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The Bioanalytical LC/MS Techniques in Studying the Drug-Juices Interactions for Pharmacokinetics Evaluations

Wael Abu Dayyih*[1], Nisreen T. Qaisi[1], Tarteel Altarawneh[1], Zainab Zakaraya[2]

[1]Faculty of Pharmacy, Mutah University; Al Karak –Jordan.
[2]Faculty of Pharmacy, AL-Ahliyya Amman University; Amman –Jordan.

Abstract— For a proper activity of the drug, researchers study all factors that could impact the pharmacological action of the drug, including interactions between drug and juices which are the most important factor that alters the effect of a medicine. HPLC/MS technique helps analyzing the concentration of drugs in plasma to identify the impact of co-administrated substances on it. In our review article, we concentrated on citrus fruit juices (Grape fruit, Seville orange and Pomelo), Cranberry juice and pomegranate and its effect on pharmacokinetics of studied drugs (Cyclosporine, Warfarin and Colchicine). In this review it found that some of the interactions showed several changes in pharmacokinetics parameters Like T *max*, C *max*, *AUC* and modification in *Half life*. While others remained without any interference. In conclusion, the complexity of the fruit juice's composition makes it difficult to study, but healthcare providers should be aware about any possible side effects or unusual interactions that may occur while taking medication with juices.

Keywords: Interactions, Juice(s), Drug(s), Pharmacokinetics, HPLC-MS technique, Cyclosporine, Warfarin, Colchicine, Pomelo, Seville orange, Grapefruit, Cranberry, Pomegranate.

Introduction:

Fruit juices contain a large number of phytochemicals that, in combination with certain drugs, can cause food–drug interactions that can be clinically significant and lead to adverse events. The mechanisms behind such interactions are in most cases related to phytochemical interference with the activity of cytochrome P450 metabolizing enzymes (CYPs) or drug transporters. Moreover, alterations in their activity can have a clinical relevance if systemic exposure to the drug is decreased or increased, meaning that the pharmacological drug effects are suboptimal, or the drug will cause toxicity Pharmaceutical drugs are manufactured in order to cure, treat or prevent disease [1].To have a proper activity of the drug, researchers study all factors that could impact the pharmacological action ofthe drug, including interactions between a drug andother drugs,food [2],andjuices which are the most important factorthat altersthe effect ofa medicine. [3]

Drug interactions are classified as pharmacodynamics (PD) or pharmacokinetics (PK) interactions. The Pharmacodynamics interactions occur whendrugsare taken with other drugs, food, or juices and that can result in the drug having additive or eliminative effects of the drug onthe human body. Pharmacokinetics interactions occur when there is a change absorption, distribution, metabolism, or excretion.These studies are critical in order to reduce the possibility of such an interaction. [4]

Juices are fluids extracted from fruits that contain 100% fresh [5], e.g. grapefruit, grape, cranberry , apple , pomegranateand blueberry,they contain vitamins and minerals that induce immunity of the body which meanspeopleconsumed juices regularly for their benefit, whoever, medication could be taken with different juices without being aware if there is any interference with each other,[6] scientists made an effort to study such interactions using different techniques and develop a number of methods and analytical devices.[7]

High-PerformanceLiquid Chromatography (HPLC),a widely used method of separation that analyzes chemical componentsin mixture based on theiraffinity to interfere with mobile phase or stationary phase, then detects the component under ultraviolet light, [8]and this technique is widely used for the determining the amount of active ingredient in tableted drug such ketoconazole and isoconazole.[9]

Mass Spectrometry(MS) isa device that detectsthe quantity of the components even if they are in nanograms, by ionizing the atoms,it canmeasure the amount of any chemical substance based on mass-to-charge ratio.[8]

HPLC/MS technique,which is a rapid, highly sensitive, and simple method, can easily helpto analyze, identify impurities,and being the most ideal tools in pharmaceutical analysis in drug discovery, pharmaceutical preparation, and studies of pharmacokinetic and pharmacodynamics of drug interactions.[10]

To evaluate drug interactions,HPLC/MS was used to detect drug–juice interaction [11], anddifferent fruit juices such as licorice and grapefruitchosen to be analyzed, [12,13]to learn more about what is theingredients and their amounts,juices can affect the region below the curve (AUC), maximum plasma concentration time (T_{max}),bioavailability, metabolism, excretion and other factors. [14,39]

This review researchaims to summarize the effect of Pomelo, Cranberry, Seville orange, and Grape fruit juices on immunosuppressant agent specifically cyclosporine, Pomegranate, cranberry juiceseffect on warfarin, Grape fruit and Seville orange juices effect on colchicine, as shown on *Table1*, using HPLC-MS technique to determine the extent of effect on PK parameters.

