

REVIEW

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Pomegranate variety and pomegranate plant part, relevance from bioactive point of view: a review

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Abstract

Pomegranate (*Punica granatum* L.) belongs to the Punicaceae plant family. It is an important fruit due to its nutritional and medicinal properties. Pomegranates are widely distributed around the world and, therefore, have a broad genetic diversity, resulting in differences in their phytochemical composition. The scientific community has focused on the positive health effects of pomegranate as a whole, but the different varieties have rarely been compared according to their bioactive compounds and bioactivity. This review aims to provide a holistic overview of the current knowledge on the bioactivity of pomegranate trees, with an emphasis on differentiating both the varieties and the different plant parts. This review intends to provide a general and organized overview of the accumulated knowledge on pomegranates, the identification of the most bioactive varieties, their potential consumption pathways and seeks to provide knowledge on the present gaps to guide future research.

Keywords: *Punica granatum* L., Bioactive compounds, Pomegranate varieties, Pomegranate parts

Highlights

- Pomegranate varieties differ in phytochemical composition and bioactive capacity
- In most studies, the variety was unspecified, making its replicability difficult
- Wonderful was the variety with the highest number of bioactivities in last years
- Peel was the part that presents the most substantial amount of bioactive compounds
- It is necessary that future studies specify the varieties and parts used.

Introduction

Pomegranates (*Punica granatum* L.) originated in the Middle East, and their cultivation was extended to different regions in the world through the propagation of its seeds, which resulted in a broad genetic diversity. The largest pomegranate germplasm collection is presently found at the Garrygala Research Station in Turkmenistan with 1117 accessions, followed by India with 810, Russia with 800, Iran with 770, Ukraine and Turkey with 370, China with 289, the USA with about 200, and Israel with 150 accessions (Still 2006; Holland and Bar-Ya'akov 2018). In the European Union, the largest germplasm collection is located in Spain, with more than 140 accessions (Zuriaga et al. 2017). New accessions have been characterized in the last few years, demonstrating the wide diversity and the growing interest on this fruit around the world (Zarei 2017; Khadivi et al. 2018). The total area of pomegranate production worldwide is estimated to be well above 300,000 ha, with more than 76% found in 5 countries (India, Iran, China, Turkey, and the

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USA) (Melgarejo et al. 2015). Iran, India, and China are responsible for 80% of the global production, estimated to be about 3 million tons (Ambigaipalan et al. 2016; IVIA 2017).

The primary use of pomegranate is fresh consumption; however, in the last decades, there has been an increase in demand for industrially-processed products such as juices, alcoholic drinks, jams, dehydrated seeds, nutritional fiber, dry rind for making infusions, and extracts from its different parts (Hmid et al. 2017). This growing interest in the use of pomegranate and its parts is motivated both the increasing demand by the nutrition, pharmaceutical, and cosmetic industries (Karimi et al. 2017) in addition with the incipient interest of consumers for its fresh consumption. During 2018, the consumption of fresh fruit in Spain accounted for 9.3% of the average budget of a household devoted to food (MAPA 2019).

This increasing importance may be due to the latest scientific research studies, which have indicated that pomegranates contain substances with antimicrobial, anti-cancer, cardio-protective, and anti-inflammatory activity. Also, the plant could be used for the treatment of diabetes mellitus and obesity, and can also improve sperm quality, among other uses (Govindappa 2015; Hosseini et al. 2016; El-Sheshtawy et al. 2016; Ghavipour et al. 2017; Gbinigie et al. 2017; Khwairakpam et al. 2018; Lepionka et al. 2019; Mohamad Sukri et al. 2019).

The pomegranate fruit is considered to be part of the so-called *Super Fruits* group, which is a term used to highlight the excellent nutritional qualities and health-promoting phytochemicals of certain fruits (Fischer et al. 2011; Czieczor et al. 2018; Kumar and Neeraj 2018). This is perhaps the reason why pomegranates have been used for pharmaceutical purposes, since ancient times, and it continues today, as pharmaceutical companies are extracting the bioactive compounds of the fruit to create capsules for dietary supplementation (Sidhu and Zafar 2012; Karimi et al. 2017).

Pomegranates contain many bioactive compounds such as alkaloids, ellagic acid, punicalagin among other ellagitannins, anthocyanins, flavonoids, tannins, and other phytochemicals that may play an essential role in human health and the prevention and treatment of many illnesses (Setiadhi and Sufiawati 2017). Different varieties normally have different physico-chemical characteristics and may, therefore, differ in the amount and types of bioactive compounds (Li et al. 2015; Hmid et al. 2017). Thus, the bioactive profile is influenced by the cultivar, growing region, climate, maturity, cultivation practice, and storage conditions (Fernandes et al. 2017).

The aim of this review is to analyze and summarize the recent research studies conducted with pomegranates to identify the main bioactive compounds present

in the different varieties and plant parts (fruits, flowers and leaves). This will allow us to elucidate the consumption trends and/or preferences in relation with both the pomegranate variety and pomegranate part consumed (that is related with the type of consumption) to obtain health benefits.

Evolution of scientific interest

A brief systematic literature search was carried out which aimed to identify the evolution of pomegranate scientific research, its applications, areas of interest, characteristics, and pomegranate varieties. The study was performed through the analysis of results from the online databases Scopus and Web of Science, in April, 2019, using "*Punica granatum*" AND "pomegranate" as the main search keywords, although the complete term "*Punica granatum* L." was also utilized. This study followed the PRISMA guidelines for systematic reviews (Moher et al. 2015).

The search results showed a considerable increase in scientific studies focused on pomegranate. Thus, since 1967, more than 6000 works have been published. The most remarkable increase was in the last 20 years (> 90%), indicating the relevance and current nature of the subject. Relevant differences were observed depending on the database consulted (WoS > Scopus) and the keywords analyzed (pomegranate > *Punica granatum* > *Punica granatum* L.). The most significant number of articles were for the generic word "pomegranate" (7143 papers in WoS) when compared to "*Punica granatum* L." (1362 papers in WoS). This difference may be motivated by the aims of the publications, as most of them perhaps only focused on a specific part, function, and/or characteristic and not on the plant itself, hence the use of its generic nomenclature. Regarding the part of the plant, even though all the parts were represented, "fruit" (36%) was the most repeated term in the articles, followed by "juice" (23%), "peel" (13%), "seed" (11%), "aril" (6%), "leaves" (5%), "flower" (3%), "rind" (3%), and "pericarp" (1%).

In addition, 11,921 patents related to pomegranate and its compounds were identified, which indicate its potential for use and applications in the pharmaceutical, nutritional, medical, cosmetic, and/or industrial sectors. Therefore, general reviews such as the present one are necessary for systematizing the accumulated knowledge and for indicating further research gaps.

Bioactive compounds

Bioactive compounds in food may be defined as phytochemicals that have an impact on metabolic processes and that may result in health benefits (International Food Information Service 2009). When assessing the health benefits of pomegranate, it is important to carry out chemical analysis that aims to identify the compounds

and to elucidate whether one or several compounds, together or alone, are responsible for the effects. This is possible when specific experiments that isolate compounds are carried out, but it should also be considered that the synergistic actions of different constituents may be greater than those of single compounds (Olapour and Najafzadeh 2010).

The main bioactive compounds identified in pomegranate in the last decades and attributed, directly or indirectly, to health benefits, are summarized in Table 1, which also shows in which part of the pomegranate fruit (peel, juice, seed and rind) and tree (leaves and flowers) the compound was found and the specific bioactivities ascribed to them. It should be noted that among the studies specified in Table 1, 91% are pre-clinical studies (51% using cell models and 40% using animals) and only 9% are studies in humans. This result faithfully identifies the general trend of accumulated knowledge about bioactive compounds in pomegranate, where the laboratory knowledge is bigger than its real apply in humans health.

