

## Evaluation of the Impact of Orange Juice on Apixaban Pharmacokinetics in Healthy Rats

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### ABSTRACT

Juice derived from the "sweet orange" cultivar is widely consumed and is considered one of the most popular juices globally. It contains many bioactive compounds that can interact with pharmaceutical agents. This study aimed to assess the impact of oral co-ingestion of orange juice (OJ) and Apixaban (AP) on the fundamental pharmacokinetic characteristics of AP, C<sub>max</sub>, and AUC<sub>0-t</sub>. Two groups of Wistar rats were used in this study: one was given the drug alone, and the other was given the drug with OJ. Each animal was given 10 ml of freshly squeezed orange juice two hours before the administration of AP at a dose of 5 mg/kg and 10 ml concurrently with it. The plasma samples were withdrawn up to 72 hours later and analyzed using the LC/MS technique, and pharmacokinetic parameters were analyzed using Winnonlin version 8.3. The findings indicated a statistically significant increase in C<sub>max</sub> of AP from 28.12±3.78 ng/mL to 56.97±9.8 ng/mL, as well as an increase in AUC<sub>0-12</sub> levels from 285.04±24.5 ng. hr/mL to 827.17±46.58 ng.hr/mL when ingested with OJ, without a significant change in T<sub>max</sub> and half-life (t<sub>1/2</sub>). The results determined that consuming sweet OJ exhibits a noteworthy interaction with orally administered AP.

**Keywords:** AP (AP); HPLC; method validation; orange juice (OJ); Citrus sinensis pharmacokinetic interactions.

### INTRODUCTION

Over the last two decades, one of the most significant challenges confronting pharmaceutical and clinical studies has been food-drug interactions. This has become a matter of concern for many researchers, especially when it relates to life-saving or narrow therapeutic window medications [1,2].

Food-drug interactions can be defined as changes in the pharmacokinetics and/or pharmacodynamics of a medication or any dietary component, or they may compromise nutritional status associated with, or as a result of, combining food and medication [3,4,5]. Older patients and those with chronic diseases are particularly at risk as this population group consume more than one-third of prescribed medications [6]. Consequently, failure to identify drug-food interactions may lead to complex or harmful consequences [7].

Therefore, food-drug interactions can lead to a

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decrease in the absorption of some oral medications and may result in a suboptimal concentration of the drug at the site of action. Ultimately, it can lead to an unfortunate failure of the patient's treatment process [8].

The inhibition or induction of chemical mediators, specifically enzymes present in the gut through food nutrients, can lead to significant changes in the pharmacokinetics and bioavailability of many medications [9]. The most common example is grapefruit juice, which specifically inhibits CYP3A4 in the intestine. This can result in an over fivefold increase in the total exposure to some medications, such as talinolol, when taken with grapefruit juice [10]. Consequently, there is an increased risk of unwanted side effects. Certain medications can impair gastrointestinal functionality and cause electrolyte and fluid losses. To mitigate these unfavorable drug-nutrient interactions, it is important to restrict the use of prescribed medications to those strictly necessary and to regularly reevaluate prescribed therapies [11].

Uncontrolled consumption of a large quantity of sweet orange juice (OJ) may decrease the absorption of celiprolol (Celocard), thereby reducing its effectiveness. To avoid this interaction, a minimum of four hours should separate the consumption of the medication and the juice [12].

Vanapalli et al. reported a reduction in the oral bioavailability of ivermectin when consumed with orange juice (OJ). In their study involving 16 healthy volunteers, 150µg/kg of ivermectin was administered with either water or OJ (750 mL over 4 hours), followed by plasma analyses up to 72 hours later. Their findings indicated a significant reduction in both C<sub>max</sub> and AUC, with T<sub>max</sub> remaining relatively consistent – suggesting a decrease in the extent of drug absorption [13].

Another viewpoint concerns medications transported via cellular pumps. OJ could alter the mechanism or activity rate of these pumps, which in turn could change the amount of medication absorbed by the body. This could potentially make these drugs either less or more active. Lilja et al. observed several interactions of this kind

with anti-allergic and other medications such as fexofenadine, levofloxacin, celiprolol, and atenolol [14].