Table 1. A summary of comparison between Pharmacokinetic Parameters and Drugs-Juices interactions studied in this article.

Drug-juice evaluated \ PK parameters		**AUC_{0-t}***	**AUC_{0-inf}****	**C_{max}*****
Cyclosporine	Pomelo juice[16]	19.4%↑	18.9%↑	12.1%↑
	Cranberry juice[16]	5.0%↓	6.6%↓	4.8%↓
	Seville orange juice[17]	No change	No change	No change
	Grape fruit juice[18]	55%↑	55%↑	~27%↑
Warfarin	Pomegranate juice [31]	Significantly reduced		
	Cranberry juice[36]	No Significant Change		
Colchicine	Grape fruit juice[36,37,38]	~5%↓	~3%↓	~7%↓
	Seville orange juice[37]	~25%↓	~20%↓	~25%↓

* AUC_{0-t} (maximum plasma concentration timecurve)
** AUC_{0-inf} (maximum plasma concentration timecurve to infinite time)
*** C_{max} (maximum plasma concentration)

1. METHODOLGY:

By conducting a thorough search of all available studies, obtained the drinks effect data, beverages, and juices on the pharmacokinetics of some drugs. In our studies, we concentrated on the Liquid chromatography/mass spectrometry (LC/MS) technique, that used to explain changes in pharmacokinetic parameters. PubMed(https://pubmed.ncbi.nlm.nih.gov) and Science Direct (https://www.sciencedirect.com) were used in the search.

2. Discussion:

2.1.1. Cyclosporine:

Cyclosporine is a cyclic undecapeptide derived from fungi, it is a well-known immunosuppressant that is used to avoid organ rejection after transplantation, as well as to treat severe rheumatoid arthritis and psoriasis.[15] Cyclosporine is also metabolized by the CYP3A enzymes contain in dihydropyridine metabolism.[16]It has a limited therapeutic window and ranging of variable bioavailability from 20% to 50%, through the metabolism in liver and kidney system, Cyclosporine is a cytochrome P450 enzymes (CYP3A4 and CYP3A5) and P-glycoprotein (P-gp) substrate, interaction with co-administrated medicines, foods and juices leads to therapeutic drug monitoring has been advised for cyclosporine.[17]

Pomelo juice contains furanocoumarins, which can inhibit the CYP3A enzymes. [18,19] The substantial increase in cyclosporine bioavailability is known to be caused by these enzymes. Pomelo is a citrus fruit with common furanocoumarins that is closely linked to grapefruit. 6,7-dihydroxybergamottin and 6,7-dihydroxybergamottin are two of them. [20] It is also known that pomelo can increase cyclosporine bioavailability in pigs and impede of digoxin transport by P-gp in Caco-2 cells in vitro. [21]
(JulieGrenier et al., 2006) [15]investigate crossover to assess the single oral dose effects of cyclosporine administered with pomelo juice, cranberry juice, and water according to their fasting circumstances on healthy male participants. The concentrations were calculated by a liquid chromatography and mass spectrometry process. *(Figure 1)* shows the effects of various treatment juices on the pharmacokinetics of cyclosporine were presented through 3 periods of sample analysis, the results of this study statically compared the difference between AUC_t, AUC_{inf} and C_{max} of juices vs water. Pomelo juice increased the total exposure of cyclosporine by 19.4% for AUC_t, 18.9% for AUC_{inf}, and 12.1%for C_{max}.[15]
Cranberries have indeed been proven to reduce the activity of cytochrome P-450 isoenzymes. [22] However, the impact of cranberry juice on the pharmacokinetics of cyclosporine were not significant, also there is no effect on the drug's levels of plasma. The reduction in AUC_t was 5.0%, and the reduction in C_{max} was 4.8%; nevertheless, these results were not significantly different. Besides from the AUC_{inf}, the ratio difference was only 6.6%, but it was statistically significant. [15]
The pharmacokinetic parameters of cyclosporine are also affected by the grapefruit amount juice, and Seville orange juice that is given to the volunteers. When given with water and Seville orange juice, the pharmacokinetic parameters of cyclosporine there are no change was obtained. The mean AUC of cyclosporine administered with grapefruit juice was increased by 55% when compared with water in healthy individuals [18] and 38% in renal allografts. [23] Although both Seville orange juice and grapefruit juice can minimize the intestinal concentration of CYP3A4, exclusively grapefruit juice increase the oral bioavailability of cyclosporine [18].The interaction between the two is evidenced by the presence of P-glycoprotein in the gut. This finding supports the notion that the enhanced