In general, the most essential pomegranate compounds can be divided into two major groups: phenolic compounds and fatty acids.

Phenolic compounds consist of a hydroxyl group (–OH), known as phenol, bonded to an aromatic hydrocarbon group as a common part of their structure. Based on the number of phenols in the molecules, the compounds can be simple phenols or polyphenols. As shown in Table 1, there are many different types of phenolic compounds in all parts of the pomegranate tree. Hydrolyzable tannins and flavonoids are the most important subgroups.

Hydrolyzable tannins are polyphenolic substances derived from gallic acid (3, 4, 5-trihydroxybenzoic acid), including gallotannins and ellagitannins. The most abundant type of ellagitannin is punicalagin. While punicalagin can be hydrolyzed into smaller phenolic compounds such as ellagic acid, the gallotannins can be hydrolyzed into gallic acid.

Ellagic acid is an important phenolic acid in pomegranate fruit. It can be found everywhere in the fruit such as the juice, peel, and seeds, among other unspecified pomegranate parts (Table 1), and is responsible for the highest number of bioactivities. Pomegranate ellagic acid has been reported to have positive effects against breast cancer, colon cancer, prostate cancer, and hepatocarcinogenesis (Bishayee et al. 2013; Ahmed et al. 2017; Tamamm et al. 2018; Mansoury 2019). It has also been shown to have anti-allergic, anti-diabetic, anti-inflammatory, antimicrobial, and anti-tyrosinase activity, and has also been linked to the protection against Alzheimer's Disease (AD) (Panichayupakaranant et al. 2010; Kar et al. 2011; Kerimi et al. 2017; Nirwana 2018; Suman and Bhatnagar 2019; Zehra et al. 2019).

The broad presence of ellagic acid in all parts of the fruit may indicate that all types of pomegranate consumers would benefit from its bioactive capacity. However, ellagic acid absorption may be controversial. Seeram et al. (2004) showed a rapid increase of ellagic acid in human plasma, reaching maximum levels in the plasma after 1 h of pomegranate juice consumption. Nevertheless, in another study (Cerdá et al. 2006), no polyphenols were detected in the plasma or urine of the human patients after pomegranate juice ingestion.

However, the ellagitannins bioavailability can be considered poor mainly due to their low solubility in gastric environments, limited intestinal absorption among other factors (González-Sarriás et al. 2015). Recent reports indicate that the ellagitannins biological effects are associated with its derivate metabolites: the urolithins (urolithin A, B, C and D) (Tomás-Barberán et al. 2017). The urolithins result of the ellagitannins transformation through lactone-ring cleavage, decarboxylation and de-hydroxylation reactions by intestinal microbiota (García-Villalba et al. 2020). Although numerous studies indicate the positive health effects of pomegranate urolithins, most of the both in vitro and in vivo studies (animal and human) do not specify the pomegranate variety used in the trial (Larrosa et al. 2010; Yuan et al. 2016; Les et al. 2018; Mazumder et al. 2019; Kujawska et al. 2019). The pomegranate cultivar omission can compromise the homogeneity and replicability of the tests, since the ellagitannins content depends of several factors such as the pomegranate variety, the fruit part used, the extraction method, etc. (García-Villalba et al. 2015). On the other hand, similar to ellagic acid, but only with one phenol ring, we find *gallic acid*. In pomegranates, gallic acid is found mainly in the peel and juice (Table 1). The bioavailability of this compound seems to be high, and its absorbability fast and good (Lafay and Gil-Izquierdo 2008). Also, some scientific works have indicated that gallic acid bioavailability from pomegranates, in the shape of food or as a pure compound, seems to be similar (Shahrzad and Bitsch 1998; Shahrzad et al. 2001). This favors the independence of the food matrix for the bioavailability of acid gallic, and therefore, dietary supplementation from industrially-produced pomegranate compounds may be as effective as fruit consumption, at least regarding this particular compound. In general, gallic acid has been observed to have anti-diabetic, antimicrobial and anti-tyrasianel activity, and positive effects against colon cancer and hepatocarcinogenesis (Kasimsetty et al. 2010; Bishayee et al. 2013; Hosseini et al. 2016; AlMatar et al. 2019).

Flavonoids are a large group of secondary plant metabolites defined by a diphenylpropane structure and categorized as polyphenolic compounds (Gullon et al. 2016).

Table 1 Summary of the main bioactive pomegranate compounds found in the pomegranate peel (PP), juice (PJ), seed (PS), flower (PF), leaves (PL) and not specified part (NS) and the references, where they were found and/or studied

	Alzheimer's disease	Anti-allergic	Anti-anxiety	Anticonvulsant	Anti-diabetic	Anti-inflammatory	Antimicrobial	Antinoniceptive	Anti-tyrosinase	Breast cancer	Colon cancer	Hepatocarcinogenesis	Prostate cancer	Lung cancer	References
Phenolic compounds															
Protocatecholic acid ^{PI,NS}										X					(Poyrazoğlu et al. 2002; Bishayee et al. 2011)
Caftaric acid ^{PI,NS}			X												(Bishayee et al. 2011; AlMatar et al. 2019)
Ferulic acid ^{PI,NS}			X												(Bishayee et al. 2011; Wang et al. 2014; Hmid et al. 2018)
Trans-p-coumaric acid ^{NS}															(Bishayee et al. 2011)
Unspecified phenols ^{PP}		X													(Jayakumar et al. 2012)
Unspecified Tannins ^{PP,PL}			X				X								(Das and Barman 2012; Ouachrif et al. 2012; Fawole et al. 2012)
Hydrolyzable tannins & derivatives															
Unspecified ^{NS}				X											(Kutan Fenercioglu et al. 2010; Larrosa et al. 2010)
Coriagin ^{NS}						X									(Bishayee et al. 2011; Khwairakpam et al. 2018; Zehra et al. 2019)
Gallagyl/dilactone ^{PI}	X			X											(Kasimsetty et al. 2010; Yuniarti et al. 2018)
Gallagic acid ^{PI,PP}															(Kasimsetty et al. 2010; Heena et al. 2018)

Table 1 (continued)

	Alzheimer's disease	Anti-allergic	Antianxiety	Anticonvulsant	Anti-diabetic	Anti-inflammatory	Antimicrobial	Antinoniceptive	Anti-tyrosinase	Breast Colon cancer	Hepatocarcinogenesis	Prostate Lung cancer	References
Punicalagins (α and β) ^{PP} PP, NS	X	X					X		X	X		X	(Rosas-Burgos et al. 2017; Suman and Bhatnagar 2019)
Punicalins ^{PJ}	-		X		X		X		X	X		X	(Kasimsetty et al. 2010; Giarnogarte et al. 2018)
Galic acid ^{PP} PJ, NS			X	X	X		X		X	X		X	(Kasimsetty et al. 2010; Arun and Singh 2012; Fawole et al. 2012; Bishayee et al. 2013; Wang et al. 2014; Banihani et al. 2014; Diudla et al. 2018)
Ellagic acid ^{PP} PJ, NS	X		X	X	X		X		X	X		X	(Makino-Wakagi et al. 2012; Wang et al. 2012, 2014; Fawole et al. 2012; Bishayee et al. 2013; Rojanathammahee et al. 2013; Banihani et al. 2014; Tamamm et al. 2018; Yuniarti et al. 2018)
Flavonoids													
Unspecified ^{PP} PL	X	X	X	X	X		X					X	(Kutan Fenercioglu et al. 2010; Das and Barman 2012; Ouachrif et al. 2012; Fawole et al. 2012)
Catechin ^{PP}									X				(Fawole et al. 2012; AlMatar et al. 2019)

Table 1 (continued)

