

Chapter

Phytochemistry, Pharmacological Activities, and Drug Interactions of Pomegranate, *Punica granatum* L. (Punicaceae)

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Abstract

Pomegranate (*Punica granatum* L.) is a Mediterranean plant that has been used in various countries for the treatment of various diseases in traditional medicine for many generations. These reported medicinal properties of pomegranate are mainly attributed to the presence of various phytochemical compounds in the plant. Scientific literature search was done in PubMed and Google Scholar databases. Full articles published in English for the last 25 years were selected. Pomegranate juice is the widely studied product of a plant. This is because of its wide medicinal and dietary use. Approximately 500 pure compounds have been isolated and characterized from different parts of the plant species. Phytochemically, the juice, seeds, flowers, and peels of *P. granatum* are the most studied parts of the plant. Major phytochemical compounds isolated from the plant include alkaloids, flavonoids, phenolics, tannins, sterols, and terpenes. Most of the compounds isolated from *P. granatum* belong to ellagitannins (punicalagins) and gallotannins. Medicinally, the use of different parts of pomegranate for the treatment of different types of cancer and cardiovascular diseases is the most widely reported in both preclinical and clinical researches. The herb/food-drug interactions of pomegranate juice with approved drugs have shown that pomegranate juice has the potential to inhibit some drugs, especially those metabolized by cytochrome CYP3A and CYP2C9. The current chapter gives a broad overview of the phytochemical, pharmacological, and herb/food-drug interactions of pomegranate.

Keywords: cytochrome, herb/food-drug interactions, *Punica granatum*, pomegranate, phytochemistry

1. Introduction

Punica granatum L., commonly known as the pomegranate, is an ancient plant that is associated with different cultures and religions in the world. Pomegranate is mentioned in the authorized King James Bible version (eight times in the Old Testament), the Koran (three times) [1], and in Buddhist and Chinese arts [2]. The plant is

considered native to regions across central Asia, especially Iran and northern India. Its medicinal, nutritional, and ornamental properties have led to its popularity and widespread medicinal use [2, 3].

Since the pomegranate has been known for over 4000 years [4], its medicinal use has been widely studied at both preclinical and clinical levels. Various reviews have been done previously and in recent years on pomegranate; phytochemistry [5], therapeutic/health benefits [6–10], nutritional benefits [11], ethnobotany [8–11], and pharmacokinetics (PK) of different parts of the plant [5]. Related research studies and reviews continue to be published. Therefore, research on pomegranate is still at the exploratory stage and therefore still incomplete [5].

The genus *Punica* has only two species, *P. granatum* (the common pomegranate) and its sister plant, *P. protopunica* Balf. [3]. Most research articles have focused on *P. granatum* and seem to have overlooked *P. protopunica*. Most people are not even aware of the existence of *P. protopunica*. The taxonomy, phytochemical, medicinal, and nutritional values of the forgotten “sister” plant should also be explored [3]. The continued research studies on *P. granatum* depict a potential plethora of medicinal, phytochemical, and nutritional knowledge in the plant species. Consequently, further in-depth study and reporting of research findings on pomegranate is necessary. This will contribute to resolving unclear issues on the plant species and contribute to knowledge in the medical world [5].

The phytochemistry, pharmacokinetics (PK), and pharmacodynamics (PD) of different parts of *P. granatum* (the common pomegranate) have recently been compiled [5]. However, review studies on the effects of *P. granatum* on the metabolism and pharmacokinetics of drugs are limited, and we could only access two that were reported in 2013 and 2023 [12, 13]. This requires an update on previous and current research to guide the current concomitant use of pomegranate with drugs. This happens when people get sick and use *P. granatum* in traditional medicine for the treatment of various diseases [8]. When they are not healed, they seek orthodox treatment in hospitals. Similarly, people also take pomegranate juice during drug medication. This could lead to herb/food-drug interactions [14]. This chapter focuses on the reported effects of pomegranate phytochemicals and pomegranate juice on the PK/PD of approved medicinal drugs since the herb/food-drug interactions are likely to affect the overall pharmacological effects of the co-administered drug.

