Healthy properties of proanthocyanidins

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Abstract.

Proanthocyanidins, also named condensed tannins, are the result of flavanols condensation. Oligomers and polymers of proanthocyanidins can widely be found in the plant kingdom, as in fruits and berries, seeds, flowers, and leafs. They have a putative role as antioxidants, and they affect the inflammatory process via calcium-dependent release of nitric oxide and protect against H_2O_2-induced lipid peroxidation. They also demonstrated a role in cardiovascular diseases via vessel relaxation and LDL oxidation inhibition. These condensed tannins have also shown activities that improve diabetic complications, such as neuropathy, retinopathy, or nephropathy, including a decrease in serum glucose and advanced glycation end products. Furthermore, proanthocyanidins have evidenced anticancer properties by mitigating tumor development through induction of apoptosis or inhibition of cell proliferation. Finally, they are able to produce antiadhesive actions against bacteria in urinary and dental infections, including *Escherichia coli* and *Streptococcus mutans*. Hence, proanthocyanidins are considered as beneficial molecules in preventing or treating many diseases and pathological conditions. Therefore, finding out more about condensed tannins bioavailability, and understanding the regulatory genes and pathways involved in their effects should be aimed in future research.

1. Introduction

Phenolic compounds have recently attracted much attention in relation to its health benefits [1]. They are known as the most abundant natural antioxidants and provide protection against different diseases such as diabetes, cancer, or stroke [2]. Phenolics are a diverse group of compounds characterized by the presence of at least one aromatic ring with one or more hydroxyl groups in addition to other substituents [3].

Flavonoids, which are being studied due to their medicinal properties, especially their antioxidant activity, are the most common group of polyphenolic compounds in the human diet [4]. Thus, the consumption of flavonoid-rich foods, in particular fruits and vegetables, is associated with a lower incidence of heart disease, ischemic stroke, cancer, and other chronic diseases [5]. All plant flavonoids (both flavonols and flavanols) share a common 15-carbon structural backbone designated as C6–C3–C6, with two aromatic rings connected by a three-carbon bridge [3]. Differences in the structure of the heterocyclic C ring result in distinct classes of flavonoids, including flavanols, flavanones, flavones, isoflavonols, and anthocyanidins [3].

