







Review

Healthy Effects of Pomegranate (*Punica granatum* L.) in Internal Medicine and Dentistry

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Abstract: *Punica granatum* L., commonly known as pomegranate, is a typical fruit of Asia, Mediterranean countries, the Middle East and the USA. While in ancient times pomegranate was considered an ornamental plant, nowadays numerous scientific studies have highlighted its antioxidant and anti-radical activities, making it a “superfood”. Pomegranate presents a high content of natural bioactive compounds (NBCs), and its consumption appears to exert numerous healthy effects, in particular, in several pathological conditions as metabolic syndrome, cancer, nephrolithiasis, urinary tract infections and neurodegenerative diseases. Moreover, recent studies have pointed out the possible beneficial action of pomegranate on oral health. For these reasons, the utility of pomegranate in internal medicine and dentistry represents a promising field, as it could enable the development of innovative natural adjuvant therapies and empower standard pharmaceutical therapies.

Keywords: ellagitannins; ellagic acid; circular economy; chronic non-communicable diseases; cancer; metabolic syndrome; oral health; periodontitis



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1. Introduction

The pomegranate (*Punica granatum* L.) is a typical crop in Asian and Mediterranean countries, the Middle East, and some USA areas [1,2]. Pomegranate fruit is composed of about 80% water and 15% carbohydrates, mainly sugars (such as fructose, sucrose, and glucose), and the remaining part is represented by fibers, vitamins (such as vitamin C), and natural bioactive compounds (NBCs), namely polyphenols [3].

Although the pomegranate has been present in our territories since ancient times, the data of the Italian “Istituto Nazionale di Statistica” (ISTAT) show that until 10 years ago, this kind of crop was uncommon in Italy [4]. Initially, pomegranate was considered a simple ornamental plant, but now it has registered a growing trend in its consumption, and this is due to the healthy properties that emerged from numerous scientific studies that have highlighted the antioxidant and anti-radical activities of this “superfood”. Thanks to

the high content of NBCs, the consumption of pomegranate appears to exert significant beneficial effects on human health, allowing it to strengthen the immune system and counteract free radical formation, which is responsible for many pathophysiological processes [5].

According to Aviram et al. [6], it is estimated that in 1 kg of pomegranate, about 40% is represented by juice, while the components discarded amount to up to 60%. Of the latter, 50% is represented by mesocarp, endocarp, and exocarp, while 10% is represented by the seeds of the arils. These matrices, considered wastes from the agro-industrial sector, if properly managed, represent a precious resource, as they are a source of bioactive polyphenolic molecules, such as flavonoids, anthocyanins, tannins, and in particular ellagitannins (ETs) (such as punicalagin) [1,7–9]. These compounds have been identified using various analytical techniques of liquid chromatography–mass spectrometry (LC-MS), such as liquid chromatography–tandem mass spectrometry (LC-MS/MS) and liquid chromatography–high-resolution–mass spectrometry (LC-HR-MS) [10,11]. In recent years, the use of LC-HR-MS instrumentation has increased rapidly for the qualitative identification of polyphenolic compounds present in plant matrices, such as pomegranate, the object of this review, which is particularly rich in ETs.

The chemical composition of pomegranate differs based on the variety and cultivation conditions. The peel, comprising 50% of the fruit's weight, is rich in phenolic compounds, such as phenolic acids, flavonoids, and tannins, which identify the biological activity of the pomegranate. Flavonoids, notably anthocyanins in arils, contribute to the red color and offer antimicrobial and antioxidant properties. Pomegranate components, including tannins, punicalagin, punicalin, strictinin A, and granatin B, inhibit nitric oxide production and suppress inflammatory cytokine expression due to ellagic acid (EA) ($C_{14}H_6O_8$) action [12].

The use of pomegranate bioactive compounds for the realization of innovative products in the nutraceutical and biomedical sectors is partly based on the results deriving from tests aimed at the evaluation of their toxicity. In detail, *in vivo* toxicity tests were conducted on rats, administering a standardized pomegranate fruit extract (PFE) at a dose of 600 mg/kg body weight/day. At the end of the study, this extract did not induce any toxic effects. In particular, the authors found “no observed adverse effect level” (NOAEL) for the doses examined [13].

This review focuses on the biological activities of the polyphenolic compounds present in pomegranate, such as those antioxidant, anti-inflammatory, antiproliferative, and antimicrobial that can induce beneficial effects in internal medicine (such as in metabolic syndrome (MetS), cancer, urinary tract infections (UTIs), nephrolithiasis, inflammatory bowel diseases (IBDs), and neurodegenerative diseases) and in dentistry (such as in stomatitis, chronic periodontitis, dental caries, tooth decay, gingivitis, and gingival bleeding).

2. Search Literature Methods

The strategy of the literature search was performed using three online databases, such as PubMed, Scopus, and the Cochrane Library (Figure 1).

The search was conducted according to the relevant terms: “pomegranate” in combination with “internal medicine” AND “diabetes mellitus” AND “metabolic syndrome” AND “arterial hypertension” AND “dyslipidemia” AND “cancer” AND “bowel inflammatory diseases” AND “nephrolithiasis” AND “neurodegenerative disorders” AND “urinary tract infections” AND “pomegranate” in combination with “oral health”. The full search was manually retrieved.

The inclusion criteria of the studies were limited to reviews, meta-analyses, and original articles written in the English language, while the exclusion criteria were represented by a different language from English: studies conducted before 1991, articles without abstracts, and studies of no interest.

The collected articles were composed between 1991 and 2023.

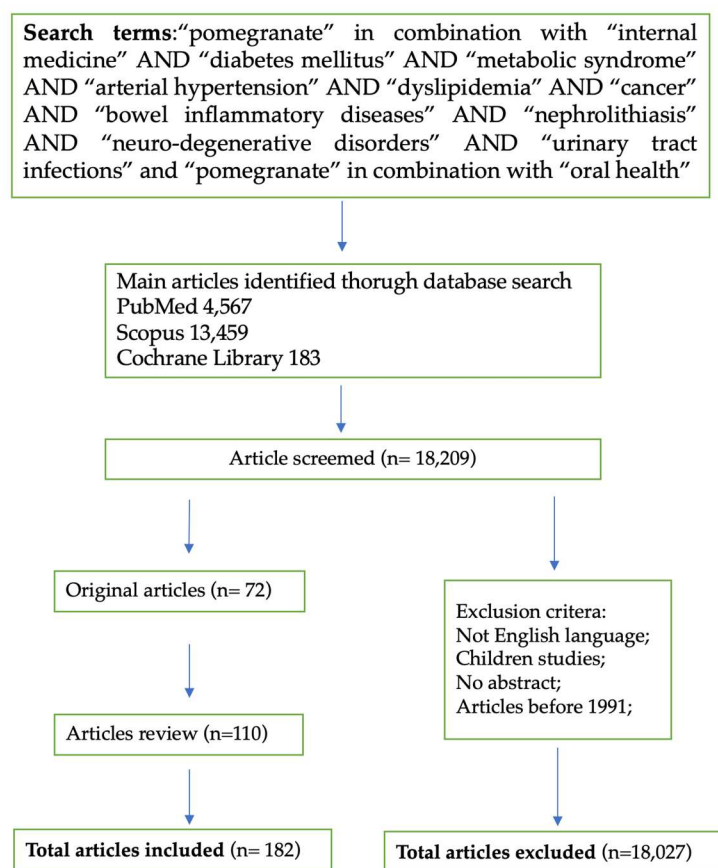


Figure 1. Search methods.

3. Bioactive Polyphenolic Compounds of Pomegranate and Their Biological Activities

Bioactive polyphenolic compounds of pomegranate exert numerous biological activities, as demonstrated by several in vitro and in vivo studies (Figure 2).

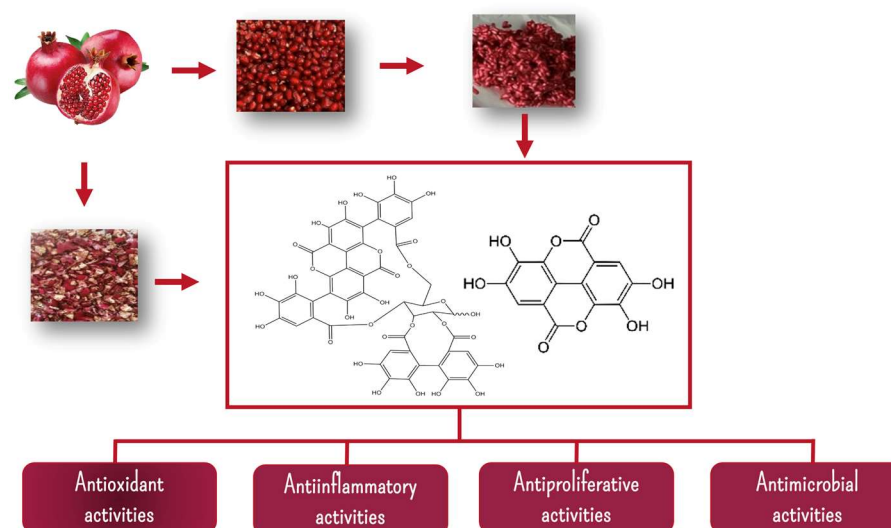


Figure 2. Biological activities of bioactive polyphenolic compounds of pomegranate (punicalagin and ellagic acid).

