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Proanthocyanidins: A comprehensive review

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ABSTRACT

Proanthocyanidins are condensed tannins with various pharmacological properties. These phytochemicals are considered as 'offense and defense molecules because of their human health benefits. The validation of their diverse health aspects, namely, antioxidant, anticancer, antidiabetic, neuroprotective, and antimicrobial has earned them repute in thermochemistry. Proanthocyanidins are oligo- or polymers of monomeric flavan-3-ols produced as an end product of flavonoid biosynthetic pathway. Agricultural wastes and food processing wastes contain immense amount of proanthocyanidins, exploitation of which can be a sustainable source of dietary supplements and functional ingredients. The current review article discusses recent developments in the health promoting properties of proanthocyanidins and the associated hurdles.

1. Introduction

Flavonoids are a class of polyphenolic compounds having significant human health benefits [1]. Some of the flavonoids such as the flavan-3-ols catechin and epicatechin polymerize to form tannins. Tannins are plant secondary metabolites, which can be hydrolysable or condensed. Hydrolyzable tannins include gallotannins and ellagitannins yielding gallic acid and ellagic acid, respectively when hydrolyzed. These tannins are actually esters of gallic acid and polyol, primarily D-glucose. Gallotannins contain gallic acid as a base unit whereas ellagitannins possess gallic acid and hexahydroxydiphenol moieties subunits [2].

The condensed tannins are also known as proanthocyanidins [3]. Proanthocyanidins are present in flowers, nuts, fruits, bark, and seeds of various plants, as a defense against biotic and abiotic stressors. Their astringency protects the plants from pathogens and predators. They are oligomeric and polymeric products of the flavonoid biosynthetic pathway. The building blocks of proanthocyanidins include catechin and epicatechin [4]. Leucoanthocyanidin reductase catalyzes the synthesis of catechin, which serves as the first committed step in proanthocyanidin biosynthesis [5]. Proanthocyanidin degree of polymerization can range between 3 and 11. In these polymeric flavan-3-ols, the elementary units are linked by C—C and occasionally C—O—C bonds. Oxidative condensation occurs between carbon C_4 of the heterocycle and carbons C_6 or C_8. Several of the doubly linked ring-A proanthocyanidins are known to be sweet tasting. For example, selligueain A, a proanthocyanidin trimer of the propelargonidin type, from the rhizome of the fern *Selliguea feei* is intensely-sweet [6]. Based on their B-rings, four most common B- type proanthocyanidins dimers are B_1, B_2, B_3 and B_4 related to C_4-C_8 chemical bonding whilst, B_5, B_6, B_7 and B_8 contain C_4–C_6 interflavan linkages [2].

Procyanidins is made of catechin and epicatechin, while prodelphinidins are made of epigallocatechin [7]. Anthocyanins are derived from anthocyanidins by the addition of sugars. On heating in acidic media, proanthocyanidins generate anthocyanins. Both proanthocyanidins and anthocyanins are products of flavonoid pathway and require the same metabolic intermediates. Total proanthocyanidin content reached the maximum level at the red-to-black stage but dramatically decreased during the last ripening process, while anthocyanin peaked.

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Studies on blackberry fruits reveal that in different developmental stages, proanthocyanidin and anthocyanin content vary [8].

Berries and fruits are the best sources of proanthocyanidins, Lingonberry, cranberry, black elderberry, black chokeberry, black currant, blueberry are some of the edible berries with predominant of proanthocyanidin content [9]. Persimmon, banana, carob bean, and Chinese quince, when raw are highly astringent because of the abundant proanthocyanidin. As per a study, the highest contents per fresh weight were determined in chokeberries, rose hips, and cocoa products [10,11]. Proanthocyanidins is present in medlar, mulberry, plum, apricot, walnut, silverberry, pomegranate as well i.e. its ubiquitous to all most all fruits [12]. Grape seed proanthocyanidins are consumed as dietary supplements. Persimmon peel proanthocyanidin showed antidiabetic properties [13]. In a study, persimmon leaf tea containing peculiar proanthocyanidins, suppressed blood glucose elevation after starch intake [14]. A commercial product pycnogenol from pine tree bark contains oligomeric proanthocyanidins, catechin, epicatechin, ferulic acid, caffeic acid, and taxifolin [15]. Triticale straw proved to be a rich source of proanthocyanidins, containing 862.5 mg/100 g [16].

Proanthocyanidins can impart astringency, bitterness, sourness, sweetness, salivary viscosity, aroma, and color formation. Anthocyanins are less astringent than proanthocyanidin because of the association of different sugars. It's savor taste can be used in fruit juices, teas, beverages and -also for enhancing the shelf life of several food products like wine [17]. They are used as additives in food preparations for enhancing microbial stability, foamability, oxidative stability, and heat stability. Proanthocyanidins have a wide range of health beneficial properties. Antioxidant, antitumor and immunostimulating properties of these compounds have come forth. Studies have shown that proanthocyanidins help to protect the body from sun damage, to improve vision, to improve flexibility in joints, arteries, and body tissues such as the heart, and to improve blood circulation by strengthening capillaries, arteries, and veins [18]. Oligomeric proanthocyanidin complexes (OPCs) have been reported to demonstrate antioxidant, antibacterial, antiviral, anticarcinogenic, anti-inflammatory, anti-allergic, and vasodilatory actions. They can inhibit lipid peroxidation, platelet aggregation, and capillary hyperpermeability [19]. The effect of proanthocyanidins on apoptosis, gene expression and transcription factors, such as NF-k B has also been reviewed [20].

2. Biological potential of proanthocyanidins

The sections below outline the therapeutic potentials of various proanthocyanidins. Fig. 1 presents proanthocyanidins and their ameliorative mechanisms.

3. Antioxidant

Oxidative stress is a primary cause of cellular injury even in normal physiological conditions. In this respect, cellular injury and oxidative stress mediated metabolic disorders can effectively be managed using antioxidants. Antioxidant compounds provide shield against oxidative stress by assuaging the free radicals' load and protect from molecular and cellular injuries [21]. Proanthocyanidins have been endorsed to possess significant antioxidant capacities [22]. Grape seed extract depressed H_2O_2-induced phosphorylation of the p38 and c-Jun N-terminal kinase (JNK) proteins of the NF-κB and MAPK signaling in human lens epithelial B-3 HLE-B3 cells, protecting against cataractogenesis [23]. Grape seed proanthocyanidin extract at 400 mg/kg has dose-dependent protective effects against induced rat testicular toxicity [24]. Moderate dose ingestion of grape seed proanthocyanidin extract of GSPE can lower oxidative stress and improve mitochondrial function, as observed in rat models [25]. Grape seed proanthocyanidin extract reduced liver glutathione alteration in obese rat models [26].