Based on the wide medicinal use of *P. granatum* in treating various diseases in traditional medicine, coupled with its concurrent use with conventional drugs, a knowledge of the effects of pomegranate on the therapeutic activity of the co-administered drugs remains vital. Moreover, the chapter provides an overall abstract view of previous research on phytochemical, pharmacological, and herb/food-drug interactions of pomegranate that is expected to guide further research on pomegranate and perhaps contribute to a healthy life for its users.

2. Discussion

2.1 Taxonomy

The spelling of the botanical name of pomegranate, *Punica granatum* L. (Punicaceae), was confirmed by checking the *World Flora Online* (WFO) website, <https://www.worldfloraonline.org/> (accessed on August 31, 2023). The plant species has 36 heterotypic synonyms, according to the *Plants of the World Online* of the Royal

Botanical Gardens-KEW (accessed on August 31, 2023). The plant is a native of the region covering Iran to the Himalayas of Northern India. This region is considered to be the origin of pomegranate, but the plant has spread to Asia, Europe, America, and Africa (especially North Africa, East Africa, and South Africa) [3, 15]. Pomegranate belongs to a monogeneric family, Punicaceae, which has only two species, *Punica granatum* L. and its sister *P. protopunica* Balf. [3, 16]. *Punica protopunica* is considered the ancestral species of the family. It is less common and occurs only in the northwestern parts of the Indian Ocean, while *P. granatum* is most common and occurs in most parts of the world (Guerrero-Solano et al., 2020). Some of the distinguishing morphological features of the two species include (i) axile placentation in flowers of *P. protopunica*, whereas flowers of *P. granatum* have both axile and parietal, (ii) leaves of *P. protopunica* are dark green while *P. granatum* has shiny green leaves, and (iii) the fruits of *P. protopunica* are less palatable, while those of *P. granatum* are more palatable [3, 16].

Punica granatum grows up to 10 meters high with a pale-brown bark and shiny evergreen leaves. The leaves are oblong with wavy margins, opposite or sub-oppositely arranged, and can grow up to 7 cm long and 2 cm wide (**Figure 1**). Phenological studies of buds and leaves of *P. granatum* revealed that the plant is heterophyllous, having two types of leaves whose shape can be differentiated especially at the apex in dormant stages [17]. The anatomical features of the leaves are similar, but they develop differently to form lanceolate and obcordate final shapes [17]. The flowers are actinomorphic, with a hypanthium that is brightly colored [16]. Pomegranate has three types of flowers: the male flowers, hermaphrodite, and intermediate forms. Heterostyly is the most common form of arrangement of the flowers. The fruit of



Figure 1.
Punica granatum leaves, fruits, and flower.

pomegranate is globose with a thick tubular calyx. The pericarp is smooth, and the mesocarp is spongy and divided into several parts filled with many seeds [16]. The fruit changes its color from green when young to sun-kissed orange-red (**Figure 1**), which makes it attractive [18].

2.2 Materials and methods

This is a book review chapter on the phytochemistry, pharmacological properties, and herb-drug interactions (HDIs) of *Punica granatum* (pomegranate). Based on the wide medicinal use of pomegranate and published articles and review papers, the current book chapter aimed to compile the phytochemistry, pharmacology, and HDIs of the plant. A review of scientific and relevant literature was therefore selected from PubMed and Google Scholar databases using the following subject headings as keywords: “pomegranate,” “*Punica granatum*,” “pomegranate phytochemistry,” “pomegranate pharmacological properties,” “pomegranate herb/food-drug interactions,” “pomegranate taxonomy,” “pomegranate ethnobotany,” “pomegranate anticancer,” “pomegranate cardiovascular,” “pomegranate antimalarial,” and “pomegranate toxicity.” Relevant papers were selected based on the following inclusion criteria: full-text original papers written in English, published within the last 25 years for research articles, and last 10 years for review articles. The exclusion criteria included abstracts and articles written in languages other than English. No article was excluded because of affiliation.