Among the polyphenolic classes of pomegranate, there are ETs. They belong to the subclass of hydrolysable tannins (HTs) and represent one of the most diverse groups of

polyphenols derived from plant matrix, as they comprise over 1000 identified NBCs [14]. Tannins, in general, exert a function of defense for the plant against attack by pathogens and herbivores. In fact, these compounds are found in the vacuoles and in the cytoplasm of plant cells and play an important protective role in natural growth conditions [15]. Furthermore, these compounds, with strong astringent properties, are capable of complexing proteins and polysaccharides [15]. They have a molecular weight between 300 and 20,000 Da and are found in the form of monomers (C-glycosidic ETs with an open-chain glucose portion), oligomers, and complex tannins [16,17]. All these molecules have in common the presence in the chemical structure of at least one hexahydroxydiphenic acid (HHDP) unit esterified in a polyol, generally glucose or quinic acid [18]. Several antimicrobial and antiviral properties are recognized in this subclass that also exert beneficial effects in the prevention of chronic degenerative non-communicable diseases [14,19–23].

To have a complete picture of their use in the biomedical field, scientific studies have also taken into account the bioavailability of these molecules, which are characterized by a complex structure that does not permit their absorption from the gut microflora [24,25]. Their effect can be attributed to the fact that these compounds undergo a hydrolysis process in the digestive system, which transforms ETs into smaller and less complex compounds, such as EA and urolithin, whose main effect on human health is attributable to their antioxidant and antiradical capacity. These molecules are able to counteract the action of free radicals and reactive oxygen species (ROS) [26].

The main bioactive compound present in pomegranate wastes is punicalagin [27,28], which, like the various polyphenolic compounds present in plant matrices, shows to have numerous biological and functional properties: antioxidant [21,29], antiviral [29], anti-inflammatory [30,31], antidiabetic [32], anticancer [33–35], cardio-protective [36–38], and antimicrobial [39–44].

The punicalagin ($C_{48}H_{28}O_{30}$) is part of the subclass of ETs and is the most representative compound within the pomegranate waste; in fact, it represents about 70% of the total ETs in the peel of the fruit. Punicalagin is a water-soluble polyphenolic compound with a high degree of hydroxylation and a high molecular weight, equal to 1084.7 Da. This compound is naturally found in the forms of two α and β reversible anomers [10,45–47].

Another of the most representative compounds in pomegranate fruit is EA, which is a dimeric derivative of gallic acid (GA) ($C_7H_6O_5$) [48]. EA is a thermostable molecule with a melting point of 350.3 C and a molecular weight of 302.19 g/mol, which is chemically identified as 2,3,7,8-tetrahydroxy-chromium [5,4,3-cde]chromene-5,10-dione [22]. EA is a natural bioactive polyphenolic compound; in particular, it is a secondary metabolite in many plant matrices [49–51].

This compound, identified as a dilacton (cyclic diester) of HHDP, showed beneficial effects in *in vitro* and *in vivo* models, and it is characterized by high free radical scavenging activity, as reported by Fischer et al. [28].

In addition to its antiradical ability, this compound has attracted particular attention from the scientific world in consideration of its antioxidant, anti-inflammatory, antimutagenic, antiproliferative, cardioprotective, hepatoprotective, nephroprotective, and neuroprotective properties [5,21–23].

Punicalagin and EA are the main compounds present in pomegranate wastes and are shown to have inhibitory activity against α -glucosidase [52], while another compound present in pomegranate wastes, in lower amounts, is GA.

Furthermore, some scientific studies have compared the antioxidant activity *in vitro* on cell lines of single analytical standards (namely punicalagin and EA) and of pomegranate extracts. The authors demonstrated the superior bioactivity of the latter [21], and this evidence confirms, as highlighted in tests relative to other vegetal matrices, that the phyto-complex has greater effectiveness compared to the purified standard.

4. Sustainable Application of a Circular Economy Model for Pomegranate Wastes Recovery

In recent years, scientific evidence has led to an increased demand for sustainable products with remarkable health properties, highlighting the need to recover polyphenolic compounds. The latter originates from waste matrices in order to promote sustainability goals through the application of circular economy principles based on the “zero waste” concept. Waste materials come from pomegranate cultivation and mainly consist of plant tissues, such as exocarp, mesocarp, endocarp, and seeds found in the arils.

Literature data showed that pomegranate wastes present several biological activities, as previously described. For this purpose, the recovery models of pomegranate peel through the integration of extraction and purification phases, during the transformation processes, have been developed. These processes aim to obtain concentrated fractions rich in HTs as active principles for various purposes. In fact, these compounds can be used primarily as food additives and secondarily as functional food ingredients, useful in the formulation and prototyping of products bound for different markets [53–56].

The extraction methods currently existing on a laboratory scale for obtaining polyphenolic extracts from pomegranate waste are different and are based on the use of high temperatures, ultrasound, pressure, and solvents.

Recent studies have carried out a comparative evaluation of pomegranate extracts obtained with different methods. In particular, the comparison was based on the examination of free and bound phenols, extracted using thermal and non-thermal methods. Polyphenolic compounds were analyzed by high-performance chromatographic techniques such as ultra-high-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UHPLC-QTOF-MS) and ultra-performance liquid chromatography coupled to a triple quadrupole mass spectrometer (UPLC-QQQ-MS).

The total content of free phenolics, approximately 10 times higher compared to the bound phenolics, did not show significant differences in the concentration obtained by different extraction methods. The highest yield of bound phenols was obtained by heating and high-pressure methods, and the composition was strictly dependent on the degree of alkaline hydrolysis. The high-pressure method allowed for obtaining an extract with a higher percentage of compounds and larger dimensions, thus highlighting that this process alters to a lesser extent the initial composition of the plant matrix [57].

Moreover, as for pomegranate, as well as for other plant matrices, it is possible to use dried and micronized wastes in order to avoid the extraction process [58].

Beyond the primary utilization of high-quality fruits in the fresh market, the cultivation of *Punica granatum* L. can involve various processes. These include the innovative production of arils through functional green withering, the production of juices obtained through cold pasteurization, as well as concentrates or innovative-based gels, and finally, the production of depleted seed oil and/or flours for feed and food use. An appropriate dried process of fresh peels can lead to the production of powders such as micronized, natural pigmenting principles, and standardized phytocomplexes in the HTs content, extending up to energy production (Figure 3).

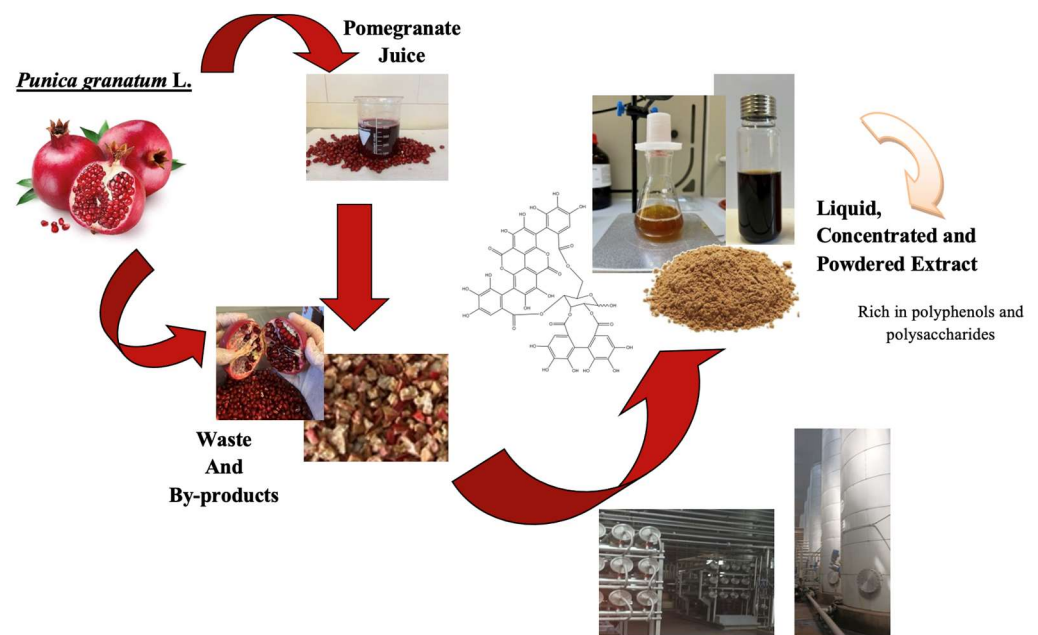


Figure 3. Circular economy model for pomegranate waste recovery.