Flavanols (or flavan-3-ols) have a saturated C3 element in the heterocyclic C ring and, unlike flavonols, isoflavones or anthocyanidins are nonplanar molecules [3]. They can exist as monomers, such as catechin, epicatechin, gallocatechin, and epigallocatechin or in oligomeric and polymeric forms referred to as proanthocyanidins [3,6]. These flavanol-based oligomers/polymers were discovered in the late 1940s by French researcher Jacques Masquelier, who first developed techniques for their extraction [7]. He named them vitamin P but, nowadays, they are known as proanthocyanidins or condensed tannins. These molecules consist of a group of polyhydroxy-flavan-3-ol (or flavanol) oligomers and polymers (up to 50 units) linked by carbon–carbon bonds from the four position of one flavanol subunit to the eight position (C4–C8) of another and to a lesser extent through a C4–C6 linkage [2,8]. In the studies by Gu et al., the degree of polymerization (DP) of these molecules was determined in selected foods and a large variation in the average DP was observed [9,10]. In black currants, for example, the average DP was 47.9 ± 5.1, whereas it was only 7.3 ± 0.2 and 2.1 ± 0.0 in wine and beer, respectively [10]. Of the estimated total daily intake of proanthocyanidins, about 73% had a DP > 3.
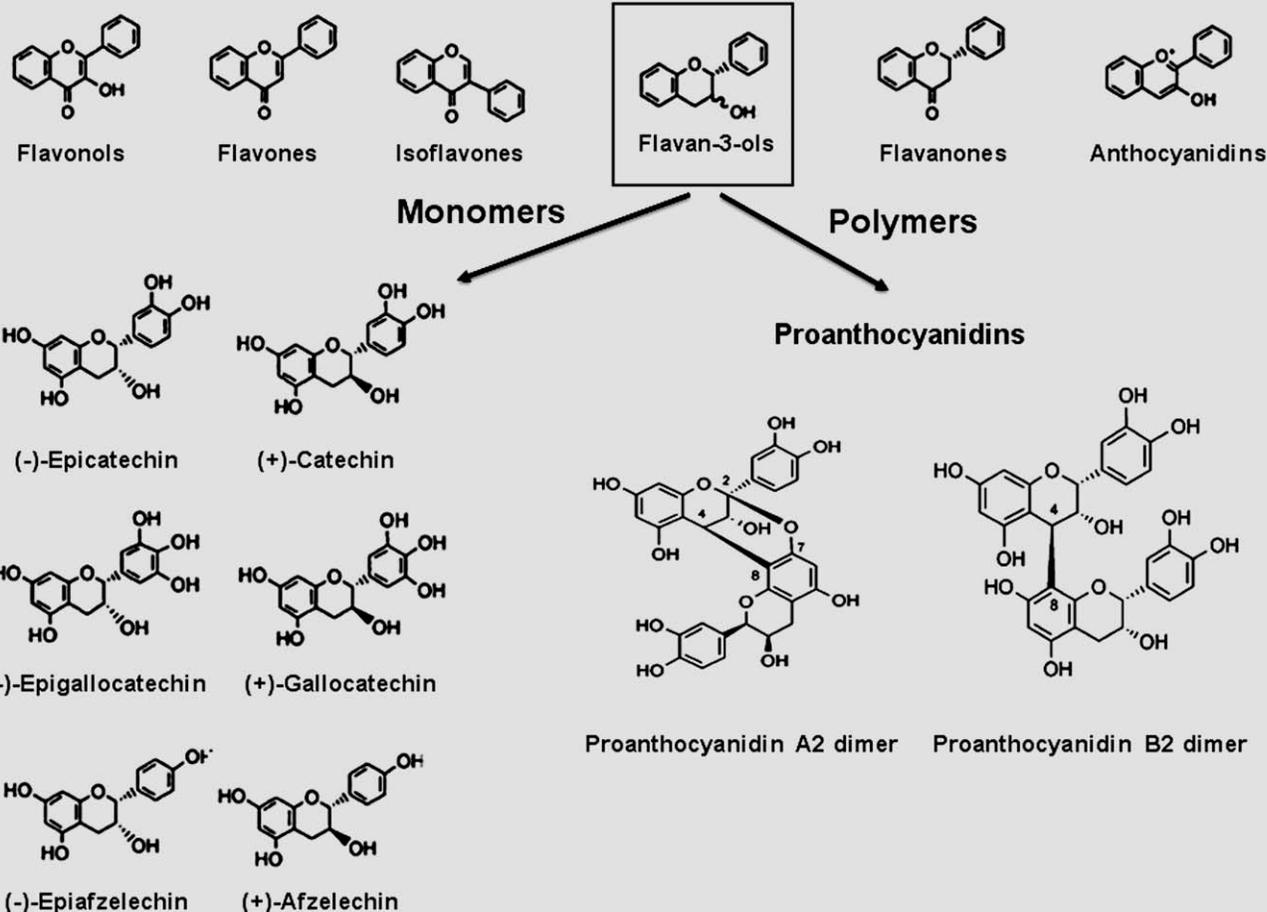
Fig. 1. Classification of flavonoids.

There are two kinds of flavanol-based oligomers: type B proanthocyanidins, which are formed from (+)-catechin and (−)-epicatechin with oxidative coupling occurring between the C4 of the heterocycle and the C6 or C8 positions of the adjacent unit, whereas type A have an additional ether bond between C2 and C7 [2]. Proanthocyanidins that consist exclusively of (epi)catechin units are called procyanidins and are the most abundant type in plants. On the other hand, the less common proanthocyanidins, containing (−)-epiafzelechin and (+)-afzelechin or (epi)gallocatechin subunits, are called propelargonidins and prodelphinidins, respectively [2] (Fig. 1).