Proanthocyanidin from *D. kaki* peels reduced oxidative damage by improving the expression of the silent information regulator, the sirtuin 1/SIRT1 gene which is a regulator of the apoptotic response to DNA damage. The orally-administrated proanthocyanidins from grape seed extract (200–300 mg) on daily bases prevented epigastric pain, significantly reduced the pain severity, the frequency of episodes, and the need of narcotic analgesics. Oxidative stress cause decline in pH, and creates acidosis [27]. Grape seed-derived procyanidins significantly attenuated gout pain and suppressed ankle swelling. In mice models of gout, procyanidins inhibited monosodium urate-induced activation of the NLRP3 inflammasome and the elevation of IL-1β. Also, it decreased ROS levels in Raw 264.7 cells [28]. In mice model, procyanidins suppressed the activity of MMP-2/9, blocked the maturation of IL-1β, decreased the phosphorylation of p38 MAPK and inhibited the translocation of NF-κB in microglia, resolving neuropathic pain [29]. Responding to the acidic pH, and inflammatory markers (IL10, C-reactive protein), acid-sensing channel are activated, which cause pain perception. Suppression of the inflammasomes in macrophages are one of the many interventions by proanthocyanidins, which alleviate pain [30].

4. Cardioprotective

Heart function can be affected by artery tonicity loss, plaque deposition, calcification or viscous blood, among other reasons. Proanthocyanidins ease cardiovascular diseases via vessel relaxation and the inhibition LDL oxidation [3,31]. Proanthocyanidins can inhibit the binding of oxidized LDL to the lectin-like oxidized LDL receptor (lectin-like oxidized LDL receptor-1 (LOX-1), which is involved in the pathogenesis of arteriosclerosis [32]. Several proanthocyanidins are involved in endothelium-dependent relaxing activity which includes endothelial NO release and subsequent increase in c-GMP levels in the vascular smooth muscle cells. Procyanidins from grape seed extract modulate NO/cyclic GMP pathway exerting cardiovascular protection [33]. Procyanidin fractions from cocoa has shown the LDL oxidation lowering ability [34].

5. Neuroprotective

Proanthocyanidins ameliorated the pesticide rotenone-induced mitochondrial respiration anomalies in a dopaminergic cell line [35]. As dopaminergic cell death lead to Parkinson's disease, a diet rich in proanthocyanidins should be neuroprotective. D-Galactose is used to induce cognitive impairment and brain aging. The supplementation of proanthocyanidins (30, 60, and 90 mg/kg) ameliorated the learning and memory abilities impaired by D-galactose as well as significantly lowered the concentrations of MDA, NO, content of β-amyloid peptide, monoamine oxidase B, acetylcholinesterase, neuronal NO synthase, and total NO synthase alongside enhancing concentrations of glutathione peroxidase and SOD in brain. Also, these reduced P53 protein expression and protected from neuron damage in hippocampus [35–38]. Numerous research data exhibited the neuroprotective effect of proanthocynidins in Alzheimer's disease (AD) via suppressing the amyloid-beta aggregation, decreasing amyloid-beta production, amyloid plaques and microgliosis, and preventing from amyloid-beta neurotoxicity in brain of mice [39,40]. Cadmium has been known to cause toxicity to neural cells via decreasing the acetylcholinesterase (AChE) levels, enzymatic and non-enzymatic antioxidants concentrations, and enhancing the oxidative stress markers. Proanthocyanidins (100 mg/kg/day) reversed these changes in rats where Cd excitotoxicity was induced. These also activated Akt phosphorylation, decreased the caspase-3 level and improved the neuronal cell survival rate [4]. The neuroprotective role of proanthocyanidins in senescence-accelerated mouse prone/8 (SAMP8) model has been reported through various mechanisms including improvement of spatial and object recognition impairment, increment in MAP-2a and 2b levels, phosphorylated neurofilament (PNF)-H and synaptophysin. Particularly, proanthocyanidins enhanced the levels of PNF-H, and phosphorylation of VEGFR-2 in brain

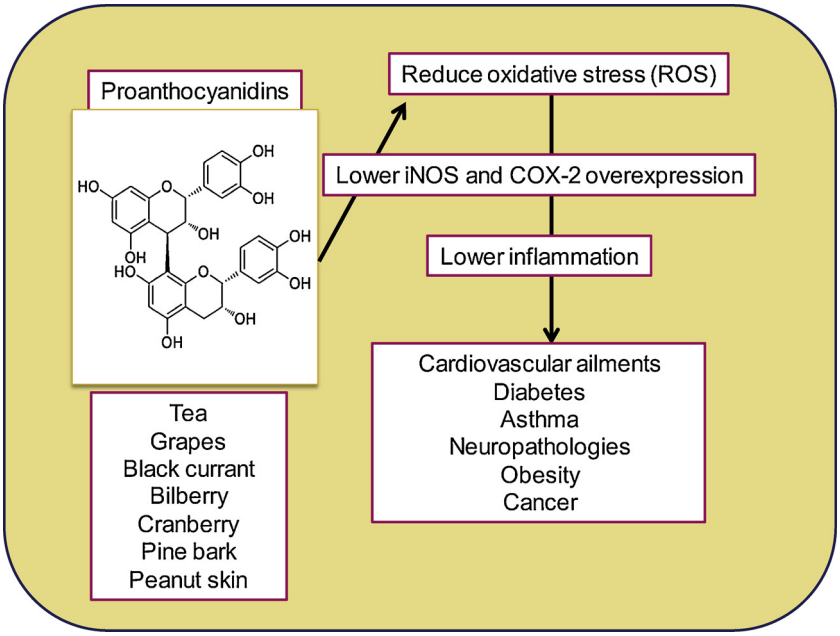

Fig. 1. Proanthocyanidins and their ameliorative mechanisms.

regions of SAMP8 [41].

6. Immunomodulatory

Grape seed proanthocyanidins could stimulate lymphocyte transformation, enhance lysosomal enzyme activity and phagocytic capability of peritoneal macrophages. They promoted the production of TNF-α [42]. Proanthocyanidins have been shown to lower inflammation in airways of murine asthma models, by reducing inflammatory cells, Th2 cytokines and serum IgE levels [43]. In rat model of osteoarthritis, grape seed proanthocyanidin extract reduced the loss of chondrocytes and proteoglycan [44]. OPC inhibited the IL-1β-induced apoptosis in chondrocytes by decreasing ROS content and matrix metalloproteinase (MMP) levels [45].