Neuhoff et al. reported a significant 23% reduction in ciprofloxacin's C<sub>max</sub> when given with OJ, with an even steeper 41% reduction when consumed with calcium-fortified OJ. The AUC of ciprofloxacin over 24 hours diminished by 38% and 22% with each form of the OJ respectively [15]. Kamath et al. further reported that sweet orange might decrease the amount of fexofenadine absorbed by the body [16].

Such research has numerous limitations due to factors like the absence or deficiency of complete evidence or information, inaccuracies in medical reports, significant lack of clinical documentation, and awareness about the effect food may have on drug pharmacodynamics or pharmacokinetics. Therefore, studying food-drug interactions from every perspective is crucial – even when there are no reports on the topic, or concerns directly linked to the medicine being studied – especially when such a drug falls into the narrow therapeutic window or critical medications, as previously mentioned [17].

## **MATERIAL AND METHODS**

The following materials were used: Apixaban (with 99.7% purity, from Sigma), AP13C (kindly provided by the Triumpharm Research Center of Clinical Studies, Amman, Jordan), formic acid and acetonitrile (HPLC grade, from Merck, Germany), and sweet oranges from local farms.

### **2.1 Method Development**

Apixaban (AP) in rat plasma was detected and quantified using HPLC/MS. The optimal mobile phase for AP separation was found to consist of acetonitrile, deionized water, and formic acid in a 70:30:0.1 ratio (v/v). An internal standard, AP 13C, was employed. The analysis was conducted using a suite of Shimadzu instruments, including an SCL-10A VP system controller, LC-10AT VP pump, SIL-10AD VP auto-injector with a sample cooler, DGU-14A VP degasser, and SPD-10A VP

ultraviolet detector (all supplied by Kyoto, Japan). Data were collected and processed using Shimadzu VP software (version 5.03). The analytical column was an ACE C18 column, measuring 4.6x100mm with a 5.0µm particle size.

## 2.2 Extraction Method

Unknown samples and/or spiked plasma were thawed at room temperature before pipetting and were mixed until homogeneous. A total of 30 µL of the internal standard (0.5 g of AP 13C in D3/mL) and 600 µL of the precipitation agent (methanol or MeOH) were added to the tube containing 100 µL of the blank or spiked plasma. The mixture was vortexed for 5 seconds, followed by an additional minute of vortexing. After centrifuging for 7 minutes at 14,000 rpm, approximately 300 µL of each sample was injected into a glass vial with a flat-bottom insert.

## 2.3 Method Validation

Validation was conducted following the International Council for Harmonisation (ICH) guidelines and acceptance criteria. Aspects such as matrix effect, recovery, linearity, precision, accuracy, and detection limit were optimized in the method.

### 2.3.1 Matrix Effect

Matrix effects often occur due to alterations in the ionization efficiency of target analytes, typically in the presence of co-eluting substances within the same matrix [18]. This can either increase or decrease the response due to enhancement or suppression of the ionization state. For this reason, the labeled internal standard (IS) was employed in this method and calculated by

$$\text{Equation 1: MF of the analyte} = \frac{\text{peak area in the presence of matrix}}{\text{peak area in the absence of matrix}}$$

$$\text{Equation 2: IS – normalized Matrix effect (MF) =}$$

$$\frac{\text{MF of analyte}}{\text{MF of internal standard}}$$

### 2.3.2 Precision, Accuracy, and LLOQ (lower limit of quantification)

The method's accuracy was determined by comparing

the actual quantities recovered from the control samples with the expected values present in the samples (theoretical values) [19]. As per the ICH guidelines, the permissible relative standard deviation (RSD) limit should be less than 15%. The QC<sub>low</sub> (3 ng/mL), QC<sub>MID1</sub> (24 ng/mL), QC<sub>MID2</sub> (80 ng/mL), and QC<sub>High</sub> (160 ng/mL) samples were extracted.