	Alzheimer's disease	Anti-allergic	Antianxiety	Anticonvulsant	Anti-diabetic	Anti-inflammatory	Antimicrobial	Antinoniceptive	Anti-tyrosinase	Breast cancer	Colon cancer	Hepatocarcinogenesis	Prostate cancer	Lung cancer	References
Epicatechin ^{PP}					X	X	X		X						(Wang et al. 2012; Fawole et al. 2012)
Kaempferol ^{PP}					X										(Wang et al. 2012)
Luteolin ^{PJ}					X	X	X		X	X			X		(Lopez-Lazaro 2009; Wang et al. 2012; Rocha et al. 2012)
Quercetin ^{PP}					X										(Wang et al. 2012)
Rutin ^{PP}							X		X						(Fawole et al. 2012; Gullon et al. 2016)
Cyanidin 3,5-diglucoside ^{PP}							X		X						(Fawole et al. 2012)
Delphinidin 3,5-diglucoside ^{PP}							X		X						(Fawole et al. 2012)
Fatty acids							X		X						(Fawole et al. 2012)
Octadecatrienoic acids ^{PS}					X							X			(Bishayee et al. 2011; Coursodon-Boydiddle et al. 2012)
Punicic acid ^{PJ,PS}					X	X			X	X			X		(Vroegrijk et al. 2011; Coursodon-Boydiddle et al. 2012; Wang et al. 2012; Rocha et al. 2012; Nekooeian et al. 2014; Banihani et al. 2014; Mphahlele et al. 2017)
Other compounds															
17- α -estradiol ^{PS}												X			(Bishayee et al. 2011)
5-hydroxy-methylfurfural ^{NS}												X			(Bishayee et al. 2011)

Table 1 (continued)

	Alzheimer's disease	Anti-allergic	Antianxiety	Anticonvulsant	Anti-diabetic	Anti-inflammatory	Antimicrobial	Antinoniceptive	Anti-tyrosinase	Breast Colon cancer	Hepatocarcinogenesis	Prostate cancer	Lung cancer	References
Alkaloids ^{PP}					X		X							(Ouachrif et al. 2012)
Hexahydroxydiphenic acid ^{PI}										X				(Kasimsetty et al. 2010)
Glycosides ^{PL}	X		X											(Das and Barman 2012)
λ-tocopherol ^{PS}											X			(Bishayee et al. 2011)
Quinones ^{PP}				X			X							(Ouachrif et al. 2012; Setiadihi and Sufiawati 2017)
Saponins ^{PP}				X			X							(Ouachrif et al. 2012; Govindappa 2015)
Sterols ^{PS}										X				(Bishayee et al. 2011)

PP, Peel; PJ, juice; PS, seed; PF, flower; PL, leaves and NS, Not Specified part

In pomegranate trees, flavonoids are present in the peel, leaves, and juice. The main pomegranate flavonoids are catechin, epicatechin, kaempferol, quercetin, luteolin, rutin, and anthocyanins (cyanidin and delphinidin). From the number of bioactivities point of view, the most relevant seems to be luteolin (Table 1).

Anthocyanins are responsible for the red color of the pomegranate fruit and its seeds, from which the juice is obtained; this color depends on the type of anthocyanin and its concentration, where the delphinidin derivatives are responsible for the blue and violet color, while pelargonidin is related to the orange-red color (Harborne 1982). All of these compounds have high antioxidant activities. Commercial pomegranate juices show an antioxidant activity that is three times greater as compared to red wine. The main antioxidant compounds in pomegranate juice are hydrolyzable tannins (around 10% of the total antioxidant activity), but anthocyanidins and ellagic acid derivatives also contribute to the pomegranate's total antioxidant capacity (Melgarejo-Sánchez et al. 2015; Gil et al. 2000). In this sense, it can be confirmed that pomegranate juice is one of the beverages with the most antioxidant capacity in the following order: pomegranate juice > red wine > grape juice > blueberry juice > blackberry juice = juice of lingonberries > orange juice = cold tea drinks = apple juice (Seeram et al. 2008).

Luteolin is a type of flavonoid that is characterized by a double bond between C2 and C3. It is one of the most common flavonoids and is mainly found in pomegranate juice, and due to this, it could be established that pomegranate juice and fresh fruit consumers will benefit from its bioactive capacity. Pomegranate luteolin has been shown to have anti-cancer activity due to its interference of cancer metastasis, suppression of cell growth, increase of cell adhesion, inhibition of cell migration, and suppression of chemotaxis towards the proteins involved (Rocha et al. 2012). It has also been shown to inhibit the progression of prostate cancer (Wang et al. 2012). Lastly, some research studies indicate that luteolin has antimicrobial and anti-inflammatory activity (Prithviraj 2018).

Some studies suggest that luteolin may be quickly absorbed (with the highest peak level after 1 h of ingestion) and slowly eliminated, thereby demonstrating the possibility of accumulation in the body (Chen et al. 2006). On the other hand, as with gallic acid, it has been suggested that the bioavailability of luteolin may be higher when ingested in food form when compared with the pure compound (Zhou et al. 2007). This favors the hypothesis that pomegranate fruit consumption may be healthier than the industrially produced supplements that contain pomegranate compounds.

Another equally important pomegranate biocompound are *Fatty Acids*. A fatty acid is a carboxylic acid with a

long chain that can either be saturated or unsaturated. Almost all fatty acids found in food have an even number of carbon atoms in an unbranched chain conformation (Coultrate 2009). Pomegranates are especially interesting due to the composition of their essential fatty acids (linoleic, linolenic and arachidonic, punicic acid). These are mainly polyunsaturated fatty acids, and play an important role in the prevention of cardiovascular diseases, among other heart problems (Grande 1988; De Hoya and Mata 1989). Among others, the major pomegranate fatty acid studied is punicic acid (Mphahlele et al. 2017).

Punicic acid can be described as a polyunsaturated fatty acid and a conjugated α -linolenic acid. It is mainly found in pomegranate seed oil (up to 95% of the total amount of fatty acids) (Arun and Singh 2012), and this is why it was named after *Punica granatum*. In addition, it may be found in small amounts in pomegranate juice, perhaps added during the extraction process. Preclinical studies indicated that punicic acid interfere in the metastasis of breast cancer, having effects against prostate cancer, and showing anti-diabetic, anti-oxidant, and anti-inflammatory activities (Verma et al. 2010; Wang et al. 2012; Rocha et al. 2012; Banihani et al. 2014; Sahebkar et al. 2016). These positive results are being studied and confirmed in several clinical trials with humans; however, in these cases, as a common rule, the pomegranate varieties are not specified (Mirmiran et al. 2010; Asghari et al. 2012).

Based on this evidence, it could be established that the intake of punicic acid by fresh pomegranate consumers may be high because of the ingestion of the whole seeds, in contrast with pomegranate juice consumers, as the content of this acid may be lower and, therefore, may not benefit from its bioactive capacity.

Studies regarding the absorption of punicic acid in animals have shown that it is slowly absorbed in an unchanged state, while part of it may be quickly converted to Conjugated Linoleic Acid (CLA) (Tsuzuki et al. 2006), with both of these compounds found in tissues and plasma 24 h after ingestion (Yuan et al. 2009). CLA is important, because it has been attributed to several positive health benefits (Lopez-Lazaro 2009). In a 28-day study in humans, PA was also partially converted to CLA, and the authors suggested the possibility that ePA or the derived CLA could induce lipid peroxidation in humans (Yuan et al. 2009).

Even though pomegranate punicic acid has been attributed to having several bioactivities, their mechanisms of action are unclear, and therefore, the bioactive capacity associated with punicic acid may be due to its conversion into conjugated linoleic acid. In this sense, punicic acid would be a precursor of the bioactive compounds and related bioactivities, and more studies are needed to fully understand the underlying mechanisms.