In mice models, proanthocyanidin inhibited the LPS-induced iNOS and COX-2 overexpression, by modulating modulating NF-κB in the hippocampus, prefrontal cortex, and amygdala. These anti-inflammatory effects assuaged depressive behaviors [46]. Oligomeric proanthocyanidin could protect oxidative stress-injured retinal ganglion cells by inhibiting apoptotic process [47].

7. Lipid lowering and anti-obesity

Ingestion of high-carbohydrate and high-fat food can result in postprandial hyperglycaemia, which can affect endothelial function [48]. Proanthocyanidins can improve metabolic impairment due to postprandial hypertriacylglycerolaemia. Grape seed proanthocyanidin extract induces hypotriacylglycerolaemic actions by repressing lipoprotein secretion [49]. Obesity is a result of metabolic disturbance, and obesity can fuel the perturbation further. In a cohort, tablets containing grape seed extract, reduced oxidized LDL level, lowering the risk of arteriosclerosis [50].

8. Antidiabetic

Diabetes is a chronic metabolic disease where glucose metabolism is impaired, which originates due to toxicity on pancreas gland and resultant deficit in insulin level [51]. Severe diabetic condition may result in neuropathy, retinopathy, or nephropathy. Its therapy requires the inhibition of excess digestive enzymes and formation of advanced glycation end product (AGE) [52].

Grape seed proanthocyanidins increased normal insulin content and decreased the number of apoptotic cells in diabetic pancreatic islets [53]. Endoplasmic reticulum (ER) stress results in the accumulation of misfolded proteins and alters calcium homeostasis. ER stress is switched on during diabetic state [54]. The proanthocyanidin treatment partially alleviated ER stress. The supplementation of grape seed proanthocyanidin extract attenuated oxidative stress through the inhibition of lipid peroxidation, restored endothelial function, and reduced the risk of vascular disease in diabetes [55]. Diabetic encephalopathy results from long-term hyperglycemia. Grape seed proanthocyanidin extract can reduce the injuries in the cerebral cortex of diabetic rats by modulating AGEs/the receptor for AGEs (RAGE)/NF-kB p65 pathway [56]. Proanthocyanidins may slow the progression of diabetic retinopathy.

9. Anticancer

Cancer is uncontrolled cell growth that can be directly induced by oxidative stress which may eventually be controlled using antioxidant rich diet [21]. Being anticancer agents, oligomeric proanthocyanidins (OPCs) alter genes involved in cell cycle and DNA replication. They significantly decreased xenograft tumor growth, and inhibited the formation of organoids in colorectal cancer [57]. Grape seed proanthocyanidins inhibit colon tumor growth by inhibiting the expression of both VEGF and Ang1 through the scavenging of ROS [58,59]. In a study, grape seed proanthocyanidins with a control diet significantly inhibits UV-induced skin tumor development [60]. Grape seed proanthocyanidins inhibited MMP-2 and MMP-9 secretion, VEGF and angiopoietin 1 signaling, which blocked angiogenesis [61]. In A431 and SCC13 human squamous cell carcinoma cell line models, grape seed proanthocyanidins decreased histone deacetylase activity, and led to the re-expression of silenced tumor suppressor genes, RASSF1A, p16(INK4a) and Cip1/p21 [62]. Oral squamous cell carcinoma cell lines CAL27 and SCC25 proliferation was inhibited by 24 h incubation with proanthocyanidins at 50–70 μg/mL. The treatment increased the expression of apoptosis-specific molecules, such as caspase-2 and caspase-8 [63]. The administration of procyanidin-rich extract from sorghum inhibited tumor growth and metastasis by suppressing VEGF production [64]. Oligomeric procyanidins B2 displaced testosterone from mARs, decreasing the *in vitro* growth of androgen-sensitive (LnCaP) and

androgen-resistant (DU145) human prostate cancer cell lines [65]. Reduction in the mAR (protein-conjugated testosterone) by the procyanidin is the anticancer mechanism. Litchi pericarp extract proanthocyanidin B2 had cytotoxicities towards human breast cancer cell MCF-7 and human embryolic lung fibroblast, though to a lesser degree than paclitaxel [66].

10. Antimicrobial

Polyphenols with significant antimicrobial properties are gaining popularity due to their natural origins and relatively safer nature. Novel natural antimicrobial agents are being preferred because of the development of antibiotics-resistant in microbes and wide spread proclaimed side-effects of conventional pharmaceutical antibiotics [67]. In this respect, proanthocyanidins dimers have been found potent antimicrobial agents [68,69]. Grape seed extract rich in proanthocyanidins reduced the viable cell counts for *Listeria monocytogenes* [70]. They exert produce antiadhesive actions against bacteria in urinary and dental infections, including *Escherichia coli* and *Streptococcus mutans*. Proanthocyanidin exhibited anti-adherence property towards multidrug resistant strains of uropathogenic P-fimbriae-expressing *E. coli* [57]. A-type cranberry proanthocyanidins reduced the adherence properties of *Candida albicans* by attenuating the inflammatory response, interfering with NF-κB p65 activation and the phosphorylation of specific signal intracellular kinases. This intervention might is useful for oral candidiasis mitigation [71]. Peanut skin-derived proanthocyanidin trimer disrupted cell membrane and wall integrity of *Bacillus cereus* [72]. Ellura, a proanthocyanidin-rich commercial product from cranberry is used for the treatment of urinary tract infection (UTI) [73]. Proanthocyanidin from diverse plants, especially pomegranate peel, is given to children suffering from diarrhea.

11. Discussion

Proanthocyanidins are oligo- or polymers of monomeric flavan-3-ols produced as an end product of flavonoid biosynthetic pathway. Proanthocyanidins are basically condensed tannins and produced by the action of cytosolic multi-enzyme complex along phenylpropanoid pathway. This upstream pathway produces basic skeleton of all flavonoids starting 3 molecules of malonyl-CoA and one 4-coumaroyl-CoA. The central intermediate colorless flavanone known as naringenin is produced by condensation upon the action of chalcone synthase and chalcone isomerase enzymes. it then produces various classes of flavonoids which on series of oxidation, hydroxylation, reduction and deoxygenation produces proanthocyanidins [2]. Majorly, the building blocks of proanthocyanidins include catechin and epicatechin [74]. Grape seed proanthocyanidins extract exerted antioxidant, anti-cancer, anti-hyperglycemic, cardioprotective properties through its anti-oxidative and anti-inflammatory effects [75].