### 2.3.3 Linearity and Calibration Curve

The Apixaban (AP) Calibration Curves and Linearity Test Concentrations were set at 1, 5, 10, 20, 50, 100, and 200 ng/mL. The Lower Limit of Quantification (LLOQ) was also calculated.

### 2.3.4 Recovery

Recovery is the percentage of the quantity of an analyte existing in or added to the analytical component of the test material that is extracted and prepared for measurement (ICH guidelines), as illustrated in Equation 3.

$$\text{Equation 3: Recovery \%} = \frac{\text{Area of extracted plasma sample}}{\text{Area of blanks spiked with the analyte post extraction}} \times 100\%$$

### 2.3.5. Method Selectivity

The method's selectivity was assessed by evaluating the blank sample (plasma) and the experiment's zero samples (immediately prior to medication administration).

## 2.4 Pharmacokinetic Study

### 2.4.1. Animals and Dosing

The study protocol was approved by the ethics review board. The research utilized Wistar rats weighing approximately 200±15 g, all of which were male and 8 weeks old. The animals were prepared for the experiment by fasting overnight (roughly 12 hours), with water access only. All rats were identified by tail tags before being divided into two groups, each containing six rats. Group 1 received an oral dose of AP (prepared in a distilled water suspension) at 5 mg/kg, whereas Group 2 was given 10 mL of orange juice (*Citrus sinensis*) both two hours prior to the experiment and concurrently with an oral dose of AP (prepared in a distilled water suspension) at 5 mg/kg.

### 2.4.2 Preparation of Doses and Juice

AP doses were prepared by suspending 10 mg of AP in 10 mL of distilled water and stirring before administration. The linear pharmacokinetics of AP was confirmed by Frost et al. [20]. The analysis method was designed in a range of 1-200 ng/mL, which made detecting smaller concentrations after administration and during elimination challenging. Each animal received the designated dosage by oral gavage. Freshly squeezed orange juice was made using a press squeezer and measured with a volumetric cylinder before being administered to the animal by oral gavage. The fruits used were purchased from Al-Gour, near the Jordan River, and were freshly picked in February 2021.

### 2.4.3 Samples of Plasma

Samples were collected from the rat tail. Before each collection, the rat tail was warmed for half a minute using a hot pad. A total of 250  $\mu$ L was drawn at the following time intervals: zero, 20, 40, 1.5, 3, 5, 8, 12, 24, 36, and 72 hours. Blood samples were drawn into heparinized tubes,

centrifuged for 15 minutes at 3500 RPM to separate the plasma, and then frozen at  $-25^{\circ}\text{C}$  for subsequent analysis.

### 2.4.4 Non-compartmental analysis (NCA) of plasma Concentration-time Data

The basic bioavailability parameters used in this study were the maximum drug concentration in plasma ( $C_{\text{max}}$ ), observed time to reach maximal concentration ( $T_{\text{max}}$ ), drug elimination rate constant derived from the slope of the later points in the elimination phase ( $K_{\text{el}}$ ), and  $\text{AUC}_{0-t}$ . These parameters were calculated using Winnonlin software (version 8.3), and statistical comparisons were performed using ANOVA with a 10% CI as the significance limit.

## 3. RESULTS

### 3.1 Method Development and Validation

AP was measured in rat plasma samples using the described technique. A sample of AP chromatograms is shown in Figure 1, with a retention time of 1.08 minutes (A), and (B) represents the blank plasma.

