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Proanthocyanidins (PC) - A Novel Approach

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Abstract
An ever increasing number of pharmacological effects have become known through the discovery of new plant flavonoid with variations in chemical structure and related derivatives. A new group of phytochemicals that has been attracting much attention from both the general public and health professionals is a novel drug proanthocyanidins. This review emphasize various properties of proanthocyanidin , pertaining to various diseases of proanthocyanidins.

INTRODUCTION

An ever increasing number of pharmacological effects have become known through the discovery of new plant flavonoid with variations in chemical structure and related derivatives. A new group of phytochemicals that has been attracting much attention from both the general public and health professionals is proanthocyanidins(PC). PC are found in leaves, fruits, bark of

trees, seeds, flowers and roots of many plants and it is predominantly present in tea, honey, wines, grape seed, vegetables, nuts, olive oil, cocoa, pine bark and cereals. Grape seed extract (GSE), the richest source of PC, has potent antioxidants and exhibits numerous pharmacological activities. PC, one of the most abundant flavonoid in the plant kingdom, are extracted generally from grape seeds and they have antioxidant[(1)], free radical scavenging[(2)] and anticarcinogenic[(3)] property etc .

Chemistry Of PC

PC, also known as condensed tannins, are widely distributed in the plant kingdom and it represents a ubiquitous group of plant phenolics which take the form of oligomers or polymers of polyhydroxy flavan-3-ol units such as (+)-catechin, (-)-epicatechin and (-)-epicatechin-3-gallate. The fundamental structural unit of PC is the phenolic flavan-3-ol nucleus. The flavan-3-ol consists of a C15 (C6-C3-C6) structure characterized by a phenylbenzopyran moiety. Proanthocyanidins consist of flavanol units linked by two C-4 and C-8 interflavan bonds[(4)].

PC In Oral Diseases

Despite the recently reported drop in the overall death rate from cancer, the estimated survival rate and number of deaths from oral cancer remain virtually unchanged. PC administration might induce apoptosis in cervical and oral cancer cell lines, while acting merely to suppress proliferation of the normal cell line control[(5)] Administration of grape seed PC is shown to have a beneficial effect on physical health, specifically the health of bone. The effects of PC on mandibular bone are assessed by examining trabecular and cortical bone density, mineral content and noninvasive bone strength in low calcium diet rats and an increase in both bone formation and bone strength in rat mandibles has been observed after PC administration[(6)]. Houde *et al*., (2006)[(7)] have demonstrated that PC have potent antioxidant properties and it should be considered as a potential agent in the prevention of periodontal diseases. Green tea catechin (monomeric unit of PC) shows a bactericidal effect against gram negative anaerobic rods and is effective in improving periodontal status[(8)] Alveolar bone resorption is a characteristic feature of periodontal diseases and it involves removal of both the mineral and the organic constituents of the bone matrix, a process mainly carried out by multinucleated osteoclast cells. MMPs produced by resident and inflammatory cells in response to Gram (-) periodonto-pathogens play a major role in the tissue destruction observed during periodontitis. Also, GSE dose-dependently inhibits the activity of MMP-1 and MMP -9 and this study suggests that GSE may be potentially used in the development of novel host-modulating strategies for the treatment of MMP-mediated disorders such as periodontitis[(9)].

MECHANISM OF ACTION OF PC

Antioxidant Property

Free radicals have been implicated in the causation of several diseases such as liver cirrhosis, atherosclerosis, cancer, diabetes, periodontitis etc. and compounds that can scavenge free radicals have great potential in ameliorating these disease processes. PC have been shown as antioxidants through the following mechanisms viz., 1) Free radicals scavenging property and 2) Metal chelating activity**.**

