

## The Impact of Pomegranate Juice on the Pharmacokinetic of Different Drugs



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**Abstract**— The consumption of herbal beverages, such as pomegranate juice (PJ), has experienced a notable surge in recent years. The concomitant utilization of prescription medications and herbal products is prevalent, which may have implications on therapeutic outcomes and adverse effects. Numerous studies have demonstrated that different juices can alter enzymes and transporters that regulate pharmacokinetic parameters, leading to clinically significant and unpredictable effects. Despite being extensively studied for its medicinal properties and potential health benefits, the interactions of pomegranate (*Punicagranatum*) with conventional medications are still under investigation. This fruit, which has a long history of traditional medicinal use for various therapeutic purposes, is widely consumed globally. Pomegranate comprises a diverse range of chemical constituents that include sugars, organic acids, polyphenols, fatty acids, anthocyanins, flavonoids, alkaloids, sterols, triterpenes, and vitamins. These constituents can vary based on factors like agricultural practices, geographical region, fruit ripeness, and storage conditions. The polyphenolic compounds found in pomegranate, such as tannins and flavonoids, are particularly rich and possess potent anti-inflammatory, antioxidant, antibacterial, antidiabetic, cardio protective and anticarcinogenic properties. Due to the multifaceted therapeutic properties and extensive chemical composition of pomegranate, researchers have been investigating its complex interactions with various medications. Co-administration of different drugs with pomegranate has resulted in insignificant changes in pharmacokinetic parameters. For instance, pomegranate has been shown to inhibit cytochrome P450 enzymes, including CYP3A and CYP2C9, which may impact the metabolism of drugs that depend on these enzymes for processing and breakdown in the liver and intestines. This may lead to increased drug levels and potential adverse effects. Examples of this interaction include carbamazepine, tolbutamide, nitrendipine, metronidazole, sildenafil, warfarin, metformin, and theophylline. It is important to note, however, that individual responses to drug interactions can vary, and findings from animal or *in vitro* studies may not always directly translate to human effects. Therefore, it is crucial to consult health care professionals before making any changes to medication regimens or incorporating pomegranate juice or other herbal products.

**Key words:** Pomegranate juice, Beverages, Drug interactions, Pharmacokinetic properties, Conventional medications.

## Objective

The objective of this investigation is to examine the plausible interactions that may exist between pomegranate juice (PJ) and various conventional medications. Specifically, this search aims to scrutinize the effects of co-administering pomegranate juice with different drugs on their pharmacokinetic properties. The purpose is to evaluate whether pomegranate juice has the potential to modify the absorption, distribution, metabolism, or elimination of these medications, which may result in alterations in their efficacy, safety, and therapeutic outcomes. By meticulously analyzing specific drug interactions, such as carbamazepine, tolbutamide, nitrendipine, metronidazole, sildenafil, warfarin, metformin, and theophylline, the study endeavors to provide valuable insights into the potential hazards and implications of consuming pomegranate juice concurrently with these medications. The ultimate aim is to make a significant contribution towards enhancing the comprehension of the interactions between pomegranate juice and conventional drugs, thereby disseminating this information to healthcare professionals and patients, and guiding appropriate clinical management.

## Introduction

In recent years, there has been a significant increase in consumption of herbal beverages. Research studies have indicated that a considerable percentage, roughly 20% of populations in Asia consume prescription medications concurrently with one or more herbal products (Wael Abu Dayyih, 2021). The impact of consuming herbal beverages along with approved medications can result in therapeutic failures or adverse effects, leading to unpredictable and clinically significant outcomes (Dayyih WA, Awad R, Awad M, Hamad MF, 2021) (Alanbaki, 2019). Various investigations have evinced that different types of juices possess the capability to modify enzymes and transporters responsible for the regulation of pharmacokinetic parameters. Consequently, such modifications may culminate in undesirable pharmacodynamic effects (Mallah, 2017).

Pomegranate (*Punicagranatum*) is a fruit that has been extensively studied for its potential health benefits and medicinal properties of interactions yet to be investigated, among those the interaction between pomegranate and different conventional medications, between natural pomegranate (Abdel-Halim, H 2020) the family Punicaceae includes the pomegranate, which is endemic to the area ranging from Iran to the northern Indian Himalayas. Since time immemorial, this fruit has been farmed and adjusted to the whole Mediterranean region (Viuda-Martos, Fernández-Lóaez and Pérez-álvarez, 2010). This particular fruit is consumed extensively around the world and has a vast historical usage in traditional medicinal practices for multiple therapeutic objectives (Hidaka, Okumura, K.I. Fujita, 2005). The plant exhibits an array of distinctive medicinal properties in its various components including the fruit, bark, leaves, and fruit rind. It is pertinent to note that a mere 52% of the total fruit weight is deemed edible, while 22% is comprised of seeds. There main in portion, a significant 78%, constitutes juice (Lansky, Neeman and Shubert, 2000).

