

Review

Pomegranate: nutraceutical with promising benefits on human health

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Abstract: The pomegranate, an ancient plant native to Central Asia, cultivated in different geographical areas including the Mediterranean basin and California, consists of flowers, roots, fruits and leaves. Presently, it is utilized not only for the exterior appearance of its fruit but above all, for the nutritional and health characteristics of the various parts composing this last one (carpellary membranes, arils, seeds and bark). The fruit, the pomegranate, is rich in numerous chemical compounds (flavonoids, ellagitannins, proanthocyanidins, mineral salts, vitamins, lipids, organic acids) of high biological and nutraceutical value that make it the object of study for many research groups, particularly in the pharmaceutical sector. Its interest is mainly addressed to the knowledge of its biological and functional properties and the research of new formulations to apply it in a wide range of diseases such as neoplastic, cardiovascular, viral, inflammatory, metabolic, microbial, intestinal, reproductive and skin diseases. In this review we highlight the health-promoting properties of pomegranate and its bioactive compounds against human diseases.

Keywords: Pomegranate; *Punica granatum* L.; Pomegranate skin extract; Pomegranate fruit extract; Nutraceutical properties; Biological properties.

1. Introduction

In the last few years, interest in pomegranate (*Punica granatum* L. puniceae) has grown, due to its nutritional and health benefits, the external appearance of the fruit and also for cosmetic and pharmaceutical purposes [1].

Among the varieties known to date, the five most popular in the world are: *Wonderful*, of American origin; *Hicanzar*, of Turkish origin; *Acco*, of Israeli origin; *Bagua*, of Indian origin; *Mollar de Elche* and *Valenciana*, of Spanish origin [2]. Moreover, there is a dwarf variety of pomegranate, called *Punica granatum Nana*, characterized by a smaller size and inedible fruits, that is usually used as a small decorative pot plant [3].

Thanks to its different health properties, various parts of the pomegranate plant, such as fruits, bark, flowers, roots and leaves have been used for medical and medicinal treatments for a wide range of diseases and health disorders [4].

The chemical composition of the fruit can vary and depends, above all, on cultivation area, climate, ripeness, cultivation practices and storage conditions [4].

The pomegranate is a source of numerous chemical compounds of high biological and nutraceutical value (e.g. phenolic acids, tannins, vitamins, antioxidants and lipids), that are present

in skin, carpellar membranes, arils and seeds. The most important product, derived from it, is the juice obtained from the arils or the whole fruit [5].

About 50% of the total weight of the pomegranate corresponds to the skin and skin membranes that represent a significant source of flavonoids, ellagitannins, proanthocyanidins, mineral salts as potassium, phosphorus, sodium, magnesium and iron.

On the other hand, the grains are made up of water (85 %), sugars (10 %), particularly fructose and glucose, vitamins (including C, A and group B vitamins), antioxidant substances, organic acids, as ascorbic, citric and malic acid, lipids. The seeds contain fatty acids, whose content ranges from 12 to 20 % of the total weight (dry weight).

Amongst them, a higher presence of alpha-linolenic acid (omega 3), linoleic acid (omega 6) and oleic acid, (omega 9) has been detected, together with stearic acid, which may lower cholesterol levels, and palmitic acid [6].

Seeds, are rich in protein, crude fiber, vitamins, minerals, pectins, sugars, polyphenols, isoflavones (especially genistein), coumestrol, sex steroids as estrone [5].

Today, the nutraceutical properties of the pomegranate arouse considerable interest in the scientific community and literature data reported several studies in which functional activities of the pomegranate and its derivatives, such as juice, seed oil, peel, etc. are highlighted [7]. This review provides an update of the current knowledge of the potential health benefits of pomegranate.

2. Pomegranate health-promoting properties

2.1. Anticancer Properties

Cancer is the leading cause of death in both developed and developing countries. This disease has higher mortality rates among low and middle-income populations. The higher mortality rates in poorer countries are mainly related to the absence of adequate health systems [8-11]. Reactive oxygen species (ROS) overproduction are considered key factors for the development of several diseases, including cancer. Tumor biology has revealed that most neoplasms have a much higher amount of reactive oxygen species than healthy ones, such as superoxide anion, H₂O₂ and hydroxyl radicals [12]. These reactive oxygen-containing chemicals react with nucleic acids, proteins and lipids, contributing significantly to tumor cells proliferation, DNA alterations, apoptosis, metastasis and angiogenesis [13-16].

Because of the problems generated with existing chemotherapeutic agents, nowadays there is an increasing interest in the search for herbal formulation with cancer preventive effect. Indeed, studies are focusing particularly on fruits rich in polyphenols due to their anticancer potential [17].

To evaluate the efficacy of pomegranate and its derivatives as anti-proliferative, anti-invasive and pro-apoptotic agents, several studies have been conducted on various cell lines, such as breast cancer lines (MCF-7 and MDA-MB-231), uterine cancer lines (HeLa and Ishikawa), colorectal adenocarcinoma lines (RKO), and animal models [18-20]. Some research groups have shown that the simultaneous use of skin, seed and pomegranate juice extracts has a synergistic action in inhibiting cell proliferation [21,22].

This result has been confirmed by M.Y. Hong et al. [23], who demonstrated that pomegranate extracts and juice components have a more potent action than the individual isolated polyphenols, suggesting that it is a synergistic and additive effect of several phytochemical compounds, including proanthocyanidins, anthocyanins, flavonoids and ellagitannins.

The proanthocyanidins are strongly antioxidant compounds that, after acid hydrolysis, can release catechins as (+)-(2R,3S)-catechin (1, Table 1). They act synergistically with ascorbic acid that gives therapeutic potential against neoplastic and cardiovascular diseases, since it is able to inhibit the action of free radicals, as well as to protect the body from the development and metastasis of cancer (which in part depends on the damage caused to the DNA).

The anthocyanins are derivatives of phenyl-4H-benzopyran-4-one and are present in the vacuoles of the epidermal cells of many plants [24]. These are characterized by a high chemical

reactivity and very low toxicity. They have, in fact, an anti-free radical action and they modulate the arachidonic acid cascade by inhibiting cAMP-phosphodiesterase [24].

There is a great variety of anthocyanins present in the pomegranate juice and the main ones are shown in Table 1: cyanidine (2), delphinidine (3) and pelargonidine-3-O-glucoside (4). Anthocyanins decrease the proliferation of colon cancer cells, HT-29, in a dose-dependent manner [25].

The flavonoids, present in the bark and skin responsible for the red color, have a very high antioxidant activity and are useful for blood circulation [26]. The main flavonoids are quercetin (5), which, in addition to an antioxidant action [27], also showed antiviral and cardioprotective effects [28,29], canferol (6), with anticancer properties, and the rutin (7), a molecule with antithrombotic properties [30].

Among the ellagitannins, ellagic acid (8), a highly thermostable molecule, can be extracted from pomegranate skin and possesses important biological activities including antitumor, antiviral, antimicrobial [31].