5. Pomegranate in Internal Medicine

The bioactive polyphenolic compounds of pomegranate are able to exert numerous beneficial properties useful in internal medicine (Figure 4).

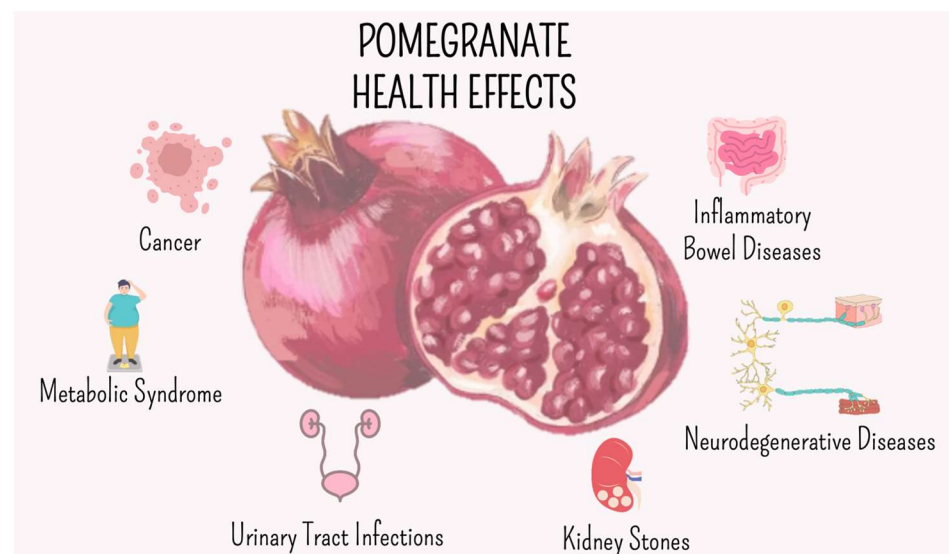


Figure 4. Beneficial effects of pomegranate in internal medicine.

5.1. Metabolic Syndrome

MetS is a chronic pathology characterized by the concomitant presence of at least three of the following conditions: (i) Abdominal obesity, (ii) alteration of glucose metabolism, (iii) arterial hypertension (AH), (iv) low high-density lipoprotein (HDL) cholesterol, and (v) hypertriglyceridemia. These conditions contribute to the onset of a low-grade inflammatory state and oxidative stress, typical of this syndrome [59]. The risk factors for MetS can be both genetic and environmental; the latter are often related to incorrect lifestyles, such as poor or no physical activity and unhealthy eating habits [60]. In recent years, the use of functional foods or oral food supplements (OFSs), based on NBCs, has become relevant

for the clinical management of MetS patients [61], and currently it represents an adjuvant therapy to be associated with traditional pharmacological treatments [59,62,63].

Some different pomegranate extracts, such as peels, flowers, juice, and seeds, are able to regulate the lipid metabolism, as confirmed by some *in vivo* studies [64]. In fact, a study conducted on hypercholesterolemic mouse models nourished with feed supplemented by 15% pomegranate seed oil (PSO), for 28 days, highlighted a decrease in the plasma levels of triglyceride, total cholesterol, and low-density lipoprotein (LDL) cholesterol compared to the control group. This lipid-lowering effect was already highlighted by a previous study conducted on hypercholesterolemic type 2 diabetes mellitus (T2DM) patients, in which the supplementation of concentrated pomegranate juice (PJ), for 8 weeks, was able to reduce the atherogenic indices, such as LDL-cholesterol/HDL-cholesterol and cholesterol total/HDL cholesterol (Table 1) [65]. Moreover, in a following study, conducted on 23 MetS women, the possible effect of the daily consumption of 300 mL of PJ, for 6 weeks, on lipid peroxidation (LPO) and the phospholipid fatty acid composition of plasma and erythrocytes was investigated. The authors highlighted a significant decrease in arachidonic acid and an increase in mono-unsaturated fatty acids in the erythrocyte membrane. They also showed a decrease in LPO, evaluated by the reduction in levels of thiobarbituric acid-reactive substances in erythrocytes, in the treatment subjects compared to the control group. These results suggest a potential antioxidant, anti-inflammatory, and cardio-protective action of pomegranate in dyslipidemia patients [66].

Further studies have demonstrated the effectiveness of pomegranate fruit in the treatment of T2DM, as it contains fiber, minerals, vitamins, and other NBCs useful in glycemic control [67]. In this context, in an animal study, it has been demonstrated that the anti-diabetic effects of pomegranate extracts are exerted through the stimulation of the peroxisome proliferator-activated receptor (PPAR)- γ , a transcription factor involved in glucose metabolism [68]. Furthermore, PJ, rich in punicalagin, seems to be able to stimulate the release of insulin by β -cells, suggesting its potential role as an adjuvant treatment in anti-diabetic therapy [69]. To support these hypotheses, a study conducted by Hashemy et al. described the beneficial effects of the pomegranate seed powder assumption, at a dose of 5 g, twice per day, for 8 weeks, in T2DM patients. At the end of the study, the treated group showed a significant reduction in fasting blood glucose and glycated hemoglobin levels compared to the control group, suggesting that pomegranate can be used to control glycemia in diabetic patients [70]. A meta-analysis that included 32 clinical trials demonstrated that pomegranate consumption was able to reduce fasting blood glucose, insulin resistance, and the homeostasis model assessment of insulin resistance (HOMA-IR) [71].

The bioactive polyphenolic compounds of pomegranate appear to play a crucial role in reducing body weight and improving body composition in overweight or obese subjects [72,73]. In fact, a study conducted on obese non-diabetic premenopausal female patients, who daily consumed 300 mg of PSO, for 16 weeks, showed a significant reduction in body weight, waist circumference, and liver fat content, as well as in serum triglycerides and C-reactive protein (CRP) levels, of treated women compared to the control group [74].

Regarding blood pressure, pomegranate has also proven useful in counteracting AH, thanks to its anti-oxidative polyphenolic compounds. To confirm this, a single-blind placebo-controlled randomized study, conducted on 60 T2DM patients, who consumed 200 mL/day of PJ, for 6 weeks, highlighted a significant reduction in systolic and diastolic blood pressure, compared to the control group [75]. Recently, a meta-analysis analyzed 14 clinical trials for a total of 573 subjects and demonstrated a reduction in systolic blood pressure and diastolic blood pressure secondary to the PJ assumption. Interestingly, this beneficial effect was dose-dependent and observed when the daily intake was >300 mL, but this antihypertensive effect was lost after two months of PJ assumption [76].

Table 1. Effects of pomegranate in internal medicine.

Type of the Study	Study Population	Activities Exerted by Pomegranate	Natural Bioactive Compounds	Future Applications	Reference
In human study	22 patients	↓ total cholesterol ↓ LDL-cholesterol ↓ total/HDL-cholesterol LDL-↓ cholesterol/HDL-cholesterol	– Oleanolic acid – Anthocyanin	Lipid-lowering effects	[65]
In human study	23 women patients	↓ arachidonic acid ↑ mono-unsaturated fatty acids ↓ lipid peroxidation	– Ellagic acid – Anthocyanin	- Antioxidant effects - Anti-inflammatory effects - Cardioprotective effects	[66]
In animal study	Rats	↑ PPAR- γ	Pomegranate Flower: – Punicalagin – Ellagic acid – Gallic acid – Oleanolic acid – Ursolic acid – Anthocyanin	Antidiabetic effects	[68]
In animal study	Mice	↑ insulin release by β -cells	– Punicalgin	Antidiabetic effects	[69]
In human study	60 patients	↓ fasting blood glucose ↓ glycated hemoglobin	– Punicalagin – Ellagic acid – Ursolic acid – Anthocyanin	Glycemic control in diabetic patients	[70]
In human study	151 women patients	↓ body weight ↓ waist circumferences ↓ liver fat content ↓ triglycerides ↓ C-reactive protein	– Punicic acid – Palmitic acid – Stearic acid – Oleic acid – Linoleic acid – Linolenic acid	Improvement in metabolic syndrome	[74]
In human study	60 patients	↓ systolic blood pressure ↓ diastolic blood pressure	– Anthocyanin – Ellagic acid	Amelioration of blood pressure control	[75]
In human study	48 patients	↓ IL-6 ↓ C-reactive protein ↓ total cholesterol ↓ LDC cholesterol ↓ triglycerides ↓ glucose ↓ insulin	– Ellagic acid – Stearic acid	Amelioration of low-grade inflammatory status, fasting serum glucose, insulin, HOMA-IR, triglycerides	[77]
In vitro study	Breast cancer cell line	↓ proliferation ↓ estrogenic activity ↓ aromatase activity	– Ellagic acid – Gallagic acid – Urolithins	Antiproliferative effects on cell lines	[78]
In vitro study	Breast cancer cell line	↓ inflammation ↓ pro-inflammatory cytokines ↓ chemokines	– Ellagic acid	Anti-inflammatory effects	[79]

Table 1. Cont.