### **1. Pomegranate is composed of a variety of chemical constituents.**

The diverse range of compounds present in pomegranate's chemical composition encompasses numerous constituents, including but not limited to sugars, organic acids,

polyphenols, fatty acids, anthocyanins, flavonoids, alkaloids, sterols, triterpenes, and vitamins such as vitamin C, B1, B2, and beta-carotene (El-Nemr, Ismail and Ragab, 1990). It is of utmost importance to take note that the specific composition of these aforementioned constituents may display variations contingent upon an array of factors, ranging from the geographical region of cultivation, the ripeness of the fruit, the agricultural practices employed, as well as the storage conditions. One must acknowledge these variables to grasp the entirety of the fruit's composition (Akbarpour, Hemmati and Sharifani, 2009). After the separation of fatty acids from pomegranate seeds, the two most prevalent fatty acids were identified as linolenic acid and linoleic acid. In addition, small amounts of other types of fatty acids were detected, including oleic acid, palmitic acid, stearic acid, palmitoleic acid, arachidonic acid, lauric acid, and caprylic acid. The findings propose that pomegranate seeds provide an ample supply of multiple types of fatty acids (Amri, 2017) and rich in polyphenolic compounds like tannins (specifically ellagitannin), flavonoids (specifically anthocyanins, flavan-3-ols, and flavonols), all of which possess powerful anti-inflammatory, antioxidant, antibacterial, antidiabetic, cardio protective and anticarcinogenic (Asgary, Javanmard and Zarfeshany, 2014). The voluminous and extensive assortment of diverse chemical compounds discovered in the pomegranate fruit, combined with its varied and multifaceted therapeutic properties, has sparked the curiosity and interest of researchers and scholars alike, in the investigation of the intricate and complicated interactions between pomegranate juice and a variety of medications. The co-administration of pomegranate with different drugs has resulted in numerous noteworthy changes and modifications in the pharmacokinetic (Abu Dayyih, 2016)

## **2. The administration of pomegranate juice can have an impact on the pharmacokinetic properties of different drugs.**

Concurrent use of meals and medications can have a major impact on the pharmacokinetic properties of drugs. Drug release, absorption, distribution, metabolism, and elimination are some of these features. The effectiveness and safety of medications taken orally depend on each of these criteria. Therefore, when it comes to therapies that are administered orally, food-drug interactions are a serious problem (Alanbaki, 2019). Many reports pomegranate possesses the capacity to impede the operation of cytochrome P450 enzymes, namely CYP3A and CYP2C9. The inhibition of cytochrome P450 enzymes, specifically CYP3A and CYP2C9, by pomegranate may significantly affect the metabolism of drugs that require these enzymes for their processing and breakdown in the liver and intestines (Mansoor, 2023).

## **3. Carbamazepine**

The pharmacological agent, namely Carbamazepine, has been frequently prescribed by medical professionals for the purpose of therapeutic management of seizure disorders as well as neuropathic pain. It is worth noting that the anticonvulsant or antiepileptic drug category encompasses a wide range of pharmacologic agents, of which Carbamazepine is a member, and is employed in the treatment of seizures and other neurological disorders (Alrashood, 2016). The possible repercussions of CYP3A4 inhibition initiated by pomegranate are

noteworthy. This might lead to a rise in the degree of carbamazepine in the anatomy, impede the expulsion of carbamazepine from the anatomy, and hinder the creation of carbamazepine epoxide, the operative metabolite of carbamazepine. These effects might escalate the hazard of carbamazepine-related secondary effects or toxicity. These phenomena may heighten the risk of carbamazepine-associated side effects or toxicity (Hidaka, Okumura, K. Fujita, 2005).

#### **4. Tolbutamide**

Sulfonylurea medication tolbutamide is prescribed to treat diabetes mellitus. It is used orally as an anti-diabetic drug. Drugs from the pharmacological family of sulfonylureas target the sulfonylurea receptor on pancreatic beta cells, increasing the release of insulin. Tolbutamide is primarily used to treat people with type 2 diabetes whose hyperglycemia has to be controlled. Its method of action entails increasing insulin production, which lowers blood glucose levels to ideal ranges (Panten, 1986). There exists a potentiality whereby the simultaneous administration of pomegranate juice and tolbutamide may induce a modification in the pharmacokinetic profile of tolbutamide (Nagata, 2007).