In addition, ellagic acid (8) has been shown to induce cell lysis, apoptosis and thus decrease cell viability due to DNA breakage and alterations in the cell cycle. Gonzalez-Sarrias et al. [32] have demonstrated that ellagic acid and its metabolites can contribute to the prevention of colon cancer by modulating the expression of multiple genes in the epithelial cells lining the colon. Some of these genes are involved in key cellular processes associated with the development of cancer.

Another tannin, the punicalagin (9) is present almost exclusively in the skin. It has several pharmacological properties, among which anti-inflammatory, anti-proliferative, pro-apoptotic and anti-genotoxic [33].

It also induces apoptosis in colon cancer cells (cell lines: HT-29, HCT116) and prostate cancer cells at a concentration of 100 mg/ml [25].

A study with 46 patients with prostate cancer under experimentation showed, for 16 of them, a considerable decrease in PSA (prostate-specific antigen) during treatment with pomegranate juice [34].

Koyama et al. [35] report that treatment of LAPC4 prostate cancer cells with 10 µg/ml pomegranate extract, obtained from seedless arils and skin, and standardized to a 37% ellagitannin content in punicalagin, inhibits cell proliferation and induces apoptosis.

Furthermore, pomegranate skin extract (PoPx) with high concentration of ellagitannins has been shown to induce apoptosis in human breast cancer cells (MCF-7), estrogen receptor (ER)-positive (ER+) [36-39].

In previous studies, the application of PoPx and genistein has shown significant inhibitory effects on the proliferation of breast cancer cells MCF-7. In addition, PoPx can inhibit cell proliferation and the expression of angiogenesis markers, phosphorylation of p38 and C-Jun protein kinases activated by mitogens and the activation of pro-survival signaling pathways.

PoPx inhibits the nuclear factor NF-κB gene expression, associated with proliferation, invasion and motility in aggressive breast cancer phenotypes [40].

Aiyer, H.S. et al, reported that the treatment at a concentration of 300 mg/ml of pomegranate fruit extract (PoMx) in combination with 1µM tamoxifen is able to reverse the resistance [41].

PoPx inhibits melanocyte proliferation and melanin synthesis by inhibiting tyrosinase activity (IC₅₀=182.2 mg/ml). The amount of inhibition is comparable to Arbutin, a glycoside with isoquinolin structure capable of being hydrolyzed in glucose and hydroquinone. A large number of studies have confirmed the ability of PoPx and ellagitannins to block the generation of free radicals in UVA and UVB irradiated human skin, thus protecting it from DNA fragmentation, from skin burns and depigmentation [42,43].

In 2010 Zhaoli Dai et al reported that Pomenagrate extract (PE) is able to inhibit in time and concentration dependent manner (already at 10 µg/mL) the viability and proliferation of a mouse mammary cancer cell line (WA-4, derived from mouse MMTV-Wnt-1 mammary tumors) characterized by the presence of several cells possessing stem cells features.

In particular, the arrest of cellular growth in the G0/G1 phase and an increased level of caspase 3 enzyme was observed, suggesting the mechanism of cell death by apoptosis.

Further investigations assessed the effect of individual phytochemicals derived from PE. Indeed, ellagic acid, ursolic acid (10) and luteolin (11) could contribute to the inhibitory potential of PE, with an IC₅₀ value of 10 μ M. Instead, caffeic acid seemed to be inefficient [44].

Subsequently, in 2011, the same research group verified the arrest of cell growth due to PE but in G₂ phase by using as in vitro model the human pancreatic cells PANC-1 and AsPC-1. The inhibition of cellular growth was already observed with an IC₅₀ amounting to 50 μ g/mL in both the lines, but individual phytochemicals were slightly responsible for it.

However, data showed increased proportion levels of cells lacking of CD44 and CD24 (connected with high tumor-initiating ability) demonstrating that PE can modify cells phenotypes reducing the tumorigenicity [45].

Amira Abdel Motaal and Sherif Shaker assessed the antioxidant and anticancer properties of different PEs, highlighting that the peel extract possesses the best antioxidant activity with IC₅₀ value of 0.50 \pm 0.9 mg/mL and promising anticancer action toward MCF-7 breast cancer cells and HCT-116 colon cancer with IC₅₀ values of 7.7 \pm 0.01 and 9.3 \pm 0.06 μ g/mL, respectively [46].

In 2015 El-Awady and co-workers investigated the possible antitumor activity of two different extracts of Punica Granatum grown in Saudi Arabia. Their findings evidenced a good percentage of cellular growth inhibition at the maximum concentration tested (100 μ g/mL) from both seeds and husks extracts, tested on hepatocellular carcinoma HepG2 (values amounting to 95.8% and 98.3%, respectively) and colon cancer CACO cells (values amounting to 99% and 97%, respectively). The whole cytotoxic profile exhibited a dose-dependent trend. The percentages of cellular growth inhibition permitted to determinate the corresponding IC₅₀ values. They were 45 and 40 μ g/mL on both HepG2 and CACO cells for pomegranate seeds and husks extracts, respectively [47].

Another study, conducted by Sina Modaeinama et al in 2015, demonstrated that the peel methanolic extract possesses a potent anti-proliferative action toward several tumor cell lines as: MCF-7 (breast adenocarcinoma), A549 (lung non-small cell cancer), SKOV3 (ovarian cancer), and PC-3 (prostate adenocarcinoma).

The cytotoxicity has been investigated at different concentrations; the best antitumor effect was detected on MCF-7, with a percentage of survival inhibition amounting to 83.7% at doses of 5 μ g/ml. Instead, for the other cell lines, this percentage was 77.87, 76.54 and 63.41 for PC3, A549 and SKOV3 respectively at the same dosage used for MCF-7 [48].

A research based on the possible effect of a PE on chronic myeloid leukemia surveys that it is able to suppress cell growth by inducing apoptosis and causing cell cycle arrest. The findings of the research group led by Asmaa MS, outlined that the peel extract of Pomenagrate could inhibit K562 cells growth in a dose-dependent manner, with total cell death at the maximum concentration tested and an IC₅₀ value of 100 \pm 0.05 μ g/mL. Further investigations have assessed the ability of the extract to induce the cell cycle arrest in G₂/M phase and apoptosis. Indeed, an upregulation of proapoptotic proteins caspases 9, 7, 3, cytochrome c and a down-regulation of antiapoptotic protein Bcl-2 were detected [49].

A new approach in the use of phytochemicals for the cancer fighting lies in the knowledge of preparing, metal-based nanoparticles from the extract of different plant parts, using green synthesis procedures. Indeed, silver nanoparticles possess the capability to up and down-regulating several cellular mechanisms and this has propelled to the forefront in investigations to use them as a possible delivery system for other chemicals or as real control systems for the cellular growth [50-52].

In 2018, Sonia Sarkar and Venkatesan Kotteeswaran carried out the green synthesis of silver nanoparticles from aqueous leaf extract of pomegranate, in order to test their capability as anticancer toward human cervical cancer cells (HeLa). Their findings have proven that this kind of delivery system is able to inhibit cell proliferation in a dose-dependent manner with an IC₅₀ value of 100 μ g/mL. Moreover, they assessed the ability of these Pomenagrate nanoparticles to induce necrosis and apoptosis by detecting increased levels of lactate dehydrogenase and DNA fragmentation [53].