Though proanthocyanidins are health-promoting, their usages have certain issues. Only the monomers and smaller oligomeric procyanidins are absorbed [13]. Proanthocyanidins with a degree of polymerization over 4 are not absorbable due to their large molecular size and gut barrier [76]. Dietary benefits of proanthocyanidin is indisputable, yet it is not enough to maintain human health homeostasis, in the face of repeated stress assaults. Also, the metabolic fate and availability of proanthocyanidins are yet to be mapped adequately. A study reports that proanthocyanidins are metabolized by gut microbiota into several components.

Administration of grape seed proanthocyanidin extract to rat models dose-dependently restored the activities of antioxidative enzymes while reducing MDA, NO, and calpainII protein. It suppressed the generation of lipid peroxidation and ameliorated lens opacity [77]. This can be an example of anti-inflammatory, antioxidative as well as neuroprotective role of proanthocyanidin. Perpetual stress generates endless stream of ROS, which induce cell apoptosis and upsets all signaling pathways [78].

Rather than superficial reporting of the benefits of proanthocyanidins or other phytochemicals, it is wise to understand the mechanism governing them. Proanthocyanidins strongly interact with proteins. The protein precipitation ability of proanthocyanidin depended on the oligomer size, with increased size enhancing crosslinkages between proteins [79]. The capability of wine proanthocyanidins to bind salivary proteins, is responsible for the astringent taste. It is likely that proanthocyanidins can bind to the excess activated enzymes, characteristic of inflammatory condition. In fact, proanthocyanidin, being collagen cross-linker, inhibited matric metalloprotease and cysteine cathepsins [80]. Downregulation of aberrant protease-activity can resolve or attenuate numerous inflammatory conditions. Proanthocyanidin is precisely capable of executing the protease-blocking. Apart from proteins, the tannins can bind to polysaccharides, and mineral nutrients, interfering with digestion/absorption.

Inflammation, the ancient necessary evil, protects against infections, but when becomes chronic or acute, leads to homeostasis loss [81]. Too much and chronic inflammation cannot be corrected by dietary supplementations. The immune activation mitigation requires profound lifestyle changes. Despite overwhelming positive results derived from phytochemicals research, diseases keep tormenting mankind, even more intensely in each successive decade, as lifestyle and environment are getting too inflammatory. A diet, however superfood-enriched it might be, cannot rescue from the hazards of the collective inflammatory agents. Proanthocyanidin consumption is beneficial, but in a limited manner. The protective functions of proanthocyanidins have been clustered into groups for ease, but they all merge in oxidative stress quenching and anti-inflammation.

Cardiovascular dysfunctions, gastrointestinal distress, pancreatitis, neurological disorders, neoplastic processes are resultant of acute and chronic inflammations. Metabolic acidosis activates acid-sensing ion channels [30,82,83]. Proton-gated sodium channels are some example of the acid-sensing ion channels. Also, the acidic milieu alters membrane polarization state, affects mitochondrial function [84], imposes ER stress [85]. Stress and inflammation are interlinked by acidosis and hypoxia. Proteins play critical roles, for the execution of which they must maintain their structural integrity. Acidosis impairs their structures. A number of enzymes are switched in acidic conditions. Excess cytochrome P450 (CYP) enzymes lead to hormone disruption [86,87]. One metabolite 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone could prevent THP-1 monocyte-endothelial cell adhesion by downregulating TNF-α-stimulated expressions of vascular cell adhesion molecule-1 and monocyte chemotactic protein-1. So, this metabolite is likely to attenuate atherosclerosis risk [88].

Diabetes can cause the inflammation of vasculature and endothelial dysfunction, which grape seed proanthocyanidin extracts can attenuate [89]. Proanthocyanidin could heal myocardial damage via antioxidant and anti-inflammatory effects [90]. Proanthocyanidin-rich fraction of *Stryphnodendron adstringens*, when tested on HeLa and SiHa cells via MTT assay, exerted oxidative stress and mitochondrial damage, triggering apoptosis [91]. However, this cancer cell inhibitory effect could be a case of osmotic alterations. The lack of immune surveillance in the in vitro test medium could have led to the death of the cancer cells, which is not likely in a cancerous body.

Literature on health aspects of proanthocyanidins is ample. But the mechanism cited is often confounding. In some studies, oxidative stress elimination of proanthocyanidin is cited as the reason of health benefit, whereas in some studies, oxidative stress induction is cited as the reason of health benefit. For example, a study reports that grape seed extract-generated oxidative stress initiated an apoptotic response [92]. Proanthocyanidin increased the antitumor activity of doxorubicin by enhancing lymphocyte proliferation, NK cell cytotoxicity, CD4+/CD8+ ratio, IL-2 and IFN-gamma productions [93]. As per another study, grape seed polyphenols catechin and proanthocyanidin B4 pretreatment protected cardiomyocytes against doxorubicin-induced

toxicity by decreasing ROS generation [94]. On the other hand, the polyphenols are hindering the anticancer activity of doxorubicin. So, the reports are biased and need to be re-examined.

A relevance of this review article is that numerous agricultural wastes such as the peels of persimmon, litchi, pomegranate, and mangosteen have proanthocyanidin. Even pine bark, witch hazel bark, almond skin, peanut skin is a good source of proanthocyanidin. Epicatechin-(4β → 6)-epicatechin-(2β → O → 7, 4β → 8)-catechin is a proanthocyanidin trimer from peanut skin [72]. Tapping of these nutrients from the refuses or abundant nature resources can be a sustainable way of dietary supplement and functional food development.

Apart from proanthocyanidins, the phenolic acids, anthocyanins are also antioxidants [31]. They act as hypoglycemic agents, inhibiting IL-1β and COX-2 gene expression. Lycopene, a carotenoid, can reduce ROS and confer antioxidant property just like proanthocyanidin [95]. So, proanthocyanidin is not a miracle phyto-molecule, but one of the several plant secondary metabolites with salutary roles.

12. Conclusion

Proanthocyanidins have been known to confer significant health benefits as reported by several studies using human and animal models. These exert protective effects against cardiovascular ailments, metabolic disorders, and oncogenic event. Hence, proanthocyanidins are expected to potential pharmaceutical agents for the treatment of such disparities. In this direction, large double-blind clinical studies need to be conducted on proanthocyanidins to provide more information on their clinical efficacy and safety so that clinical implication of proanthocyanidins can be suggested as therapeutic remedies supported by sufficient scientific evidences.