Oligomers and polymers of proanthocyanidins can widely be found in the plant kingdom, especially in fruits and berries (persimmon, acerola, apple, cranberry, blueberry, and black raspberry), nuts (almond), seeds (grape seed, *Antidesma thwaitesianum* seed, *Oenothera* seed, cocoa beans), trees (maritime pine, *Croton palanostigma, Croton celtidifolius*), flowers (longan flower), tubers (onion), leafs (green tea, parsley), or legumes (pea, Jamapa bean) [9–17]. Apples (32%), chocolate (17.9%), and grapes (17.8%) were found to be the major contributors to the proanthocyanidin intake in the USA [10].

With regards to proanthocyanidins bioavailability, the number of studies concerning this aspect is still scarce, since the interest in the health benefit of these complex molecules is recent and bioavailability assays are not easy [18]. Latest studies suggest that only the low-molecular-weight oligomers (DP $\leq$ 3) are absorbed intact in the gastrointestinal tract. There is evidence in support of absorption of monomeric catechins and proanthocyanidins up to trimers through the human intestinal caco-2 epithelial cells [19,20], and some studies confirm that (epi)catechins appear in urine and plasma mainly as glucuronidated, methylated, and sulfated metabolites after the ingestion of diet containing monomeric catechins and proanthocyanidins up to trimers [21–25]. However, the permeability of a proanthocyanidin polymer with a mean DP of 6 was 10 times lower suggesting that only the monomers, dimers, and trimers are easily absorbed [19]. Concerning the absorption site, several studies emphasize that the majority of the dietary proanthocyanidins are remarkably stable in the stomach environment

and pass unaltered through the small intestine, suggesting that they are degraded into small phenolic acids by the colonic microflora in the cecum and large intestine [6,26–28]. Furthermore, it is reported that only proanthocyanidins with DP $\leq$ 2 result in the production of significant amounts of phenolic acid metabolites in the gut [29]. Therefore, despite their high abundance in our diet, proanthocyanidins are poorly absorbed. It is suggested that, except the low-molecular-weight oligomers and the phenolic acids produced by their microbial degradation, proanthocyanidins may mainly exert local effects in the gastrointestinal tract [30].

Concerning target tissues of these molecules, a series of *in vivo* studies have investigated the bioavailability of grape seed proanthocyanidins to multiple organs, including liver, kidney, heart, spleen, and the brain [25,31–35]. However, more quantitative studies are needed to assess absorption, metabolism, and excretion of proanthocyanidins as there is still no clear consensus among studies [18].

2. Antioxidant and anti-inflammatory properties of proanthocyanidins

Oxidative stress is caused by an imbalance between antioxidant and pro-oxidant systems and has been associated to some pathologies and metabolic disturbances such as aging, cancer, cardiovascular diseases, diabetes, obesity, cataracts, and neurodegenerative diseases (Alzheimer, Parkinson) [36–38].

The defence system in humans has been connected to the levels of dietary antioxidants intake [39]. Polyphenols are powerful antioxidants, being able to scavenge or quench a wide range of free radical species and to inhibit their formation [40,41]. Among them, we can find proanthocyanidins, which have been reported to exhibit a broad spectrum of biological and pharmacological activities against free radicals formation and oxidative stress [42].

Thus, oligomeric-condensed tannin-enriched fractions from red wine are reported to act directly on endothelial cells causing calcium-dependent release of nitric oxide (NO) [43]. In 2007, Ho et al. reported that a fraction of longan flower extract rich in olygomers of proanthocyanidins had potent antioxidative and anti-inflammatory activities via NO [44]. Moreover, a reduction of reactive oxygen species generation and elevation of the reduced glutathione/oxidized glutathione ratio were observed in groups of rats that were administered proanthocyanidins [45]. A year later, Lee et al. (2008) used an aging model of H_2O_2-induced cellular senescence to investigate the protective potential of proanthocyanidins from persimmon peel against oxidative damage in the nucleus of normal human lung diploid fibroblasts and concluded that proanthocyanidins would modulate oxidative DNA damage under H_2O_2-induced cellular senescence [12].