2.2. Anti-inflammatory properties

Inflammation, the first physiological defense mechanism in humans, can protect against injuries caused by physical agents, poisons and others. [25,54-56]. The defense system, the so-called primary inflammation, neutralizes infectious microorganisms, eliminates irritation and maintains normal physiological functions [57]. The inflammatory process is triggered by various chemical and biological agents, including pro-inflammatory enzymes and cytokines, such as eicosanoids or degradation products of inflamed tissue.

According to recent reports, pomegranate showed potential as an anti-inflammatory medicine in several experimental models.

Some extracts of pomegranate, especially the cold pressed seed extract, reduce the action of cyclooxygenase and lipoxygenase enzymes *in vitro*. Cyclooxygenases are useful enzymes for the degradation of arachidonic acid into prostaglandins, important mediators of inflammation. Lipoxygenase, on the other hand, mediates the transformation of arachidonic acid into leukotrienes and it is reduced by extracts of pomegranate seeds [58,59].

Bousetta et al. [60] report that punicalic acid (12), a fatty acid present in pomegranate seed oil, has an anti-inflammatory effect due to the inhibition of neutrophil activation and therefore limits lipid peroxidation.

Lee et al. [57] analyzed some hydrolyzable tannins, including punicalagin (9), punicalin (13), isolated from pomegranate by fractionation. Following *in vitro* studies, each of these compounds exerted a dose-dependent inhibitory effect on nitric oxide synthesis with an important anti-inflammatory effect [61].

De Nigris et al. [62] have shown that the dietary inclusion of pomegranate fruit extract has led to a significant decrease in expression of the markers of vascular inflammation, thrombospondin and cytokine transforming growth factor (TGF- β 1) in obese Zucker rats, a model of metabolic syndrome.

Larossa et al. [63] indicated that pomegranate composition could provide prevention against colon inflammation before and during the disease process. They evaluated the effects of pomegranate intake and its main microbiota-derived metabolite urolithin-A (UROA) on colon inflammation. Results suggested that UROA could be the most active anti-inflammatory compound derived from pomegranate ingestion in healthy subjects, whereas in colon inflammation, the effects could be due to the nonmetabolized ellagitannin-related fraction.

Besides, pomegranate extract supplementation has been shown to lead to decreased levels of prostaglandin E2 in the colon mucosa due to reduced cyclooxygenase-2 (COX-2) overexpression and diminished levels of prostaglandin synthetase E (PTGES) due to high ellagic acid (8) content [64].

S. Park et al. examined the effects of pomegranate peel extract (PPE) on THP-1 monocytic cells exposed to PM10, air borne particulate matter with a diameter of $<10\mu\text{M}$ (PM10) that are known to induce cytotoxicity and ROS production and also to increase the expression and secretion of inflammatory cytokines, such as TNF- α , IL-1 β . This study demonstrated that PPE at 10–100 $\mu\text{g mL}^{-1}$ attenuated the production of ROS and the expression of TNF- α , IL-1 β , MCP-1, and ICAM-1 thus preventing inflammatory events due to particulate matter [65].

A recent study by Xu et al. investigates the inflammation effects of pomegranate flower (PFE) ethanol extract in LPS-induced RAW264.7 cells. LPS is a component of the Gram-negative bacteria cell wall that has been often used in inflammatory response because it can activate macrophages. Their findings suggest that PFE is able to inhibit the production of NO, PGE2, and pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β), as well as the protein expression of iNOS and COX-2 in LPS-stimulated RAW264.7 macrophages. Moreover, PFE treatment significantly inhibited LPS-induced NF- κ B activation through blocking nuclear translocation of NF- κ B and I κ B α degradation and PFE treatment also inhibited the phosphorylation of MAPKs [66].

Kim et al. demonstrated the beneficial protective outcomes of pomegranate beverages, in comparison with those of mango in a preclinical model of colitis. The results obtained suggested that extracts rich in gallo- and ellagitannins act on different molecular targets in the protection against ulcerative colitis. Mango polyphenols inhibited the IGF-1R- AKT/mTOR axis, and pomegranate polyphenols downregulate the mTOR downstream pathway through reductions in ERK1/2 [67].

The systemic effects of PE on the formalin-induced nociceptive behaviour and against gastric injury caused by non-steroidal anti-inflammatory drugs and ethanol in mice have been investigated. PE produced antinociceptive and anti-inflammatory activities without producing gastric damage and even exerting gastroprotection, possibly by modulation at central and peripheral levels, suggesting its utility in the therapy of pain [68].

The topical anti-inflammatory potential of a standardized pomegranate rind extract (SPRE), against a mouse model of contact dermatitis has been evaluated, in comparison with its marker compound ellagic acid, by J. Mo et al. The results revealed the strong anti-inflammatory effect of topical application of SPRE, being ellagic acid responsible for the extract activity as its major antioxidant constituent. The study suggests the topical formulation of SPRE as promising therapy for contact dermatitis and as an alternative treatment for cutaneous disorders [69].

2.3. Antioxidant activity

ROS, produced during normal cellular metabolic processes or derived from exposure to ionizing or xenobiotic radiation, are recognized as concausal factors in a large number of chronic diseases. The toxic effects of ROS depend on their ability to damage relevant and sensitive biological substrates, such as DNA, RNA, proteins and membrane lipids.

ROS include superoxide radicals, lipoperoxide oxides, hydrogen peroxide and hydroxyl free radicals [70]. An antioxidant is generally defined as a natural (fruit and vegetables) or artificial substance that can neutralize or protect a biological system from free radicals, such as oxygen, nitrogen and lipid radicals [71,72]. These antioxidant properties make fruit and vegetables elements with good health properties, avoiding or reducing the risk of suffering from certain degenerative diseases [73-80].

Anthocyanins, phenols [81] and vitamins as A (14), C (15) and E (16) (Table 1) [82] are responsible for the high antioxidant power of pomegranate that have been studied by several authors in both *in vitro* and *in vivo* models [83].

Some authors [84] state that the antioxidant activity of phenolic compounds is due to their ability to capture free radicals and their chelating ability of metal cations.

Gil et al. [85] reported that the antioxidant capacity possessed by pomegranate juice is 3 times higher than that of red wine or green tea and 2, 6 and 8 times higher than that found in red berries, grapefruit and orange juice respectively.

In 2013, a comparison of total phenolic content and antioxidant properties between different extraction solvents of pomegranate seed (PS) and pomegranate defatted seed (PDS) was carried out. Data revealed this trend, in decreasing order, for the used solvents regarding the radical scavenging activity methanol > water > acetone > butanol > ethyl acetate > hexane (EC₅₀ antiradical potential amounting to 0.14 µg/g for PS and 0.19 µg/g for PDS). Similarly, the reducing activity test, decreed that methanol extract of PS an PDS possessed the greater reducing strength [86].

Derakhshan et al in 2018 investigated the antioxidant activity and the total phenolic content of pomegranate peels, juice and seeds from three regions of Natanz, Shahreza, and Doorak using as solvent ethanol. The best antioxidant activity was obtained by Doorak's seed and peel, as well as for the higher total phenolic content [87].

