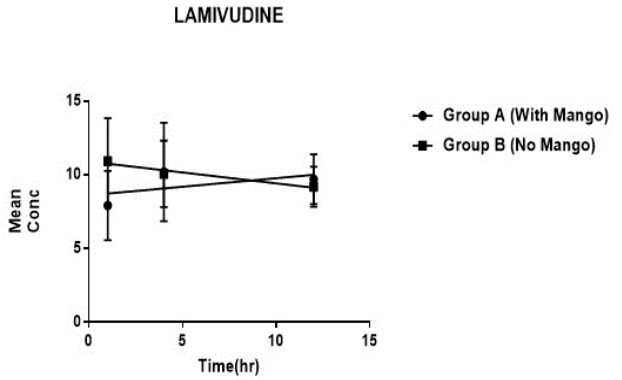

Figure 2b. Mean Concentration-Standard deviation plot of Group A and Group B at Period 1(Group A 'with Mango' against Group B 'No Mango').

3.1.1.1.2 Period 2 (group A 'No Mango' against group B 'with Mango')

At the Period 2, group B demonstrates a generally higher mean plasma concentration than group A (Fig.2c). At 1 h, group A has a mean concentration of 11.79 ± 3.31 while group B has 124.21 ± 8.87. At 4 h, group A has a mean concentration of 13.47 ± 5.54 while group B has 20.62 ± 8.03. At 12 h, group A has a mean plasma concentration of 10.78 ± 2.05 while group B has 24.69 ± 7.77. It is worthy to highlight that subjects in group B demonstrate higher mean concentration across the three time points, and are statistically significant (P<0.05) at 1 and 12 h, following their exposure to Mango fruit.

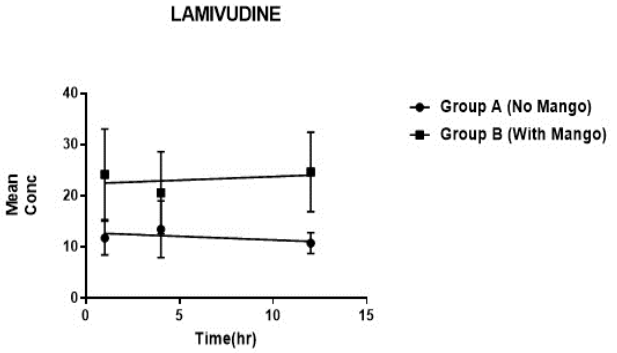

Figure 2c. Mean Concentration-Standard deviation plot of Group A and Group B at Period 2 (Group A 'No Mango' against Group B 'with Mango).

3.2 Plasma concentration of zidovudine; baseline (no treatment), period 1 and period 2

Fig. 3a-3c Show the Mean Concentration –Standard Deviation Plots for group A and B at the baseline, Period 1 and Period 2.

3.2.1 Plasma concentration of zidovudine

3.2.1.1 Baseline (no treatment in the two groups)

Across the three time points, group A demonstrates consistently higher mean plasma concentrations than the group B. The mean concentration is 0.42 ± 0.28 at 1 h, in group A while group B has 0.39 ± 0.13. At the 4 h, group B has only 0.13 ± 0.06 while group A has 0.28 ± 0.16. At the 12 h, group A records 0.22 ± 0.14 as against 0.14 ± 0.12 presented by the B group. On the overall, only the difference between the groups at the 4 h, time point is statistically significant (P<0.05) while that of 1 h, and 12 h, are not statistically significant (Fig.3a).

3.2.1.1.1 Period 1 (group A 'with Mango' against group 'No Mango')

At 1 h, time point, in the presence of Mango, group A presents a lower mean concentration of 0.34 ± 0.21 compared to the group with 'No Mango', 0.50 ± 0.25. At 4 h, there is also a slight depression of the mean plasma concentration with group A presenting 0.17 ± 0.10 compared to group B with 'No Mango' with 0.20 ± 0.13. At 12 h, there was a reversal of the mean concentration lowering trend as group A presents a higher concentration of 0.22 ± 0.17 as against 0.20 ± 0.21 of group B (Fig.3b). However, none of the differences is statistically significant (P<0.05).