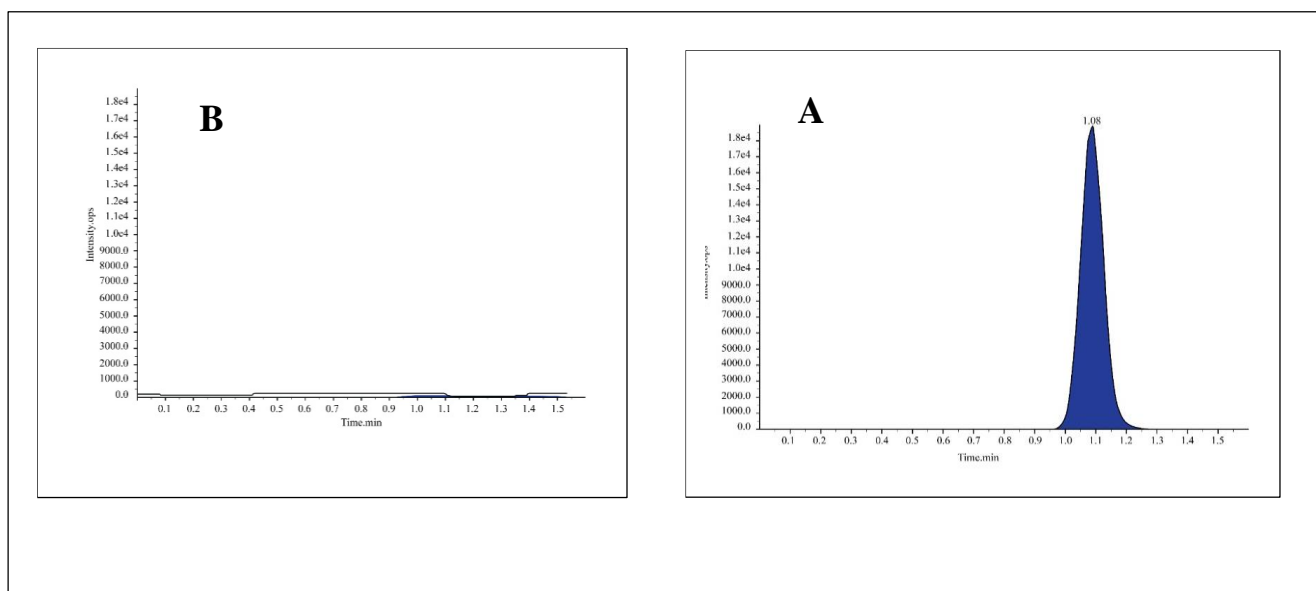


Figure 1: Chromatogram of AP (A blank plasma B AP showing retention time at 1.08 minutes)

### 3.2 Method Validation

**3.2.1 Matrix Effect:** The matrix effect results for Apixaban (AP) indicated that the calculated Relative Standard Deviation (RSD) was less than 15%, adhering to the limit set by the ICH guidelines.

#### 3.2.2 Precision, Accuracy, and (lower limit of quantification) LLOQ

An acceptable accuracy range of 85–115% was achieved for all concentrations [21]. The "within-run" accuracy results display that AP in plasma can be quantified with sufficient accuracy and precision across the entire concentration spectrum. As the results from the LLOQ demonstrate, quantities larger than the LLOQ can be precisely and accurately quantified using the AP

analytical method. The results are provided as supplementary data.

#### 3.2.3 Linearity and Calibration Curve

Using the mean of three linearity test runs, AP concentrations ranging from 5.00 ng/mL to 200 ng/mL yielded a linear regression with a correlation coefficient of  $R = 0.9992$ , demonstrating the linearity of the concentration used with the area under the curve (AUC) measured for the drug and internal standard (IS). This is depicted in Figure 2. The RSD of back calculation was as follows: 12.64 (1 ng/mL), 1.41 (5 ng/mL), 5.25 (10 ng/mL), 7.84 (20 ng/mL), 2.27 (50 ng/mL), 6.98 (100 ng/mL), and 2.77 (200 ng/mL). The LLOQ was determined to be 2 ng/mL.

