Review

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

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

1. Introduction

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

Although the pomegranate is 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, while now it has registered a growing trend in its consumption and this is due to the healthy properties 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

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exert significative beneficial effects on human health, allowing to strengthen the immune system and to counteract the free radicals formation, 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 up to 60%. Of the latter, the 50% is represented by mesocarp, endocarp and exocarp, while the 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 (like punicalagina) [1,7-9]. These compounds have been identified using various analytical techniques of liquid chromatography-mass spectrometry (LC-MS), like the liquid chromatography-tandem mass spectrometry (LC-MS/MS) and the liquid chromatography-high-resolution-mass spectrometry (LC-HR-MS) [10,11]. In recent years, the use of LC-HR-MS instrumentation is increased rapidly for the qualitative identification of polyphenolic compounds present in plant matrices, such as the cultivation object of this work, which is particularly rich in ellagitannins.

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. Flavonoids, notably anthocyanins in arils, contribute to the red colour 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) action [12].

This review focuses on the biological activities of the bioactive polyphenolic compounds present in pomegranate and on the possible beneficial effects of these compounds in internal medicine and dentistry.

2. Materials and Methods

The purpose of this review is to analyze the scientific articles that put in evidence the possible positive and protective role of pomegranate in internal medicine and in dentistry. A literature search was conducted using three online databases, such as PubMed, Scopus and Cochrane Library.

The search was limited to peer-reviewed journals written in the English language and the search terms were “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.

3. Bioactive Polyphenolic Compounds of Pomegranate and Their Biological Activities

Pomegranate is rich in bioactive polyphenolic compounds, which exert numerous biological activities, demonstrated by several i*n vitro* and *in vivo* studies (Figure 1).

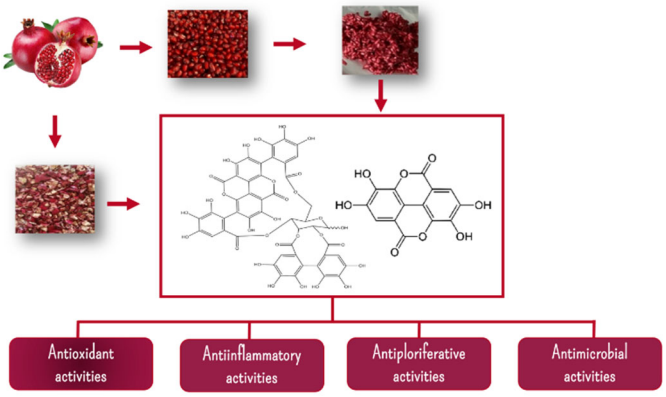

Figure 1. Biological activities of bioactive polyphenolic compounds of pomegranate.

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Among the polyphenolic classes of pomegranate, there are Ellagitannins. They belong to the subclass of hydrolysable tannins and represent one of the most diverse groups of polyphenols derived from plant matrix, as they comprise over 1,000 identified NBCs [13]. Tannins, in general, exert a function of defense for the plant against attack by pathogens and herbivores. In fact, these compounds, including ellagitannins, are found in the vacuoles and in the cytoplasm of plant cells and play an important protective role in natural growth conditions [14]. 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 ellagitannins with an open chain glucose portion), oligomers and complex tannins [15,16] but all these molecules have in common the presence in the chemical structure of at least one HHDP unit esterified in a polyol, generally glucose or quinic acid [17]. Several antimicrobial and antiviral properties are recognized in this subclass [18-21] that exert also beneficial effects in the prevention of chronic non-communicable diseases [13,18-22].

To have a complete picture of their use in the biomedical field, scientific studies have also taken into account the bioavailability of these molecules, characterized by a complex structure that does not permit their absorption from the gut microflora [23,24]. Their effect can be attributed to the fact that these compounds undergo a hydrolysis process in the digestive system, which transforms ellagitannins into smaller and less complex compounds, such as EA and urolithin, whose main effect on human health is attributable to the antioxidant and antiradical capacity. These molecules are able to counteract the action of free radicals and reactive oxygen species (ROS) [25].

The main bioactive compound present in pomegranate wastes is punicalagin [26,27], which, like the various polyphenolic compounds present in plant matrices, shows to have numerous biological and functional properties: antioxidant [20,28], antiviral [28] anti-inflammatory [29,30], antidiabetic [31], anticancer [32-34], cardio-protective [35-37] and antimicrobial [38-43].