bioavailability of cyclosporine is due to the interaction between the drug and juice. [15]

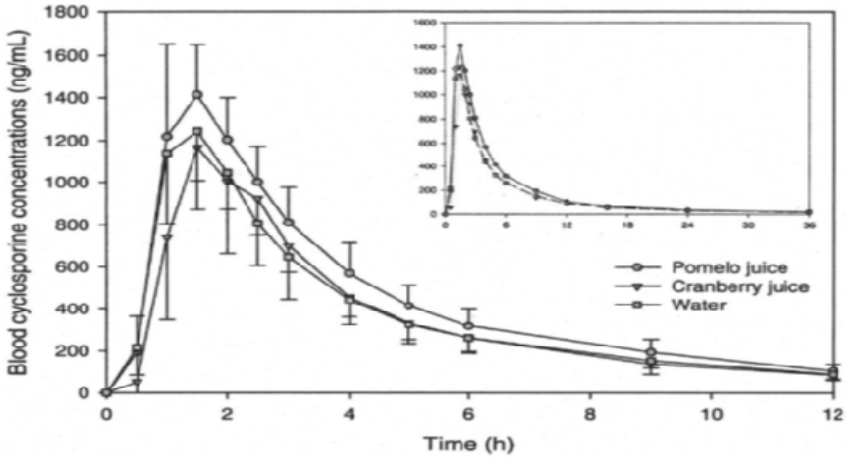

Figure 1. Cyclosporine mean blood concentrations after 200-mg dose of Neoral 100-mg soft gelatin capsules given with water, pomelo juice, or cranberry juice in healthy volunteers. *Error bars* indicate SD. [15]

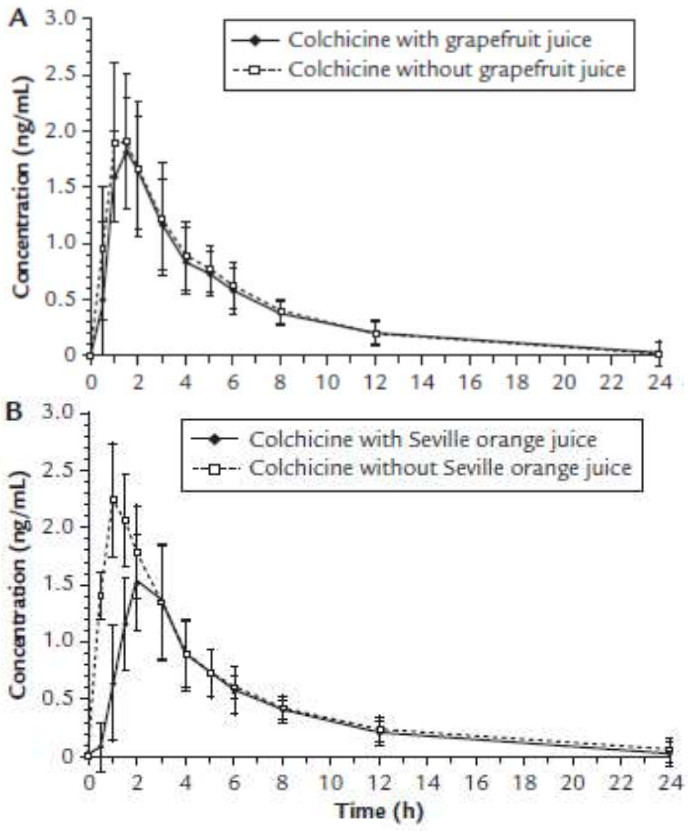

Figure 2. Mean plasma colchicine concentration after the administration of a single oral dose of colchicine 0.6mg with (A) grapefruit juice (n=21) and (B)Seville orange juice (n=23) in healthy subjects. [18]