Pomegranate bioactivity potential

As mentioned above, from the scientific point of view, the term "bioactive" is a synonym of "biologically active". In that sense, the bioactivity of an element could be represented by one, or more, substances that have biological activity, that is, it causes a specific effect, response and/or reaction (Abdelkarim et al. 2014).

The potential bioactivity of pomegranate has been traditionally attributed to the exceptional antioxidant activity of the fruit (Glazer et al. 2012). In the last few years, the total antioxidant capacity of different varieties has been reported by several studies as part of their characterization process (Hmid et al. 2017, 2018; Silva et al. 2019).

The total antioxidant capacity of pomegranate reflects the total amount of antioxidant compounds, but it does not specify their nature. For instance, a variety with a high total antioxidant capacity could be missing the specific compound responsible for the mechanism that improves type II diabetes, while a low total antioxidant capacity variety could have the necessary compound (Dludla et al. 2018). Therefore, the total antioxidant capacity will be given little importance in the present report. The potential bioactivity of pomegranate is highly dependent on the variety and the part of the fruit due to the substantial variability of compounds found in each variety and part of the plant. Thus, the present article focuses on these.

Pomegranate varieties

Even though pomegranate has been widely studied, few studies have compared the level of intensity of an activity (i.e., anti-diabetic, or anti-breast cancer) among different varieties. In some studies, the variety has been unspecified, giving it little importance. It is possible that the most common commercial varieties are used, although this is unknown. The phytochemical composition of many plants has changed over time due to domestication (Holland and Bar-Ya'akov 2018). Therefore, it seems logical to find different nutraceutical effects among varieties. In fact, when the phenolic profile of different pomegranate varieties were studied at the same time, statistical differences were found (Di Stefano et al. 2019). It has also been proven that health effects (bioactive compounds content) and attractiveness factors (color, size, flavor) of pomegranate fruit are not correlated with each other, and will vary with variety and season (Hmid et al. 2017; Derakhshan et al. 2018).

Pomegranate varieties can be divided into 3 groups: sweet, sweet-sour, and sour varieties (Watson and Preedy 2013), and this classification depends on the sugar:acid ratio (Hmid et al. 2018). Whether a variety is sweet or sour is not given any importance in the clinical

studies on the bioactive capacities of pomegranate. The sweet and sour varieties have been compared for a certain bioactivity only in very few occasions. Sour varieties have been found to have greater bactericidal effects than the sweet ones (Fazeli et al. 2011; Naziri et al. 2012). However, due to the lack of studies, it is difficult to conclude whether there are differences or not in the bioactive capacity between sweet, sweet-sour, and sour varieties or if it is just a variability between varieties.

Between the varieties with bioactive capacity mentioned in the preclinical studies from the last decades, a high diversity was observed, as shown in Table 2, where it is possible to observe the different bioactive capacities of varieties and if the studies were carried out in vitro or in vivo (animal and human models). Note that, as in the identification of the bioactive compounds present in the different pomegranate parts (Table 1), most of the studies are carried out in vitro, and among the in vivo studies, only a small portion are studies with human models.

However, aware of the human studies are limited and based on the studies available, it was possible to define a bioactivity range according to the number and intensity of activities found aiming to identify the pomegranate varieties more used and/or studied. In this sense, the most bioactive varieties identified, in terms of the number of scientific studies, were Wonderful > Gabsi > Mollar de Elche > Ganesh > Ruby. As for the type of tests conducted, it is possible to highlight that for the Wonderful variety, almost half of the studies were carried out in vivo (26% clinical studies), while for Gabsi, Mollar de Elche, Ganesh, and Ruby, these were in vitro. The same trend was observed for the varieties with the least bioactivity, where the studies were carried out predominantly in vitro.

Nevertheless, this predominance of preclinical studies (in vivo and in vitro) over clinical trials in humans is reversed when were considered studies in which the pomegranate variety was not specified (Table 3). In most cases, the references on the article for the pomegranate variety was simply "acquired at the local market". Considering that a significant proportion of these studies were carried out in vivo, and even with humans, it can be affirmed and highlighted an important mistakes and deficiencies of these studies, since it can imply serious difficulties for future replications and/or standardization of results based on the compositional pomegranate varieties variations.

In addition, Table 4 shows the specific bioactivities related to each variety, but also for unspecified varieties, aiming to maintain the global view both of the bioactive compounds in pomegranate and varietal identification as a relevant part of the study.

Table 2 Bioactive among different pomegranate parts and varieties. Alphabetically ordered according to variety

Variety	Peel	Fruit	Juice	Seed	Flower	Leaves	Bioactivity	In vitro	In vivo		References
									Animals	Humans	
Acide	X						+	X			(Abid et al. 2017)
Amrouz	X						+		X		(Ouachrif et al. 2012)
Anar	X						+			X	(Kamali et al. 2015)
Arakta	X						+	X			(Fawole et al. 2012)
Badana	X						+	X			(Khalil et al. 2017)
Bhagwa			X				+	X			(Opara et al. 2009)
			X				+		X		(Husain et al. 2018)
	X							X			(Fawole et al. 2012)
Borde de Albatara	X						+	X			(Rosas-Burgos et al. 2017)
Borde de Beniél	X						+	X			(Rosas-Burgos et al. 2017)
Chetoui					X		+	X			(Bekir et al. 2016)
					x		+	X			(Bekir et al. 2013b)
Daqingpi							+	X			(Zhang et al. 2010)
Dente di Cavallo				X			+	X			(Lucci et al. 2015)
Desi	X	X	X				+	X			(Altieri et al. 2019)
Egypt	X		X				+	X			(Khalil et al. 2017)
Espagnoule							+	X			(Opara et al. 2009)
Gabsi	X				X		+	X			(Bekir et al. 2016)
							+	X			(Abid et al. 2017)
							+	X			(Bekir et al. 2016)
	X							X			(Kharchoufi et al. 2018a)
	X		X		X			X			(Elfalleh et al. 2012)
	X				X			X			(Bekir et al. 2013a)
						X		X			(Bekir et al. 2013a)
Ganesh	X							X			(Mansour et al. 2013)
	X						+	X			(Malviya et al. 2014)
Garsi	X						+	X			(Fawole et al. 2012)
							+	X			(Bekir et al. 2016)
					X		+	X			(Bekir et al. 2013b)
Helow		X					+		X		(Subash et al. 2014)
Hicaznar	X						+	X			(Rosas-Burgos et al. 2017)
Indian white			X				+	X			(Opara et al. 2009)
Kabul			X				+	X			(Vaithyanathan et al. 2011)

Table 2 (continued)

Variety	Peel	Fruit	Juice	Seed	Flower	Leaves	Bioactivity	In vitro	In vivo		References
									Animals	Humans	
Kandhari	X						+	X			(Khalil et al. 2017)
Mollar de Elche	X	X	X				++	X			(Altieri et al. 2019)
	X						+	X			(Gullon et al. 2016)
	X							X			(Fawole et al. 2012)
Nana	X			X	X		+	X	X		(Rosas-Burgos et al. 2017)
Nebli	X						+	X			(Wafa et al. 2017)
Omani			X				++	X	X		(Abid et al. 2017)
			X					X			(Subash et al. 2015)
Piñón Tierno de Ojós			X				+	X			(Opara et al. 2009)
Rabbab-e Neyriz	X		X				+	X			(Rosas-Burgos et al. 2017)
			X				+	X		X	(Bazargani-Gilani et al. 2015)
Rafrafi					X		+	X			(Barati Boldaji et al. 2020)
Ruby	X						++	X			(Bekir et al. 2016)
	X							X			(Fawole et al. 2012)
	X							X			(Arun et al. 2017)
								X			(Opara et al. 2009)
Sefri	X						+	X	X		(Ouachrif et al. 2012)
Shishe Kab	X			X	X		+	X			(Tehraniifar et al. 2011)
Tounsi	X						+	X			(Abid et al. 2017)
Valenciana de Albatera	X						+	X			(Rosas-Burgos et al. 2017)
Wonderful	X						++++	X			(Martinez et al. 2019)
	X							X			(Glazer et al. 2012)
	X							X	X		(Ashoush et al. 2013)
								X			(Verotta et al. 2018)
			X					X			(Velagapudi et al. 2016)
	X							X	X		(Mastrogiovanni et al. 2019)
	X							X	X		(Gupta et al. 2019)
	X							X			(Shirode et al. 2015)
			X					X			(Gil et al. 2000)
		X								X	(Heber et al. 2007)