More recently, the analysis of five pomegranate juices genotypes ('Mollar', 'Kingdom', 'Dente di Cavallo', and two old populations 'Francofonte' and 'Santa Tecla') assessed that the total phenolic content ranged between 741.9 ± 55.8 and 424.2 ± 47.5 mg GAE/100 mL and the Francoforte genotype exhibited the higher amount. Furthermore, twenty-three phenolic compounds were identified. In particular, cyanidin-3,5-O-diglucoside and pelargonidin-3,5-O-diglucoside were the kind of anthocyanins present in all genotypes; the Santa Tecla population had the highest content of these anthocyanins with values of 97.64 mgL⁻¹ and 40.29 mgL⁻¹ respectively, whereas in the Francoforte population, ferulic acid hexoside was the most abundant compound (391.18 mgL⁻¹). The antioxidant activity values ranged between 221.5 and 36.73 µmol Trolox equivalents/100mL of juice and the higher one was recorded for the Santa Tecla pomegranate population [88].

A new and interesting study conducted by Hanani et al, addressed this issue by another perspective. Indeed, pomegranate peel powder was incorporated into fish gelatin film-forming solution (FFS) with the aim to create an active packaging film. They found that the addition of 1% of pomegranate peel powder significantly increased the DPPH radical-scavenging activity to 59.74% whereas the addition of 5% led to a percentage of 71.82% whereas the fish gelatin film without pomegranate peel powder used as control achieved only the 53% [89].

In 2019 deeper analysis were conducted on the main enzymatic antioxidants (peroxisomal catalase and SOD isozymes) and the NADPH-regenerating system of pomegranate and their possibility to vary for different cultivar and genotypes. In the reported study were analysed seeds and juices from two pomegranate varieties (Valenciana and Mollar) grown in two diverse Spanish locations. The evaluations of the isoenzymatic superoxide dismutase (SOD) activity pattern showed one Mn-SOD and five CuZn-SODs (I–V) whose abundances depended on the variety while immunoblot assays exhibited at least one additional Fe-SOD with a subunit size of about 23 kDa in both varieties. Moreover, a strong metabolism of ROS could be due to the presence of the H₂O₂-scavenging peroxisomal catalase in seeds and juice [90].

2.4 Antidiabetic activity

Diabetes is the most widespread metabolic disease in the world and its incidence is constantly increasing. According to the World Health Organization, it is the third most common disease after cardiovascular and oncological diseases [91].

Diet is one of the ways to control diabetes mellitus and pomegranate fruit and its derivatives are part of it [32].

The main components with antidiabetic properties are polyphenols; these compounds lower blood glucose through numerous mechanisms including the reduction of glucose absorption through the intestine or peripheral tissues, although the most likely mechanism is the decrease of the enzyme glucosidase [92].

Li et al. [93] have hypothesized that pomegranate flowers extract (PGF) improves post-prandial hyperglycemia in type 2 diabetes and obesity, at least partially, due to inhibition of intestinal α -glucosidase activity.

Huang et al. [94], instead, reported a potential mechanism of the antidiabetic activity of the PGF involving the activation of PPAR- γ .

In addition, caffeic acid (17) or 3,4-dihydroxycinnamic acid another component of PE, increases the uptake of glucose by adipocytes in rats and myoblasts in mice [25].

Finally, McFarlin et al. [95] studied the effect of pomegranate seed oil on fat accumulation in mice and observed an improvement in insulin sensitivity.

Hamendra Singh Parmar and Anand Kar went into the possible effect of pomegranate peel extract on tissue lipid peroxidation (LPO), the concentration of thyroid hormones, insulin, and glucose in male rats starting from in vitro evaluations, which proved an inhibition of H₂O₂-induced LPO in red blood cells of rats by 0.25, 0.50, 1.0, and 2.0 μ g/mL in a concentration-dependent manner. The maximum was achieved at 2.0 μ g/mL. In vivo, *P. granatum* decreased LPO in hepatic, cardiac, and renal tissues and serum glucose concentration. These data suggested a potential regulatory role of this peel extract on thyroid function and glucose metabolism [96].

Another study assessed the ability of pomegranate fruit extract (PFE) to decrease the serum resistin levels (adipocytokine, seen as a possible connection between obesity and type 2 diabetes) in ovariectomized mice, an animal model with elevated resistin levels in serum and upregulated resistin mRNA expression in white adipose tissue. Furthermore, PFE was able to reduce the secretion and intracellular levels of resistin in differentiated murine 3T3-L1 adipocytes, without altering resistin mRNA expression. Other findings suggested that PFE promoted the degradation of resistin. All these activities could be mainly attributed to ellagic acid [97].

Several studies agree that oxidative stress induced by diabetes mellitus leads to brain damages. Indeed, Cambay Z. et al indicated that the co-administration of pomegranate flower extract and antidiabetics led to improvements in learning and memory performances of diabetic rats. Moreover,

in test subjects in which LPO was increased and glutathione (GSH) content was decreased in hippocampal tissue, the supplementation of PGF was able to restore these levels. Besides, daily PGF intake decreased glial-fibrillar acidic protein contents induced by diabetes in the hippocampus [98].

On the contrary, in 2016, a research team questioned these findings, corroborating that daily consumption of pomegranate seed oil in patients suffering from diabetes mellitus 2, did not significantly affect the levels of parameters such as fasting blood sugar (FBS), insulin, HbA1c, alanine transferase, and homeostasis model assessment-insulin resistance [99].

PGF has been, over the years, part of the Chinese dietary as an ally against Type 2 diabetes mellitus (T2DM). For this reason, Tang et al tried to explore the possible mechanism of action implied in the antidiabetic effect. The rat model (Male Sprague-Dawley rats, SD rats) diet was implemented with PGF polyphenols extract at doses of 50 and 100 mg/kg for a period of 4 weeks. Several assays as oral glucose tolerance test (OGTT), insulin tolerance test (ITT) and homeostasis model assessment of insulin resistance (HOMA-IR) were performed, revealing an improvement of insulin sensitivity. Deeper molecular investigations established that insulin signalling activity was enhanced with an elevation in insulin-stimulated phosphorylation of insulin receptor substrate (IRS-1), Akt and GSK-3 β . Besides, they assessed a decrease, after the treatment, of endoplasmic reticulum (ER) stress signals including phosphorylation of inositol-requiring kinase1 (IRE1) and activation of X box binding protein (XBP-1) splicing. In addition, regarding the blood lipid profile, liver glycogen content and antioxidant status were improved by PGF in the rats [100].

Similar results were found for pomegranate fruits aqueous extract as a noticeable reduction in fasting blood glucose (FBG) by 28.1% and 67.9% in short-term and long-term treatment models (Alloxan-diabetic male Wistar rats) and an increase in the mRNAs expression levels of IRS-1, Akt, Glut-2, and Glut-4, suggesting an improvement of glucose uptake and storage [101].