2.3 Pomegranate phytochemistry

Plants produce various phytochemical compounds that contribute to the pharmacological activities of medicinal plants. These compounds can act in synergism, especially when the plant is used in its crude form or when isolated compounds are combined. About 500 compounds have been isolated and characterized from different parts of *P. granatum* (leaves, fruit rind, peel, seeds, juice, flowers, and stem bark) [5]. Most of these compounds have been isolated from pomegranate juice. Isolation and characterization of these compounds have been done in various ways. Structure elucidation of 92 compounds such as punicalagin, punicalin, and corilagin was done through nuclear magnetic resonance (NMR) and mass spectroscopy (MS) [5], and recently, other compounds like ellagic acid have been isolated through reverse iontophoresis [19]. In a single study, 88 compounds (flavonoids, coumarins, and phenolic acids) were isolated and identified from pomegranate seeds through ultra-high-performance liquid chromatography (UHPLC) coupled with quadrupole orbitrap high-resolution mass spectrometry (Q Orbitrap HRMS) [20].

Various phytochemical compounds have been isolated from different parts of *P. granatum*: pomegranate juice (180 compounds), seeds (164 compounds), flowers (113 compounds), and peels (108 compounds), based on the basic structures. About 41 compounds have also been isolated from pomegranate leaves and six from the stem bark of the plant species [5]. These compounds include flavonoids, alkaloids, sterols, tannins, ellagitannins, gallotannins, lignans, organic acids, fatty acids, saccharides, anthocyanins, anthocyanidins, proanthocyanidins, coumarins, terpenes, triterpenes, terpenoids, phenolics, phenolic acids, xanthones, xanthonoids, ellagic acid and hydroxycinnamic acid [5, 21, 22], and punicalagin [23]. Based on the review by [5], most compounds belong to ellagitannins and gallotannins.

A total of 88 ellagitannins and 31 gallotannins have been isolated and identified from seeds, juice, flowers, and fruit peels of pomegranates. Most of these compounds

have ≥ 2 constitutional isomers with similar major MS fragments, the same molecular formula, and the same name but different structures [5]. These phytochemicals have shown high health benefits, especially in fruits (pomegranate, strawberry, blackberry, raspberry, and muscadine grapes) and nuts (walnuts) that contain ellagitannins [6].

About 45 anthocyanins have been isolated from *P. granatum*. Considering that these anthocyanins are pigments, they are responsible for the diversified pomegranate flowers and fruit colors [24]. Different substitutions of monosaccharides and disaccharides with aglycone structures corresponding to different chemical structures of anthocyanins have also been isolated from pomegranate. For example, glucose, galactose, xylose, rutinose, and caffeoyl moieties are usually located at different positions of aglycone structure therefore yielding different anthocyanin structures [5].

Pomegranate is also considered a flavonoid-rich plant. Most of these flavonoids have been isolated from pomegranate juice and fruit peel [22]. The study [22] reported that 19 flavonoids have been isolated; however, a later review reported that 171 flavonoid compounds have been isolated from the plant species [5]. Other major compounds like phenolic acids (124 compounds) have also been isolated from pomegranate [5]. These phytochemicals play a major role in the therapeutic effects of *P. granatum* against various human diseases.

2.4 Pharmacological properties of pomegranate

Pomegranate is considered as an ancient medicinal plant in various traditional and complementary systems of treatment for various diseases and disease conditions [4]. To validate this, various research studies have been done at preclinical and clinical levels using various parts (juice, flowers, leaves, fruit rind, bark, peel, seeds, and seed oils) of *P. granatum*. Pomegranate juice is the most widely used pharmacologically.

2.4.1 Ethnobotany of pomegranate

Pomegranate is one of the most ancient plants that have been widely used in traditional medicine, homeopathic medication, and complementary systems of treatment such as Unani Tibb/Islamic, Persian [1, 25], Ayurvedic, Chinese medicine [2], and African traditional medicine [24, 26]. Its current use in traditional medicine for the treatment of several types of cancers, diabetes, hypertension, and stomach ulcers dates back to its native use in Asian cultures [2, 3].