Conflict of interest

There is no conflict of interest in submission of the manuscript.

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References

[1] D. Ravishankar, A.K. Rajora, F. Greco, H.M. Osborn, Flavonoids as prospective compounds for anti-cancer therapy, Int. J. Biochem. Cell Biol. 45 (2013) 2821–2831.
[2] I. Ky, A. Le Floch, L. Zeng, L. Pechamat, M. Jourdes, P.L. Teissedre, Tannins, in: B. Caballero, P.M. Finglas, F. Toldrá (Eds.), Encyclopedia of Food and Health, Academic Press, Oxford, 2016, pp. 247–255.
[3] R. de la Iglesia, F.I. Milagro, J. Campión, N. Boqué, J.A. Martínez, Healthy properties of proanthocyanidins, Biofact 36 (2010) 159–168.
[4] C. Dong, Protective effect of proanthocyanidins in cadmium induced neurotoxicity in mice, Drug Res. 65 (2015) 555–560.
[5] C. Liu, X. Wang, V. Shulaev, R.A. Dixon, A role for leucoanthocyanidin reductase in the extension of proanthocyanidins, Nat. Plants 2 (2016) 16182.
[6] N.-I. Baek, M.-S. Chung, L. Shamon, L.B. Kardono, S. Tsauri, K. Padmawinata, J.M. Pezzuto, D.D. Soejarto, A.D. Kinghorn, A. Selligueain, A novel highly sweet proanthocyanidin from the rhizomes of *Selliguea feei*, J. Nat. Prod. 56 (1993) 1532–1538.
[7] D. Ferreira, D. Slade, Oligomeric proanthocyanidins: naturally occurring *O*-heterocycles, Nat. Prod. Rep. 19 (2002) 517–541.
[8] Q. Chen, X. Zhang, H. Yu, H. Tang, Changes of total anthocyanins and proanthocyanidins in the developing blackberry fruits, Int. J. Chem. Tech. Res. 4 (2012) 129–137.
[9] L. Krenn, M. Steitz, C. Schlicht, H. Kurth, F. Gaedcke, Anthocyanin-and proanthocyanidin-rich extracts of berries in food supplements–analysis with problems, Die Pharmazie—Int. J. Pharm. Sci. 62 (2007) 803–812.
[10] J.K. Hellström, A.R. Torronen, P.H. Mattila, Proanthocyanidins in common food products of plant origin, J. Agric. Food Chem. 57 (2009) 7899–7906.
[11] S. Patel, Rose hip as an underutilized functional food: evidence-based review, Trends Food Sci. Technol. 63 (2017) 29–38.
[12] Y. Qin, F. Che, J. Li, B. Hu, Analysis of content of proanthocyanidin from featured fruit of Xinjiang, Xinjiang Agric. Sci. 46 (2009) 484–487.
[13] Y.A. Lee, E.J. Cho, T. Tanaka, T. Yokozawa, Inhibitory activities of proanthocyanidins from persimmon against oxidative stress and digestive enzymes related to diabetes, J. Nutr. Sci. Vitaminol. 53 (2007) 287–292.
[14] K. Kawakami, S. Aketa, M. Nakanami, S. Iizuka, M. Hirayama, Major water-soluble polyphenols, proanthocyanidins, in leaves of persimmon (*Diospyros kaki*) and their α-amylase inhibitory activity, Biosci. Biotechnol. Biochem. 74 (2010) 1380–1385.
[15] Pycnogenol, in: M. Ebadi (Ed.), Pharmacodynamic Basis of Herbal Medicine, CRC Press, 2010, pp. 509–511.
[16] F. Hosseinian, G. Mazza, Triticale bran and straw: potential new sources of phenolic acids, proanthocyanidins, and lignans, J. Funct. Foods 1 (2009) 57–64.
[17] P.M. Aron, Composition of Flavonoid Phenolic Polymers Isolated From Red Wine During Maceration and Significance of Flavan-3-Ols in Foods Pertaining to Biological Activity, Oregon State University, 2007.
[18] J. Shi, J. Yu, J.E. Pohorly, Y. Kakuda, Polyphenolics in grape seeds—biochemistry and functionality, J. Med. Food 6 (2003) 291–299.
[19] A.M. Fine, Oligomeric proanthocyanidin complexes: history, structure, and phytopharmaceutical applications, Altern. Med. Rev. 5 (2000) 144–151.
[20] P. Cos, T.D. Bruyne, N. Hermans, S. Apers, D.V. Berghe, A. Vlietinck, Proanthocyanidins in health care: current and new trends, Curr. Med. Chem. 11 (2004) 1345–1359.
[21] Iahtisham-Ul-Haq, M.S. Butt, A. Shamshad, H.A.R. Suleria, Heath benefits of anthocyanins in black carrot (*Daucus carota*), in: M.R. Goyal, H.A.R. Suleria (Eds.), Human Health Benefits of Plant Bioactive Compounds: Potentials and Prospects, Apple Academic Press, New York, USA, 2019.
[22] R. Lai, D. Xian, X. Xiong, L. Yang, J. Song, J. Zhong, Proanthocyanidins: novel treatment for psoriasis that reduces oxidative stress and modulates Th17 and Treg cells, Redox Rep. 23 (2018) 130–135.
[23] Z. Jia, Z. Song, Y. Zhao, X. Wang, P. Liu, Grape seed proanthocyanidin extract protects human lens epithelial cells from oxidative stress via reducing NF-κB and MAPK protein expression, Mol. Vis. 17 (2011) 210.
[24] Y.-m. Zhao, L.-p. Gao, H.-l. Zhang, J.-X. Guo, P.-p. Guo, Grape seed proanthocyanidin extract prevents DDP-induced testicular toxicity in rats, Food Funct. 5 (2014) 605–611.
[25] D. Pajuelo, H. Quesada, S. Díaz, A. Fernández-Iglesias, A. Arola-Arnal, C. Bladé, J. Salvadó, L. Arola, Chronic dietary supplementation of proanthocyanidins corrects the mitochondrial dysfunction of brown adipose tissue caused by diet-induced obesity in Wistar rats, Br. J. Nutr. 107 (2012) 170–178.
[26] A. Fernández-Iglesias, D. Pajuelo, H. Quesada, S. Díaz, C. Bladé, L. Arola, M.J. Salvadó, M. Mulero, Grape seed proanthocyanidin extract improves the hepatic glutathione metabolism in obese Z ucker rats, Mol. Nutr. Food Res. 58 (2014) 727–737.
[27] S. Patel, Stressor-driven extracellular acidosis as tumor inducer via aberrant enzyme activation: a review on the mechanisms and possible prophylaxis, Gene 626 (2017) 209–214.
[28] H.-J. Liu, X.-X. Pan, B.-Q. Liu, X. Gui, L. Hu, C.-Y. Jiang, Y. Han, Y.-X. Fan, Y.-L. Tang, W.-T. Liu, Grape seed-derived procyanidins alleviate gout pain via NLRP3 inflammasome suppression, J. Neuroinflammation 14 (2017) 74.
[29] C. Pan, C. Wang, L. Zhang, L. Song, Y. Chen, B. Liu, W.-T. Liu, L. Hu, Y. Pan, Procyanidins attenuate neuropathic pain by suppressing matrix metalloproteinase-9/2, J. Neuroinflammation 15 (2018) 187.
[30] W.-G. Li, T.-L. Xu, Acid-sensing ion channels: a novel therapeutic target for pain and anxiety, Curr. Pharm. Des. 21 (2015) 885–894.
[31] M.J. Kruger, N. Davies, K.H. Myburgh, S. Lecour, Proanthocyanidins, anthocyanins and cardiovascular diseases, Food Res. Int. 59 (2014) 41–52.
[32] M. Mizuno, I. Nakanishi, S. Matsubayashi, K. Imai, T. Arai, K.-i. Matsumoto, K. Fukuhara, Synthesis and antioxidant activity of a procyanidin B3 analogue, Bioorg. Med. Chem. Lett. 27 (2017) 1041–1044.
[33] D.F. Fitzpatrick, B. Bing, D.A. Maggi, R.C. Fleming, R.M. O'malley, Vasodilating procyanidins derived from grape seeds, Ann. New York Acad. Sci. 957 (2002) 78–89.
[34] M.M. Bearden, D.A. Pearson, D. Rein, K.A. Chevaux, D.R. Carpenter, C.L. Keen, H. Schmitz, Potential cardiovascular health benefits of procyanidins present in chocolate and cocoa, ACS Symposium Series vol. 754, (2000) 177–186.
[35] K.E. Strathearn, G.G. Yousef, M.H. Grace, S.L. Roy, M.A. Tambe, M.G. Ferruzzi, Q.-L. Wu, J.E. Simon, M.A. Lila, J.-C. Rochet, Neuroprotective effects of anthocyanin- and proanthocyanidin-rich extracts in cellular models of Parkinson's disease, Brain Res. 1555 (2014) 60–77.
[36] J. Wang, M.G. Ferruzzi, L. Ho, J. Blount, E.M. Janle, B. Gong, Y. Pan, G.N. Gowda, D. Raftery, I. Arrieta-Cruz, Brain-targeted proanthocyanidin metabolites for Alzheimer's disease treatment, J. Neurosci. 32 (2012) 5144–5150.
[37] H. Guo, M. Cao, S. Zou, B. Ye, Y. Dong, Cranberry extract standardized for proanthocyanidins alleviates β-amyloid peptide toxicity by improving proteostasis through HSF-1 in Caenorhabditis elegans model of Alzheimer's disease, J. Gerontol. Ser. A: Biomed. Sci. Med. Sci. 71 (2015) 1564–1573.
[38] Y.-S. Gong, J. Guo, K. Hu, Y.-Q. Gao, B.-J. Xie, Z.-D. Sun, E.-N. Yang, F.-L. Hou, Ameliorative effect of lotus seedpod proanthocyanidins on cognitive impairment and brain aging induced by D-galactose, Exp. Gerontol. 74 (2016) 21–28.
[39] Y.-J. Wang, P. Thomas, J.-H. Zhong, F.-F. Bi, S. Kosaraju, A. Pollard, M. Fenech, X.-F. Zhou, Consumption of grape seed extract prevents amyloid-β deposition and attenuates inflammation in brain of an Alzheimer's disease mouse, Neurotox. Res. 15 (2009) 3–14.
[40] W. Li, Y. Jiang, T. Sun, X. Yao, X. Sun, Supplementation of procyanidins B2 attenuates photooxidation-induced apoptosis in ARPE-19 cells, Int. J. Food Sci. Nutr. 67 (2016) 650–659.