A recent study reported the potential combination of pomegranate juice and *Lactobacillus casei* NRRL-B-1922 (used as fermenting agent) to create a functional juice able to combat T2DM. The results highlighted that pomegranate could support the growth of *L. casei* even without nutrient supplementation. Further analysis demonstrated that the glucose and fructose content were steadily reduced with the consumption rate of 0.51 g/L/h and 0.37 g/L/h, respectively in bioreactor. Moreover, the possible antidiabetic mechanism of action could be attributable to the dipeptidyl peptidase-4 (DPP4) inhibition (with a rate of 80%). Indeed, DPP4 is a well-known target of many antidiabetic agents [102].

2.5 Antimicrobial activities

Antimicrobial agents mainly act on microorganisms that cause food poisoning (infected or toxin-producing agents) and on microorganisms that alter food by producing final metabolic products (catabolites) or enzymes with bad odour, unpleasant taste, problems of persistence, different colouring and/or health risk [103].

The antimicrobial activity of pomegranate and its products has been demonstrated in numerous studies [104], in particular, polyphenols, flavonoids and condensed and hydrolysable tannins, extracted from the fruit, have been studied as potential agents to treat or prevent a wide range of infections [105].

The antimicrobial mechanisms of phenolic compounds involve the reaction of phenols with sulfhydryl groups of membrane proteins of the microbial cell inducing bacterial death due to membrane protein precipitation and inhibition of enzymes such as glycosyltransferase [106].

Food-borne diseases and urinary tract infections are treated conventionally in the Indian subcontinent using PoPx, while ellagitannins, punicalagina (9), ellagic acid (8) and gallic acid (18) present in the pomegranate skin, as natural antimicrobial agents, have been widely exploited against *Staphylococcus aureus* and *Escherichia coli* haemorrhagic for their ability to precipitate membrane proteins and inhibit enzymes such as glycosyltransferase, leading to lysis.

In vivo and in situ application of an 80% pomegranate skin (PoP) methanol extract presented an inhibitory effect against *Listeria monocytogenes*, *Staphylococcus aureus*, *Escherichia coli* and

Yersinia enterocolitica. However, it has been reported that higher doses of PoPx (24.7 mg/ml) represent the lowest bactericidal concentration of *Listeria monocytogenes* [107].

Another study, evidenced the powerful activity of *Punica granatum* L. peels ethanolic extract (Tunisian Nana variety) against two *Salmonella* strains, *Salmonella* Enteritidis and *Salmonella* Kentucky, microorganisms resistant to the majority of antibiotics. MIC values ranged from 10.75 to 12.5 mg/mL regarding both strains. In particular, the inhibitory effect achieved by peel extract (using hydroethanolic and hydromethanethanolic mixtures) on *Salmonella* Kentucky achieved inhibition diameters of 22.2 mm and 22 mm, respectively [108].

Višnjevec et al. explored and evaluated the antimicrobial properties of ethanol and water extracts of pomegranate exocarp and mesocarp from Istria. The best antibacterial activity was recorded, here too, for ethanolic extract. Indeed, the microorganisms more susceptible to this extract were *C. albicans*, *C. parapsilosis*, *R. mucilaginosa*, *E. dermatitidis* and *S. aureus*, with MIC ranging from 0.156 to 1.25 mg/mL. Instead, the best antimicrobial activities of the exocarp and mesocarp water extracts were found toward *S. aureus*, followed by *E. coli* without any antifungal activity [109].

Another use of pomegranate as antimicrobial agent involved its participation in the synthesis of silver nanoparticles. These last, thanks to the use of transmission electron microscopy (TEM) and scanning electron microscopy (SEM), showed to be equally distributed in the solution, with a spherical shape and size ranging from 20 to 40 nm and with an average particle size of 26.95 nm. Subsequently, tests evidenced the capability of nanoparticles to substantially inhibit Gram-negative and Gram-positive bacteria as *E. coli*, *P. aeruginosa*, *P. vulgaris*, *S. typhi*, *S. aureus*, *S. epidermidis* and *K. pneumonia* already at 25 and 50 µg/mL [110].

2.6 Prevention of cardiovascular diseases

One of the main risk factors for the development of coronary diseases is dyslipidemia, characterized by an excessive increase in low-density lipoproteins (LDL) and/or low levels of high-density lipoproteins (HDL) [111,112].

It is known that LDL oxidation contributes to atherosclerosis and the development of cardiovascular diseases [29,113].

Inhibition of LDL oxidation is considered a good strategy to prevent the accumulation of foaming cells and, ultimately, cholesterol deposits in the arteries.

Thanks to its excellent antioxidant activity, the extract obtained from the pomegranate skin has the potential to inhibit LDL oxidation and thus delay the progression of atherosclerosis with a significant reduction in foaming cell levels at the artery level.

The polyphenols present in pomegranate, punicalagin (9), Gallic Acid (18) and, to a lesser extent, ellagic acid (8), increase the expression and secretion of the liver enzyme paraoxonase 1 in a dose-dependent manner, thus reducing the risk of developing atherosclerosis [114].

Riaz and Khan in 2016 gave an insight into the anticoagulant, antiplatelet and antianemic effects of *Punica granatum* by studying the hematological profile of the rabbits used as in vivo model. Their findings evidenced a substantial increase in erythrocyte count, mean corpuscular hemoglobin concentration after 30 days of treatment whereas red cell distribution width was significantly reduced. Instead, leucocyte count, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and platelet count (PLT) were not altered at any dose. Furthermore, there was highly significant increase in bleeding time both after 30 and 60 days, and a significant rise in thrombin time (TT) and activated partial thromboplastin time (α PTT) after 60 days whereas prothrombin time did not change. Comparing the pomegranate ability in lowering cholesterol and the prolonged α PTT time, they speculated that the cholesterol reduction induced by *P. granatum* may lead to a decrease in the concentration of coagulation factors, influencing, in this way, α PTT. In conclusion, data illustrated that *P. granatum* significantly inhibited aggregation of platelets induced by adenosine diphosphate ADP and epinephrine (Epi) in the blood samples of animals treated already at 2 ml/kg for 30 and 60 days [115].

The hypothesis that pomegranate ameliorates the cardiac function has been also supported by Razani et al. Indeed, they administered 220 mL of pomegranate juice to one hundred hospitalized

patient suffering from unstable angina or myocardial infarction for a period of 5 days in order, at the end, to evaluate cardiac markers and parameters. The results indicated a significant reduction in the intensity, occurrence, and duration of angina pectoris in patients with unstable angina. Moreover, the measurement of serum levels of troponin and malondialdehyde revealed a decrease of these factors. Nevertheless, other parameters like interleukin-6, tumor necrosis factor alpha, blood pressure and heart rate were not affected [116].

More recently, the possible interaction between ethanolic peel extract of *Punica granatum* and Doxorubicin (well known for its cardiotoxicity) was evaluated. The assessment was performed by measuring heart weight/body weight ratio, biochemical parameters and histopathological changes. After the treatment with 100 mg/kg body weight an increased heart weight/body weight ratio in comparison with Doxorubicin treated group was observed as well as blood and tissue glutathione, superoxide dismutase and catalase levels. On the contrary, creatine kinase, lactate dehydrogenase enzyme and malondialdehyde levels appeared significantly reduced. Concerning the histopathological morphology, the only assumption of Doxorubicin led to a massive change in the myocardium with vacuolar alterations in the heart muscle and necrosis of heart muscle with remote cells showing features of increase in the size in between the necrotic and fragmented muscle fibers. Instead, treatment with *P. granatum* peel extract displayed a protective effect with less histological changes such as irregular and spreaded vacuolation limited to subendocardial layers [117].

