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Pomegranate Juice-Drug Interactions: Pharmacokinetic ParametersStudiedUsing Different Liquid ChromatographyTechniques

Heba Abdel-Halim[1], Wael Abu Dayyih[1*]

[1]Departmenr of Pharmaceutical Medicinal Chemistry and Pharmacognosy; Faculty of Pharmacy and Medical Sciences –University of Petra

Abstract— Pomegranate (*Punica granatum*L.)is an ancient fruit that is still part of diet all over the world. Health-promoting effects have long been attributed to this fruit; modern research supports the use of pomegranate as a folk remedy for diabetes, metabolic syndrome, and many other ailments. Many interactions have been reported between different food substances and drugs that would alter the effect of the drug, and some are known to cause serious consequences on the health. The importance of diet-drug interactions has prompted the study of the effect of concurrent admiration of different food substances to determine drugs' dosing, timing, and formulation for new drug candidates before being marketed. This review provides an overview of current knowledge of the effect of pomegranate juice on different enzymes and transporters that modulate the pharmacokinetic parameters by using different liquid chromatographic bioanalytical methods.

Keywords— Pomegranate, drug interactions, pharmacokinetic properties, high performance liquid chromatography, liquid chromatography–mass spectrometry, liquid chromatography–mass spectrometry.

1. Introduction

Punica granatum L. (pomegranate) has been one of the traditional medicine remedies used for centuries in different regions of the world [1]. Different parts of the plant are consumed including: fruit, bark, leaves, and fruit rind, with each part having special medicinal effects. Only 52% of the total fruit weight is edible, it contains 22% of seeds, and the majority (78%) is juice[2]. Over the years, this fruit was used to treat various complaints such as rheumatoid arthritis and different inflammation conditions, dental plaque, dysentery, and to fight malarial parasites and intestinal infections [1]. In addition, pomegranate was found to have antioxidant, antibacterial, antidiabetic, cardioprotective and anticarcinogenic activities [3-6].

Pomegranate is very rich in phytochemical compounds (phytocompounds) [7]. Phytocompounds are low molecular weight compounds that are usually produced by plants as a defense mechanism. A diversity of phytocompound families were identified and many were explored for their therapeutic effects [3-6].Seeds are considered a rich source of lipids, proteins, and fibers, while the main contents of the juice are sugars (10.6%), and pectin (1.4%). In general the different minerals content of the seeds is higher than that of the juice with the exception of potassium [8, 9]. The active constituents and the medicinal properties of pomegranate extensively studied and reported in many previous research[10-12]. Pomegranate's wide therapeutic effects are believed to be through a number of mechanisms, however, the different effects may be mainly attributed to its antioxidant, anticarcinogenic, and anti-inflammatory properties.

1.1 Chemical Constituents of Pomegranate

The chemical constituents of the different parts of pomegranate differ with fluctuations of the planting region, maturity upon harvest, agriculture practice, and storage conditions [13, 14]. A variety of chemical compounds were reported to be found in pomegranate fruit, tree, leaves and/or juice and belong to different chemical classes including: sugars, organic acids, polyphenols, flavonoids, anthocyanins, fatty acids, alkaloids,sterols, triterpenes, and vitamins. The main sugars included pomegranate extract were found to be: glucose, fructose, sucrose, and maltose. While this fruit is rich in the vitamins e C, B1, B2, and beta-carotene[8].

Saturated and unsaturated fatty acids were extracted from pomegranate seeds, the predominant fatty acids to be found were linolenic and linoleic acid, while other fatty acids were found in smaller amounts and included: oleic acid, palmitic acid, stearic acid, palmitoleic acid, arachidonic acid, lauric acid, and caprylic acid [15]. In addition, the rare *trans*-18-carbon fatty acid, punicic acid, was found in the seed extract of the fruit [16].

1.3 Therapeutic Effects of Pomegranate

It was recently reported that the therapeutic effects of pomegranate are mainly attributed to ellagic acid ellagitannins (including punicalagins), punicic acid, flavonoids, anthocyanidins, anthocyanins, and estrogenic flavonols and flavones [17]. Phenolic compounds that were reported to be found in pomegranate include[18]:

- Flavonoid: anthocyanins (pelargonidin, delphinidin, cyaniding), anthoxanthins (catechin, epicatechin and quercetin)
- Tannins: ellagitannins, and ellagic acid derivatives (punicalagin, punicalin and pedunculagin)
- Phenolic acids (chlorogenic, caffeic, syringic, sinapic, p-coumaric, ferulic, ellagic, gallic and cinnamic acid)

The presence of flavonoids and tannins has contributed to the fruit's anticancer activity [19]. The antioxidant activity can be attributed to the high total phenolic, flavonoid and flavonol content. It has been reported that highest antioxidant activity was that of the fruit's peel extract that contained the highest total phenolic content [20]. Ellagic tannins, ellagic acid, and gallic acid are the main compounds responsible for this antioxidant activity [21]. In addition, ellagic acid shows antimutant, antiviral activities[22]. Pomegranate fruit is also enriched with punicalagin, a strong antioxidant that exert its mechanism through controlling superoxide and other free radicals of DPPH (1,1-diphenyl-2-picrylhydrazyl)[23].Among different acids found in pomegranate, the ascorbic acid content adds to the reported antioxidant activity [24].