The punicalagin is part of the subclass of ellagitannin and is the most representative compound within the pomegranate waste, in fact it represents about 70% of the total ellagitannins in the peel of the fruit. Punicalagin ($C_{48}H_{28}O_{30}$) is a water-soluble polyphenolic compound, with a high degree of hydroxylation and high molecular weight, equal to 1084.7 Da. This compound is naturally found in the forms of two α and β reversible anomers [10,44-46].

Another of the most representative compounds in pomegranate fruit is EA ($C_{14}H_6O_8$), which is a dimeric derivative of gallic acid ($C_7H_6O_5$) [47]. 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 [21]. EA is a naturally occurring bioactive polyphenolic compound that is a secondary metabolite in many plant matrices.

This compound, identified as a dilatton of hexahydroxydiphenic acid (HHDP), showed beneficial effects in *in vitro* and *in vivo* models and it is characterized by a high free radical scavenging activity, as reported by Fischer et al. [27].

In addition to the 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.

Both compounds most present in pomegranate wastes, such as punicalamine and EA, show to have an inhibitory activity of α-glucosidase [48], while another compound present in pomegranate wastes, in lower amounts, is gallic acid (GA).

Individual samples of pomegranate extracts can give different responses in tests for the evaluation of functional and biological activities and properties. This is due to the fact that these properties are related to the content of the polyphenolic compounds in the extracts, which can vary depending on the cultivars, as well as on the extraction procedures [40,49].

Furthermore, some scientific studies have compared the antioxidant activity *in vitro* on cell lines of single analytical standard of punicalagin and EA and of *Punica granatum* L. extracts. The authors demonstrated a superior bioactivity of the latter [20] and this evidence confirms, as highlighted in

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tests relative to other vegetal matrices, that the phytocomplex has a greater effectiveness, compared to the purified standard.

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

In recent years, scientific evidences have led to an increased demand for sustainable products with remarkable healthy properties, highlighting the need to recover polyphenolic compounds. The latter origin from waste matrices in order to promote the sustainability goals, through the application of circular economy principles based on "zero waste" concept. Waste materials coming 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 biological activities; among these, there are antioxidant, anti-inflammatory, antiproliferative and antimicrobial ones. 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 hydrolysable tannins as active principles for various purposes. In fact, these compounds can be used primarily as food additives, secondarily as functional foods ingredients, useful in the formulation and in the prototipation of products, bound to different markets [50-53].

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 [54].

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 a 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 phyto-complexes in the hydrolysable tannin content, extending up to the energy production (Figure 2).

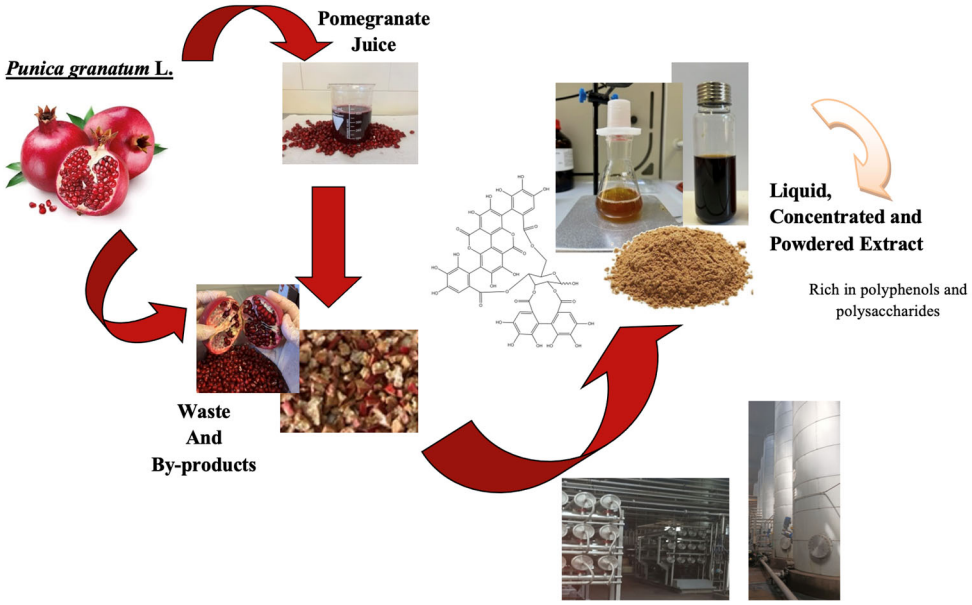

Figure 2. Circular economy model for pomegranate wastes recovery.