2.7 Antiviral activities

The hydrolysable tannins of pomegranate, including punicalin (13), punicalagin (9), gallic acid (18) and ellagic acid (8), have antiviral properties capable of modulating respiratory infections and influenza.

The antiviral properties of the polyphenolic extract of pomegranate have been attributed to inhibition of influenza virus RNA replication [114,118].

Similarly, phenols in the skin inactivate viruses through direct structural damage and indirect intercellular inhibition of viral replication.

The virucidal effects of pomegranate phenolic compounds are associated with their interaction with the antigenic glycoprotein, hemagglutinin, present on the surface of some viruses (es. influenza viruses), which produces a loss of red blood cell agglutination [119].

In particular, Mehran Haidari et al argued that punicalagin (9) is the effective component of pomegranate polyphenol extract able to block replication of the virus RNA, inhibit agglutination of chicken RBC's by the virus and had viricidal activity. They have also investigated the potential synergistic effect of pomegranate polyphenol extract (PPE) and Oseltamivir (a well-known antiviral agent), outlining that Oseltamivir in association with PPE amplified its anti-influenza power [120].

Aarthi Sundararajan et al. in 2010, confirmed and implemented these data strengthening that the direct anti-influenza activity of pomegranate polyphenols (PPs) is primarily a consequence of PP-induced virion structural damage. Indeed, the PP component of pomegranates rapidly inactivates the influenza virus through a direct effect on the viral particle. They also suggested that this action might be distinct from effects on hemagglutinin (HA) function. Moreover, they demonstrated the efficacy of pomegranate PPs against H1N1 and H3N2 influenza viruses and against the reassortant H5N1 virus rg-VN/04 [119].

Furthermore, another study attributed to punicalagin the power to reduce the viral cytopathic effect on rhabdomyosarcoma cells, calculating an IC₅₀ value of 15 µg/ml. This effect was also assessed in vivo, noticing a decrease of mortality in mice treated with a lethal dose of enterovirus 71 [121].

B. Uma Reddy et al focused on the potential effect against Hepatitis C virus (HCV) of the ellagitannins extracted from Pomegranate (*Punica granatum*) fruit peel. In particular, pure compounds punicalagin, punicalin, and ellagic acid exhibited in vitro the capability of blocking the HCV NS3/4A protease activity in a concentration dependent manner with IC₅₀ values of less than 0.1 mM (for punicalagin and punicalin) whereas IC₅₀ for ellagic acid was achieved at 1.0 mM. These data were confirmed through in silico studies and observing a consistent reduction of HCV

replication in cell culture systems. Data *ex vivo* pointed out the optimal bioavailability and the toxicity absence of these compounds [122].

Besides, a good activity of pomegranate extract toward Adenovirus has been found. The 50% inhibitory concentration (IC₅₀) and 50% Cytotoxicity Concentration (CC₅₀) have been estimated on HeLa cells with values of 165±10.1 and 18.6±6.7 µg/mL, respectively whereas the selectivity index (SI, calculated as the ratio of CC₅₀ and IC₅₀) on adenovirus amounted to 8.9 [123].

In their analysis, David M. J. Houston et al investigated the co-administration effects of pomegranate rind extract in conjunction with zinc (II) salts in order to challenge Herpes simplex virus HSV-1 and its aciclovir-resistant. Data showed a potentiation factor by up to 5.5 fold. Regarding aciclovir-resistance, pomegranate rind extract exhibited an EC₅₀ value amounting to 0.02 µg mL⁻¹, whereas acyclovir showed no activity [124].

Given the several reported studies that have proven the antiviral effects of pomegranate, Arunkumara and Rajarajanb surmised the possible inhibitory effect of *Punica granatum* against Herpes simplex virus – 2 (HSV-2). In effect, their findings assessed that ethanolic peel extract was able to significantly inhibit HSV-2 at a concentration of 62.5 µg/ml. In order to understand the real responsible of this action, the extract was subjected to bioactive compounds separation by bioassay-guided fractionation. Then, the single components were tested as antivirals. The key component for the activity seemed to be punicalgin, showing a total inhibition rate at 31.25 µg/ml. Moreover, bioactive compounds analysis using ADMET tool, established that human intestinal absorption (HIA) properties of acyclovir (ACY), gallic acid (GA) and ellagic acid (EA) had moderate adsorption values of 63.77%, 53.69% and 61.39% respectively, and punicalgin presented very strong plasma protein binding. Besides, docking studies highlighted that the most active component could interact with HSV-2 amino acids through several hydrogen bonds [125].

The global pandemic due to the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has dramatically shaped queries on the necessity to find as soon as possible a cure for this disease. With this in mind, many efforts, also with the aid of artificial intelligence, have been made to discover molecules able to interact with the viral proteins and cause the Sars-CoV-2 inhibition. Several compounds of natural origin were found to be able to do this. Among them, docking studies revealed that the ellagic acid, one of the already mentioned main component of pomegranate, has the potentiality to interact with important proteins involved in Sars-CoV-2 as RNA-dependent RNA polymerase (RdRp), angiotensin-converting enzyme 2 (ACE2), spike glycoprotein (SGp) and Main Protease (3CLpro) [126,127].

Furthermore, another study conducted on the viral main protease (3-chymotrypsin-like cysteine enzyme), held responsible for the COVID-19 control of duplication and life cycle management, assessed the potential of hydrolysable tannins (present also in pomegranate) as its natural inhibitors. Indeed, punicalin seems to establish H-bonds with the crucial catalytic residues of pocket Spatial position [128].

2.8 Other properties

2.8.1 Obesity

Obesity is a chronic disease of multifactorial origin characterized by excessive accumulation of fat or general hypertrophy of adipose tissue in the body [129]. Obesity can, therefore, be so described when the natural energy reserve of humans or other mammals stored in the form of body fat increases to such an extent that it is associated with a series of complications, health problems, diseases and even an increase in the mortality rate [130].

Studies have been carried out showing that the consumption of pomegranate extracts, in particular punicalagine (9), diminishes the sense of hunger and body weight [131] and that the extract inhibits the development of obesity and hyperlipidemia. These effects seem to be due partly to inhibition of pancreatic lipase and partly to a decreased calorie intake [132].

Khabeer et al went through the anti-obesity potential of SHAMstat3pg, a fatty acid composite extracted from pomegranate seeds oil, made up of punicalic acid, oleic acid and linoleic acid. Their

findings established that the treatment of 10 µg/ml of SHAMstat3pg (24 hr) inhibited in a dose-dependent manner adipogenesis of human adipose derived mesenchymal stem cells (HADMSC), ameliorated inflammation, attenuated ATP production, and glucose uptake. Also, the extract favorably regulated the mRNA expression of the studied obesity-associated gene transcripts [133].