Type of the Study	Study Population	Activities Exerted by Pomegranate	Natural Bioactive Compounds	Future Applications	Reference
In vitro study	Breast cancer cell line	↓ pro-inflammatory cytokines (IL-2, IL-6, IL-12, IL-17, IP-10, TNF- α , MIP-1 α , MIP-1 β , MCP-1, VEGF)	– Punicic acid – Palmitic acid – Stearic acid – Oleic acid – Linoleic acid – Linolenic acid	Reduction in VEGF levels, antioxidant effects and anticytotoxic effect	[80]
In vitro study	Lung carcinoma cell line	↓ proliferation ↓ migration anti-metastasis	– Punicalagin – Ellagic acid	Antiproliferative and anti-metastasis effects	[81]
In animal study	Lung	↓ IL-1 β ↓ IL-6 ↓ TNF- α	– Ellagic acid – Gallic acid – Anthocyanin – Caffeic acid	Pomegranate juice reduces acute lung injury	[82]
In vitro study	Lung carcinoma cell line	↓ cell viability ↓ cell growth ↑ antioxidant capacity G ₁ cell cycle arrest	– Punicalgin – Ellagic acid	Chemopreventive/chemotherapeutic action of pomegranate	[83]
In vitro study	Primary lung tumors	↓ cell proliferation ↓ angiogenesis ↓ mTOR signaling ↓ PI3K activation ↓ lung tumor multiplicity	– Punicalgin – Ellagic acid	Chemopreventive action of pomegranate	[84]
In vitro study	Colon cancer cell line	↓ cell proliferation G _{0/1} cell cycle arrest G ₂ /M cell cycle followed by apoptosis	– Ellagitannins	Pomegranate induces apoptosis and inhibits cell proliferation	[85]
In vitro study	Colon cancer cell line	↓ TNF- α ↓ NF- κ B	– Ellagitannins – Punicalgin	Modulation of inflammatory cell signaling	[23]
In animal study	Rats	↓ onset of colonic tumors ↑ expression of PPARgamma protein	– Punicic acid – Palmitic acid – Stearic acid – Oleic acid – Linoleic acid – Linolenic acid	Reduction in colon carcinogenesis (induced by azoxymethane)	[86]
In vitro study	LNCaP, PC-3, and DU 145 human cancer cell lines	↓ cell proliferation ↑ apoptosis	– Ellagic tannins – Gallic acid	Possible antitumor activity of pomegranate-derived materials against human PC	[87]
In vitro study	Metastatic castration-resistant PC cells	↓ signal transducer and activator of transcription 3	– Ellagic acid	Pomegranate may be effective in treating metastatic castration-resistant PC	[88]
In vitro study	Human prostate cancer DU145 cell	↓ proliferation of human prostate cancer ↑ apoptosis	– Ellagic acid – Gallic acid – Anthocyanin	Develop a novel mechanism-based chemopreventive strategy for prostate cancer.	[89]

Table 1. Cont.

Type of the Study	Study Population	Activities Exerted by Pomegranate	Natural Bioactive Compounds	Future Applications	Reference
In vitro study	LNCaP-AR cell line	↓ HSD3B2, AKR1C3, and SRD5A1 gene expression	– Ellagitannin	Pomegranate polyphenols inhibits the gene expression involved in androgen-synthesizing enzymes in androgen-independent prostate cancer cells	[90]
In vitro study	66 multidrug resistant strains of major urinary tract pathogens	Antibacterial activity against <i>E. coli</i>	– Ethanol extract of Pomegranate	Economic and safe alternative treatment for urinary tract infections	[91]
In human study	23 UTI patients and 7 healthy subjects	↑ 10% in PON1 activity ↓ supersaturation of calcium oxalate	– Punicalgin	Reducing the risk of calcium oxalate stone formation in UTI patients	[92]
In animal study	56 rats	↓ ethylene glycol-induced crystal depositions in renal tubules	– Punicalgin – Ellagic acid – Gallic acid – Ursolic acid – Anthocyanin	Effective alternative treatment for Urinary Tract Infections	[93]
In human study	36 patients with IBD involving the colorectum in remission	↓ fecal calprotectin levels ↓ systemic inflammatory markers	– Ellagitannin	Useful adjuvant treatment in long-term maintenance in IBD patients with a high risk of clinical relapse	[94]
In animal study	Rats fed a high-fat diet	↓ IL-6, TNF- α	– Punicalagin – Urolithin A	Pomegranate protects against the inflammatory damage of a high-fat diet	[95]
In animal study	Female mice with UC	↓ IL-6, TNF- α , and IFN- γ ↓ COX-2	– Ellagic acid	Pomegranate could represent an adjuvant anti-inflammatory treatment in UC patients	[96]
In vitro study	Microglial BV-2 cells	↓ LPS-induced neuroinflammation	– Punicalagin	Improvement in memory via anti-inflammatory and anti-amylogenic mechanisms in AD patients	[97]
In animal study	Mice with age-related deterioration in memory and learning	↓ IL-1 β , IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10 ↓ TNF- α ↓ amyloid-beta accumulation	– Ellagic acid – Gallic acid – Anthocyanin	Pomegranate beneficial effects against neurodegenerative diseases	[98]
In vitro study	SK-N-SH cells	↓ COX-2-dependent PGE2 production	– Punicalagin – Ellagic acid	Slowing the progression of neurodegenerative disorders	[99]

Table 1. Cont.

Type of the Study	Study Population	Activities Exerted by Pomegranate	Natural Bioactive Compounds	Future Applications	Reference
In animal study	Pregnant mice	↓ brain tissue loss ↓ caspase-3 activation	– Ellagic acid	Maternal supplementation with pomegranate could exert neuroprotection in the newborn	[100]
In animal study	18 AD transgenic mice	↓ neuroinflammatory activity ↓ β -site cleavage of amyloid precursor protein	– Ellagic acid – Gallic acid – Anthocyanin	Long-term supplementation with pomegranates can attenuate AD by reducing inflammation	[101]
In animal study	12 mice with double Swedish APP mutation	↓ LPO ↓ protein carbonyl levels ↑ SOD ↑ catalase ↑ GPx ↑ GSH ↑ GST	– Anthocyanin – Hydroxycinnamic – Acid derivatives – Ellagic acid – Punicalin – Gallic acid – Protocatechuic acid	Pomegranate could represent a valid adjuvant strategy for AD	[102]

Abbreviations: AD, Alzheimer's disease; AKR1C3, aldo-keto reductase family 1 member C3; COX, cyclooxygenase; GPx, glutathione peroxidase; GSH, glutathione; GST, glutathione S transferase; HDL-cholesterol, high-density lipoprotein cholesterol; HSD3B2, 3 beta-hydroxysteroid dehydrogenase type 2; IBD, inflammatory bowel disease; IL-6, interleukin-6; IL, interleukin; LDL-cholesterol, low-density lipoprotein-cholesterol; LPO, lipid peroxidation; LPS, lipopolysaccharide; MIP-1 α , macrophage inflammatory protein-1 α ; NF- κ B, nuclear factor kappa-light-chain enhancer of activated B cells; PC, prostate cancer; PG, prostaglandin; PI3K, phosphatidylinositol 3-kinase; PPAR- γ , peroxisome proliferator-activated receptor- γ ; SOD, superoxide dismutase; SRD5A1, steroid 5 alpha reductase type 1; TNF- α , tumor necrosis factor- α ; TNF, tumor necrosis factor; UC, ulcerative colitis; UTI, urinary tract infection; VEGF, vascular endothelial growth factor; ↑ increase; ↓ decrease.