In Ayurvedic (traditional Indian) medication, pomegranate is described as the “dalim fruit” (Sanskrit name), and it is used to cure different parasitic diseases and as a blood tonic. In this respect, people in this Asian culture, regard the plant as “a pharmacy unto itself” [25]. Similarly, in the Chinese ethnomedicine systems (traditional Chinese medicine, Uygur medicine, Mongolian medicine, and Tibetan medicine), most people in these regions use different parts of the plant mostly as a sour flavor to treat diarrhea and stomach upsets [4]. The use of pomegranate for the treatment of various diseases in these and other systems of medication has been studied at preclinical and clinical levels.

2.4.2 Pharmacological properties of pomegranate phytochemicals

Pomegranate has various bioactive substances. These phytochemicals have shown potential preventive and curative pharmacological properties when tested at both preclinical and clinical levels [27]. The preventive activities of pomegranates are

displayed by improving the immune response and avoiding infection. The synergistic effect of both preventive and prophylactic activities of pomegranate phytochemicals is greater when these phytochemicals are tested in combination than when they are tested alone [28]. While phytochemicals isolated from pomegranates have been used for the treatment of various ailments, most studies have reported on their use against different types of cancers, treatment of cardiovascular diseases, and some for the treatment of malaria.

2.4.3 Anticancer activities of pomegranate phytochemicals

Cancer is considered one of the leading causes of global mortality. The disease caused 9.6 million deaths, with 18.1 million cases reported in 2018 alone [29, 30]. As part of battling this life-threatening disease, pomegranate has been widely used for the treatment of different types of cancers.

A systematic, comprehensive, and critical review by Wong et al. [27] reported on various research studies on the uses of *P. granatum* for the prevention and treatment of various types of cancer. Furthermore, phytochemicals isolated from different parts of the plant species have shown potential use for the treatment of various types of cancers when tested at both the preclinical (*ex vivo*, *in vitro*, and *in vivo*) and clinical levels [27]. Polyphenols isolated from natural products have shown anticancer activities. A recent review by Teniente et al. [31] reported on anti-cervical cancer properties of polyphenols from pomegranate peels. Phenolic acids such as punican, punicalagin, ellagic acid, gallic acid, caffeic acid, rutin, and quercetin isolated from pomegranate peels showed *in vitro* activity against cervical cancer [30]. Other phenolics isolated from pomegranate seed oil have also shown *in vitro* antioxidant and anticancer activities against lung and colon cancer [32]. A similar review on the *in vitro* anticancer properties of pomegranate polyphenols has also shown preclinical and clinical therapeutic anticancer activity of various polyphenols against breast cancer [33]. Various studies indicated that these polyphenols have different mechanisms of action such as inhibition and arrest of the cell cycle [34], regulation of cellular redox balance [35], modulation of different signaling pathways [36], and antiproliferative, antiestrogenic, antiangiogenic, and antimetastatic activities [33, 37].

A recent review on anticancer activities of pomegranate by Rahman et al. [38] reported that extracts and pure compounds isolated from different parts of the plant have preventive and therapeutic activities against different types of cancers such as breast, skin, colon, bladder and lung cancers when tested at preclinical (*in vitro* and *in vivo*) and clinical levels. Similarly, galactomannan isolated from the fruit rind showed *in vitro* and *in vivo* anticancer activities against skin and lung cancers [38, 39]. Other pomegranate phytochemicals such as luteolin, ellagic acid, and punicic acid have shown therapeutic activity against prostate cancer [40]. Furthermore, ellagic acid and urolithins A and B showed *in vitro* inhibition activity against breast cancer. *In vitro* and *in vivo* anticancer prevention activities have also been depicted in pomegranate phytochemicals like tannins and punicalagin against colon cancer [38].