2.8.2 Intestinal regulation

The consumption of pomegranate products leads to a significant accumulation of ellagitannins in the large intestine, where they interact with the intestinal microflora [134]. Bialonska et al. [135] report that the beneficial effects on microflora are mainly due to Popx.

A well-known cause of intestinal damage is represented by high-intensity-exercise. In order to overcome this risk, Chaves et al studied the consequences of the assumption of fermented milk supplemented with whey protein (approximately 80% protein), probiotic (*Bifidobacterium animalis* subsp. *lactis* BB12) and pomegranate juice (*Punica granatum* L.) on the physical performance, intestinal motility and villi structure, inflammatory markers and intestinal microbiota of in vivo model Wistar rats under high-intensity acute exercise. The group only subjected to exercise went through changes in the intestinal villi interspace, in the proportion of *Lactobacillus* species and an increase in *Clostridium* species, as well as a decrease in intestinal motility. The treated group, instead, increased intestinal motility and maintained the intestinal villi interspace and the natural microbiota proportions, but the physical performance was not improved [136].

2.8.3 Effect on the male reproductive system

According to Türk et al. [137], the consumption of pomegranate juice produces an increase in the concentration of sperm in the epididymis, higher sperm mobility and density and a reduction of poor quality sperm compared to the reference or control group. In a more recent study, this same group of researchers suggested that ellagic acid (8) has a protective effect on both testicles and sperm. This effect may be related to the powerful action of ellagic acid against oxidative stress [138]. Concerning erectile dysfunction or impotence, the continued inability to achieve or maintain an erection sufficient to maintain satisfactory sexual intercourse, Forest et al. [139] stated that after four weeks of treatment with pomegranate juice patients showed better erectile activity than others who had received a product with a placebo effect.

2.8.4 Antidiarrheal effects

Qnais et al. [140] have assessed the antidiarrheal effects of the water extract of pomegranate fruit skin on rats. The results revealed that the extract dose-dependently inhibits spontaneous ileum movements and attenuates acetylcholine-induced contractions.

In other studies, the antidiarrheal effects of fruit skin on rats were evaluated by administering an oral dose of 400 mg/kg. The results show that pomegranate extract decreases the number of defecations and stool weight [141].

These previous findings were also supported by Zhao et al in 2018 by studying the aqueous extract of pomegranate peels and, in particular, its bioactivity-guided fractions and bioactive components. The fraction considered responsible of the antidiarrheal activity was the ethyl acetate one, mainly composed by punicalagin, corilagin, and ellagic acid. Data also revealed that the administration of the ethyl acetate fraction at 100, 200, and 400 mg/kg was able to decrease gastrointestinal transit in charcoal meal tests in mice as well as inhibit castor oil-induced enteropooling compared to control animals. From histopathological evaluations emerged that small intestine lesions of mice treated with the ethyl acetate fraction were alleviated compared to those in mice treated with castor oil [142].

2.8.5 Effects on oral health

Currently, science recognizes that chronic periodontal inflammatory disease is closely related to the worsening of cardiovascular disease [143].

DiSilvestro et al. [144] have demonstrated that an oral rinse based on extracts of pomegranate would significantly reduce (about 84%) the number of microorganisms from the dental plaque.

Sastravaha et al. [145] have highlighted the effectiveness of a toothpaste containing pomegranate extracts as an additional treatment to complement routine periodontal therapies and have demonstrated that pomegranate flavonoids have an *in vitro* antibacterial action against the microorganisms responsible for gingivitis.

3. Toxicological aspects of pomegranate and potential interaction with drugs

Recent studies have shown that pomegranate fruit, in various forms, can be considered part of a healthy diet and lifestyle without any risk or toxic reaction [25]. Studies have shown that two doses of pomegranate extract (0.4 and 1.2 mg/kg body weight) produced no toxic effects in rats in terms of food intake, weight changes and behavioral or biochemical factors [146].

Heber et al. [147] have carried out studies on 64 overweight subjects to assess the safety of the use of extracts in humans. Following the intake of 710 mg and 1420 mg capsules (containing 435 mg and 870 mg gallic acid equivalents respectively) no adverse events occurred and no significant differences in toxicity were found in all subjects studied.

Other studies have been carried out on patients with carotid artery stenosis, showing that the consumption of pomegranate juice (121 mg/l ellagic acid equivalent) for more than 3 years did not cause any toxic effect on blood parameters and liver, kidney and heart functions [148].

Based on current research on pomegranate, considering its beneficial effects in cancer, cardiovascular diseases, etc., it was interesting to determine the effects of pomegranate extracts on the cytochrome P450-3A, a liver enzyme system responsible for the metabolism of many drugs [7].

Studies in rats show that the administration of pomegranate juice has an inhibitory effect on the pharmacokinetics of carbamazepine, an anticonvulsant drug also metabolized by the cytochrome P450-3A [7].

A single-dose randomized trial in healthy volunteers showed that treatment with pomegranate juice had no effect on the half-life and distribution time of intravenous administration of benzodiazepines with anxiolytic, hypnotic, anticonvulsant and muscle relaxant properties and no effect on maximum concentration and clearance after oral administration [7].

4. Conclusion

Nowadays it is well known that the beneficial effects of fruit and vegetables in preventing disease depend on the composition of the bioactive compounds they contain [5,7,149-154].

In particular, among them, pomegranate emerges, as well as nutritional resources, for its extensively documented health properties in several application fields (neoplastic, cardiovascular, viral, inflammatory etc) that make it a promising tool in medicinal treatments.

Certainly, the juice is the most widespread type of pomegranate based product in stores for its ease of consumption, followed by capsules with a concentration of ellagic acid of 40% [3]. From what emerges from the various studies analyzed, the interest in the consumption and production of pomegranate has greatly increased in recent years [155-158].

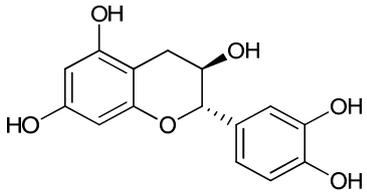
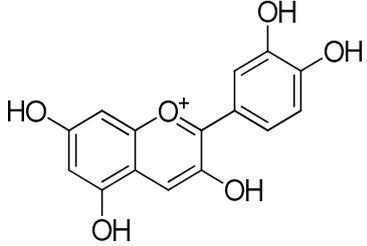
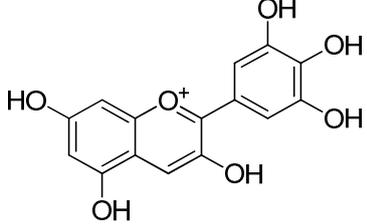
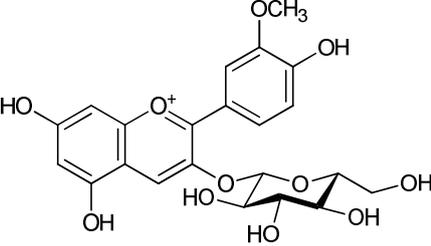
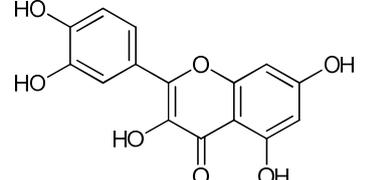
Indeed, prior research has thoroughly supported the beneficial effects of pomegranate regarding not only the phytocomplex but also the single components, among which stand out the various tannins and the ellagic acid.