5. Pomegranate in Internal Medicine

The bioactive polyphenolic compounds of pomegranate are able to exert numerous beneficial properties useful in internal medicine (Figure 3).

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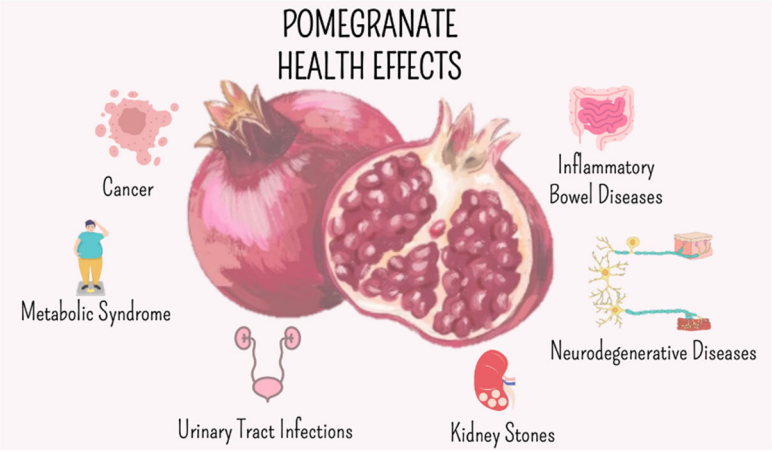

Figure 3. Beneficial effects of pomegranate in internal medicine.

5.1. Metabolic Syndrome

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) cholesterols and iv) hypertriglyceridemia. These conditions contribute to the onset of a low-grade inflammatory state and oxidative stress, typical of this syndrome [55]. The risk factors of 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 [56]. In recent years, the use of functional foods or oral food supplements, based on NBCs, has become relevant for the clinical management of MetS patients [57] and currently it represents an adjuvant therapy to be associated with traditional pharmacological treatments [55,58,59].

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 [60]. In fact, a study conducted on hypercholesterolemic mouse models nourished with feed supplemented by 15% of pomegranate seed oil (PSO), for 28 days, highlighted a decrease in the plasma levels of triglyceride, total cholesterol and low-density lipoprotein (LDL) cholesterols, 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, like LDL-cholesterol/HDL-cholesterol and cholesterol total/HDL cholesterol [61]. Moreover, in a following study, conducted on 23 MetS women, it was investigated the possible effect of the daily consumption of 300 ml of PJ, for 6 weeks, on lipid peroxidation and on phospholipid fatty acid composition of plasma and erythrocytes. The authors highlighted a significant decrease of arachidonic acid and an increase of mono-unsaturated fatty acids in the erythrocyte membrane. They also showed a decrease of lipid peroxidation, evaluated by the reduction of levels of thiobarbituric acid reactive substances in erythrocytes, in the treatment subjects compared to control group. These results suggest a potential antioxidant, anti-inflammatory and cardio-protective action of pomegranate in dyslipidemic patients [62].

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 [63]. In this context, *in vitro* studies have demonstrated the anti-diabetic effects of pomegranate extracts, exerted through the stimulation of the peroxisome proliferator-activated receptor (PPAR)-γ, a transcription factor involved in glucose metabolism. [64]. 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 also in anti-diabetic therapy [65]. To support these hypotheses, a study conducted by Hashemy et al. described the beneficial effects of the pomegranate seeds powder assumption, at the dose of 5 g, twice *per* day, for 8 weeks, in T2DM patients. At the end of the study, the treated group showed a

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signifycant reduction of fasting blood glucose and glycated hemoglobin levels, compared to control group, suggesting how pomegranate can be used to control glycaemia in diabetic patients [66].

The bioactive polyphenolic compounds of pomegranate appear to play a crucial role also in reducing the body weight and improving the body composition in overweight or obese subjects [67,68]. In fact, a study conducted on obese non-diabetic premenopausal female patients, who daily assumed 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 control group [69].