#### **5. Nitrendipine**

Nitrendipine, a dihydropyridine, functions as a calcium channel blocker predominantly utilized for the management of hypertension. The mechanism of action of nitrendipine involves hindering the entry of calcium ions into smooth muscle cells of blood vessels. This leads to the relaxation and dilation of blood vessels by virtue of calcium channel blockade (Mengden, 1992). It has been noted that Pomegranate juice can obstruct the operation of CYP3A4 in both the gastrointestinal tract and liver upon consumption. This consequential inhibition can lead to heightened systemic exposure to drugs, which are metabolized by the aforementioned enzyme, such as nitrendipine. It has been observed that this augmented systemic exposure can potentially result in elevated blood levels of nitrendipine, thereby increasing the probability of adverse effects (Voruganti, 2012).

#### **6. Metronidazole**

Metronidazole, a pharmacological agent categorized as an antibiotic, is employed in the management of a myriad of infections that arise from specific bacteria and parasites. Its efficiency is predominantly aimed at anaerobic microorganisms, a group of living organisms that can flourish and spread in an environment deprived of oxygen (Freeman, Klutman and Lamp, 1997). The concurrent usage of pomegranate juice and metronidazole might have an influence on the pharmacokinetics of metronidazole, leading to a change in its absorption, distribution, metabolism, or elimination, which could increase the concentrations of the medicine in the systemic circulation (Haifa T. Abu Tbeekh, Wael A. Abu Dayyih, Eyad M. Mallah, Nidal A. Qinna, Riad M. Awad, 2014).

#### **7. Sildenafil**

Sildenafil is a pharmaceutical agent that is employed for the management of erectile dysfunction among the male gender. It is categorized among a set of therapeutic agents denominated phosphodiesterase type 5 inhibitors. The modus operandi of Sildenafil include

the inhibition of the enzyme PDE5, leading to an increased blood flow to the male genitalia during sexual arousal (Bressler, Marmor and Kessler, 1999). The co-administration of pomegranate has the potential to impact the absorption, distribution, metabolism or elimination of sildenafil within the human body. This may result in altered pharmacokinetic properties of the drug and may have significant implications for patient safety and efficacy of treatment (Mallah, 2016).

### **8. Warfarin**

The usage of Warfarin to avert blood clots in people with atrial fibrillation has been widespread for a considerable amount of time. A prevalent cardiac arrhythmia known as atrial fibrillation can increase the likelihood of blood coagulation in the heart, thereby engendering the possibility of stroke or systemic thromboembolism (Singer, Chang and Go, 2010). The consumption of pomegranate juice has been suggested to have the potential to result in an increase in warfarin levels within the bloodstream, thus leading to the enhancement of its anticoagulant effects and subsequently elevating the probability of experiencing bleeding events (Komperda, 2009).

### **9. Metformin**

Metformin, a member of the biguanides category, is a highly prevalent medication. Its primary function is to combat type 2 diabetes, with its efficacy being well-known and established. Furthermore, it has also been deemed useful in the treatment of polycystic ovary syndrome and prediabetes in specific circumstances, thus expanding its range of applications (Pernicova and Korbonits, 2014). The simultaneous administration of pomegranate and metformin has the potential to impact the pharmacokinetics of metformin, particularly with regards to its absorption and/or distribution within the human body (Awad, 2016).

### **10. Theophylline**

The medication, Theophylline, falls under the category of methylxanthines which is a class of drugs. Its primary purpose is to manage asthma, chronic obstructive pulmonary disease (COPD), and other respiratory conditions. Theophylline performs its function by easing the smooth muscles present in the airways, thereby enhancing the breathing process and improving the airflow. It is an effective medication for respiratory disorders and the benefits of its usage should be taken into consideration while determining the treatment plan (Barnes, 2013). Pomegranate juice may not interfere with Theophylline (Mansoor, 2023).

### **Conclusion**

Conclusively, co-administration of pomegranate juice with conventional medications may potentially result in significant interactions and alterations in pharmacokinetic properties. The heterogeneous chemical composition of pomegranate juice, which includes polyphenolic compounds and enzymes inhibitory effects, can affect the metabolism of specific drugs, leading to changes in their bioavailability, maximum plasma concentration, and overall efficacy. Numerous medications, such as carbamazepine, tolbutamide, nitrendipine, metronidazole, sildenafil, warfarin, and metformin, have been discovered to be influenced by

the consumption of pomegranate juice. These interactions may lead to higher drug levels, increased systemic exposure, and possible adverse effects or therapeutic failures. It is imperative for healthcare practitioners and patients to be cognizant of these interactions and consider them when administering or using these medications in conjunction with pomegranate juice. Further investigation is required to acquire a more profound understanding of the mechanisms underlying these interactions and to determine specific dosing recommendations or precautions for patients consuming pomegranate juice. Overall, caution should be exercised when combining pomegranate juice with conventional medications, and healthcare providers should be proactive in assessing and managing potential drug interactions to ensure optimal therapeutic outcomes and patient safety

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