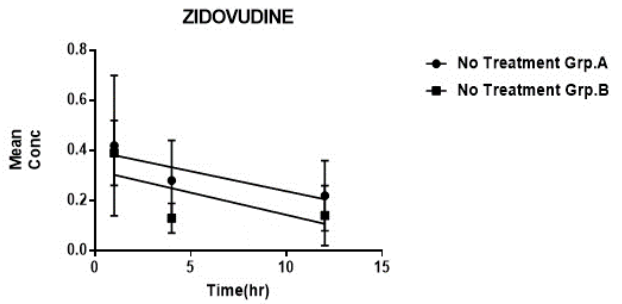

Figure 3a. Mean Concentration-Standard deviation plot of groups A and B at baseline (No treatment in the two groups)

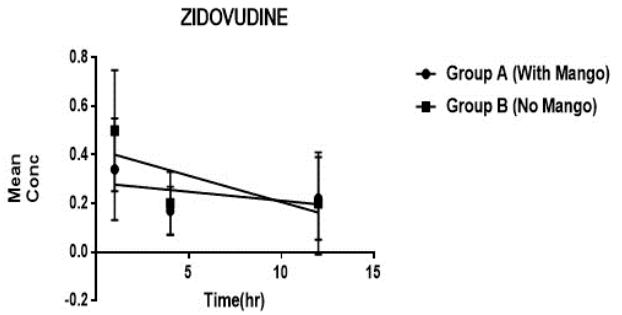

Figure 3b. Mean Concentration-Standard deviation plot of groups A and B at Period 1(Group A 'with Mango' against Group 'No Mango').

3.2.1.1.2 Period 2 (group A 'No Mango' against group B 'with Mango')

At 1 h, group B 'with Mango' demonstrates a higher mean plasma concentration of 0.35 ± 0.13 while group A 'no Mango' has 0.24 ± 0.12. At 4 h, group B 'with Mango' presents a lower mean plasma concentration of 0.20 ± 0.16 compared to group A 'No Mango' which presented a mean concentration of 0.26 ± 0.14. At 12 h, there is a slight rais in the mean concentration of group B in the presence of Mango while group A, 'No Mango' has 0.14 ± 0.13. But generally, all the differences reported were not statistically significant (P>0.05) (Fig.3c).

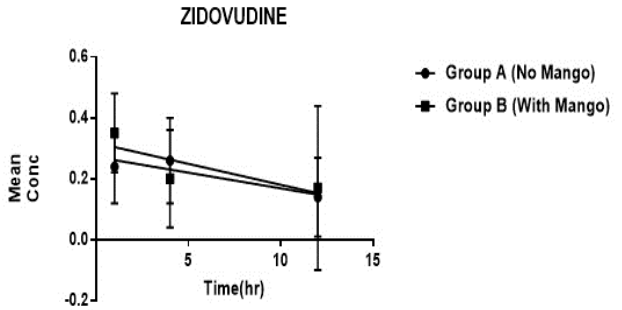

Figure 3c. Mean Concentration-Standard deviation plot of group A and B at Period 2(Group A 'No Mango' against Group B 'with Mango').

3.3 Plasma concentration of nevirapine: baseline (no treatment), period 1 and period 2

Fig.4a-4c Show the Mean Concentration –Standard Deviation Plots for group A and B at the baseline, Period 1 and Period 2.

3.3.1 Plasma concentration of nevirapine

3.3.1.1 Baseline (no treatment in the two groups)

At 1 h, group B shows a tendency for a lower mean plasma concentration of 5.88 ± 3.87 while group A has 10.43 ± 4.13. At 4 h, group A demonstrates a higher mean concentration of 10.21 ± 6.11 as against group B that present 7.29 ± 2.97. At 12 h, group A has a slightly higher mean concentration of 7.20 ± 4.81 as against group B with a mean plasma concentration of 5.49 ± 3.85. The difference is statistically significant (P<0.05) at 1 h, time point between group A and group B (Fig.4a).