Regarding the blood pressure, pomegranate has also proven useful in counteract AH, thanks to their anti-oxidative polyphenolic compounds. To confirm this, a single-blind placebo controlled randomized study, conducted on 60 T2DM patients, who have assumed 200 ml/day of PJ, for 6 weeks, highlighted a significant reduction in systolic and diastolic blood pressure, compared to control group [70].

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 oral food supplement (OFS) based on pomegranate, on inflammatory and oxidative stress biomarkers in overweight and obese individuals. In particular, 40 obese and overweight subjects have assumed 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 the total cholesterol, glucose and insulin serum levels. This might suggest that pomegranate OFS may reduce those complications related to obesity, like low-grade chronic systemic inflammation [71].

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" [72]. Cancer was conceptualized as a disease of genetic origin, however the research, over the last several decades, has established how environmental factors with epigenetic effects play a pivotal role in the phenomenon of carcinogenesis [73]. These environmental factors, capable of altering the spatial conformation of chromatin to regulate gene expression, include unhealthy nutrition, chemicals and industrial pollutants and poor lifestyle [74] (such as smoking, alcohol consumption and physical inactivity) [75]. However, while an unbalance diet, such as the Western Diet, increases the risk of cancer onset, on the other hand a balance diet, rich in fruit and vegetables, such as the Mediterranean Diet (MD), is an important factor in cancer prevention [76,77]. MD, thanks to the ability to guarantee a wide variety of micronutrients and other NBCs, is able to counteract the cancer [78,79]. Among NBCs are certainly included polyphenolic molecules, of which the pomegranate is rich. These molecules are capable to exert chemo-preventive and chemotherapeutic effects through their antioxidant, anti-radical and anti-inflammatory activities and through anti-mutagenic and anti-proliferative properties. The latter include the induction of apoptosis in cancer cells, the stimulation of the immune system [80,81], 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) [82].

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 [83]. Many exogenous and endogenous risk factors could affect the onset and development of BC [84]. Among exogenous factors include early menarche, nulliparity, oral contraceptive use, never having or short duration of breast feeding, use of hormone replacement therapy, circadian disruption and unhealthy lifestyle (including smoking, alcohol consumption, imbalanced diet, *etc*). Endogenous risk factors, namely

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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 to counteract the breast cancer carcinogenesis would be to modify the lifestyle and the nutritional choices, in order to guarantee a proper prevention for this type of cancer. Several *in vitro* studies have highlighted how pomegranate by-products, namely pomegranate fruit extract (PFE), PJ and PSO, are able to take part in the process of breast carcinogenesis, exhibiting the following effects: (i) the anti-proliferative, anti-aromatase and anti-estrogenic activities [85]; (ii) the regulation of the transforming growth factor beta (TGF-ß)/Smads pathway [86]; (iii) the anti-inflammatory effects, through the reduction of pro-inflammatory cytokines and chemokines; (iv) the reduction of vascular endothelial growth factor (VEGF) levels [87]; (v) the downregulation of the expression of the genes, involved in the damage of DNA and the estrogen-responsive genes [88]; (vi) and the disruption of ER and Wnt/ß-catenin signaling pathways [89].

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 [90]. 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 radiations, occupational exposures (such as asbestos and indoor air pollution) [91]. 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, to repair DNA from the oxidative damage, to inhibit tumor cell proliferation and to induce tumor cell apoptosis, caused by smoking [92]. 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) have potential anti-proliferative, antimigratory [93] and anti-metastasis properties against the lung carcinoma, while pomegranate peel extract (PPE), PJ and PSO, tested both *in vitro* and *in vivo* studies, have shown strong anti-inflammatory activities, reducing the proinflammatory cytokine levels (IL-1β and IL-6), and strong antioxidant properties inactivating cellular oxygen radicals in the lungs [94]. 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 the inhibition of several signaling pathways against lung cancerous cells, including NF-κB expression, MAPK phosphorylation, PI3K and mTOR pathway activity and Akt phosphorylation, leading to reduced cell proliferation and angiogenesis in lungs [95,96].