Table 2 (continued)

Variety	Peel	Fruit	Juice	Seed	Flower	Leaves	Bioactivity	In vitro		In vivo		References
								Animals	Humans	Animals	Humans	
	X		X						X			(Al-Jarallah et al. 2013)
		X							X			(Hartman et al. 2006)
		X	X					X				(Kim et al. 2002)
		X	X						X			(Seeram et al. 2007)
			X							X		(Pantuck et al. 2006)
			X					X				(Adams et al. 2006)
	X		X	X				X				(Lansky et al. 2005)
	X		X	X				X				(Aslam et al. 2006)
			X					X				(Seeram et al. 2005)
	X				X				X			(Aviram et al. 2008)
	X							X				(Shirode et al. 2014)
										X		(Sumner et al. 2005)
			X					X				(Velagapudi et al. 2016)
			X					X				(Khateeb et al. 2010)
	X							X				(Fawole et al. 2012)
	X								X			(Morzelle et al. 2016)
			X					X				(Kasimsetty et al. 2010)
			X							X		(Bookheimer et al. 2013)
			X								X	(Siddarth et al. 2020)
			X						X			(Makino-Wakagi et al. 2012)
			X					X		X		(Rojanathammanee et al. 2013)
Zaghwani					X			X				(Bekir et al. 2016)
					X			X				(Bekir et al. 2013b)
Zehri					X			X				(Bekir et al. 2016)

Table 3 Bioactive among different pomegranate part in unspecified pomegranate variety

Variety	Pomegranate part						Experimental			References	
	Peel	Fruit	Juice	Seed	Flower	Leaves	In vitro	In vivo			
								Animals	Humans		
Unspecified	X			X			X			(Heena et al. 2018)	
	X						X			(Liu et al. 2014)	
	X						X			(Du et al. 2019)	
	X								X	(González-Sarrías et al. 2015)	
			X						X	(Bookheimer et al. 2013)	
			X						X	(Banihani et al. 2019)	
			X						X	(Sohrab et al. 2019)	
			X						X	(Fuster-Muñoz et al. 2016)	
			X						X	(González-Ortiz et al. 2011)	
				X					X	(Asghari et al. 2012)	
				X					X	(Mirmiran et al. 2010)	
	X							X			(Deng et al. 2017)
	X								X		(Al-Megrin 2017)
			X						X		(Kujawska et al. 2019)
				X			X	X			(Li et al. 2016)
				X				X			(Les et al. 2018)
				X						X	(Rosenblat et al. 2006)
				X					X		(Kaplan et al. 2001)
	X							X			(Arunkumar and Rajarajan 2018)
		X							X		(Syeda et al. 2018)
	X							X			(Hanani et al. 2019)
	X							X			(Kharchoufi et al. 2018b)
				X					X		(Gabizon et al., 2019)
	X								X		(González-Trujano et al. 2015)
	X								X		(Kumar et al. 2013)
						X			X		(Mithun et al. 2012)
						X			X		(Nasiri et al. 2017)
	X						X		X		(Janardan Salwe et al. 2014)
		X							X		(Yuniarti et al. 2018)
	X							X			(Sudheesh et al. 2018)
						X		X			(Elbatanony et al. 2019)
					X			X			(Al-Huqail et al. 2018)
			X						X	(Matthaiou et al. 2014)	
			X						X	(Achraf et al. 2018)	
			X						X	(Davidson et al. 2009)	
		X							X	(Hosseini et al. 2016)	
					X		X			(Giamogante et al. 2018)	
			X						X	(Sohrab et al. 2019)	
X							X			(Panichayupakaranant et al. 2010)	
X			X				X			(Pagliarulo et al. 2016)	
X								X		(Althunibat et al. 2010)	
		X			X	X	X			(Kiraz et al. 2016)	
				X			X			(Mandal et al. 2017)	
X								X		(Larrosa et al. 2010)	
					X		X			(Durgawale and Datkhile 2016)	
X							X			(Šavikin et al. 2018)	
			X						X	(Aharoni et al. 2015)	
X							X			(Al-Bahadily et al. 2019)	
X	X	X					X			(Altieri et al. 2019)	

Pomegranate parts

In general, the pomegranate fruit is comprised by the pericarp, mesocarp and seeds arranged in eight carpels superimposed in two whorls and protected by the carpel membranes (Gilg and Schürhoff 1959; Strasburger et al. 1986). Based on the bibliographical review, when the bioactive compounds and nutraceutical value of pomegranate fruits are studied, the pericarp or skin is commonly named peel (PP). The PP could comprise up to a maximum of 50% of the total fruit weight, and it is an important source of bioactive compounds (Viuda-Martos et al. 2010). In Spanish pomegranate varieties, Melgarejo (1993) determined that the pomegranate seeds comprised about 60–70% of the total weight, while the PP remained in the 25–40% range (Melgarejo 1993).

The seeds are the edible part of the fruit, and are formed by a hard inner part, which contains the cotyledons, the embryo, and the testa, a pulpy membrane from which the juice (PJ) is extracted. In most of the published articles on pomegranate seeds, the authors focused on the hard inner part of the seed without taking the pulpy membrane into consideration.

Accordingly, to facilitate the comprehension of this review, the commonly used terminology for the pomegranate parts, although botanically inaccurate (Gilg and Schürhoff 1959; Melgarejo and Salazar 2003), was maintained. Therefore, in the present review, the term pomegranate seed (PS) will be used only for the hard inner part of the seed. These differences in the terminology of the pomegranate fruit parts can be due to the objective of the articles consulted, which were more focused on the biochemical part than the botanical one, but could also be related with the area of training and research of the authors (pharmaceutical, nutritional, medical, etc.).

Although the fruit parts were the most commonly used plant part on the bibliography, other parts of the pomegranate tree have also been used, such as the pomegranate leaves (PL) and flowers (PF). Even though the literature shows that every part of pomegranate has been used in several scientific assays, a clear predominance of studies employing pomegranate peel and juice was observed (Tables 2 and 3).

The identification of the bioactive capacity of the different parts of the fruit is greatly important, as different consumers have different eating habits. However, it also affects the form and the mode in which its use could be enhanced in different sectors such as the pharmaceutical, food, or cosmetic sectors, among others. Based on the evidence found in Tables 2 and 3, it could be confirmed that in both specified and unspecified pomegranate varieties, the PP was the most studied bioactive part of the fruit. It was followed by PJ, PS, and other parts (PL and PF), perhaps due to the high content of biological

compounds found in this part of the fruit (Orak et al. 2012).

Pomegranate peel (PP)

Thus, in terms of bioactivity, the PP was the most studied part of the fruit. Based on the review of the literature, it was observed that the antioxidant activity of PP was the most widely studied for all pomegranate varieties. This was followed by antimicrobial, anti-inflammatory, and antifungal activities, among others.