Furthermore, a proanthocyanidin-rich fraction, derived from Jamapa bean methanolic extract, evidenced an antiradical capacity according to Aparicio-Fernández et al. (2008) [16] and other researchers reported that *A. thwaitesianum* seeds and marcs, rich in proanthocyanidins, exhibited antioxidant activity and had the ability to protect against H_2O_2- induced lipid peroxidation assays [46]. This proanthocyanidin antioxidant activity has also been reported by other articles [16,47].

3. Proanthocyanidins cardiovascular effect

Prevalence of cardiovascular diseases is one of the most important problems of the world and is rising every year [40]. In fact, as of 2007, it is the leading cause of death in the United States [48,49], England, Canada, and Wales [50]. The causes, prevention, and/or treatment of all forms of this disease are active fields of biomedical research. In this context, heart attacks and strokes are mainly caused by a blockage that prevents blood from flowing to the heart or the brain [51]. Proanthocyanidins have demonstrated a preventing role in cardiovascular diseases via activities against vessel constriction and inhibiting LDL oxidation [47,52–55].

In rat mesenteric arterial bed and in isolated mesenteric artery, both precontracted with phenylephrine, proanthocyanidin-rich fraction obtained from *C. celtidifolius* barks induced a concentration-dependent relaxation [52]. This finding can lead to future treatments with proanthocyanidin extracts to reduce blood pressure in patients with hypertension.

It has also been described excellent antioxidant activities in inhibiting or increasing the lag time of human LDL oxidation by proanthocyanidins from cranberry fractions and longan flowers [47,53–55].

Finally, it has been reported that proanthocyanidins play a role in the stabilization of collagen and maintenance of elastin, two key proteins in connective tissue that support organs, joints, muscle, and blood vessels [56]. Proanthocyanidins develop an inhibitory action on collagenase, elastase, hyaluronidase, and beta-glucuronidase that can be involved in the protective cardiovascular effect of proanthocyanidins.

4. Proanthocyanidins benefits on diabetic complications

Type 2 diabetes is associated to glucotoxicity and lipotoxicity caused by hyperglycemia and hyperlipidemia and leading to a chronic oxidative stress [57–59]. Chronic hyperglycemia also participates in the development of diabetic complications such as atherosclerosis, cardiac dysfunction, nephropathy, and retinopathy [57,60,61]. Thus, the direct interaction of glycation end products with their specific cell-surface receptors (RAGE) may play a key role in the development of cardiovascular diseases [62], as it has been implicated in the pathogenesis of diabetic vascular complications via an induction of reactive oxygen species and subsequent alteration of many gene expressions [63]. There are several articles that show the positive role of proanthocyanidins in type 2 diabetes [47,63–66].

Thus, Zhang et al. (2007) found that grape seed proanthocyanidin extract markedly downregulated RAGE expression. Interestingly, these effects have been corroborated in different subsequent studies [63].

The elevation of lipid peroxidation in the kidney and serum under the diabetic condition was decreased by the administration of proanthocyanidins in diabetic rats [45]. These investigations demonstrated that proanthocyanidins affected the inflammatory process via regulation of related protein expression, inducible NO synthase (iNOS), cyclooxygenase-2, and upstream regulators, nuclear factor κB, and inhibitor-binding protein κB-α. Proanthocyanidins also decreased serum glucose, glycosylated protein, serum urea nitrogen, urinary protein, and renal advanced glycation end products [45].

The effects of proanthocyanidins preparations from persimmon on hyperlipidemia, hyperglycemia, and oxidative stress in a mouse model of type 2 diabetes were also investigated concluding that these polyphenolic compounds improve the high blood sugar status, the oxidative stress, and, specially, the hyperlipidemia [13].