Finally, pomegranate seems useful for counteracting the oxidative stress and the chronic low-grade inflammatory state typical of MetS. In fact, in a study by Hossein et al., the authors described the beneficial effect of an OFS based on pomegranate on inflammatory and oxidative stress biomarkers in overweight and obese individuals. In particular, 48 obese and overweight subjects have consumed 1000 mg of pomegranate extract daily for 30 days. The pomegranate extract has significantly reduced interleukin (IL)-6 and high-sensitivity CRP levels, as well as total cholesterol, glucose, and insulin serum levels. This might suggest that pomegranate OFS may reduce those complications related to obesity, such as low-grade chronic systemic inflammation [77].

For the reasons previously discussed, the long-term daily assumption of pomegranate, both as fresh fruit and/or as OFS, can be considered an adjuvant therapy in subjects at risk of developing MetS or in patients affected by it.

5.2. Cancer

According to the current National Cancer Institute (NCI) definition, “cancer is a disease, in which some of the body's cells grow uncontrollably and spread to other parts of the body” [103]. Cancer was conceptualized as a disease of genetic origin; however, research over the last several decades has established how environmental factors with epigenetic effects play a pivotal role in the phenomenon of carcinogenesis [104]. These environmental factors, capable of altering the spatial conformation of chromatin to regulate gene expression, include unhealthy nutrition, chemicals and industrial pollutants, and a poor lifestyle [105] (such as smoking, alcohol consumption, and physical inactivity) [106]. However, while an imbalanced diet, such as the Western diet, increases the risk of cancer onset, on the other hand, a balanced diet rich in fruit and vegetables, such as the Mediterranean diet (MD), is an important factor in cancer prevention [107,108]. MD, thanks to the ability to guarantee a wide variety of micronutrients and other NBCs, is able

to counteract the cancer [109,110]. Among the NBCs are certainly included polyphenolic molecules, of which the pomegranate is rich. These molecules are capable of exerting chemo-preventive and chemotherapeutic effects through their antioxidant, anti-radical, and anti-inflammatory activities and through their anti-mutagenic and anti-proliferative properties. The latter include the induction of apoptosis in cancer cells, the stimulation of the immune system [111,112], the modulation of hormonal concentration and metabolism, the cell cycle arrest, the enzymatic detoxification, the activation of transcription factors and the induction of apoptosis, the cell adhesion, and finally, the production of growth factors against different type of cancer, such as breast cancer (BC), lung cancer (LC), colorectal cancer (CRC), and prostate cancer (PC) [113].

5.2.1. Pomegranate and Breast Cancer

BC, generally categorized into estrogen receptor (ER) positive and ER negative, is the most diagnosed cancer and the major cause of cancer-related death among females [114]. Many exogenous and endogenous risk factors could affect the onset and development of BC [115]. Among exogenous factors are early menarche, nulliparity, oral contraceptive use, never having or short duration of breast feeding, use of hormone replacement therapy, circadian disruption, and an unhealthy lifestyle (including smoking, alcohol consumption, an imbalanced diet, etc.). Endogenous risk factors, namely genetic factors, such as mutations on breast cancer gene 1 (BRCA1) and BRCA2, only account for approximately 5–10% of all BC incidences. For this reason, a possible strategy capable of counteracting BC carcinogenesis would be to modify the lifestyle and nutritional choices in order to guarantee proper prevention of this type of cancer. Several in vitro studies have highlighted how pomegranate by-products, namely PFE, PJ, and PSO, are involved in the process of breast carcinogenesis, exhibiting the following effects: (i) the anti-proliferative, anti-aromatase, and anti-estrogenic activities [78]; (ii) the regulation of the transforming growth factor beta (TGF- β)/Smads pathway [79]; (iii) the anti-inflammatory effects, through the reduction in pro-inflammatory cytokines and chemokines; (iv) the reduction in vascular endothelial growth factor (VEGF) levels [80]; (v) the downregulation of the expression of the genes involved in the damage of DNA and the estrogen-responsive genes [116]; (vi) and the disruption of ER and Wnt/ β -catenin signaling pathways [117].

5.2.2. Pomegranate and Lung Cancer

LC is the most common cancer and the leading cause of death worldwide, due to its diagnosis at an advanced stage [118]. In addition to a positive family history of LC, other important risk factors for this type of disease are tobacco smoking, unhealthy eating habits (such as high intake of fried or well-cooked red meat and alcohol consumption), chronic inflammation related to infections, exposure to ionizing radiation, and occupational exposures (such as asbestos and indoor air pollution) [119]. Thanks to their countless nutrients, such as vitamins, minerals, phytochemicals, and dietary fibers, fruits could play a pivotal role in the prevention of LC and in the risk reduction in current smokers, thanks to the ability of these micronutrients to exert antioxidant activities, repair DNA from oxidative damage, inhibit tumor cell proliferation, and induce tumor cell apoptosis, caused by smoking [120]. It was highlighted how pomegranate polyphenols have potent chemotherapeutic properties that exert anti-cancerous activities on lung carcinoma. In more detail, several in vitro studies have pointed out how pomegranate leaf extract (PLE) has potential anti-proliferative, antimigratory [81], and anti-metastasis properties against lung carcinoma, while pomegranate peel extract (PPE), PJ, and PSO, tested both in vitro and in vivo have shown strong anti-inflammatory activities, reducing proinflammatory cytokine levels (IL-1 β and IL-6), and strong antioxidant properties inactivating cellular oxygen radicals in the lungs [82]. In addition to the effects described above, PFE seems to play a pivotal role against the LC. In fact, both in vitro and in vivo studies have shown how PFE is involved in the downregulation and inhibition of several signaling pathways against lung cancerous cells, including nuclear factor kappa-light-chain enhancer of activated

B cells (NF- κ B) expression, mitogen-activated protein kinase (MAPK) phosphorylation, phosphoinositide 3-kinases (PI3K), and mechanistic target of rapamycin (mTOR) pathway activity and Akt phosphorylation, leading to reduced cell proliferation and angiogenesis in lungs [83,84].

5.2.3. Pomegranate and Colon Cancer

CRC is the third most common cancer and the fourth most frequent cause of cancer deaths worldwide. Several risk factors are thought to contribute to its etiopathogenesis, such as older age, genetics, and environment, including a diet rich in meat and fats and poor in fiber, folate, and calcium, a sedentary lifestyle, obesity, high alcohol intake, smoking, etc. [121]. It is well known through several clinical studies that a highly fiber-rich diet based on the computation of plant-based foods, such as fruits and vegetables, is a protective factor associated with a decrease in CRC incidence [122]. Dietary fiber is composed of plant-based carbohydrates that cannot be metabolized by digestive enzymes encoded in the human genome, such as amylase. However, this macronutrient, through an anaerobic fermentation process, can be metabolized by certain species of gut microbiota, producing short-chain fatty acids (SCFAs), which include acetate, propionate, and butyrate [123]. It has been shown that the latter may have anti-neoplastic properties in the colon, modulating the immune response, and thereby resulting in protection against CRC [124]. Moreover, the production of SCFAs reduces the colonic pH, preventing the conversion of bile acid metabolites into more toxic forms [125].

As well as being rich in vitamins, such as vitamins A, E, C, B1, and B2, minerals, and phytochemicals, namely polyphenolic compounds, the pomegranate micronized peel is a rich reservoir of dietary fiber. Thereby, it represents a byproduct useful in CRC prevention, thanks to its remarkable bioactivity [126]. It is also worth emphasizing how the gut microbiota plays a crucial role in polyphenol catabolism. Indeed, when colon bacteria degrade dietary fiber, the ETs, obtained from pomegranate, are hydrolyzed to form EA and transformed into urolithin by the gut microbiota. Thus, these compounds exert their action in the prevention of CRC carcinogenesis by remodeling the gut microbiota [127]. Furthermore, the consumption of PJ is capable of releasing ETs and urolithins in the colon, potentially reducing the risk of CRC development by inhibiting cell proliferation and inducing apoptosis [85]. Several studies have also highlighted how PJ plays an important role in the downregulation of the inflammatory signaling pathways in colon cancer cells through the inhibition of cyclooxygenase (COX)-2 expression [23,128]. The activity of this enzyme is increased in many cancers, such as CRC [129]. Moreover, PJ suppresses Akt activation, which is needed for NF- κ B DNA binding. Finally, several *in vitro* studies have emphasized the PJ anti-proliferative and pro-apoptotic effects against CRC cells [23]. As regards the PSO, *in vivo* studies have shown how its consumption is significantly correlated with the inhibition of colon tumorigenesis due to the up-regulation of PPAR γ protein expression in the rat colon [86].