[41] Y.A. Lee, E.J. Cho, T. Yokozawa, Oligomeric proanthocyanidins improve memory and enhance phosphorylation of vascular endothelial growth factor receptor-2 in senescence-accelerated mouse prone/8, Brit. J. Nutr. 103 (2010) 479–489.

[42] H. Tong, X. Song, X. Sun, G. Sun, F. Du, Immunomodulatory and antitumor activities of grape seed proanthocyanidins, J. Agri. Food Chem. 59 (2011) 11543–11547.

[43] T. Lee, H.-S. Kwon, B.-R. Bang, Y.S. Lee, M.-Y. Park, K.-A. Moon, T.-B. Kim, K.-Y. Lee, H.-B. Moon, Y.S. Cho, Grape seed proanthocyanidin extract attenuates allergic inflammation in murine models of asthma, J. Clin. Immunol. 32 (2012) 1292–1304.

[44] Y.J. Woo, Y.B. Joo, Y.O. Jung, J.H. Ju, M. La Cho, H.J. Oh, J.Y. Jhun, M.K. Park, J.S. Park, C.M. Kang, Grape seed proanthocyanidin extract ameliorates monosodium iodoacetate-induced osteoarthritis, Exp. Mol. Med. 43 (2011) 561.

[45] M.H. Yin, Y.T. Wang, Q. Li, G.F. Lv, Oligomeric proanthocyanidins inhibit apoptosis of chondrocytes induced by interleukin-1β, Mol. Med. Rep. 16 (2017) 4195–4200.

[46] X. Jiang, J. Liu, Q. Lin, K. Mao, F. Tian, C. Jing, C. Wang, L. Ding, C. Pang, Proanthocyanidin prevents lipopolysaccharide-induced depressive-like behavior in mice via neuroinflammatory pathway, Brain Res. Bull. 135 (2017) 40–46.

[47] H. Wang, C. Zhang, D. Lu, X. Shu, L. Zhu, R. Qi, K.-F. So, D. Lu, Y. Xu, Oligomeric proanthocyanidin protects retinal ganglion cells against oxidative stress-induced apoptosis, Neural Regen. Res. 8 (2013) 2317.