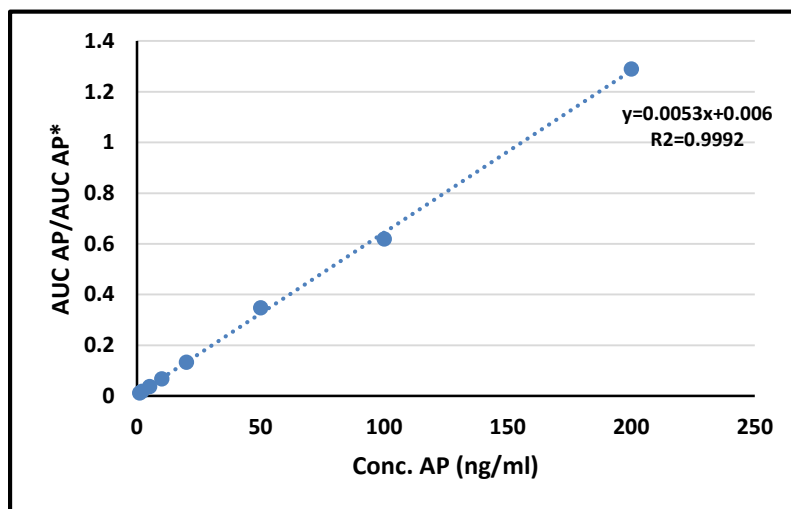


Figure 2: Calibration curve of AP

#### 3.2.4 Recovery

As per the International Council for Harmonisation (ICH) guidelines for measuring Apixaban (AP) concentrations in rat plasma, the method was sufficiently reliable for pharmacokinetic studies. The average recovery was 85.13% with a relative standard deviation (RSD) of

5.72%, satisfying the guideline criteria of 85–115%. These results are presented in Table 1. The methodology's selectivity was confirmed, as no AP peak was detected in the blank plasma.

**Table 1: Results of the recovery test.**

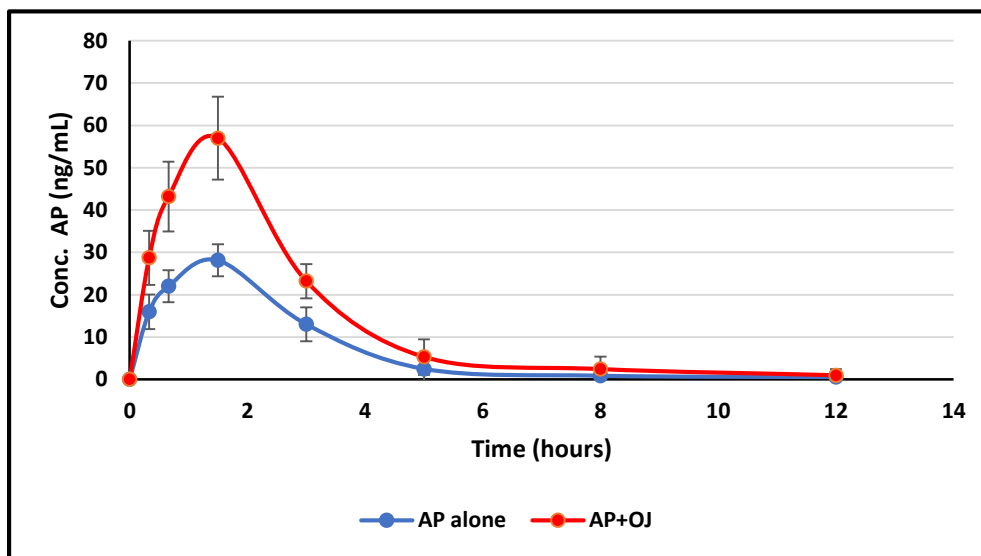
Replicate	IS (Peak Area) in QC Low (Peak Area)		IS (Peak Area) in QC <sub>Med-1</sub> (Peak Area)		IS (Peak Area) in QC <sub>Med-2</sub> (Peak Area)		IS (Peak Area) in QC <sub>High</sub> (Peak Area)	
	Extracted	Post Spiked	Extracted	Post Spiked	Extracted	Post Spiked	Extracted	Post Spiked
1	65246	67151	64293	69782	62828	79096	60947	77844
2	61481	69647	59061	72886	64377	74397	63556	77851
3	60775	67771	59816	70956	59171	71847	61234	75292
Mean	<b>62501</b>	<b>68190</b>	<b>61057</b>	<b>71208</b>	<b>62125</b>	<b>75113</b>	<b>61912</b>	<b>76996</b>
Recovery %	<b>91.66</b>		<b>85.74</b>		<b>82.71</b>		<b>80.41</b>	
Mean	<b>85.13</b>							
SD	<b>4.870</b>							
RSD	<b>5.72</b>							

**3.3 Pharmacokinetic Study**

**3.3.1 Construction of Plasma Level Time Profiles**

The C<sub>max</sub> and AUC were higher in group 2 than in group 1, as depicted in Figure 3. Plasma analysis at 24, 36,

and 72 hours yielded no results as they fell below the Lower Limit of Quantification (LLOQ). Therefore, the results are presented up until the 12-hour mark.