The effects of a grape seed proanthocyanidin extract in nephropathy and retinopathy were observed in diabetic rats [64,65], where body weight, advanced glycation end products [64,65], blood urea nitrogen, and creatinine were significantly reduced [64] but not fasting blood glucose and glycosylated hemoglobin [64,65]. This extract also significantly suppressed the glomerular hypertrophy and decreased interstitial fibrosis [64], repressed vascular lesions of central regions, and decreased angiogenesis [65]. Furthermore, in the kidney of diabetic rats, it was found that 25 proteins were significantly changed in comparison to normal; among them, nine proteins were backregulated to normal level after the proanthocyanidin extract treatment [64]. On the other hand, seven of the 18 proteins, which were found either up or downregulated in the retina of STZ-induced diabetic rats, were found backregulated to normal levels after the extract therapy [65]. Finally, complex I was found to be upregulated in the kidney of diabetic rats and backregulated to normal after the proanthocyanidin extract administration [64].

Furthermore, in a study by Cui et al. (2008), the grape seed proanthocyanidin extract showed significant protection in diabetic neuropathy. This extract could apparently improve the mechanical allodynia and the sciatic-tibial nerve conductive velocity and alleviate nerve impairment of diabetic rats without affecting the body weights or plasma glucose levels [66].

Finally, treatment of insulin-resistant rats with a proanthocyanidin-rich extract from longan flower, decreased the systolic blood pressure, and enhanced the expression of insulin signaling pathway-related proteins, including insulin receptor substrate-1 and glucose transporter 4 [47].

5. Proanthocyanidins anticancer properties

Proanthocyanidins have evidenced some neoplasic disease prevention properties by exhibiting cytotoxicity against many types of tumors, including colon, breast, and prostate cancers [17,67]. There are also several studies concerning cranberry extracts with putative anticancer activities, such as apoptosis and inhibition of proliferation that implicate the proanthocyanidins as major contributors [67–70].

The biosynthesis and metabolism of polyamines (spermidine and spermine) involved in cell proliferation is controlled by enzymes such as ornithine decarboxylase, whose activity can be affected by dietary polyphenols, as has been reported for grape seed and cranberry proanthocyanidins [70,71]. Thus, a cranberry proanthocyanidin fraction appears to selectively inhibit the proliferation of H460 human large cell lung carcinoma, HT-29 colon adenocarcinoma, and K562 chronic myelogenous leukemia cells in vitro. Moreover, the number of new tumor colonies decreased in HT-29 and HCT-116 colon tumor cell lines in a dose-dependent manner, when treated with a cranberry proanthocyanidin fraction prepared from Early Black variety cranberry fruit [72].

5.1. Effect of proanthocyanidins on apoptosis and cell proliferation

Apoptosis plays a major role in establishing a natural balance between cell death and cell renewal by destroying excess, damaged, or abnormal cells [6]. Aparicio-Fernández et al. showed that Jamapa bean methanolic extract, which consisted of a mixture of anthocyanins, proanthocyanidins, and flavonols, inhibited the proliferation of HeLa cells by increasing DNA molecule breakage (as cytometry analysis showed) and apoptosis. In this study, western blot analysis revealed an increment in the expression of Bax and caspase-3 proteins [73]. Caspase-3 is required for DNA fragmentation and some of the typical morphological changes of cells undergoing apoptosis [74], whereas Bax is a proapoptotic member of the Bcl-2 protein family that resides in the outer mitochondrial membrane [32].

5.2. Oral cancer

Proanthocyanidins exhibit chemopreventive and chemotherapeutic potential in many stages of oral carcinogenesis [75]. Thus, studies involving raspberry-, grape-, and grape seed-derived proanthocyanidins have recently demonstrated selective inhibition of oral cancer phenotypes, particularly in oral squamous cell carcinomas (OSCC) [76,77].

The administration of proanthocyanidins by grape seed and cranberry extracts reduced cell growth and proliferation of OSCC, CAL27, and SCC25 cell lines in a dose-dependent manner [17,75]. Moreover, the effects of the grape seed extract were more selective, and intensely specific, for the OSCC cell line compared with noncancerous controls, suggesting a possible selective effect that may render oral cancers more susceptible to the apoptosis-inducing and proliferation-inhibiting effects of proanthocyanidins [75]. A further analysis revealed a common, dramatic upregulation of mRNA expression in the apoptosis initiator, caspase-2, and the apoptosis effector, caspase-8 from CAL27 and SCC25 cell lines by the administration of grape seed and cranberry proanthocyanidins extracts [17].