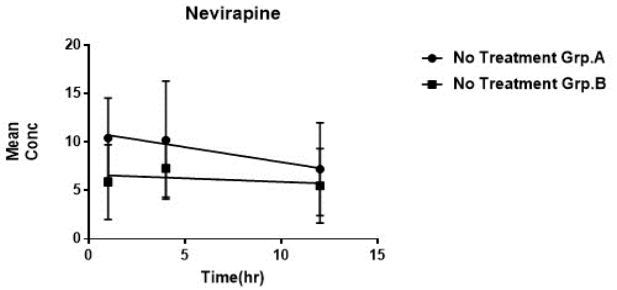

Figure 4a. Mean Concentration-Standard deviation plot of groups A and B at Baseline (No treatment in the two groups)

3.3.1.1.1 Period 1 (group A 'with Mango' against group B 'No Mango'

At 1 h, the mean concentration of group A in the presence of Mango, 9.08 ± 5.36 is lower than 10.23 ± 5.37 recorded in group B. At the 4 h, time point, group A presents a higher mean concentration of 11.60 ± 3.63 than 9.69 ± 6.22 presented by group B. At 12 h, group A still maintained a higher mean plasma concentration of 10.43 ± 8.00 which is higher than 9.31 ± 5.55 in group B. However, the differences across the groups are not statistically significant (P>0.05) (Fig.4b).

3.3.1.1.2 Period 2 (group A 'No Mango' against group B 'with Mango')

At 1 h, group B that consumed mango demonstrated a slightly lower mean concentration of 9.67 ± 4.66 while group A did not take Mango had 10.68 ± 3.71. At 4 h, the Mango treated group B has a higher mean concentration of 14.52 ± 11.70 while group A without Mango, has 10.69 ± 4.80. At 12 h, the Mango treated group B showed a lower mean concentration of 7.07 ± 6.7 while group A, without Mango demonstrates a

higher mean plasma concentration of 11.46 ± 3.57. However, all the reported differences are not statistically significant (P>0.05) across all three time points (Fig.4c)

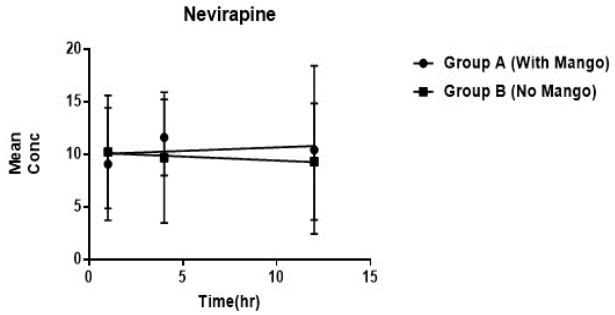

Figure 4b. Mean Concentration-Standard deviation plot of groups A and B at Period 1 (Group A 'with Mango' against Group B 'No Mango')

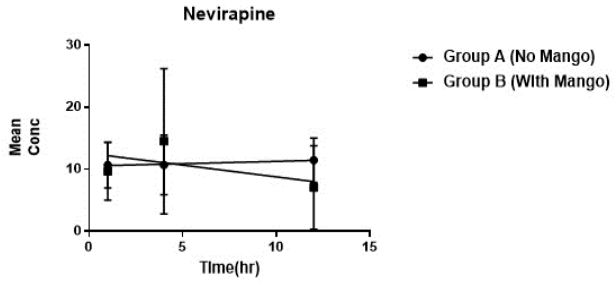

Figure 4c. Mean Concentration-Standard deviation plot of groups A and B at Period 2 (Group A 'No Mango' against Group B 'with Mango')

4. Discussion

Specific foods or drinks can affect how a medicine is absorbed, metabolised, or utilised by the body. This is referred to as a drug-food interaction. These interactions may alter how effectively a treatment works or have unintended consequences [16, 17]. Numerous medications, including statins (used to lower cholesterol), blood pressure medications, and psychiatric medications, have been shown to interact with grapefruit juice. It may impair the function of gastrointestinal enzymes, elevating medication levels in the blood and increasing the risk of toxicity or bad effects [18, 19].

The drugs zidovudine, lamivudine, and nevirapine are all used to treat HIV (Human Immunodeficiency Virus) infection. These medications are often administered as part of a combination antiretroviral therapy (ART) regimen to manage the virus and reduce the progression of HIV to AIDS (Acquired Immunodeficiency Syndrome) [20].

Our study investigated the effect of concurrent consumption of mango fruit on the concentration profile of patients on Highly Active Anti-retroviral Therapy (HAART) medications namely; lamivudine, zidovudine and nevirapine.