**Figure 3: Plasma level-time profile of AP in rats' plasma (G1 "AP only" and G2 "AP with OJ").**

**3.3.2 Calculation of Pharmacokinetic Parameters**

Table 2 shows the pharmacokinetic parameters of AP with and without OJ. Statistical analysis showed that C<sub>max</sub>

increased significantly as well as AUC<sub>0-12</sub>, while elimination rate constant (K<sub>el</sub>) and half-life (t<sub>1/2</sub>) showed non-significant difference in their values by ANOVA.

**Table 2. AP basic pharmacokinetic characteristics in the examined groups**

Group no.	C <sub>max</sub> ±SD (ng/mL)	T <sub>max</sub> (hr) (median)	AUC <sub>0-12</sub> ±SD (ng. hr.mL <sup>-1</sup> )	Kel ±SD (h <sup>-1</sup> )	Half-life T <sub>1/2</sub> (h)
G1, AP alone	28.12±3.78	1.5	285.04 ± 24.5	0.0698 ± 0.098	10.07±0.6
G2, AP+ OJ	56.97 ±9.8 *	1.5	827.17 ± 46.58*	0.0687 ± 0.085	10.08±0.92

\* significant (0.1 CI)

#### 4. DISCUSSION

The C<sub>max</sub> of Apixaban (AP) alone was found to be 28.12±3.78 ng/mL and increased to 56.97±9.8 ng/mL when consumed with orange juice (OJ). ANOVA results revealed that the increase in C<sub>max</sub> with OJ was statistically significant (CI = 0.1). Although C<sub>max</sub> is an extent and rate parameter, without knowing T<sub>max</sub> and AUC, it's impossible to determine whether the interaction is due to the quantity or rate of drug absorption. The variance could have been affected by a change in pace, magnitude, or both. The T<sub>max</sub> (median) was 1.5 hours (90 min) for both groups, indicating no difference between them. This suggests that the absorption rate remained constant, with the same amount of AP being absorbed no matter how it was taken. When administered alone, AP has an AUC<sub>0-t</sub> of 285.04±24.5 ng.hr/mL, which significantly increased to 827.17±46.58 ng.hr/mL when consumed with citrus sinensis OJ, as depicted in Figure 3. This implies that more AP was absorbed when taken with OJ, resulting in a larger C<sub>max</sub>. The elimination rate constant (Kel) for AP was calculated for both groups, and the results showed no significant difference in Kel between the two groups. This indicates that OJ did not affect the elimination pattern of AP.

Interactions between food, juices, and drugs at the site of absorption frequently occur at three levels: the first and most common being intestinal cytochrome P3A4, the second being intestinal uptake of organic anion-transporting polypeptides (OATPs), specifically OATP2B1, and thirdly, the efflux transporter, P-glycoprotein (P-GP) [22]. This study revealed that when orange juice (OJ) was co-administered with Apixaban (AP), there were significant increases in the C<sub>max</sub> and AUC of the drug. This could potentially be due to OJ

inhibiting the P-GP efflux mechanism [23], leading to greater drug absorption and thus a higher C<sub>max</sub> and AUC. The drug absorption rate remained consistent between both groups, indicating that the interaction primarily influenced the extent of absorption, as manifested by the higher AUC<sub>0-t</sub>.

Breast cancer resistance protein (BCRP, gene ABCG2), an efflux transporter present in numerous healthy tissues, including the gastrointestinal tract, colon, liver, and kidneys, can reduce systemic exposure to several drugs — including AP — since BCRP acts as rate-limiting barrier to the absorption of its substrates from the intestine and enhances the excretion of its substrates into the bile and urine [24, 25].