5.3. Esophageal adenocarcinoma

Reflux of bile and stomach acid has been linked to esophageal adenocarcinoma in human cohorts, and recent in vitro

Table 1
Beneficial effects and healthy properties of proanthocyanidins

Diseases	Effects/Properties	References
Cardiovascular	↓ Vessel constriction	[49]
	↓ LDL oxidation	[44,50–52]
Diabetes	↓ RAGE expression	[60]
	↓ AGEs effects	[61–63]
	↓ Lipid peroxidation in kidney	[42]
	↓ Hyperlipidemia, hyperglycemia and oxidative stress	[13]
	↓ Body weight	[61,62]
	Improve nephropathy and retinopathy	[61,62]
	Improve neuropathy	[63]
	Improve insulin resistance	[44]
Cancer	↑ Apoptosis and ↓ proliferation	[14,16,17,65–67,69,72,77,104,105]
	↓ Angiogenesis	[79]
Bacterial infections	Anti-adhesive activity	[87,91,92]
	↓ Inflammatory mediators	[98]

studies have documented specific cellular responses to acid or bile exposure, including alterations in genes associated with increased cell proliferation and survival with a corresponding decrease in apoptosis [78,79].

Kresty et al. (2008) carried out a research where pretreating acid-responsive human esophageal adenocarcinoma cell line, SEG-1, with cranberry proanthocyanidins significantly inhibited cell viability in a dose- and time-dependent manner [80]. Loss of cell cycle checkpoint control and subsequent uncontrolled cell proliferation are characteristic of numerous cancers, including esophageal adenocarcinoma [80,81]. The experiment resulted in a significant increase in the percentage of cells at the first gap phase checkpoint and significant declines in the percentage of cells in S-phase, which means an antiproliferative effect. Furthermore, treatment of SEG-1 cells with proanthocyanidins resulted in significant induction of apoptosis [80]. Moreover, pretreatment of a second esophageal adenocarcinoma cell line, BIC-1, with the same polyphenols also inhibited cell proliferation. In summary, the results of this study showed that a cranberry proanthocyanidins-rich extract has potent effects on cell cycle regulation, cell viability, cell proliferation, and apoptosis of esophageal adenocarcinoma cells [80].

5.4. Prostate cancer

Oligomeric proanthocyanidin complexes inhibit the activity of enzymes such as lipoxygenase and cyclooxygenase [82]. These effects may have a role in cancer prevention since 12-lipoxygenase increases the expression of vascular endothelial growth factor and angiogenesis in prostate cancers [82].

In this context, Neuwirt et al. (2008) presented evidence that these oligomeric proanthocyanidin complexes cause inhibition of growth of prostate cancer cells through the activation of mechanisms that lead to a G1 growth arrest and induction of apoptosis. They showed this antiproliferative and proapoptotic effect in three prostate cancer cell lines: LNCaP, receptor-negative PC3, and DU145 cells [14].

These growth inhibition and apoptosis induction effects on LNCaP and DU145 prostate cancer cell lines were previously reported by other authors [83–85].

5.5. Lymphoma

Non-Hodgkin lymphoma is the fifth most common cancer in the United States among both men and women and the lifetime cumulative risk of developing it is one in 50 [86]. This type of cancer include a heterogeneous group of malignancies that arise primarily from lymphoid tissue throughout the body [87] and is characterized by the presence of Hodgkin and Reed-Sternberg cells that generally constitute less than 1% of the total tumor cell mass [88]. The intake of flavonols, epicatechins, anthocyanidins, proanthocyanidins, and total flavonoids is inversely associated with the risk of this type of cancer [15].

Specifically, Mackenzie et al. (2008) presented evidence that dimeric procyanidin B2 inhibits the binding of nuclear factor κB to DNA process that is involved in Hodgkin and Reed-Sternberg cell proliferation and resistance to apoptosis [88].