For lamivudine, at the baseline (no treatment phase) there is a tendency for the mean plasma concentrations in group B to be higher than those of group A, but the differences demonstrated are not statistically significant across the three time points of the study. The groups are therefore considered balanced. This suggests that the randomization done at the beginning of this study was adequate and any difference observed between groups A and B going further in this study will be significant and are not biased by baseline differences.

At Period 1, there was a statistically significant (P<0.05) difference in the 1 h, mean plasma concentration with group B (No Mango) having 10.92 ± 2.91 tending to be higher than group A (With mango) with 7.91 ± 2.35 mean plasma concentration. Taken alone, this suggests Mango lowers the plasma concentration of Lamivudine at 1 h. However, in Period 2, this trend was neither altered nor reversed even after the group B subjects were exposed to mango fruit for I week. In essence, if Mango fruit was responsible for lower mean concentrations in group A when exposed to mango in Period1 it should have done so in group B (With Mango) in Period 2. Instead, group B (with mango) in period 2 tends to present a significantly higher (P<0.05) mean value of 24.21 ± 8.87 at 1 h, time point when compared with group A (No Mango) having 11.79 ± 3.31 mean concentration. Since the plasma concentration suppression effect did not move with the mango in period 2 as observed in period 1, apparently, the presence of mango fruit cannot be considered responsible for the mean concentration value lowering i.e. other factors other than the mango effect might have been responsible for our observation. In vitro study by Rodeiro *et al.* [21], suggests that Mango and its components lowere the activities of CYP 450 enzymes, but it has also been established that there is little or no possibility of Lamivudine interaction with drug or herbal (phytocomponents) sharing the CYP 450 metabolic pathway due to low extent of metabolism and low protein binding, hence justifying our observation that mango fruit does not alter the concentration profile of Lamivudine.

For Zidovudine and Nevirapine, the study did not demonstrate any statistically significant difference in the mean plasma concentrations of Zidovudine and Nevirapine across all the three phases of this study. This suggests mango fruit may affect the concentration profile of zidovudine and nevirapine. This could be because zidovudine and nevirapine are easily absorbed through the gastrointestinal tract. Food can influence zidovudine absorption. Taking Zidovudine with a meal, particularly a high-fat meal, can reduce absorption.For optimum absorption, Zidovudine is recommended to be taken on an empty stomach. Nevirapine, unlike Zidovudine, can be taken with or without food because food does not affect its absorption [22].

5. Conclusions and limitation

The results of our study show that the concentration profile of the subjects with respect to the ARV medications (Lamivudine150mg, Zidovudine 300mg, and Nevirapine 200mg) were not significantly altered in the presence of mango fruit. Therefore, patients taking Mango fruit with these medications are not likely to experience any negative or unfavourable food-drug interaction that can be of any clinical importance.

The design is deliberately 'data poor technique' for ethical reasons as the subjects are ill patients with active Human Immunodeficiency Virus (HIV) and may not be able to withstand too many blood samples. Also, the study was done on patients who have been on these medications for varying length of time, and are already at their steady state concentrations, and it was considered ethically inappropriate to stop them temporarily for the main purpose of carrying out proper pharmacokinetic profiling. The design was therefore targeted at the trough concentrations which were the concentrations just before the next dose.

Abbreviations

ADME–Absorption-Distribution-Metabolism-Elimination.
ART-Anti-retroviral therapy
ARVs-Anti-Retrovirals
AUC –Area Under the Curve
CI –Confidence Interval
C Max-Maximum Plasma Concentration
FDA- Food and Drug Administration
HAART - Highly Active Anti-Retroviral Therapy.
HIV/AIDS-Human Immunodeficiency Syndrome
HPLC-UV-High Performance Liquid Chromatography-Ultra Violet
MTCT-Mother-to Child-Transmission
NNRTI–Non-nucleoside Reverse Transcriptase Enzyme Inhibitor
NRTIs–Nucleoside Reverse Transcriptase Enzyme Inhibitor
OTC –Over the Counter
PK-Pharmacokinetic
TDM-Therapeutic Drug Monitoring
T Max-Time to Maximum Concentration
WHO-World Health Organization

Authors' contributions

All the authors contributed equally to writing the content.

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Availability of data and materials

All relevant data are within the paper and its supporting information files. Additional data will be made available on request according to the journal policy.

Conflicts of interest

The authors have no conflicts of interest to declare.

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