Antioxidant capacity provides, in addition to health and medical applications, and mainly due to its influence on the tyrosinase-inhibitor mechanism, the suitable characteristics for use in other sectors such as food preservation, development of functional dietary food, and agriculture improvement (Tehranifar et al. 2011; Khalil et al. 2017; Abid et al. 2017; Heena et al. 2018; Kharchoufi et al. 2018a; Šavikin et al. 2018; Altieri et al. 2019).

In addition, the pomegranate pericarp has proven to be effective against many types of bacteria. The compound isolated from the PP have been shown to be effective against Gram-negative bacteria (*Escherichia coli*, *Salmonella sp*, *Pseudomonas aeruginosa*, *P. putida*, *Enterobacter aerogenes* and *Klebsiella pneumonia*), and Gram-positive bacteria (*Bacillus subtilis*, *Listeria innocua*, *L. monocytogenes*, *Taphylococcus aureus*, and *Staphylococcus aureus*) (Wafa et al. 2017; Kharchoufi et al. 2018a). In one experiment, PP extracts also showed effects in preserving meat against 8 different strains of *Listeria monocytogenes* (Hayrapetyan et al. 2012). In the mentioned study, the various extracts had different strengths, attributed to variability in the raw materials (different varieties). In a complementary manner, antifungal (*Penicillium digitatum*, *P. italicum*, *Botrytis cinerea*, *Rhizopus stolonifer*, and *Saccharomyces cerevisiae*) (Kharchoufi et al. 2018a) and antiviral (HSV-2) (Arunkumar and Rajarajan 2018) activities were also reported.

The anti-inflammatory and antinociceptive activity of PP extract has been verified through different manners of administration: oral, gel, nano-emulsions, intraperitoneal, and intra-cerebroventricular (Lansky and Newman 2007; Janardan Salwe et al. 2014; González-Trujano et al. 2015; Nirwana 2018). This is in agreement with other studies regarding in vivo and in vitro assays (Verotta et al. 2018; Sudheesh et al. 2018; Mastrogiovanni et al. 2019). An extract of the whole pericarp also showed anti-inflammatory activity in damaged mice and albino rats (Syeda 2018; Wang et al. 2014).

Regarding the anti-cancer activity, PP extract showed suppressive effects on two types of human cancer, prostate cancer (Deng et al. 2017) and breast cancer (Shirode et al. 2015), and also on stimulated apoptosis. It could be highlighted that the last studies indicated that the growth

Table 4 Specific bioactivities linked to pomegranate varieties and pomegranate parts as peel (PP), juice (PJ), seed (PS), flower (PF) and leaves (PL)

Variety	Pomegranate part	Related activities													References	
		Medical	Hepatoprotective	Cardioprotective	Antinociceptive	Anti-diabetic	Antioxidant	Antimicrobial	Antifungal	Neurodegenerative	Anti-allergic	Anti-cancer	Anti-inflammatory			
Acide	PP						X									(Abid et al. 2017)
Anrouz	PP				X										X	(Ouachrif et al. 2012)
Anar	PP														X	(Kamali et al. 2015)
Arakta	PP	X					X									(Fawole et al. 2012)
Badana	PP						X									(Khalil et al. 2017)
Bhagwa	PJ PP	X					X									(Opara et al. 2009; Fawole et al. 2012; Husain et al. 2018)
Borde de Albarera	PP						X				X					(Rosas-Burgos et al. 2017)
Borde de Beniuel	PP						X			X						(Rosas-Burgos et al. 2017)
Chetoui	PF					X							X		X	(Bekir et al. 2013b, 2016)
Daqingpi	PL									X						(Zhang et al. 2010)
Dente di Cavallo	PP PF PJ	X					X			X					X	(Lucciet al. 2015; Alitieri et al. 2019)
Desi	PP						X									(Khalil et al. 2017)
Egypt	PJ								X							(Opara et al. 2009)
Espagnoule	PF											X				(Bekir et al. 2016)

Table 4 (continued)

Variety	Related activities											References		
	Pomegranate part	Medical	Hepatoprotective	Cardioprotective	Antinociceptive	Anti-diabetic	Antioxidant	Antimicrobial	Antifungal	Neurodegenerative	Anti-allergic		Anti-cancer	Anti-inflammatory
Gabshi	PP PS PF PL	X				X	X	X		X			X	(Elfalleh et al. 2012; Mansour et al. 2013; Bekir et al. 2013a, 2016; Abid et al. 2017; Kharchrouf et al. 2018a) (Fawole et al. 2012; Malviya et al. 2014) (Bekir et al. 2013b, 2016) (Subash et al. 2014) (Rosas-Burgos et al. 2017) (Opara et al. 2009) (Vaithyanathan et al. 2011) (Khalil et al. 2017) (Fawole et al. 2012; Gullon et al. 2016; Rosas-Burgos et al. 2017; Altieri et al. 2019) (Wafa et al. 2017) (Abid et al. 2017) (Opara et al. 2009; Subash et al. 2015)
Ganesh	PP	X				X	X							
Garsi	PF PF				X	X				X		X		
Helow	PJ					X		X						
Hicaznar	PP						X	X						
Indian white	PJ						X							
Kabul	PJ							X						
Kandhairi	PP					X								
Mollar de Elche	PP PJ PF	X				X			X					
Nana	PP PS PF						X							
Nebli	PP					X								
Omani	PJ						X			X				

Table 4 (continued)

Variety	Pomegranate part	Related activities													References	
		Medical	Hepatoprotective	Cardioprotective	Antinociceptive	Anti-diabetic	Antioxidant	Antimicrobial	Antifungal	Neurodegenerative	Anti-allergic	Anti-cancer	Anti-inflammatory			
Piñón Tierno de Ojós	PP						X					X				(Rosas-Burgos et al. 2017)
Rabbab-e Neyriz	PJ							X								(Bazargani-Gilani et al. 2015)
Rafrafi	PF				X							X				(Bekir et al. 2016)
Ruby	PP PJ	X		X		X										(Opara et al. 2009; Favole et al. 2012; Arun et al. 2017)
Sefri	PP													X		(Ouachrif et al. 2012)
Shishe Kab	PP PS PL								X			X				(Tehraniifar et al. 2011)
Tounsi	PP								X							(Abid et al. 2017)
Unspecified	PP PS								X							(Heena et al. 2018)
Unspecified	PP PF													X		(Syeda et al. 2018; Du et al. 2019)
Unspecified	PP PL													X		(Li et al. 2016; Deng et al. 2017)

Table 4 (continued)

Variety	Related activities													References
	Pomegranate part	Medical	Hepatoprotective	Cardioprotective	Antinociceptive	Anti-diabetic	Antioxidant	Antimicrobial	Antifungal	Neurodegenerative	Anti-allergic	Anti-cancer	Anti-inflammatory	
Unspecified PP	X					X	X	X	X	X			X	(Alhuniyat et al. 2010; Kumar et al. 2013; Al-Megrin et al. 2017; Sawikin et al. 2018; Avunkumar and Rajarajan 2018; Kharchoufi et al. 2018b; Sudheesh et al. 2018; Al-Bahadily et al. 2019; Hanani et al. 2019)
Unspecified PJ	X			X				X						(Kaplan et al. 2001; Rosenblat et al. 2006; Davidson et al. 2009; Sohrab et al. 2019)
Unspecified PS										X		X	X	(Mandal et al. 2017; Gabizon et al. 2019)
Unspecified PP PF PL					X								X	(Mithun et al. 2012; Janardan Salwe et al. 2014; González-Trujano et al. 2015)
Unspecified PF														(Nasiri et al. 2017; Yuniarti et al. 2018)

Table 4 (continued)