5.2.4. Pomegranate and Prostate Cancer

PC is the second-most common form of cancer in men [130]. Non-modifiable risk factors for PC include age, genetic predisposition, and ethnicity, while modifiable risk factors include environmental factors, such as obesity, smoking, low physical exercise, and an unhealthy diet that play a pivotal role in the initiation, promotion, and progression of PC. In fact, several studies have highlighted how an excessive intake of saturated fats from dairy products and ultra-processed meat is associated with an increased risk of PC [131,132]. As for other types of cancer, a considerable number of *in vitro* and *in vivo* studies have shown how PJ and PFE possess anti-proliferative, proapoptotic, and anti-metastatic actions, decreasing the levels of pro-inflammatory cytokines and chemokines and inhibiting angiogenesis through a reduction in VEGF levels [87]. Moreover, these compounds are capable of acting on the canonical signaling pathways, namely NF- κ B and PI3K/Akt/mTOR, in human PC cell lines and/or in mouse PC tumor models [88,89].

Moreover, the possible chemopreventive and chemotherapeutic effects exhibited by the ETs contained in PJ and PE against PC have also been found in both in vivo and in vitro studies. These studies demonstrated a reduction in the expression of androgen genes, which play a crucial role in PC cell growth and progression [90]. Several studies have highlighted the association between PC and gut microbiota dysbiosis, suggesting that the latter might be involved in not only gastrointestinal cancers (GC) but also in PC. In fact, there could exist a “microbiota–gut–prostate axis” so that the pro-inflammatory cytokines and the pathogen bacteria of the gut microbiota enter systemic circulation, thanks to the increased permeability of the gastrointestinal tract barrier and the altered tight junctions. These alterations seem to be induced by gut microbiota dysbiosis and local inflammation, suggesting the potential role of the diet on PC [133]. Different in vivo studies have focused attention on how PPE reshapes the gut microbiota thanks to the countless properties exerted by the phytochemical compounds contained therein, thus constituting a possible adjuvant therapy for PC [134].

5.3. Urinary Tract Infections

Pomegranate exerts antimicrobial effects against the main pathogens that cause UTIs [135]. In particular, it would seem that every part of the pomegranate plant has antimicrobial activity, suggesting that pomegranate-based OFSs can counteract UTIs. OFSs can also be formulated from the wastes of the pomegranate supply chain [136]. An interesting study investigated the antimicrobial activity of 17 medicinal plants in extracts of water, acetone, and ethanol against the main pathogens causing UTIs, highlighting how pomegranate ethanol extract shows strong antibacterial activity against *Escherichia coli* [91]. Among the numerous phytochemical compounds of pomegranate, those that have shown the highest antimicrobial activity are the EA and the HTs, such as punicalagin. In most studies, their combination showed the greatest benefits [136].

5.4. Nephrolithiasis

Numerous studies have highlighted a direct correlation between oxidative stress and nephrolithiasis, although the mechanism underlying the increased kidney stone development in the presence of oxidative stress has not been well defined yet [137]. In this context, PJ, which has been shown to exert important antioxidant scavenging actions against ROS, could represent a valid adjuvant strategy in the prevention of stone formation [92]. An in vitro study, conducted on tissues from murine models, observed a reduction in crystal deposits in the renal tubules in mice fed PJ compared to the control group [93]. Subsequently, Tracy et al. developed a clinical trial conducted on patients suffering from recurrent kidney stones, who had been administered a pomegranate polyphenolic extract, at a concentration of 1000 mg/day, for 90 days. The authors highlighted how patients suffering from recurrent kidney stones had high levels of oxidative stress and how the consumption of pomegranate polyphenols significantly reduced the oxidative stress itself and induced a trend in a reduction in calcium oxalate saturation levels [92]. Although these results are promising, they should be further investigated to confirm the beneficial role of pomegranate against nephrolithiasis because the data to support this thesis are not currently sufficient.

5.5. Inflammatory Bowel Diseases

IBDs are described as chronic diseases characterized by recurrent inflammation of the intestinal tract with multifactorial genesis, in which autoimmune, genetic, and environmental factors are involved. IBDs include Crohn’s disease and ulcerative colitis [138]. Numerous scientific studies highlight how a diet rich in polyphenols seems to play a key role in mitigating the chronic inflammation underlying IBDs [139]. A study conducted on murine models evaluated the effect of treatment with PJ, containing ETs and EA, in mice with colitis and colon ulceration, emphasizing how PJ is able to reduce the expression of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)- α and IL-1 β , and of

COX-2. Furthermore, the gut microbiota of mice treated with PJ at the end of the study showed an increase in Ruminococcaceae, butyrate-producing bacteria [139].

IBDs are characterized by the inflammation of the colon mucosa, accompanied by the infiltration of inflammatory cells, including neutrophils, which represent the first line of defense in the immune system and produce a series of inflammatory molecules [140]. A randomized controlled trial, conducted on a group of IBD patients with a high rate of relapses, evaluated the effects of supplementation with PJ, rich in ETs, on the modulation of local and systemic inflammation biomarkers. The authors examined whether patients treated with PJ for 12 weeks showed a reduction in the fecal concentration of calprotectin (a protein derived from fecal neutrophils, a marker of inflammation of the intestinal mucosa) and in the serum concentration of CRP, erythrocyte sedimentation rate (ESR), TNF- α , and IL-6, markers of systemic inflammation [94].

Furthermore, in this context, it has been demonstrated that the pomegranate peel polyphenols seem to reduce the gut permeability to inflammatory cells induced by lipopolysaccharide (LPS), suggesting that wastes from the pomegranate agri-food chain could also be used as effective anti-inflammatory agents in the treatment of IBDs [95].

Finally, pomegranate seems to exert a protective role against IBDs in the acute phase. In fact, in murine models with ulcerative colitis in the acute phase, the EA supplementation appears to ameliorate the severity of the disease, both through the improvement in colon ulcerations and through the reduction in the inflammatory profile [96].

5.6. Neurodegenerative Diseases

PJ seems to be able to attenuate neuro-inflammation, suggesting that this fruit can be useful in counteracting the onset and symptoms of age-associated neurodegenerative pathologies, such as Alzheimer's and Parkinson's diseases [141].

Pomegranate polyphenolic compounds reduce neuro-inflammation by several mechanisms, which include: (i) the inhibition of NF- κ B, a transcription factor involved in the inflammatory process [97]; (ii) the reduction in the pro-inflammatory cytokines, such as IL-2, IL-6, IL-1 β , and TNF- α [98]; (iii) the reduction in the beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) gene expression, responsible for the production and the deposition of the β -amyloid peptide, involved in Alzheimer's disease; (iv) the reduction in COX-2 activity [99]; (v) the reduction in the catalytic activity of caspases [100].

Pomegranate polyphenols seem to improve synaptic function during Alzheimer's disease. In fact, a study conducted on mouse models subjected to nutritional supplementation with pomegranate extracts (4% *w/w*) for 15 months highlighted the protective role of pomegranate against the proteins that improve the synaptic structure, such as synaptophysin, postsynaptic density protein-95 (PSD-95), mammalian uncoordinated-18-1 (Munc18-1) and synaptosomal-associated protein-25 (SNAP25) [101].

Finally, the supplementation with pomegranate extracts (4% *w/w*) would seem to protect the brain from oxidative damage in mouse models affected by Alzheimer's through a reduction in LPO and carbonyl levels and the restoration of antioxidant enzyme activities, such as glutathione peroxidase (GPX), superoxide dismutase (SOD) and glutathione S-transferase (GST) [102].

Although clinical studies on humans are lacking, *in vitro* and animal models studies seem encouraging and suggest that pomegranate and its phenolic compounds possess important anti-inflammatory and neuroprotective properties that could be effective against the symptoms of neurodegenerative diseases with neuro-inflammatory etiopathology [142].

6. Pomegranate and Oral Health

Pomegranate has garnered significant attention in the field of dentistry for its potential therapeutic properties, particularly in the treatment of dental plaque, gingivitis, and periodontitis. The literature data about this fruit have revealed a multitude of benefits, making it a valuable candidate for promoting oral health.