6. Proanthocyanidins antibacterial effects

Many pathogens need a positive adhesion to host cells or host tissues as a prerequisite for invasion and virulence. This adhesion is commonly mediated by carbohydrate–protein interactions between surface adhesions of microorganisms and the host cell [89,90]. Hence, antiadhesive compounds are potential prophylactic tools in alternative treatment regimes against bacterial infection [90].

Pelargonium sidoides extract, containing mainly polymeric proanthocyanidins, was found to have antiadhesive activity against *Helicobacter pylori* in a dose-dependent manner [90]. In another study by Mayer et al. (2008), after fractionation of raw extracts, proanthocyanidins and gallate

Table 2
Proanthocyanidins applied to different diseases and their dietary sources

Dietary source	Proanthocyanidins	Diseases	References
Longan flower	Proanthocyanidins A2	Cardiovascular diseases	[44,51]
	Proanthocyanidins A2	Diabetes	[44]
Croton celtidifolius	Proanthocyanidin oligomers mainly composed of catechin and epicatechin units in the ratio of 1.5–1	Cardiovascular diseases	[49]
Cranberry	A-Type proacyanidins	Cardiovascular diseases	[50]
	Oligomers composed primarily of four to seven epicatechin units with at least one or two A-type linkages between the units	Human large cell lung carcinoma, HT-29 colon adenocarcinoma, and K562 chronic myelogenous leukemia cells *in vitro*	[64]
	–	Oral squamous cell carcinomas	[17]
	–	Human tumor cell lines	[65,66]
	Epicatechin units with mainly DP of 4 and 5 containing at least one A-type linkage	Human esophageal adenocarcinoma cells	[77]
	A-type proanthocyanidins	Antibacterial against *Escherichia coli*	[91]
	Type A oligomers	Antibacterial against *Streptococcus mutans*	[89]
	–	Antibacterial against periodontopathogens	[98]
	0.35% anthocyanins and 65.1% proanthocyanidins	Antibacterial against *Porphyromonas gingivalis*	[101]
	65.1% proanthocyanidins and 0.35% anthocyanins	Antibacterial against *Peptostreptococcus micros*	[95]
Maritime pine	Oligomeric proanthocyanidins	Prostate cancer	[14]
Persimmon peel	Polymeric and oligomeric proanthocyanidins	Diabetes	[13,42]
Pelargonium sidoides	Polymeric proanthocyanidins	Antibacterial against *Helicobacter pylori*	[87]
Apple and hop	–	Antibacterial against *Porphyromonas gingivalis*	[102]
Grape seed	–	Diabetes	[60–62]
	56% dimeric, 12% trimeric, 6.6% tetrameric and small amounts of monomeric and high-molecular-weight oligomeric proanthocyanidins	Diabetes	[63]
	–	Colon aberrant crypts and breast tumors	[68]
	Oligomeric proanthocyanidins	Oral squamous cell carcinoma	[17,72]
	Oligomeric proanthocyanidins	Prostate cancer	[14]
	Procyanidins oligomers of catechin and epicatechin, some of which are esterified with gallic acid	Prostate cancer	[81]
	Oligomers of catechin and/or epicatechin	DU145 human prostate carcinoma cells	[82]
	Proanthocyanidins P2, P3, P4, and gallate esters P2G and P3G (P = proanthocyanidin consisting of catechin and epicatechin units, n = oligomerization degree, G = gallate ester)	Antibacterial against: *Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumoniae, Streptococcus pyogenes, Klebsiella pneumoniae, Escherichia coli, Haemophilus influenzae, Staphylococcus epidermidis, Enterococcus faecalis* and *Enterococcus casilliflavus*	[88]
Black Jamapa Bean	TP3 fraction: epicatechin and anthocyanins in the form of delphinidin 3-glycoside, petunidin 3-glycoside, and malvidin 3-glycoside. TP4 fraction: higher concentrations of flavan-3-ol oligomers and rich in heterogeneous dimers mainly composed of (epi)-afzelechin, (epi)catechin, and (epi)gallocatechin in addition to the above anthocyanins. SG2 fraction: a mixture of monomer-hexamer catechin-based proanthocyanidins.	Chemopreventive activity on HeLa and HaCaT Cells	[70]

esters were determined as active antibacterial agents toward 10 different pathogens [91].

