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Extended Abstract
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BABE 2018- In Vitro and In Silico Drug-Food Interaction: An Evaluation of Metformin and Green Tea Interactions- Jacob A. Kolawole, University of Jos.

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Food-drug interaction is a consequence of physical, chemical or physiological relationship between a drug and food. Failure to identify and properly manage food-drug interaction can lead to serious consequences such as reduction in absorption of certain orally administered drugs thereby leading to failure

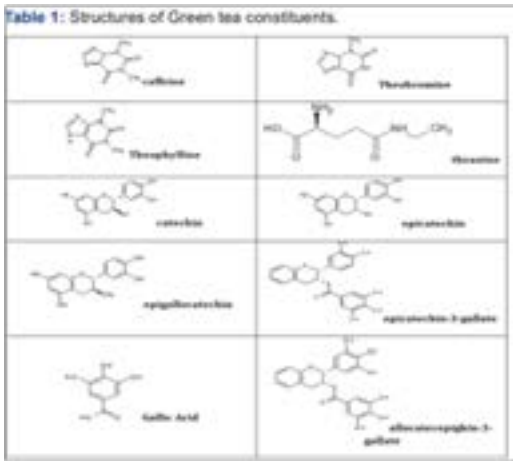
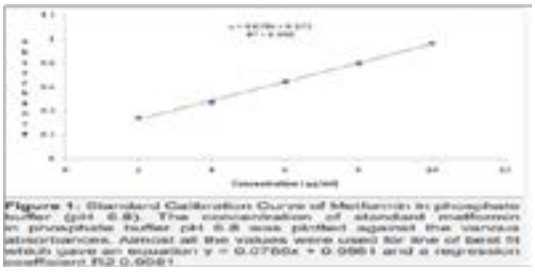


Table 1: Structures of Green tea constituents.

of treatments. This study sort to explore the effect of green tea on Metformin uses both in-vitro dissolution test and in-silico docking interactions models. Dissolution test was carried out on Metformin alone and Metformin in the presence of green tea using the official dissolution medium, phosphate buffer pH 6.8 and sampling done at USP timing intervals. Docking studies was carried out by using 10 phenolic compounds and metformin in the active site of the AMPK crystal structure, 4ZHX.pdb. Metformin alone complied with the USP requirement of 70% drug release while Metformin release in the presence of green tea was less than 70% at 45minutes. Phenolic constituents of green tea; (-)-epigallocatechine, epicatechine, theanine and theophylline were seen to form complexes with metformin through covalent bonding in the active site of AMPK. Conclusion: This study was able to establish the interaction of green tea on metformin dissolution profile and possible binding interactions in the binding site of AMPK enzyme. It was therefore concluded that green tea decreases the release and uptake of metformin by forming complexes through covalent and hydrogen bounding of some of it's phenolic constituents. Key Points i. The presence of green tea in the dissolution media along with metformin caused a decrease in its dissolution profile due to complex formation ii. The catechins and theanine constituents of green tea could possibly compete for binding site residues with metformin. Abbrevations: CAMP: Cyclic Adenosine Monophosphate; PKA: Protein Kinase A; SPSS: Statistical Package for Social Sciences; AMPK: AMP-activated protein kinase

Discussion: In-vitro food - drug interaction via dissolution test Food drug interaction is an alteration in the pharmacokinetics and pharmacodynamics of a drug by food or food ingredients. A food drug interaction can be a consequence of physical, chemical or



physiological relationship between a drug and food. Dissolution test profile provides insight into in-vivo drug release in order to establish possible bioavailability characteristics. The USP (2007) specifies at least 70% release of drug at 45 minutes in dissolution

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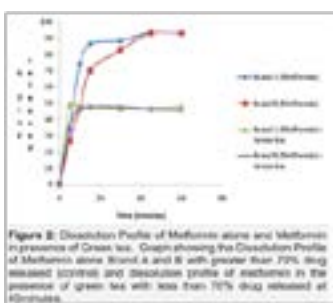
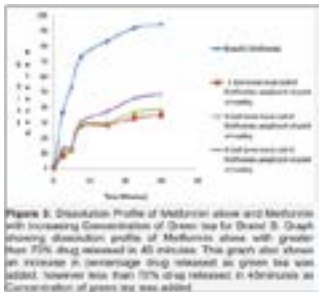
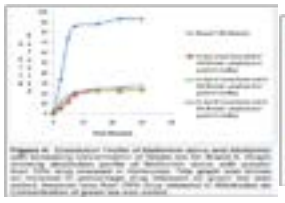
medium for oral tablet using phosphate buffer pH 6.8. The two brands of metformin used in this study showed a percentage release of 93.41% for Brand A and 93.04% for Brand B therefore complying with the USP specification

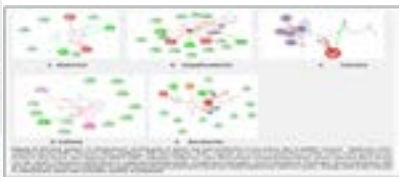
2nd and 3rd Phase: In the test sample (containing Metformin and Green Tea) there was decrease in percentage drug released of less than 70% drug released for Brand A (46.86%) and Brand B (46.46%) at 45 minutes in phosphate buffer pH 6.8. This shows that green tea interferes with the dissolution profile of metformin. The test procedure for the addition of various concentration of green tea at the point of reading, showed an increase in percentage drug released and absorbance as the concentration of green tea was increased.