[48] S. Lacroix, C. Des Rosiers, J.-C. Tardif, A. Nigam, The role of oxidative stress in postprandial endothelial dysfunction, Nutr. Res. Rev. 25 (2012) 288–301.

[49] H. Quesada, S. Díaz, D. Pajuelo, A. Fernández-Iglesias, S. Garcia-Vallvé, G. Pujadas, M.J. Salvadó, L. Arola, C. Bladé, The lipid-lowering effect of dietary proanthocyanidins in rats involves both chylomicron-rich and VLDL-rich fractions, Br. J. Nutr. 108 (2012) 208–217.

[50] A. Sano, R. Uchida, M. Saito, N. Shioya, Y. Komori, Y. Tho, N. Hashizume, Beneficial effects of grape seed extract on malondialdehyde-modified LDL, J. Nutr. Sci. Vitaminol. 53 (2007) 174–182.

[51] American-Diabetic-Association, Diagnosis and classification of diabetes mellitus, Diabetes Care 33 (2010) 62–69.

[52] F. Xiu, M. Stanojcic, L. Diao, M.G. Jeschke, Stress hyperglycemia, insulin treatment, and innate immune cells, Int. J. Endocrinol. 2014 (2014).

[53] Y. Ding, Z. Zhang, X. Dai, Y. Jiang, L. Bao, Y. Li, Y. Li, Grape seed proanthocyanidins ameliorate pancreatic beta-cell dysfunction and death in low-dose streptozotocin- and high-carbohydrate/high-fat diet-induced diabetic rats partially by regulating endoplasmic reticulum stress, Nutr. Metab. 10 (2013) 51.

[54] S.S. Rajan, V. Srinivasan, M. Balasubramanyam, U. Tatu, Endoplasmic reticulum (ER) stress & diabetes, Ind. J. Med. Res. 125 (2007) 411–424.

[55] N. Okudan, H. Barışkaner, H. Gökbel, A.S. şahin, M. Belviranlı, H. Baysal, The effect of supplementation of grape seed proanthocyanidin extract on vascular dysfunction in experimental diabetes, J. Med. Food 14 (2011) 1298–1302.

[56] M. Lu, L. Xu, B. Li, W. Zhang, C. Zhang, H. Feng, X. Cui, H. Gao, Protective effects of grape seed proanthocyanidin extracts on cerebral cortex of streptozotocin-induced diabetic rats through modulating AGEs/RAGE/NF-κB pathway, J. Nutr. Sci. Vitaminol. 56 (2010) 87–97.

[57] P. Ravindranathan, D. Pasham, U. Balaji, J. Cardenas, J. Gu, S. Toden, A. Goel, Mechanistic insights into anticancer properties of oligomeric proanthocyanidins from grape seeds in colorectal cancer, Carcinogen 39 (2018) 767–777.

[58] S. Huang, N. Yang, Y. Liu, J. Gao, T. Huang, L. Hu, J. Zhao, Y. Li, C. Li, X. Zhang, Grape seed proanthocyanidins inhibit colon cancer-induced angiogenesis through suppressing the expression of VEGF and Ang1, Int. J. Mol. Med. 30 (2012) 1410–1416.

[59] W. Wen, J. Lu, K. Zhang, S. Chen, Grape seed extract inhibits angiogenesis via suppression of the vascular endothelial growth factor receptor signaling pathway, Cancer Prev. Res. 1 (2008) 554–561.

[60] S.K. Katiyar, Proanthocyanidins from grape seeds inhibit UV–radiation-induced immune suppression in mice: detection and analysis of molecular and cellular targets, Photochem. Photobiol. 91 (2015) 156–162.

[61] S. Huang, N. Yang, Y. Liu, L. Hu, J. Zhao, J. Gao, Y. Li, C. Li, X. Zhang, T. Huang, Grape seed proanthocyanidins inhibit angiogenesis via the downregulation of both vascular endothelial growth factor and angiopoietin signaling, Nutr. Res. 32 (2012) 530–536.

[62] M. Vaid, R. Prasad, T. Singh, V. Jones, S.K. Katiyar, Grape seed proanthocyanidins reactivate silenced tumor suppressor genes in human skin cancer cells by targeting epigenetic regulators, Toxicol. Appl. Pharmacol. 263 (2012) 122–130.

[63] K. Kingsley, D. Jensen, R. Toponce, J. Dye, D. Martin, S. Phippen, D. Ross, V.S. Halthore, S. O'Malley, Inhibition of oral cancer growth in vitro is modulated through differential signaling pathways by over-the-counter proanthocyanidin supplements, J. Diet. Suppl. 7 (2010) 130–144.

[64] L. Wu, Z. Huang, P. Qin, Y. Yao, X. Meng, J. Zou, K. Zhu, G. Ren, Chemical characterization of a procyanidin-rich extract from sorghum bran and its effect on oxidative stress and tumor inhibition in vivo, J. Agric. Food Chem. 59 (2011) 8609–8615.

[65] M. Kampa, K. Theodoropoulou, F. Mavromati, V. Pelekanou, G. Notas, E.D. Lagoudaki, A.-P. Nifli, C. Morel-Salmi, E.N. Stathopoulos, J. Vercauteren, Novel oligomeric proanthocyanidin derivatives interact with membrane androgen sites and induce regression of hormone-independent prostate cancer, J. Pharmacol. Exp. Ther. 337 (2011) 24–32.

[66] M. Zhao, B. Yang, J. Wang, Y. Liu, L. Yu, Y. Jiang, Immunomodulatory and anticancer activities of flavonoids extracted from litchi (*Litchi chinensis* Sonn.) pericarp, Int. Immunopharmacol. 7 (2007) 162–166.

[67] M. Daglia, Polyphenols as antimicrobial agents, Curr. Opin. Biotechnol. 23 (2012) 174–181.

[68] A. Karioti, M. Sokovic, A. Ciric, C. Koukoulitsa, A.R. Bilia, H. Skaltsa, Antimicrobial properties of Quercus ilex L. proanthocyanidin dimers and simple phenolics: evaluation of their synergistic activity with conventional antimicrobials and prediction of their pharmacokinetic profile, J. Agric. Food Chem. 59 (2011) 6412–6422.

[69] X. Zang, M. Shang, F. Xu, J. Liang, X. Wang, M. Mikage, S. Cai, A-type proanthocyanidins from the stems of *Ephedra sinica* (Ephedraceae) and their antimicrobial activities, Molecules 18 (2013) 5172–5189.