Dental plaque, a biofilm of bacteria that forms on tooth surfaces, is a primary contributor to oral health problems. Pomegranate has been extensively studied for its ability to counteract dental plaque formation. The flavonoids present in pomegranate demonstrated a robust antibacterial action against key contributors to plaque formation, including *Streptococcus sanguis* and *Eikenella corrodens* (Table 2) [143,144]. Its antibacterial effect is attributed to tannins, compounds that enhance bacteriolysis and impair bacterial adherence to tooth surfaces. Comparative studies have highlighted the pomegranate's superior inhibition capacity towards specific bacteria compared to chlorhexidine (CHX), a commonly used oral antiseptic [145]. Despite limited research about pomegranate's impact on plaque and salivary proteins, a study conducted on adolescents revealed that pomegranate mouthrinse significantly reduced plaque accumulation and gingivitis compared to a placebo. This finding aligns with existing literature, suggesting pomegranate extract's potential as an adjunct therapy for treating gingivitis with minimal side effects [146].

Moreover, pomegranate mouthwash has proven to be effective against periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Prevotella intermedia* [147]. Notably, pomegranate plays a role in inhibiting quorum sensing in bacteria, which is a process vital for gene expression related to antibiotic resistance and biofilm development. This pomegranate function adds an intriguing dimension to its antibacterial properties [148,149].

Orthodontic patients, who often face challenges in maintaining oral hygiene, have benefited from a hydro-alcoholic extract of pomegranate, demonstrating a substantial reduction in dental plaque bacteria compared to CHX [150]. Punicalagin has been identified as a key contributor to pomegranate's antibacterial activity [21].

Beyond its antibacterial prowess, pomegranate exhibits a positive synergistic effect with antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *S. aureus*, showcasing its potential as a complementary agent in the battle against antibiotic-resistant strains [151].

Gingivitis is characterized by chronic inflammation and early clinical manifestations such as gum bleeding [152–154]. This oral ailment leads to increased salivary albumin, cystatin C, and amylase. The enhancement of the latter is due to plasma protein leakage into the gingival crevicular fluid, thus offering a non-invasive diagnostic tool.

Clinical studies affirm pomegranate efficacy in reducing gingival bleeding and in diminishing colony-forming units (CFUs) of dental plaque organisms [155,156]. Mouthrinse containing pomegranate extract has also demonstrated effectiveness in reducing bacterial protein levels and activities related to cell injury, increasing antioxidant enzyme activity, thus highlighting its potential role in oral health maintenance [136,157].

For acute periodontitis, studies emphasize pomegranate's anti-inflammatory effects and its potential as an adjuvant treatment to conventional periodontal therapy [158]. Biochemical investigations reveal significant decreases in inflammatory markers (IL-1 β and IL-6), indicating pomegranate potentiality in managing periodontal disease [159].

Pomegranate also enhances the growth of enteric probiotic bacteria, suggesting potential benefits in decreasing the periodontal pathogen load [160]. Its antibacterial activity extends to *Helicobacter pylori*, associated with deep periodontal pockets. While its anti-viral properties may contribute to treating periodontitis triggered by viral infections [161,162].

For chronic periodontitis, pomegranate-based compounds have also proven effective. In fact, clinical studies have demonstrated the effectiveness of pomegranate extract in reducing inflammation in this chronic condition and inhibiting periodontopathogens. Moreover, it has shown its action against microbial growth, including the growth inhibition of *S. aureus* and of MRSA strains [155,163–165].

Pomegranate's applications extend even further. It has demonstrated its ability in treating recurrent aphthous stomatitis, promoting wound healing, and acting as a storage medium for avulsed teeth [166–168].

An optimal therapeutic agent for plaque control must fulfill selected criteria, including specificity for plaque bacteria, substantivity, stability, lack of adverse reactions, toxic safety,

ecological safety, and user-friendly features [169]. Pomegranate seems to align well with these criteria [12].

Research supporting pomegranate’s role in oral health is primarily limited to in vitro studies, although promising in vivo studies exist. Pomegranate rinsing reduces α -glucosidase activity and increases ceruloplasmin activity in saliva [12]. Pomegranate extract effectively treats denture stomatitis, associated with candidiasis [170]. Pomegranate tannins inhibit human salivary α -amylase, a substrate for cariogenic microbes [171,172]. Studies on periodontal therapy support the efficacy of a gel containing extracts of *Centella asiatica* and *Punica granatum* L. [159]. Pomegranate chewing seems to enhance antibacterial and antioxidant effects and boost the salivary flow rate. Pomegranate flower extract inhibits the bacterial sucrose-digesting enzyme linked to dental caries and gingivitis [173]. Antioxidant agents from pomegranate are hypothesized to have preventive effects against oral cavity diseases [174]. Pomegranate extracts reduce aspartate aminotransferase activities, suggesting benefits in periodontal pathology [175]. Hydroalcoholic extracts from pomegranate fruit significantly decrease dental plaque CFUs, offering an alternative for reducing plaque bacteria [150]. Pomegranate contributes to the maintenance of oral hygiene and reduces microorganisms cultured from dental plaque in one-minute rinses with a mouthwash containing pomegranate extract [157].

Punicic acid in PSO acts as an anti-inflammatory agent by down-regulating neutrophil activation and LPO [176,177].

Tooth decay, initiated by *Streptococcus mutans* in the oral cavity, is a prevalent chronic condition affecting children and young adults. Conventional mouthwashes, such as CHX, possess antimicrobial properties but are also associated with drawbacks, such as staining and taste alterations. A recent study explored the antibacterial potentiality of pomegranate peel and guava leaf extracts, comparing them with CHX in a group of children. The results indicate a significant reduction ($p < 0.01$) in *S. mutans* count after using pomegranate and guava leaf extracts. The beneficial effects seem to be directly correlated with the concentration of these extracts. However, the efficacy of CHX outperformed both extracts, emphasizing the need for further research on a combined antimicrobial approach [178]. In fact, CHX is the gold standard for its potent antibacterial and antiplaque properties, but its use is associated with certain side effects. Among these are xerostomia (dry mouth), hypogeusia (reduced sense of taste), and discoloration of the tongue. In particular, long-term use of CHX may lead to the development of calculus on teeth and extrinsic tooth staining. In this context, it is important to explore alternative oral care solutions with fewer associated side effects [179,180]. Among these, herbal products have been investigated, and pomegranate seems to represent one of the most effective herbal remedies. In this regard, a study aimed to evaluate the effectiveness of pomegranate mouthrinse compared to 0.12% CHX mouthrinse. In detail, this study examined the impact of these solutions on the reduction in bacterial plaque and gingivitis, among individuals aged 18–25 years. The results demonstrated the antiplaque and antigingivitis effects of both mouthrinses. In particular, pomegranate showed superior antigingivitis power, but it did not match the antiplaque effectiveness of CHX. Although pomegranate mouthrinse represents a convenient and stypctic option with acceptable plaque reduction, further clinical trials are warranted to establish its real action and its advantages over CHX [181].

Table 2. Effects of pomegranate in oral health.

Type of the Study	Study Population	Activities Exerted by Pomegranate	Natural Bioactive Compounds	Future Applications	Reference
In human study	30 patients	Robust antibacterial action against key contributors to plaque formation ↓ <i>Streptococcus sanguis</i> ↓ <i>Eikenella corrodens</i>	Flavonoids	Reduction in plaque formation	[143]

Table 2. Cont.

Type of the Study	Study Population	Activities Exerted by Pomegranate	Natural Bioactive Compounds	Future Applications	Reference
In human study	40 patients	Pomegranate mouthrinse reduced the mean plaque and gingival index scores significantly at 3, 6 and 9 months follow-up compared to placebo	Hydro alcoholic extract	Antibacterial alternative to chlorhexidine	[146]
In vitro	6 bacterial strains	↓ <i>Eikenella corrodens</i> ↓ <i>A. viscosus</i>	Hydro alcoholic extract	Antibacterial alternative to chlorhexidine	[147]
In vitro study	3 bacterial strains grown in Luria Bertani broth at 30 °C with shaking	↓ <i>Chromobacterium violaceum</i> No effects on <i>Pseudomonas aeruginosa</i>	n/a	Antibacterial alternative to chlorhexidine	[149]
In human study	60 orthodontic patients (33 females, 27 males)	↓ colony-forming units per milliliter CFU/mL by 84%	Hydroalcoholic extract	Antibacterial alternative to chlorhexidine	[150]
In human study	23 patients	The gel containing 10% Punica granatum Linn extract was not efficient in preventing supragingival dental plaque formation and gingivitis	n/a	Inhibition of plaque formation and gingivitis prevention	[152]
In human study	23 patients	↓ streptococci (23%) ↓ lactobacilli (46%)	Hydroalcoholic extract	Antibacterial alternative to chlorhexidine	[155]
In human study	20 patients	↓ bleeding ↓ gingivitis score not effective in reducing plaque scores	Hydroalcoholic extract	Anti-inflammatory effects	[156]
In human study	32 patients	↓ total protein ↓ activities of aspartate aminotransferase ↓ alpha-glucosidase activity ↑ activities of the antioxidant enzyme ceruloplasmin ↑ radical scavenging capacity	Punica granatum extract PomElla	Antibacterial alternative to chlorhexidine	[157]
In human study	40 (17 males, 23 females)	↓ plaque index ↓ gingival index ↓ papillary bleeding index	Punica granatum extract	Antibacterial alternative to chlorhexidine	[158]
In human study	15 patients	Improvement in pocket depth, attachment level and gingival index	Punica granatum extract	Antibacterial alternative to chlorhexidine	[159]

Table 2. Cont.