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, genetic and environment, including a diet rich in meat and fats and poor in fibers, folate and calcium, a sedentary lifestyle, obesity, high alcohol intake, smoking, *etc*. [97]. It is well known through several clinical studies how a highly rich fibers diet based on computation of plant-based foods, such as fruits and vegetables, is a protective factor, associated with a decrease in CRC incidence [98]. Dietary fiber is composed by 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 [99]. It has been shown that the latter may have anti-neoplastic properties in colon, modulating the immune response, thereby resulting in protection against CRC [100]. Moreover, the production of the SCFAs reduces the colonic pH, preventing the conversion of bile acid metabolites into more toxic forms [101].

As well as being rich in vitamins, such as vitamin A, E, C, B1 and B2, minerals and phytochemicals, namely polyphenolic compounds, the pomegranate micronized peel is a rich

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reservoir of dietary fiber. Thereby, it represents a byproduct useful in the CRC prevention, thanks to its remarkable bioactivity [102]. It is also worth emphasizing how gut microbiota plays a crucial role in the polyphenols catabolism. Indeed, when colon bacteria degrade dietary fiber, the ellagitannins, obtained from pomegranate, are hydrolyzed to form EA and are transformed into urolithin by gut microbiota. Thus, these compounds exert their action in the prevention of CRC carcinogenesis, by remodeling gut microbiota [103]. Furthermore, the consumption of PJ is capable to release ellagitannins and urolithins in the colon, potentially reducing the risk of CRC development, by inhibiting cell proliferation and inducing apoptosis [104]. 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-2 (COX-2) expression [22,105]. The activity of this enzyme is increased in many cancers, such as CRC [106]. Moreover, PJ suppresses the Akt activation, needed for NF-κB DNA binding. Finally, several *in vitro* studies have emphasized the PJ anti-proliferative and pro-apoptotic effects against CRC cells [22]. As regards the PSO, *in vivo* studies have shown how its consumption is significantly correlated with the inhibition of the colon tumorigenesis, due to the up-regulation of the PPARγ protein expression in the rats colon [107].

5.2.4. Pomegranate and Prostate Cancer

PC is the second most common form of cancer in men [108]. Non-modifiable risk factors for PC include age, the genetic predisposition and the ethnicity, while modifiable risk factors include environmental factors, such as obesity, smoking, low physical exercise and unhealthy diet that play a pivotal role in the initiation, in the promotion and in the progression of PC. In fact, several studies have highlighted how an excessive intake of sutured fats from dairy products and ultraprocessed meat is associated with an increased risk of PC [109,110]. As for other types of cancer, a considerable amount of *in vitro* and *in vivo* studies has shown how PJ and PE possess anti-proliferative, proapoptotic and anti-metastatic actions, decreasing the levels of pro-inflammatory cytokines and chemokines and inhibiting the angiogenesis through the reduction of VEGF levels [111]. Moreover, these compounds are capable to act on the canonical signaling pathways, namely NF-kB and PI3K/Akt/mTOR in human PC cell lines and/or in mouse PC tumor models [112,113]. Moreover, the possible chemopreventive and chemotherapeutic effects exhibited by the ellagitannins contained in PJ and PE against PC, have also been found, both *in vivo* and *in vitro* studies. These studies demonstrated a reduction in the expression of androgen genes, that play a crucial role in the PC cell growth and progression [114]. Several studies have highlighted the association of PC and gut microbiota dysbiosis, suggesting that the latter might be involved in not only gastrointestinal cancers (GC) but also in PC. In fact, it could exist a "microbiota-gut-prostate axis" so that the pro-inflammatory cytokines and the pathogen bacteria of the gut microbiota enter in the systemic circulation, thanks to the increased permeability of the gastrointestinal tract barrier and to 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 [115]. Different *in vivo* studies have focused the attention on how PPE reshapes the gut microbiota thanks to its countless properties, exert by phytochemicals compounds contained therein, and thus costituting a possible adjuvant therapy for PC [116].

5.3. Urinary Tract Infections

Pomegranate exerts antimicrobial effects against the main pathogens that cause urinary tract infections (UTIs) [117]. 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 starting from wastes of the pomegranate supply chain [118]. 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 a strong antibacterial activity against *Escherichia coli* [119]. Among the numerous phytochemical compounds of pomegranate, those that have shown the highest antimicrobial activity

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are the EA and the hydrolyzable tannins, such as punicalagin. In most studies, their combination showed the greatest benefits [118].