Flavonoids were found to have estrogenic activity, they should be hydrolyzed to show this activity as no estrogenic activity was observed in their glycoside counterparts [25].Furthermore, pomegranate extracts contained steroidal estrogens (γ-tocopherol, 17-α-estradiol, stigmasterol, β-estriol sitosterol, and testosterone), and nonsteroidal compounds (compestrol, coumestrol) [26]. The presence of these estrogens prohibit the estrogenic activity of 17-β-estradiol and therefore pomegranate can inhibit breast cancer cells for both types, estrogen-dependent and estrogen-independent. The antioxidant activity of polyphenols added to this inhibitory activities have been long related to the pomegranate human breast cancer

preventive effect [27]. In general, the presence of flavonoids and tannins has contributed to the fruit's anticancer activity [19]. Additionally, due to the rich fatty acid content of pomegranate seed oil it is been recently considered to be a good source of omega-3 fatty acids [28].

The diversity of the chemical constituents and the diversity of medicinal effects of pomegranate has prompted the study of the pomegranate juice – drug interactions. Many significant pharmacokinetic (PK) properties alterations were reported with used of pomegranate with drugs such as drugs like antiarrythmic, calicium channel blockers, and statins [29]. The current review focuses on the effect of concurrent consumption of pomegranate juice on the PK properties of different drugs as was assessed different liquid chromatography techniques.

2. Effect of Pomegranate Juice on Pharmacokinetic Properties of Drugs

The concurrent consumption of food with drugs may have a significant impact on drug release, absorption, distribution, metabolism and/or elimination (collectively, PK properties)and thus, on the therapeutic outcome and safety of drugs. The observed food-drug interactions are one of the main concerns for drugs administered orally. Recently, increased efforts were made to study the mechanisms by which any food substance may alter the PK properties of drugs [30]. Different studies suggested the interference of pomegranate juice with the intestinal absorption of certain drugs, in addition, many reports suggested that pomegranate inhibits CYP3A enzymes in the body [31]. In the following examples we review the effects of pomegranate juice on PK properties of some essential drugs as was determined using liquid chromatography techniques. The different parameters of peak serum concentration (Cmax), time to reach peak serum concentration (Tmax), and area under the curve (AUC) were used as an indication of the changes of PK properties of the different drugs.

2.1 Theophylline

Theophylline is one of the most widely used drugs for the treatment of asthma and chronic obstructive pulmonary disease. It is the first-line treatment in developing countries, while inhaled β2-agonists and corticosteroids are more used in other parts of the world [32].

Pomegranate use has been reported to help in the treatment of respiratory diseases and disorders [33], therefore a potential food-drug interaction can be observed. In a recent study, high performance liquid chromatography (HPLC) method of analysis was developed in order to measure theophylline concentrations in rat plasma and to establish the effect of pomegranate juice concurrent consumption on the different PK parameters. It has been found that intake of pomegranate juice prior to the oral administration of theophylline did not cause any significant alteration of the PK parameters and thus suggesting no significant interaction [34].

2.2 Metronidazole

Metronidazole is an antibiotic that is still considered the first-line choice for treatment of infections related to the gastrointestinal tract including colitis caused by *Clostridium difficile*[35]. The metabolism of metronidazole and associated cytotoxicity is not definitively characterized yet despite the long years of use [36]. Liquid chromatography–mass spectrometry (HPLC-MS/MS) techniques were used to study the effect of pomegranate fresh juice on the metronidazole PK properties. A significant increase in the

metronidazole PK parameters (Cmax and AUC) were observed after pretreatment of rats with multiple doses of pomegranate juice. This study's findings suggested also that pomegranate is an inhibitor of intestinal but not hepatic enzymes responsible for metronidazole metabolism [37].

2.3 Glimepiride

Glimepiride is sulfonylurea oral antidiabetic drug usually used by patients with type-2 diabetes mellitus, it lowers blood glucose levels by stimulating the release of insulin from beta cells of the pancreas [38]. A rapid, and sensitive method was developed for the determination of glimepiride in rat serum, using HPLC-MS/MS. The potential pharmacokinetic interactions between glimepiride pomegranate juice were investigated in the serum of experimental rats. This study found that pomegranate juice significantly reduced the glimepiride Cmax, Tmax and AUC[39] .

2.4 Piracetam

Piracetam is a nootropic commonly used drugs for the treatment of neurodegenerative diseases [40]. The effect of pomegranate juice on the PK parameters of piracetam was determined using HPLC techniques. No significant difference was found in the PK parameters of piracetam with its concurrent administration with pomegranate juice [41].

2.5 Warfarin

Warfarin, vitamin K antagonist, is characterized with very narrow therapeutic window. Many factors may affect the body's response to warfarin resulting in the observed interindividual variability [42]. The risk of warfarin high of low blood concentrations has prompted the study of the impact of pomegranate juice on both PK and pharmacodynamics properties of warfarin. Liquid chromatography–mass spectrometry (LC–MS) method was developed to determine the concentration of warfarin plasma, the Cmax, and AUC of warfarin were significantly reduced with pomegranate juice consumption. In contrast to this decrease pomegranate juice significantly increased both the prothombin time (PT) and international normalized ratio (INR) values.This increase in PT and INR level may increase the risk of bleeding and hence the pomegranate juice should be consumed with caution by patients using warfarin [43].

2.6 Metformin

Metformin (dimethylbiguanide) is the first-line oral blood glucose-lowering agent used in the treatment of type-2 diabetes mellitus [44]. Different pomegranate products have been used traditionally to treat and manage type-2 diabetes mellitus [45]. HPLC method was used to establish the effect of pomegranate juice on PK parameters of metformin, pomegranate consumption significantly reduced metformin plasma Cmax which may result in the reduction of the efficacy of metformin administered dose and may result in the delay of metformin action [46].

3. Conclusion

Different pomegranate juice-drug interaction studies were done to evaluate the potential effects of the juice on drug's PK parameters. For some of the reviewed drugs, the juice showed significant changes in the PK parameters and hence the therapeutic and/or side effect profile of these drugs.

The study of effect of different food substance intake on drugs should be taken into consideration when deciding the appropriate dosing, timing, and formulation of new drug candidates.

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