Type of the Study	Study Population	Activities Exerted by Pomegranate	Natural Bioactive Compounds	Future Applications	Reference
In vitro study	Fecal samples	OMx exposure enhanced the growth of total bacteria, <i>Bifidobacterium</i> spp. and <i>Lactobacillus</i> spp., without influencing the <i>Clostridium coccoides</i> – <i>Eubacterium rectale</i> group and the <i>C. histolyticum</i> group	– Punicalgin – Polyphenols	Antibacterial affects	[160]
In animal study	40 dogs	↓ gingival bleeding index	n/a	Reduce dental deposit accumulation in dogs and improve gingival health	[164]
In human study	55 patients	Reducing gingival bleeding in periodontal disease, suggesting that both extracts have anti-inflammatory and antimicrobial actions similar to those of the chlorhexidine 0.12%	Punica granatum extract	Antibacterial alternative to chlorhexidine	[165]
In human study	40 patients	↓ mean time of pain elimination ↓ mean duration of complete healing	Punica granatum gel	Antibacterial and enhancer of healing processes	[166]
In animal study	Rats	↓ mean duration of complete healing	Methanolic extract of Punica granatum	Antibacterial and enhancer of healing processes	[167]
In vitro study	PDL fibroblasts	The most effective solution for maintaining PDL	n/a	Suitable transport medium for avulsed teeth	[168]
In human study	60 patients	Mycologic exam (<i>Candida</i>) after treatment	Punica granatum gel	Topical antifungal agent for the treatment of candidosis associated with denture stomatitis	[170]
In vitro study	n/a	Effective inhibitor of human salivary α -amylase as acarbose and indicate a higher stability for the enzyme–inhibitor complex than ESI	Tannins	Inhibitor of human salivary α -amylase (substrate for cariogenic microbes)	[171]
In animal study	Rats	↓ plasma glucose levels in non-fasted Zucker diabetic fatty rats	n/a	Punica granatum Linn	[173]
In vitro study	TNF α -induced neutrophil priming	Punicic acid exerts a potent anti-inflammatory effect through inhibition of TNF α -induced priming of NADPH oxidase	Punicic acid	Anti-inflammatory effect	[176]

Table 2. Cont.

Type of the Study	Study Population	Activities Exerted by Pomegranate	Natural Bioactive Compounds	Future Applications	Reference
In vitro and in animal study	Male ICR mice	Hydrolysable tannins inhibited NO production and iNOS expression in RAW 264.7 cells	– Punicalagin – Punicalin – Strictinin a – Granatin b	Anti-inflammatory effect	[181]
In human study	100 children	↓ <i>S. mutans</i> count	Pomegranate peel extract	Antibacterial alternative to chlorhexidine	[178]
In human study	55 subjects	Subjects using <i>P. granatum</i> rinse showed significant improvement in gingival scores as compared with CHX	Punica granatum extract	Antibacterial alternative to chlorhexidine	[181]

Abbreviations: CHX, chlorhexidine; CFU, colony-forming unit; iNO, inducible nitric oxide; NADPH, nicotinamide adenine dinucleotide phosphate; TNF, tumor necrosis factor; PDL, periodontal ligament, ↑increase, ↓decrease.

7. Conclusions

In conclusion, the extensive body of research on pomegranate in internal medicine and dentistry underscores its multifaceted benefits and its potential applications in addressing both internal medicine chronic diseases and various aspects of oral health (Figure 5). For its distinct anti-inflammatory, antioxidant, anti-cancerous, and antibacterial properties, pomegranate emerges as a versatile and promising candidate in the prevention and treatment of diseases of internist relevance and in oral care regimens. However, while the existing studies provide valuable insights, the need for further extensive clinical trials and long-term assessments is evident to establish its real effectiveness, safety and its advantages over conventional treatments.

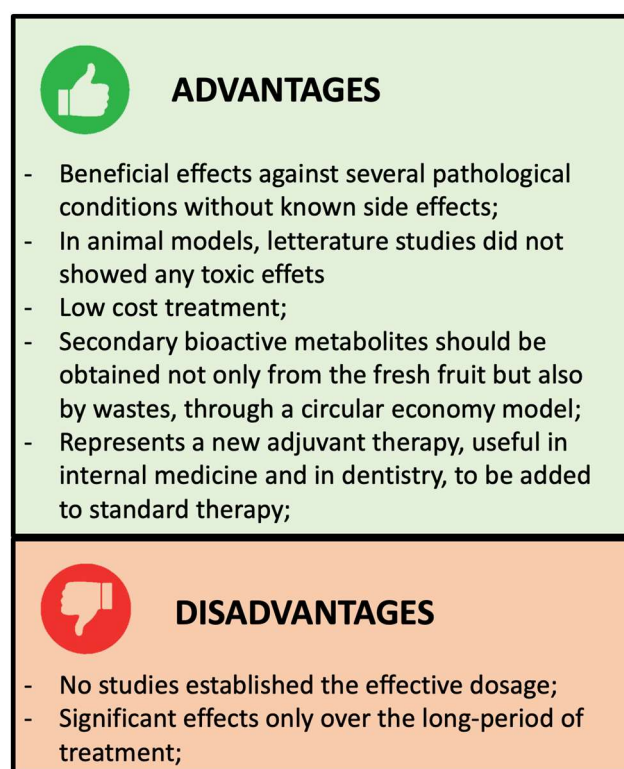


Figure 5. Advantages and disadvantages of pomegranate use.

The ongoing exploration of pomegranate in internal medicine and dentistry promises the development of innovative and natural therapeutic approaches, useful for the clinical management of several pathologies of internal relevance and oral diseases.

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Abbreviation

AH	Arterial hypertension
BACE1	Beta-site amyloid precursor protein cleaving enzyme 1
BC	Breast cancer
BRCA1	Breast cancer gene 1
CFUs	Colony-forming units
CHX	Chlorhexidine
COX	Cyclooxygenase
CRC	Colorectal cancer
CRP	C-reactive protein
EA	Ellagic acid
ER	Estrogen receptor
ESR	Erythrocyte sedimentation rate
ET	Ellagitannin
GA	Gallic acid
GC	Gastrointestinal cancers
GPX	Glutathione peroxidase
GST	Glutathione S-transferase
HDL	Low high-density lipoprotein
HHDP	Hexahydroxydiphenic acid
HOMA-IR	Homeostasis model assessment of insulin resistance
HTs	Hydrolysable tannins
IBDs	Inflammatory bowel diseases
IL	Interleukin
ISTAT	Istituto Nazionale Di Statistica
LC	Lung cancer
LC-HR-MS	Liquid chromatography-high-resolution-mass spectrometry
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDL	Low-density lipoprotein
LPO	Peroxidation
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase

MD	Mediterranean diet
MetS	Metabolic syndrome
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
mTOR	Mechanistic target of rapamycin
Munc18-1	Mammalian uncoordinated-18-1
NBCs	Natural bioactive compounds
NCI	National Cancer Institute
NF-K β	Nuclear factor kappa-light-chain enhancer of activated B cells
OFS	Oral food supplement
PC	Prostate cancer
PFE	Pomegranate fruit extract
PI3K	Phosphoinositide 3-kinases
PJ	Pomegranate juice
PLE	Pomegranate leaf extract
PPAR	Peroxisome proliferator-activated receptor
PPE	Pomegranate peel extract
PSD-95	Postsynaptic density protein-95
PSO	Pomegranate seed oil
ROS	Reactive oxygen species
SCFAs	Short-chain fatty acids
SNAP25	Synaptosomal-associated protein-25
SOD	Superoxide dismutase
T2DM	Type 2 diabetes mellitus
TGF- β	Transforming growth factor beta
TNF	Tumor necrosis factor
UHPLC-QTOF-MS	Ultra-high-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry
UPLC-QQQ-MS	Ultra-performance liquid chromatography coupled with triple quadrupole mass spectrometer
UTIs	Urinary tract infections
VEGF	Vascular endothelial growth factor

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