Anthocyanins isolated from natural products are considered as natural antioxidants. Anthocyanins isolated from flowers, leaves, and seeds of pomegranates have shown antioxidant activities [39]. The observed diversity in the chemical structure of pomegranate anthocyanins caused by internal and external factors contributes to the variation of different pomegranate anthocyanins [24]. Additionally, *in vitro* antioxidant activity of phenols, tannins, and flavonoids from pomegranate peels [40] and flowers has also been reported [41]. With the continued reports of increased

anticancer multidrug resistance [42], these pomegranate phytochemicals that have shown potential anticancer activities can be used as scaffolds for the discovery of novel anticancer drugs.

2.4.4 Anticancer properties of extracts from pomegranate

Extracts from pomegranate seed oil and fermented fruit have shown *in vitro* therapeutic activity against breast cancer [38]. Peel extracts from pomegranate have shown *in vitro* radical scavenging and Fe^{3+} antioxidant activities [43]. In a recent study, phytocomplexes isolated from pomegranate through hydrodynamic cavitation showed selective *in vitro* antiproliferative activity against human breast cancer cell lines without causing harm to healthy cells [44]. Similarly, fruit extracts of pomegranate have also shown *in vitro* and *in vivo* anticancer activities against skin and prostate cancer [38, 45–47]. The same extract showed *in vivo* antiproliferative activity against lung cancer [38, 48], with similar activity being shown in aqueous peel extracts [49]. Likewise, leaf extracts have also shown *in vitro* signaling pathway inhibition activity against lung cancer [50].

Pomegranate seed, peel extracts, and peel oil have also shown *in vitro* activity against breast cancer [38]. Similar anticancer activity against colon cancer has also been observed in pomegranate juice when tested *in vitro* and *in vivo* [51]. Since cancer is considered the most life-threatening disease globally, pomegranate promises a wide area of further research in the world of oncology. It has potential use as a chemopreventive and/or chemotherapeutic anticancer drug since it has no side effects, especially when used naturally [38].

2.4.5 Anti-cardiovascular activities of pomegranate phytochemicals

Approximately a third of the global deaths in 2019 were caused by cardiovascular (CDV) diseases. This amounted to 9.6 million deaths among men and 8.9 million deaths among women in the same year [52]. Pomegranate phytochemicals have shown potential use to prevent and cure various conditions associated with CDV diseases.

Various pomegranate phytochemicals have shown activity against CDV diseases such as atherosclerosis [53], hypertension, peripheral heart disease, and coronary heart disease [22]. Flavonoids, tannins, ellagitannins, ellagic acid, anthocyanins, punicalagin, punicalin, gallic acid, urolithins, puninic acid, and naringin isolated from *P. granatum* have shown potential vasculoprotective properties [22]. Both preclinical (*in vitro* and *in vivo*) and clinical research studies have shown that the vasculoprotective properties of these phytochemicals are generally through platelet aggregation, reduction of oxidative stress, reduced lipid uptake by macrophages [53, 54], enhanced endothelial cell function [55, 56], alleviation of myocardial ischemia [57], and regulation of blood pressure [22]. Based on the high mortality caused by CDV diseases, these and other pomegranate phytochemicals should be explored further.

2.4.6 Antimalarial activities of pomegranate

Increased resistance of malaria-causing parasites to available antimalarial drugs has made malaria one of the most prevalent parasitic diseases in the world, especially in Sub-Saharan Africa. The disease caused 627,000 deaths globally, in 2021 [58]. Different approaches have been employed to counteract antimalarial drug resistance [59]. Extracts and pure compounds isolated from pomegranate have contributed to the same warfare.

In a book on the use of simple natural remedies, Kurain and Perumal [18] reported that a decoction of the bark of pomegranate is taken for the traditional treatment of malaria [18]. Equally, in the Ayurvedic system of treatment, at a place called Orissa, in the northeastern part of India, the sun-dried rind of immature pomegranate fruits is used as a powdered formulation called OMARIA for treatment and prevention of *Plasmodium falciparum* and *Plasmodium vivax* malaria [60].