[70] B. Bisha, N. Weinsetel, B.F. Brehm-Stecher, A. Mendonca, Antilisterial effects of gravinol-s grape seed extract at low levels in aqueous media and its potential application as a produce wash, J. Food Prot. 73 (2010) 266–273.

[71] M. Feldman, S. Tanabe, A. Howell, D. Grenier, Cranberry proanthocyanidins inhibit the adherence properties of *Candida albicans* and cytokine secretion by oral epithelial cells, BMC Complement Altern. Med. 12 (2012) 6.

[72] T. Tamura, M. Ozawa, N. Tanaka, S. Arai, K. Mura, *Bacillus cereus* response to a proanthocyanidin trimer, a transcriptional and functional analysis, Curr. Microbiol. 73 (2016) 115–123.

[73] K. Sujana, K.S. Tejaswini, S.S. Lakshmi, Cranberry fruit: an update review, Int. J. Herb. Med. 4 (2016) 5–8.

[74] R.A. Dixon, D.Y. Xie, S.B. Sharma, Proanthocyanidins—a final frontier in flavonoid research? New Phytol. 165 (2005) 9–28.

[75] L. Bao, Z. Zhang, X. Dai, Y. Ding, Y. Jiang, Y. Li, Y. Li, Effects of grape seed proanthocyanidin extract on renal injury in type 2 diabetic rats, Mol. Med. Rep. 11 (2015) 645–652.

[76] K. Ou, L. Gu, Absorption and metabolism of proanthocyanidins, J. Funct. Foods 7 (2014) 43–53.

[77] X. Zhang, Y. Hu, Inhibitory effects of grape seed proanthocyanidin extract on selenite-induced cataract formation and possible mechanism, J. Huazhong Univ. Sci. Technol. 32 (2012) 613–619.

[78] H.-U. Simon, A. Haj-Yehia, F. Levi-Schaffer, Role of reactive oxygen species (ROS) in apoptosis induction, Apoptosis 5 (2000) 415–418.

[79] R.L. Kilmister, P. Faulkner, M.O. Downey, S.J. Darby, R.J. Falconer, The complexity of condensed tannin binding to bovine serum albumin—an isothermal titration calorimetry study, Food Chem. 190 (2016) 173–178.

[80] D.J. Epasinghe, C.K.Y. Yiu, M.F. Burrow, N. Hiraishi, F.R. Tay, The inhibitory effect of proanthocyanidin on soluble and collagen-bound proteases, J. Dent. 41 (2013) 832–839.

[81] M.E. Kotas, R. Medzhitov, Homeostasis, inflammation, and disease susceptibility, Cell 160 (2015) 816–827.

[82] M.-H. Li, T.-D. Leng, X.-C. Feng, T. Yang, R.P. Simon, Z.-G. Xiong, Modulation of acid-sensing ion channel 1a by intracellular pH and its role in ischemic stroke, J. Biol. Chem. 291 (2016) 18370–18383.

[83] J.A. Wemmie, R.J. Taugher, C.J. Kreple, Acid-sensing ion channels in pain and disease, Nat. Rev. Neurosci. 14 (2013) 461.

[84] X. Shi, Y. Zhao, Y. Jiao, T. Shi, X. Yang, ROS-dependent mitochondria molecular mechanisms underlying antitumor activity of Pleurotus abalonus acidic polysaccharides in human breast cancer MCF-7 cells, PLoS One 8 (2013) e64266.

[85] H. Yoshida, ER stress and diseases, FEBS J. 274 (2007) 630–658.

[86] S. Patel, Disruption of aromatase homeostasis as the cause of a multiplicity of ailments: a comprehensive review, J. Steroid Biochem. Mol. Biol. 168 (2017) 19–25.

[87] S. Patel, A. Homaei, A.B. Raju, B.R. Meher, Estrogen: the necessary evil for human health, and ways to tame it, Biomed. Pharmacother. 102 (2018) 403–411.

[88] C.C. Lee, J.H. Kim, J.S. Kim, Y.S. Oh, S.M. Han, J.H.Y. Park, K.W. Lee, C.Y. Lee, 5-(3′, 4′-Dihydroxyphenyl-γ-valerolactone), a major microbial metabolite of proanthocyanidin, attenuates THP-1 monocyte-endothelial adhesion, Int. J. Mol. Sci. 18 (2017) 1363.

[89] Z. Zhang, Y. Li, Y. Li, Grape seed proanthocyanidin extracts prevent hyperglycemia-induced monocyte adhesion to aortic endothelial cells and ameliorates vascular inflammation in high-carbohydrate/high-fat diet and streptozotocin-induced diabetic rats, Int. J. Food Sci. Nutr. 67 (2016) 524–534.

[90] S. Ma, C. Chen, T. Cao, Y. Bi, J. Zhou, X. Li, D. Yu, S. Li, Mitigation effect of proanthocyanidin on secondary heart injury in rats caused by mechanical trauma, Sci. Rep. 7 (2017) 44623.

[91] V. Kaplum, A.C. Ramos, M.E.L. Consolaro, M.A. Fernandez, T. Ueda-Nakamura, B.P. Dias-Filho, S.O. Silva, J.C.P. de Mello, C.V. Nakamura, Proanthocyanidin polymer-rich fraction of *Stryphnodendron adstringens* promotes in vitro and in vivo cancer cell death via oxidative stress, Front. Pharmacol. 9 (2018) 694.

[92] K. Raina, A. Tyagi, D. Kumar, R. Agarwal, C. Agarwal, Role of oxidative stress in cytotoxicity of grape seed extract in human bladder cancer cells, Food Chem. Toxicol. 61 (2013) 187–195.

[93] X.-Y. Zhang, W.-G. Li, Y.-J. Wu, T.-Z. Zheng, W. Li, S.-Y. Qu, N.-F. Liu, Proanthocyanidin from grape seeds potentiates anti-tumor activity of doxorubicin via immunomodulatory mechanism, Int. Immunopharmacol. 5 (2005) 1247–1257.

[94] Y. Du, H. Lou, Catechin and proanthocyanidin B4 from grape seeds prevent doxorubicin-induced toxicity in cardiomyocytes, Eur. J. Pharmacol. 591 (2008) 96–101.

[95] T. Mageshwaran, A.R. Ebenezar, M. Madhanamadhubala, S. Kavitha, S. Mahalaxmi, Counteraction of reactive oxygen species and determination of antibacterial efficacy of proanthocyanidin and lycopene when mixed with calcium hydroxide and chlorhexidine mixture: an in vitro comparative study, J. Conserv. Dent. 15 (2012) 337.