5.4. Nephrolithiasis

Numerous studies have highlighted a direct correlation between oxidative stress and nephrolithiasis, although the mechanism underlying the increased kidney stones development in presence of oxidative stress hasn't been well defined yet [120]. 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 [121]. 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 [122]. Subsequently, Tracy et al. have developed a clinical trial conducted on patients suffering from recurrent kidney stones, who had been administered a pomegranate polyphenolic extract, at a concentration of 1,000 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 the calcium oxalate saturation levels reduction [121]. Although these results are promising, they would be further investigated to confirm the beneficial role of pomegranate against nephrolithiasis, because the data to support this thesis are not sufficient, currently.

5.5. Inflammatory Bowel Diseases

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 [123]. Numerous scientific evidences highlight how a diet rich in polyphenols seems to play a key role in mitigating the chronic inflammation, underlying IBDs [124]. A study conducted on murine models evaluated the effect of a treatment with PJ, containing ellagitannins and EA, in mice with colitis and colon ulceration, emphasizing how PJ is able to reduce the expression of pro-inflammatory cytokines, like tumor necrosis factor (TNF)-α and IL-1β 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 [124].

IBDs are characterized by the inflammation of the colon mucosa, accompanied by the infiltration of inflammatory cells, including neutrophils, which represent the defense first line of the immune system and which produce a series of inflammatory molecules [125]. A randomized controlled trial, conducted on a group of IBDs patients, with a high rate of relapses, evaluated the effects of supplementation with PJ, rich in ellagitannins, in 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, 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 [126].

Furthermore, in this context, it has been demonstrated that the pomegranate peel polyphenols appear to be able to reduce 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 IBDs treatment [127].

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 of colon ulcerations and through the reduction of the inflammatory profile [128].

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5.6. Neurodegenerative Diseases

PJ would seem able to attenuate the neuro-inflammation suggesting that this fruit can be useful in counteracting the onset and the symptoms of age-associated neurodegenerative pathologies, such as Alzheimer's and Parkinson's diseases [128]. Pomegranate polyphenolic compounds reduce the neuro-inflammation by several mechanisms, which include: (i) the inhibition of NF-κB, a transcription factor involved in the inflammatory process [129]; (ii) the reduction of the pro-inflammatory cytokines, such as IL-2, IL-6, IL-1β and TNF-α [130]; (iii) the reduction of 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 of COX-2 activity [131]; (v) the reduction of the catalytic activity of caspases [132].

Pomegranate polyphenols seem able to improve the 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 a protective role of pomegranate against the proteins that improve the synaptic structure, such as synaptophysin, PSD-95, Munc18-1 and SNAP25 [133].

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 the reduction of lipid peroxidation (LPO) and carbonyl levels and the restoration of the antioxidant enzymes activities, like glutathione peroxidase, superoxide dismutase (SOD) and glutathione S-transferase (GST) [134].

Although clinical studies on humans are lacking, *in vitro* and on 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 [135].

6. Pomegranate and Oral Health

Pomegranate has garnered a 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 to promote oral health.

Dental plaque, a biofilm of bacteria that forms on tooth surfaces, is a primary contributor to oral health problems. Pomegranate has been studied extensively for its ability to counteract the dental plaque formation. The flavonoids present in pomegranate demonstrated a robust antibacterial action against key contributors to the plaque formation, including *Streptococcus sanguis* and *Eikenella corrodens* [136,137]. Its antibacterial effect is attributed to tannins, compounds that enhance bacteriolysis and impair the 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 [138]. Despite limited research about pomegranate's impact on plaque and on 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 potentiality as an adjunct therapy for treating gingivitis with minimal side effects [139].

Moreover, pomegranate mouthwash has proven to be effective against periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis* and *Prevotella intermedia* [140]. Notably, pomegranate's role in inhibiting quorum sensing in bacteria, a process vital for gene expression related to antibiotic resistance and to biofilm development. This pomegranate function adds an intriguing dimension to its antibacterial properties [141,142].

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 [143]. The ellagitannin punicalagin has been identified as a key contributor to pomegranate's antibacterial activity [20].

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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 potentiality as a complementary agent in the battle against antibiotic-resistant strains [144].

Gingivitis is characterized by chronic inflammation and early clinical manifestations like gum bleeding [145-147]. 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 [148,149]. Mouthrinse containing pomegranate extract has also demonstrated effective in reducing bacterial protein levels and activities related to cell injury, increasing the antioxidant enzymes activity, thus highlighting its potential role in oral health maintenance [118,150].