Precisely, the latter has recently aroused great interest for the potential inhibitory activity against Sars-CoV-2, demonstrated through docking studies and, for this reason, it seems clear that to continue the research with the evaluation of the activity could represent an important goal for the fight against this plague.

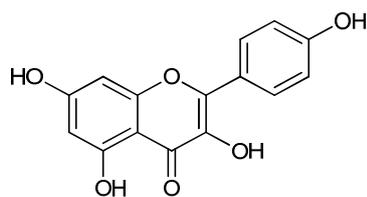
Moreover, many studies have promoted the possible use of pomegranate in combination with other drugs already available (like Doxorubicin) establishing its good influence in reverting their chemoresistance, thus overcoming their limits, lowering the toxicity and increasing the action.

In light of the reasons mentioned above, it becomes evident that pomegranate turns out to be one of the most attractive nutraceuticals and the deepening of its study could lead to the opening of new avenues for medical science domains.

Table 1. Bioactive compounds present in pomegranate.

Structure	Activity	Bibliographic Reference
 <p>(+)-(2R,3S)- Catechin (1)</p>	Antioxidant	[23]
 <p>Cyanidine (2)</p>	Antioxidant Antitumoral Anti-inflammatory	[5]
 <p>Delphinidine (3)</p>	Antitumoral Antioxidant Anti-inflammatory	[5]
 <p>Pelargonidin-3-O-glucoside (4)</p>	Antitumoral Antioxidant Anti-inflammatory	[5]
	Antiviral Antioxidant Cardioprotective Antitumoral	[28]

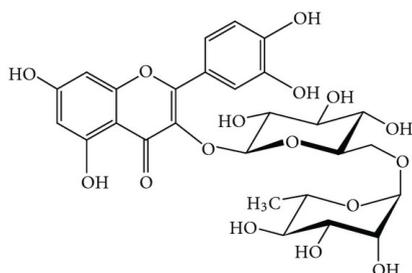
Quercetin (5)



Anti-cancerogenic

[30]

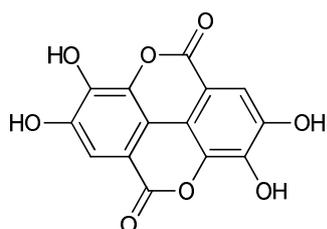
Canferol (6)



Antitumoral
Antimicrobial

[30]

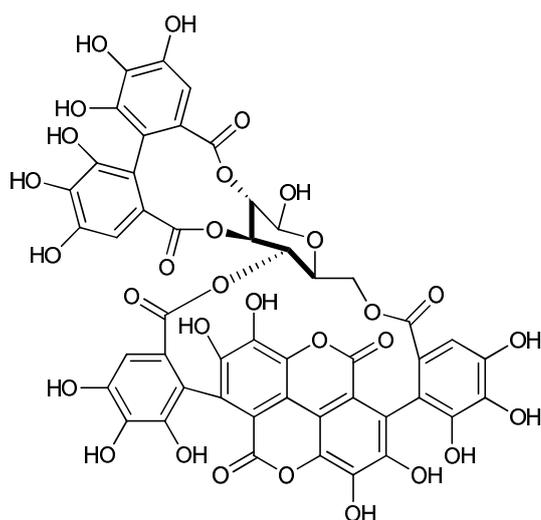
Rutin (7)



Antitumoral
Antiviral
Antimicrobial

[32]

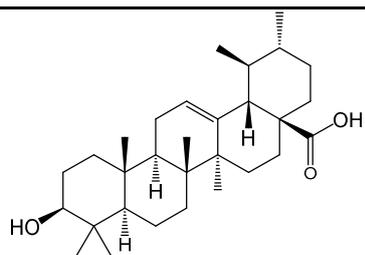
Ellagic Acid (8)



Anti-inflammatory
Antiproliferative
Pro-apoptotics
Antigenotoxic

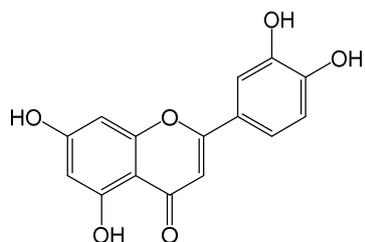
[33]

Punicalagine (9)



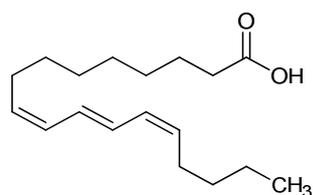
Ursolic acid (10)

Antitumoral [44]



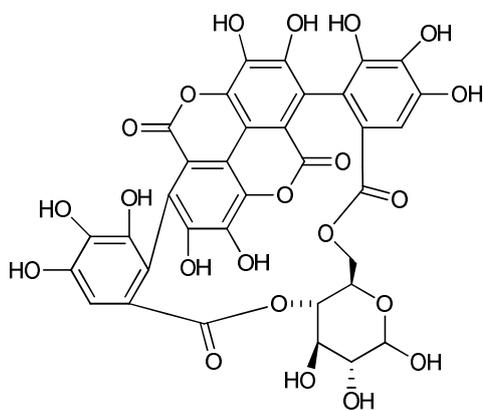
Luteolin (11)

Antitumoral [44]



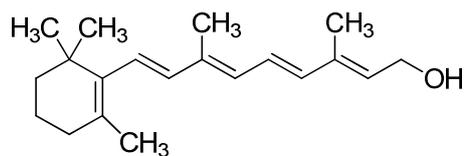
Punicic Acid (12)

Anti-inflammatory [60]



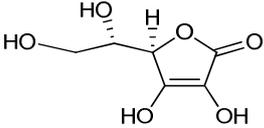
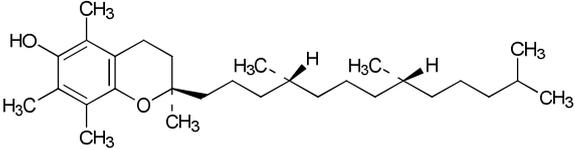
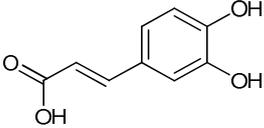
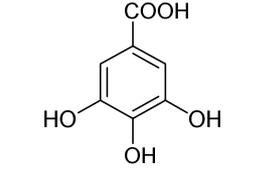
Punicalin (13)

Anti-inflammatory [57]



Vitamin A or retinol (14)

Antioxidant [82]

 <p>Vitamin C or ascorbic acid (15)</p>	Antioxidant	[82]
 <p>Vitamin E or tocopherol (16)</p>	Antioxidant Anti-inflammatory	[82]
 <p>Caffeic acid (17)</p>	Antidiabetics	[5]
 <p>Gallic acid (18)</p>	Antimicrobial Prevention of cardiovascular diseases	[107]

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