6.1. Urinary infections

Urinary tract infections (UTI) have a high incidence worldwide and a substantial share of the public health budget is spent on their treatment [92]. Ascending UTI may cause renal parenchymal damage, leading eventually to renal failure [92]. The bacterium *Escherichia coli* causes most uncomplicated UTI, whereas in complicated upper UTI, *E. coli* strains of specific uropathogenic virulence predominate [93]. Urovirulence is strongly defined by bacterial fimbriae, which mediate the firm adherence to the host's tissue. Adhesion is accomplished by the binding of lectins exposed on the surface of these fimbriae to complementary carbohydrates of the host tissue [93].

Research has identified an antiadhesive mechanism of cranberry proanthocyanidins extract that inhibit docking of bacteria on tissues "*in vitro.*" For example, it was identified to selectively possess antiadhesion activity against p-fimbriated *E. coli* [94] and even abolished the expression of this p-fimbriae when added to bacterial culture medium [95]. What is more, the reduction in biofilm formation and acidogenicity by *Streptococcus mutans* could specifically be attributed to cranberry condensed tannins and mainly to type A oligomers of epicatechin [92]. Additionally, it has been demonstrated by two clinical trials that the antiadhesive activity of cranberry ingredients is conserved in human urine, following oral ingestion of cranberry juice [96,97].

6.2. Dental infections

Tooth decay and periodontal disease are worldwide plagues caused by pathogenic bacteria resident in the oral cavity and characterized by the destruction of tooth-supporting tissues, including the alveolar bone [92,98]. The initiation and rate of progression of periodontitis involve complex interactions between periodontopathogenic bacteria, notably from the *S. mutans* group and immune and resident host cells [92,99]. The cytotoxicity mediated by bacterial cell wall components and lipopolysaccharide may contribute to periodontal tissue destruction and disease progression [100]. Within a matrix of salivary proteins, these bacteria release enzymes, for example, glucosyltransferase and fructosyltransferase, and synthesize fructanes and glucanes that facilitate further bacterial attachment [92].

It was found that a proanthocyanidin-rich cranberry fraction possesses the capacity to reduce the production of inflammatory mediators by lipopolysaccharide (LPS)-stimulated macrophages and gingival fibroblasts [101,102] and to inhibit host extracellular matrix destructive enzyme production and activity [103]. In addition, the same cranberry fraction could prevent biofilm formation by *Porphyromonas gingivalis* [104], a major etiological agent of chronic periodontitis [98]. In another report, apple and hop polyphenols that are mainly constituted of proanthocyanidins were found to protect periodontal ligament cells against *P. gingivalis* cytotoxicity [105].

Peptostreptococcus micros is one of the few Gram-positive bacterial species for which there is evidence for a role in periodontitis [106]. Pretreating cells with a cranberry fraction rich in proanthocyanidins, statistically reduced the loss of cell viability and the cell wall toxicity induced by *P. micros* in both human monocyte-derived macrophages and oral epithelial cells [98].

7. Conclusions

Proanthocyanidins, or condensed tannins, are polyphenolic compounds that are widely found in plants. These molecules have a role as antioxidants; hence, they have been applied in different research concerning diseases related with oxidative stress and free radicals.

Indeed, proanthocyanidins seem to have positive healthy effects (Table 1) by improving some complications of type 2 diabetes, cardiovascular diseases, and different types of cancer or bacterial infections. However, there are still few studies taking into account that putative therapeutic uses of proanthocyanidins are very broad and it is likely that they will continue to be used in new contexts and applications. Moreover, most of the reports up to date involve *in vitro* and animal trials but there are scarce clinical studies. Thus, future research should continue with the aim of investigating the proanthocyanidins bioavailability and understanding the regulatory genes and pathways that are involved on human health effects.

Finally, as shown in Table 2 the development of functional foods containing proanthocyanidins, as part of a healthy diet, may aid in the prevention of chronic disease and in the maintenance of good health.

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