The methanolic extracts of the fruit rind of pomegranate have also shown potent *in vitro* antimalarial activity with 50 percent inhibition concentration (IC_{50}) values of 2.8 and 4.5 $\mu\text{g/mL}$ when tested against W2 (chloroquine-resistant) and D10 (chloroquine sensitive) strains of *P. falciparum* [61–63]. These reported antimalarial activities of pomegranate rind are mainly attributed to the ellagic acid and punicalagin phytochemicals of the plant. These compounds are likely to work through the pro-inhibition of mechanisms that are involved in the onset of malaria, especially cerebral malaria [62]. Other compounds like punicalagins have also shown good *in vitro* antiplasmodial activities with IC_{50} values of 7.5 and 8.8 $\mu\text{g/mL}$, and gallagic acid with IC_{50} values of 7.5 and 8.8 $\mu\text{g/mL}$ when both were tested against D6 and W2 strains of *P. falciparum*, respectively [63]. For *in vivo* antiplasmodial assays, methanolic peel extracts of pomegranate showed a percentage chemosuppression of 50% against *P. chabaudi* using the Swiss albino mouse model [64]. Further antimalarial activities of pomegranate should be explored to validate its use in the treatment of malaria.

Other pharmacological activities of pomegranate extracts and pure compounds such as antibacterial, antifungal, antidiabetic, anti-inflammatory, and antiviral (including COVID-19 virus), and control of disease conditions like Alzheimer's disease, ulcers, and coughs are reported in a review on pharmacological activities of pomegranate [21].

2.5 Herb/food-drug interactions

Herb/food-drug interactions often occur as a result of cytochrome P540 (CYP450) and/or P-glycoprotein (Pgp inhibition). Cytochrome P450 (CYP450) is a heme-containing monooxygenase that primarily defends the body against xenobiotics. CYP450 mediates drug bioactivation to intermediates and is responsible for the metabolism of most of the approved drugs. The CYP450s are mainly hepatic and enteric. This metabolism determines the bioavailability and therefore the therapeutic effect of the orally administered drug [65]. P-glycoprotein is an efflux transporter expressed in a variety of epithelial cells such as those of the large and small intestines. P-glycoprotein in epithelial cells is important in ridding the body of xenobiotics by excretion into, for example, the urine and bile, while endothelial Pgp prevents entry of xenobiotics into organs by excretion into the blood. Herbs and food have been implicated in adverse drug reactions when consumed concomitantly with prescription drugs. Xenobiotics from natural products such as medicinal herbs and food can induce or inhibit CYP450s. Inducers of CYP450s cause increased metabolism of the co-used drugs that can lead to reduced bioavailability of the drug(s), which causes therapeutic failure, and inhibitors lead to increased concentration of the co-used drug(s), thereby enhancing its therapeutic activity or making the drug toxic [65].

People use medicinal plants in traditional medicine for the treatment of various ailments. If the condition persists, patients seek orthodox treatment in hospitals which leads to herb-drug interactions (HDIs) [14, 66]. Food-drug interactions (FDIs) can also occur when food or drinks are taken during medication. The herbs, foods, and drinks taken during drug medication can affect the pharmacokinetics and

pharmacodynamics of the drugs by modulating CYP450s [67]. In various parts of the world where pomegranate occurs, especially in Asia, the plant is used both medicinally and dietarily [21]. While most reviews and research studies have reported on the pharmacokinetics of pomegranate juice, extracts, and phytochemicals, few have focused on the effects of pomegranate on drugs. Therefore, herb/food-drug interactions of *Punica granatum* are discussed in this chapter.

2.5.1 Food/juice-drug interactions: effect of pomegranate juice on drugs

Foods or drinks taken during drug medication can lead to food-drug interactions (FDIs). The interaction between grapefruit juice (GFJ) and several drugs is one of the most extensively studied food-drug interactions. The juice was shown to increase the oral bioavailability of the dihydropyridine calcium channel blocker felodipine by inhibiting its metabolism by intestinal CYP3A4 [68]. Similarly, most studies on *P. granatum* drug interactions have focused on pomegranate juice (PJ). The juice has shown inhibition of CYP3A4 [69] and CYP2C9 [70]. Pomegranate juice is taken with drugs since it is thought to possess therapeutic and nutritional benefits [21]. Therefore, an understanding of the effects of PJ on the pharmacokinetics and pharmacodynamics and the overall therapeutic activity of the co-administered drug(s) is necessary.