For periodontitis, studies emphasize pomegranate's anti-inflammatory effects and its potentiality as adjuvant treatment to the conventional periodontal therapy [151]. Biochemical investigations reveal significant decreases in inflammatory markers (IL-1β and IL-6), indicating pomegranate potentiality in managing periodontal disease [152].

Pomegranate also enhances the growth of enteric probiotic bacteria, suggesting potential benefits in decreasing the periodontal pathogen load [153]. Its antibacterial activity extends to *Helicobacter pylori*, associated with deep periodontal pockets. While, its anti-viral properties may contribute to treat the periodontitis triggered by viral infections [154,155].

For chronic periodontitis, pomegranate-based compounds have also proven effective. In fact, clinical studies have demonstrated the effectiveness of pomegranate extract in reducing the inflammation in this chronic condition, inhibiting the periodontopathogens. Moreover, it has shown its action against microbial growth, including the growth inhibition of *S. aureus* and of MRSA strains [148,156-158].

Pomegranate's applications extend even further. It has demonstrated the ability in treating recurrent aphthous stomatitis, promoting wound healing and acting as a medium storage for avulsed teeth [159-161]. Its several applications grant pomegranate to become a promising candidate for various oral health issues.

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 [162]. Pomegranate seems to well align 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 [163]. Pomegranate tannins inhibit human salivary α-amylase, a substrate for cariogenic microbes [164,165]. Studies on periodontal therapy support the efficacy of a gel containing extracts of *Centella asiatica* and *Punica granatum* [152]. Chewing pomegranate seems to enhance antibacterial and antioxidant effects and to boost salivary flow rate. Pomegranate flower extract inhibits the bacterial sucrose-digesting enzyme linked to dental caries and gingivitis [166]. Antioxidant agents from pomegranate are hypothesized to have preventive effects against oral cavity diseases [167]. Pomegranate extracts reduce aspartate aminotransferase activities, suggesting benefits in periodontal pathology [168]. Hydroalcoholic extracts from pomegranate fruit significantly decrease dental plaque CFUs, offering an alternative for reducing plaque bacteria [143]. Pomegranate contributes to the maintaining of the oral hygiene and reduces microorganisms cultured from dental plaque in one-minute rinses with a mouthwash containing pomegranate extract [150].

Punicic acid in PSO acts as an anti-inflammatory agent by down-regulating neutrophil activation and LPO [169,170].

Tooth decay, initiated by *Streptococcus mutans* in the oral cavity, is a prevalent chronic condition, affecting children and young adults. Conventional mouthwashes, like CHX, possess antimicrobial

properties but are also associated with drawbacks, such as staining and taste alterations. A recent study explores the antibacterial potentiality of pomegranate peel and guava leaves 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 leaves 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 combined antimicrobial approach [171]. 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, 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 contest, it is important to explore alternative oral care solutions with fewer associated side effects [172,173]. Among these, herbal products have been investigated, where the pomegranate seems to represent one of the most effective herbal remedies. At this regard, a study aimed to evaluate the ability of pomegranate mouthrinse compared to 0.12% CHX mouthrinse. In detail, this study examined the impact of these solutions on the reduction of bacterial plaque and the gingivitis, among individuals aged 18–25 years. The results demonstrated antiplaque and antigingivitis effects of both mouthrinses. In particular, pomegranate showed a superior antigingivitis power, but it did not match the antiplaque effectiveness of CHX. Although pomegranate mouthrinse represents a convenient and styptic option with acceptable plaque reduction, further clinical trials are warranted to establish its real action and its advantages over CHX, the current gold standard for the plaque control [174].

7. Conclusions

In conclusion, the extensive body of research on pomegranate in internal medicine and in dentistry, underscores its multifaceted benefits and its potential applications in addressing both for internal medicine chronic diseases and for various oral health concerns. From its robust anti-inflammatory, antioxidant, anti-cancerous and antibacterial properties, pomegranate emerges as a versatile and promising candidate in the prevention and in the treatment of diseases of internist relevance and in the 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. The ongoing exploration about pomegranate in internal medicine and in dentistry promises for the development of innovative and natural solutions, useful for the clinical management of several internal medical pathological conditions and of oral diseases.

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