2.1.2. Warfarin:

Since warfarin is the main anticoagulant for preventing arterial and venous thromboembolic events, its interactions with other drugs and compounds have been studied[24].*PunicagranatumL.* (pomegranate fruit) and its various parts were used for thousands years as classic medicines. The main component of pomegranate is its seeds, which are 48% edible. It is also applied to treat different conditions like arthritis and colitis.[25-31] The method was used to determine the concentration in plasma and the C_{max} of warfarin after pomegranate juice consumption is Liquid chromatography–mass spectrometry (LC-MS), the effects of pomegranate juice on the pharmacodynamics and PK of warfarin have been studied.[31] In addition, the consumption of pomegranate juice has been associated with a decrease in plasma concentrations of the drug, a significantly higher prothrombin time and an increase in the international normalized ratio (INR). These increases may increase the risk of blood loss. Pomegranate juice should be avoided for patients on warfarin. [31]

Cranberry juice wasshown toreact with warfarin in a case study. Warfarin is mainly metabolized by the CYP enzymes and is the only known medicine that could have an interaction with cranberry juice. [15] the cranberry juice in another study show can prevent the CYP3A4 and CYP2C9 enzymes. Although it has been shown that co-administration of cranberry juice with warfarin can lead to a decrease in INR, these effects have not been observed in most studies. [32]

2.1.3. Colchicine:

Colchicine is a lipid-soluble alkaloid that has a long half-life and a high bioavailability. [33] Its potent anti-inflammatory effects last for up to 48 hours. Although its peak plasma concentration can reach 1 hour after administration, its effects last for several days.[34] The labeling for colchicine contain strict advisories concerning drug– drug and drug–food interactions, that containwarnings to drink the grapefruit or grapefruit juice through treatment. Two of the furocoumarins in grapefruit juice and Seville orange juice can prevent intestinal cytochrome P450 (CYP) isozyme 3A4 and P-glycoprotein as mentioned previously (involved in colchicine metabolism and transport).[35]

After being given colchicine by using grapefruit juice or not, the Plasma concentration versus time curves of the drug showeduncommonly similar *(Figure 2(A))*. Although consumption of grapefruit juice did not greatly affect the pharmacokinetics of colchicine, it did increase the median colchicine T_{max} by about 0.5 hour. The geometric mean of the AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} was decreased by~5%, ~3%, and ~7% respectively. Ratios was within the FDA-accepted interval (80%–125%) for establishing “no interaction” between listed drug and juice. [36]

Also, the plasma concentration of colchicine after it was administered with or without Seville orange juice showed differences *(Figure 2(B))*. Consumption of Seville orange juice resulted in a decrease in colchicine C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ by ~25%, ~25% and ~20% respectively. The geometric means for the AUC_{0-t}, C_{max}, and AUC0 indicated that a significant food-drug interaction when combined with Seville orange juice. [36]

3. Conclusion:

There are a huge number of phytochemicals in fruit juices, the literature does not provide sufficient evidence that these chemicals can interact with drugs. Drug interactions are also challenging due to the unknown quantity and complexity of the fruit juice.

Many of the drug interactions that concern us are not considered clinical. However, there are some that deserve our attention and can be avoided by taking a medication with water, further studies are still needed to analyze the exact mechanisms involved in this interaction.

Lastly, patients should always ask their healthcare professionals about any potential side effects or unusual reactions while taking their medication.

In conclusion, a better understanding of the mechanisms behind drug interactions with fruit juices, and further in order to decrease the likelihood of any unwanted effects or unsuccessful pharmacological treatments.

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