A recent preclinical and clinical review by Mansoor et al. (2023) showed the effects of PJ on drugs metabolized by CYP3A4 and CYP2C9. The review revealed the preclinical effects PJ on eight drugs: carbamazepine (used for the treatment of seizures), tolbutamide (used to reduce blood sugar), buspirone (used for anxiety disorder), nitrendipine (used for hypertension), metronidazole (antibiotic), sildenafil (male dysfunction), saquinavir (HIV/AIDS), and warfarin (anticoagulant) tested in rats and rabbits [12]. According to the analysis by these authors, these preclinical studies suggested that PJ showed intestinal inhibition of CYP3A4 and CYP2C9 rather than hepatic metabolism.

They also reviewed preclinical studies on drugs not metabolized by CYP3A4 and CYP2C9, namely metformin (antidiabetic) [71], piracetam (nootropic) [72], and theophylline (used for treatment of respiratory diseases such as asthma) [67]. There was no interaction with piracetam and theophylline, but the C_{max} of metformin was reduced while there was no change to the area under the curve (AUC). The mechanism of interaction between PJ and metformin was not due to CYP450s. Another recent study showed that PJ and GFJ increased the AUC of brexpiprazole (used for the treatment of schizophrenia and major depressive disorders) in rats [73]. Brexpiprazole is metabolized by CYP3A4 and CYP2D6. The reduction in AUC was suggested to be due to inhibition of intestinal CYP3A4. The effect from the GFJ was more pronounced (approximately twofold) than from the PJ. The review [12] further showed that most clinical studies that were done later showed no effect of PJ on flurbiprofen (an anti-inflammatory) [74], simvastatin [75], dapoxetine [76], midazolam [77], cyclosporine [78], and artemether [23].

This shows that the observed preclinical inhibition of CYP3A4 and CYP2C9 by PJ does not necessarily relate to clinical drug interactions in humans [77]. This could be because most of the clinical studies were done using a single dose of PJ [12] and therefore, further clinical studies with prolonged PJ administration of the co-administered drugs are recommended. Moreover, the observed difference in the preclinical effects of PJ on drugs compared to clinical effects could be due to differences in the drugs used across preclinical (*ex vivo*, *in vitro*, and *in vivo*) and clinical studies. Consequently, the clinical studies should be done based on previous similar

studies for possible comparison. Interestingly, the study on dapoxetine [76] compared the effects of GFJ and PJ. The GFJ was found to affect the pharmacokinetics of dapoxetine, but the PJ had no effect. This is like the brexpiprazole study in rats, where PJ was found to have a lesser effect on the PK of brexpiprazole compared to GFJ.

Most studies on herb-drug interactions of *P. granatum* focused on PJ. Considering the wide use of the plant species in the treatment of various diseases in traditional medicine and its associated use with drugs, it will be necessary to explore further the effects of the pomegranate extracts on the therapeutic activity of co-administered drugs.

2.6 Toxicity studies of pomegranate extracts

Chloroform, acetone, methanol, and water bark extracts of pomegranate have been reported to be safe in Swiss albino mice as no signs of toxicity were observed when the extracts were orally administered at a dosage of 2000 mg/kg of body [78]. Similar results were obtained when ethanolic leaves and fruit peel extracts of the plant species were orally given to Swiss albino mice at dose levels of 500, 1000, and 2000 mg/kg [79]. This suggests that the reported pharmacological activities of pomegranate are not a result of intrinsic toxicity.

3. Conclusions

Pomegranate is an ancient medicinal plant, and most people continue to use it for the prevention, treatment, and management of various diseases and disease conditions. To guide its traditional use, researchers have focused on the chemopreventive and chemotherapeutic activities of pomegranate. Most of these studies have shown that pomegranate is mostly used to treat different types of cancers and CDV diseases. The continued review reports and studies on the medicinal and phytochemical properties of pomegranate call for further plant research to unearth its medicinal potential.

Conflict of interest

The authors declare no conflict of interest.

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