Variety	Related activities											References		
	Pomegranate part	Medical	Hepatoprotective	Cardioprotective	Antinociceptive	Anti-diabetic	Antioxidant	Antimicrobial	Antifungal	Neurodegenerative	Anti-allergic		Anti-cancer	Anti-inflammatory
Unspecified	PS PJ						X							(Matthaiou et al. 2014; Al-Huqail et al. 2018)
Unspecified	PJ PF	X											X	(Hosseini et al. 2016; Achraf et al. 2018)
Unspecified	PL	X												(Giamogante et al. 2018)
Unspecified	PP						X			X			x	(Panichayupakaranant et al. 2010)
Unspecified	PP PS PL						X							(Pagliarulo et al. 2016; Elbaratony et al. 2019)
Unspecified	PP PF PL	X					X				X			(Durgawale and Datkhile 2016; Kiraz et al. 2016; Altieri et al. 2019)
Unspecified	PP PJ												X	(Larrosa et al. 2010; Aharoni et al. 2015)
Valenciana de PP Albaterra							X		X					(Rosas-Burgos et al. 2017)

Table 4 (continued)

Variety	Related activities											References		
	Pomegranate part	Medical	Hepatoprotective	Cardioprotective	Antinociceptive	Anti-diabetic	Antioxidant	Antimicrobial	Antifungal	Neurodegenerative	Anti-allergic		Anti-cancer	Anti-inflammatory
Wonderful	X	X	X	X	X	X	X	X	X	X	X	X	X	(Gil et al. 2000; Kim et al. 2002; Lansky et al. 2005; Seeram et al. 2005, 2007; Sumner et al. 2005; Adams et al. 2006; Pantuck et al. 2006; Aslam et al. 2006; Hartman et al. 2006; Heber et al. 2007; Aviram et al. 2008; Kasimsetty et al. 2010; Khateeb et al. 2010; Glazer et al. 2012; Makino-Wakagi et al. 2012; Fawole et al. 2012; Al-Jarallah et al. 2013; Rojanathammanee et al. 2013; Ashoush et al. 2013; Shirinde et al. 2014, 2015; Velagapudi et al. 2016; Morzelle et al. 2016; Verotta et al. 2018; Mastrogianni et al. 2019; Gupta et al. 2019; Martínez et al. 2019)

Table 4 (continued)

Variety	Pomegranate part	Related activities											References	
		Medical	Hepatoprotective	Cardioprotective	Antinociceptive	Anti-diabetic	Antioxidant	Antimicrobial	Antifungal	Neurodegenerative	Anti-allergic	Anti-cancer		Anti-inflammatory
Zaghwan	PF					X			X			X		(Beikir et al. 2013b, 2016)
Zehri	PF				X						X			(Beikir et al. 2016)

PP, Pee; PJ, juice; PS, seed; PF, flower and PL, leaves

inhibition of cancer cells must not only be attributed to the high antioxidant capacity of PP, as the extract may also be involved in DNA repair processes and induction of double-strand breaks. However, both the knowledge of the anticancer specific mechanism and its efficacy in humans continues to be limited, since the majority studies that indicate these activities normally are carried out using cell models.

In a study from 2010 (Olapour and Najafzadeh 2010), an antiepileptic effect of pomegranate was suggested. In that study, mice were administrated PP extract in doses of 100, 200, 400, and 600 mg/kg. Then, they were injected with strychnine, which is a competitive antagonist of the inhibitory neurotransmitter glycine at specific receptors, used to kill rodents causing muscular convulsions and death due to asphyxia. The PP extract administered had a significant anticonvulsive effect on the treated mice, and the animals suffered a lesser number of convulsions, the convulsions lasted less, and they lived for longer.

Pomegranate juice (PJ)

The PJ is the second pomegranate part with the largest number of research studies. PJ has also been linked to microbial inhibiting properties with interesting medical (Altieri et al. 2019; Silva et al. 2019) and industrial applications. Some works have demonstrated that dipping chicken in PJ reduced microbial growth under refrigeration temperatures (Bazargani-Gilani et al. 2015). Along the same line, other research studies have shown that the growth of certain Gram-positive bacteria such as *Escherichia coli*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus*, and *Clostridium perfringens* and Gram-negative bacteria such as *Helicobacter pylori* and *Vibrio parahemolyticus*, were inhibited by PJ (Pagliarulo et al. 2016; Juneja et al. 2016). The inhibition of *Helicobacter pylori* may indicate that PJ could be useful as a supplement for treating gastric ulcers, which are caused by this organism. However, *Escherichia coli*, inhibited by PP extract, has been shown to be unaffected by PJ in another study (Haghayeghi et al. 2013). Nevertheless, in another experiment, PJ seemed to inhibit the growth of *Escherichia coli* (Pagliarulo et al. 2016; Juneja et al. 2016). This controversy supports the suggestion that different pomegranate varieties are likely to have different bioactive compounds. Therefore, when considering PJ as a preservative or as a supplement against certain diseases, more in-depth research of the specific variety must be carried out first.

Moreover, cell models studies indicated that PJ interferes in metastasis of breast cancer, suppressing cell growth, increasing cell adhesion, inhibiting cell migration, and suppressing chemotaxis of proteins involved in breast cancer metastasis (Rocha et al. 2012). Prostate

cancer and colon cancer progression were also inhibited by PJ as with breast cancer (Kasimsetty et al. 2010; Wang et al. 2012). Another study conducted using cell model reported that the intestinal bacterial metabolites resulting from PJ ingestion (uroolithins) may play an essential role in the anticancer activity by inhibiting the initiation and proliferation of colon cancer (Kasimsetty et al. 2010). Nevertheless, although they are positive indications and desirable effects, and as indicated above these results are based on tests conducted with cell models. Thus, the health effects verification and validation must be improved and tested in clinical studies in humans.

Resistin, an adipocytokine, is considered the link between obesity and type II diabetes. A study with the Wonderful variety showed that PJ extract suppresses resistin secretion via a mechanism that may involve the degradation of the intracellular resistin protein in adipocytes (Makino-Wakagi et al. 2012). Another study proved that 3 h after ingestion of PJ, fasting serum glucose and insulin resistance were reduced among type II diabetes patients (Rosenblat et al. 2006; Banihani et al. 2014; Altieri et al. 2019). In addition, PJ consumption showed cardioprotective activity (Sumner et al. 2005; Al-Jarallah et al. 2013) even under clinical trial experimental conditions (Sohrab et al. 2019).

Likewise, PJ also showed representative anti-inflammatory activity in clinical trial conditions (Aharoni et al. 2015; Achraf et al. 2018). Several long-term studies (15 months) in mice and an in vitro assay suggested that supplementation with PJ extract may slow the progression of cognitive and behavioral impairments due to Alzheimer's Disease (AD) (Subash et al. 2014, 2015; Velagapudi et al. 2016). These effects were mainly found for the Wonderful variety, but also for the Omani variety.

However, based on the review of the literature, a deficient standardization of the methodology utilized for juice production was identified. Despite some works indicating if the juice was obtained manually or automatically, in the majority of cases this was not specified, and this could have an impact on the bioactive properties analyzed.

Pomegranate seed (PS)

In pomegranates, PS are significant sources of fiber (Mandal et al. 2017), although their importance lies mainly on its oil. PS oil has been reported to have a great cancer-fighting potential in the reproductive systems, both in males and females (Jasuja et al. 2012). It has also been reported to inhibit aromatase (Kim et al. 2002), the enzyme that produces estrogen from testosterone 17- β -hydroxysteroid dehydrogenase type 1, which is responsible for the conversion of estrone into estradiol. That enzymatic blockade helps to increase the

pomegranate's ability to prevent the growth of estrogen-dependent breast cancer cells in culture and also minimizes the invasiveness of cancer cells (Mandal et al. 2017). PS oil also prevents the proliferation of certain human prostate cancer lines by changing the cell growth cycle and inducing apoptosis (Lansky et al. 2005; Jasuja et al. 2012; Lucci et al. 2015).