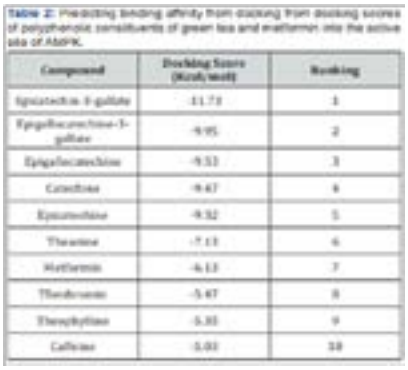
This however did not meet this USP (2007) specification showing less than 70% drug release at 45minutes for brand A and Brand B in green tea. The increase in absorbance as varying concentration of green tea was added to metformin can be due to complex formation between constituent's green tea and metformin as shown in (Figure 4 & 5).





This could also imply that constituents in green tea might not entirely stop the release of metformin, but could slow it down significantly to affect treatment outcomes in the long run.

Predicting binding affinity from docking scores The Catechins (Epicatechin-3-gallate, Epigallocatechin, catechin, Epicatechin) and Theanine were seen to have higher binding affinity as compared to metformin in (Table 2).



Theobromine, Theophylline and Caffeine were seen to have lower binding affinities than metformin. Ligand orientations are scored in relation to intermolecular energy interaction and ranked relative to other poses and ligands in the compound library. Scoring functions such as a Score [used in this study provides a fast and predictive tool for the estimation of a ligand's binding affinity from its binding energy. Similar docking scores between these Catechins can be attributed to having similarities in their structures. From these results, the catechins having a higher binding affinity than metformin could imply that they are competing with metformin for binding site residues. Binding pattern analysis From (Figure 5a), metformin can be seen interacting with active site residues, while in the presence of green tea constituents (Figure 5b-5e), there is a shared interaction between metformin and these compounds. From this study, it was observed that interactions of Epigallocatechin, Epicatechin and Theamine with metformin (Figure 5b-5e), was through covalent bonding. The complex of green tea- metformin that would be formed through these covalent bonding interactions can explain the decrease in dissolution profile of metformin. Other interaction types such as carbon-hydrogen bonding (Figure 5d) and some unfavourable bumps (Figure 5b-5e) were also observed. These interactions can in the long run affect the bioavailability of metformin, hence interfering with treatment outcomes.

Binding pattern analysis

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Materials and Methods: The official USP (2007) Pharmacopoeia for dissolution testing was adopted. Using phosphate buffer pH 6.8 at temperature of 37 ˚C±5 ˚C at 100rpm the tablets were placed in the basket and the machine was adjusted to start counting down from 60 minutes. As the procedure commenced 5mls of the dissolution sample was withdrawn at 5, 10, 15, 30, 45 and 60 minutes and immediately replaced with 5mls of phosphate buffer for control and phosphate buffer with green tea for the test, to maintain sink condition. The samples were filtered through 0.45µm syringe. The filtrate was diluted using 1 in 20 dilutions using phosphate buffer for the control and phosphate buffer together with green tea for the test. These samples were analysed by ultraviolet spectrophotometer at 232nm [13,14].

The percentage drug released was calculated using the

Formula:

% Drug released=concentration in mglml at a given time x 100

final concentration

The percentage drug released was plotted against time. 1st phase (normal dissolution testing procedure) involved the use of buffer solution and two brands of Metformin tablet 500mg (control media). 2nd phase involved combination of buffer and green tea, in the ratio of 2:1 as the medium. 3rd Phase involved the spiking of the solution from 1st phase with graded amount of tea solutions just at the point of taking absorbance.

Conclusion: Green tea significantly decreases the dissolution profile of metformin tablet due to the presence of constituents in green tea which can form a complex with metformin as indicted by the in-silico dockings. Whatever affects the dissolution profile of metformin would adversely affect its bioavailability which was seen in the interaction of metformin and green tea constituents in the active site of AMPK enzyme. Regardless of the fact that some literatures showed that green tea may have health benefits with regards to decreasing blood glucose levels in diabetic patients, concurrent administration with metformin might decrease the effectiveness of the drug?

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