This study lends further support to the growing evidence that efflux contributes to AP's low oral bioavailability. Honda et al. found in their research on Caco-cells that OJ inhibits vinblastine transport from apical to basal membrane through interaction with P-GP and multidrug resistance protein (MRP2), both found in apical membranes [26]. As AP is predominantly eliminated through bile excretion [27], the unchanged elimination rate throughout the study (identical T<sub>max</sub> in both groups) suggests that OJ primarily affected drug absorption and had no impact on AP's elimination. Therefore, when AP is co-administered with OJ as an oral anticoagulant, clinical monitoring is necessary, chiefly for bleeding symptoms such as hemorrhage and hematoma, in response to the anticipated increase in systemic AP concentration. Thus, concurrent administration of OJ from Citrus sinensis had a significant impact, namely an increase, on the extent of AP absorption.

#### CONCLUSION

A validated, rapid, and sensitive analytical method has

been successfully developed for Apixaban (AP) in healthy rat plasma, ideally suited for pharmacokinetic applications. The results of this study demonstrate that consumption of orange juice (*Citrus sinensis*) alongside AP results in increased absorption and bioavailability of AP, without any significant alteration in AP's elimination.

#### **Ethical Approval**

The study protocol was approved by the Ethics Review Board at Al-Ahliyya Amman University, as per decision no. (AUP: AAU/1/4/2021-2022), Faculty of Pharmacy,

Al-Ahliyya Amman University, Jordan.

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#### **Declaration of conflict**

The authors declare that they have no conflicts of interest.

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## تقييم تأثير عصير البرتقال على الحرائك الدوائية للأبيكسابان في الفئران السليمة

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<sup>3</sup> مجموعة الطب التكاملي، Sains@BERTAM، المعهد المتقدم للطب وطب الأسنان، جامعة سينز ماليزيا، كيبالا بيتس، بينانج، ماليزيا.

<sup>4</sup> كلية الصيدلة، جامعة الزيتونة الاردنية، الأردن.

<sup>5</sup> كلية العلوم الطبية المساندة، جامعة عمان الاهلية، الأردن.

<sup>6</sup> كلية الصيدلة، جامعة العلوم التطبيقية، الأردن.

<sup>7</sup> كلية الصيدلة، جامعة مؤتة، الأردن.

### ملخص

يستهلك العصير المشتق من صنف "البرتقال الحلو" على نطاق واسع ويعتبر من أكثر العصائر شعبية على مستوى العالم. أنه يحتوي على العديد من المركبات النشطة بيولوجيا التي يمكن أن تتفاعل مع العوامل الصيدلانية. تهدف هذه الدراسة إلى تقييم تأثير تناول عصير البرتقال والأبيكسابان عن طريق الفم على الخصائص الدوائية الأساسية للأبيكسابان. تم استخدام مجموعتين من فئران الوستار في هذه الدراسة، أعطيت إحداهما الدواء بمفرده والأخرى مع عصير البرتقال. تم تحليل عينات البلازما باستخدام تقنية LC/MS وتم تحليل المعلمات الدوائية باستخدام WinNoline الإصدار 8.3. أشارت النتائج إلى ارتفاع ذو دلالة إحصائية في  $C_{max}$  لـ Apixaban من  $3.78 \pm 28.12$  نانوغرام / مل إلى  $56.97 \pm 9.8$  نانوغرام / مل، بالإضافة إلى زيادة في مستويات AUC<sub>0-12</sub> من  $24.5 \pm 285.04$  نانوغرام. ساعة/مل إلى  $46.58 \pm 827.17$  نانوغرام ساعة/مل عند تناوله مع عصير البرتقال. حددت النتائج أن تناول عصير البرتقال الحلو يظهر تفاعلاً ملحوظاً مع أبيكسابان الذي يتم تناوله عن طريق الفم.

**الكلمات الدالة:** الابكسبان، التحليل اللوني عالي الكفاءة، مقايسة الطريقة، عصير البرتقال، معلّلات الحرائك الدوائية.

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