As with the other plant parts mentioned above, the PS oil also has anti-inflammatory activity (Mandal et al. 2017). In a study carried out in rats, it was shown to reduce inflammation at the site of the lesion (Coursodon-Boyiddle et al. 2012).

Antimicrobial activity has also been confirmed by means of assays with dried PS extract in a study with meat pâté, which showed the effectiveness of this extract against different strains of *Listeria monocytogenes* (Hayrapetyan et al. 2012), and liquid PS extract against *Salmonella enterica* (Wafa et al. 2017) and plant pathogenic fungi such as *Penicillium italicum*, *Botrytis cinerea*, and *Rhizopus stolonifer* (Tehranifar et al. 2011).

Another study carried out in rats (Nekooeian et al. 2014), showed the anti-diabetic activity of PS oil through the improvement of insulin secretion without changing fasting blood glucose. In mice, PS oil ameliorated high-fat diet-induced obesity and insulin resistance, non-aligned with changes in food intake (Shirode et al. 2014). Other studies have confirmed the pharmacological potential of PS through focused trials on its cosmetic applications for the regeneration of the skin (Aslam et al. 2006), and its medical applications through the study of its influence/treatment of neurodegenerative diseases such as Creutzfeldt—Jacob disease (CJD), multiple sclerosis (MS), Parkinson disease (PD), and Alzheimer's disease (AD) (Gabizon et al. 2019).

Among the varieties studied for PS bioactivity we mainly found the Wonderful variety, but also the Dente di Cavallo, Gabsi, Nana, Shishe Kab varieties. The vast majority of the works were conducted with unspecified varieties of pomegranate.

Pomegranate flower (PF)

Based on the bibliographic results, a significant increase in the interest of the scientific community regarding the applications and bioactivities of the pomegranate flower (PF) was observed in recent years.

PF extracts have been shown to have beneficial effects against diabetes by reducing the fasting blood glucose in rats (Bagri et al. 2009). In another study (Gil et al. 2000), a pomegranate extract made from a mixture of unspecified parts showed beneficial effects in humans with type II diabetes. The extracts antagonized the hyperglycemia-induced oxidative stress, illustrated by the drop in the levels of plasma malondialdehyde and the increase in the

total level of plasma glutathione. The PFs of seven pomegranate varieties (Chetoui, Espagnoule, Gabsi, Garsi, Raf-rafi, Zaghvani, and Zehri) were also studied in regards to their anti-cholinesterase and anti-hyperglycemic activities, finding significant differences among the evaluated varieties (Bekir et al. 2016).

Antioxidant, anti-inflammatory, and anti-breast cancer activities of Chetoui, Garsi, and Zaghvani varieties have also been investigated (Elfalleh et al. 2012; Bekir et al. 2013b).

Pomegranate leaves (PL)

Antioxidant and anti-inflammatory activities were the major bioactivities studied in PL (Elfalleh et al. 2012; Bekir et al. 2013a; Janardan Salwe et al. 2014). In addition, many works identified the potential of antimicrobial effects of the PF extract on plant pathogenic fungi (*Penicillium italicum*, *Botrytis cinerea*, and *Rhizopus stolonifer*) (Tehranifar et al. 2011), for Gram negative bacteria (*Pseudomonas aeruginosa*, *E. coli*, and *Salmonella typhimurium*), Gram positive bacteria (*Staphylococcus aureus*, *Listeria monocytogenes*, *Enterococcus fecalis*, and *Bacillus cereus*), yeast (*Candida albicans*), and fungi such as *Aspergillus niger* (Elbatany et al. 2019).

The medical application of PL extract was also studied for cancer treatment and prevention (Kiraz et al. 2016; Li et al. 2016; Giamogante et al. 2018). Another study, carried out with rats, showed anticonvulsant and antianxiety effects in the Maximal electroshock and Pentylene-tetrazole-induced seizure models (Sarma and Das 2014).

Combination of different pomegranates parts

Extracts made from mixtures of different pomegranate parts have different sets of compounds that may result in synergistic effects that are greater than those from single compounds (Seeram et al. 2005; Olapour and Najafzadeh 2010). An emulsion made from the combination of PS oil and an extract from PJ, PP, PL, and PF demonstrated evidence of having a high chemo-preventive effect against experimental hepatocarcinogenesis in rats, resulting in fewer animals with visible hepatocyte nodules and lower nodule multiplicity (Bishayee et al. 2011). According to the same study, this effect was probably due to pomegranate phytoconstituents that utilize antioxidant mechanisms to repeal the oxidative stress provoked during diethylnitrosamine-initiated hepatocarcinogenesis.

Another study showed that the same emulsion reversed the increase of inducible nitric oxide synthase (responsible of generating nitric oxide that contributes to chronic inflammatory reactions) in hepatocellular carcinogenesis, indicating a clear anti-inflammatory effect (Bishayee et al. 2013).

The anti-inflammatory activity of pomegranate extract made from different pomegranate parts showed effects against colon inflammation (Larrosa et al. 2010), due to the anti-inflammatory effects of the metabolites (in particular, urolithin-A).

A study in transgenic mouse (Rojanathammanee et al. 2013) concluded that some compounds of pomegranate extract made from PJ and PS attenuated the nuclear factor of activated T-cells in a reported cell line, decreasing A β -stimulated tumor necrosis factor α secretion by murine microglia. This indicates that pomegranate produces anti-inflammatory effects in the brain and that adding pomegranate in the diet may attenuate AD development.

Although there are many more preclinical studies available on the bibliography based on the use of pomegranate extracts with interesting bioactivities, the lack of homogeneity in the extract preparation (pomegranate part used, pomegranate part pre-treatment, additional substances among others.) and no pomegranate variety specification make it difficult, and even limit, their classification and, therefore, their comparison and replication.

Conclusions

Pomegranate varieties differ in their phytochemical compositions, thereby affecting their bioactive capacity. In most of the clinical studies, the variety was unspecified. Therefore, reproducing those studies may prove to be difficult. The variety Wonderful was the one in which the highest number of bioactivities were found throughout the last few years. Thus, it may be one of the most interesting varieties for the consumer from a health point of view.

The different parts of the pomegranate fruit have diverse bioactive capacities. The PP has the most substantial amount of bioactive compounds. Thus, the health-promoting characteristics attributed to pomegranate may mislead the consumers of fresh pomegranates, who normally discard the PP when eating the fruit. In regard to this, PJ consumers may not benefit from the bioactive compounds present in the PS.

It is, therefore, concluded that the promotion of health benefits attributed to pomegranates should be linked to variety and end-user eating habits.

It is, therefore, recommended that future studies specify the pomegranate varieties and parts utilized, as there is a high variability in the amount of bioactive compounds between them. Aside from this, more in vivo studies that isolate the bioactive compounds should be carried out to clarify the activities of single compounds and their synergistic actions with other compounds.

Abbreviations

WoS: Web of Science; S: Scopus; Pom: Pomegranate; PuGr: Punica granatum; PP: Pomegranate Peel; PJ: Pomegranate Juice; PS: Pomegranate Seeds; PL: Pomegranate Leaves; PF: Pomegranate Flower; AD: Alzheimer's Disease; CJD: Creutzfeldt–Jacob disease; MS: Multiple sclerosis; PD: Parkinson disease.

Acknowledgements

Not applicable.

Authors' contributions

PMS conceived the contextualization of work. DNG reviewed and analysed the bibliographic references, interpreted the results and drafted the manuscript. JJMN, FH, PL and PM performed the revisions and complements of the paper. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 17 June 2020 Accepted: 22 November 2020

Published online: 03 January 2021

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