Free Radicals Scavenging Property

The scavenging capacity of catechin and epicatechin molecules depends on the number of ortho-dihydroxyl and ortho-hydroxyketol groups and C2-C3 double bonds due to their hydrogen donating ability[(10)]. It is also proposed that the higher antioxidant activity is related to the greater number of hydroxyl groups on the flavonoid nucleus[(11)]. The dimeric PC are more effective than vitamin C in trapping oxygen radicals[(2)]. The protective role of PC through its free radical scavenging property both *in vitro* and *in vivo* has also been demonstrated by Ye et al., (1999)[(12)]. The electronic configuration of PC allows easy release of electrons to free radical species ($R^{\cdot}$)

such as superoxide anion, hydroxyl, peroxyl and nitric oxide radicals. By release of electrons, the radical character of the ROS is transferred to PC ($P^{\cdot}$). PC structure determines relative ease of oxidation and free radical scavenging activity[13]. PC have been suggested to be superior to flavonols in their antioxidant capacity since oxidation of PC predominantly produces semiquinone radicals that couple to produce oligomeric compounds through nucleophilic addition. In other words, the presence of electron-donating groups attached to the aromatic ring such as –OH ought to increase the ease of hydrogen atom abstraction and, consequently, antiradical performance, whereas groups with electron-withdrawing properties such as $–COO^{-}$ should have the opposite effect[14]. Although electron-donating –OH groups are attached to the aromatic ring in PC, the hydrogen atom is more easily abstracted. This could be the reason why PC shows antiradical activity at the concentrations employed as shown earlier[15]. Chemically, the important features of flavonoids, are their remarkable antioxidant properties.

The hydrogen donating substituents (hydroxyl groups) attached to the aromatic ring structures of flavonoids, enable them to undergo redox reactions scavenging free radicals more easily and the stable delocalization system, consisting of aromatic and heterocyclic rings as well as multiple unsaturated bonds, helps to delocalize the free radicals. Chemical structure determines the relative ease of flavonol or PC oxidation and free radical scavenging activity although the presence of galloyl groups and the number and position of hydroxyl groups (based on redox potential) enhance antioxidant activity[15] .

Metal Chelating Activity

The presence of free state iron and copper in biological systems catalyzes free radical reactions such as Fenton and Haber-Weiss reactions. In the Fenton reaction, iron catalyzes the generation of hydroxyl radicals. The ability of PC to bind such divalent transition metals effectively reduces the concentration of these cations and thus the extent of oxidative activity[16] . Facino et al., (1996) [17] have indicated that PC strongly complexes iron and copper cations in the ratios of Fe^{2+}/ procyanidin (2:1) and Cu^{+}/procyanidin (4:1) respectively. Results of an investigation involving the effect of PC hydroxylation patterns and degree of polymerization on aluminum chelating capacity reveal that hydroxyl groups are essential sites for metal chelation, o-dihydroxyl phenyl groups of the B ring in particular, and that increasing the degree of polymerization leads to higher stability of tannin-metal complexes[18] .

BIOLOGICAL POTENTIAL OF PC

Antiinflammatory Effects

COX and lipoxygenase (LOX) play an important role as inflammatory mediators. They are involved in the release of arachidonic acid, which is a starting point for a general inflammatory response. Selected phenolic compounds are shown to inhibit both the COX and 5-LOX pathways and this inhibition reduces the release of arachidonic acid. The exact mechanism by which flavonoids inhibit these enzymes is not clear[19]. PC efficiently restrain the inflammatory response of activated neutrophils *in vitro* and when absorbed *in vivo,* they could prevent the oxidative discharge at the sites of their adhesion[20].

Nitric Oxide Synthase (NOS) Activity

While a small amount of NO is essential to maintain normal body function (homeostasis), a significant increase of NO synthesized by inducible nitric oxide synthase (iNOS) activates inflammatory process and acts synergistically with other inflammatory mediators[21]. Catechin, EGCG, and other flavanoids repress NO production in macrophages and human peripheral blood mononuclear cells[22]. Interestingly, EGCG is shown to exert its effect on iNOS expression and reduce the activity by competitively inhibiting the binding of arginine and tetrahydrobiopterin

and it has been demonstrated that the gallate structure of this catechin is important for its action[23].

Antimicrobial Activity

PC, well known for their high levels of antioxidants and polyphenols, have also shown promise as novel antimicrobial agents The polyphenol compounds may form aggregates with the toxin, in turn preventing its receptor binding and internalization into the host cell[24]. The antimicrobial effects of several tannin extracts on yeast, filamentous fungi, bacterial and viral toxicity have been reviewed by Chung et al.,(1998)[25]. Polymeric PC may be useful as suppressors of antibiotic resistance in *Staphylococcus aureus* and they also show promise as an alternative treatment to antibiotic use against *Staphylococcus aureus* infection [26].

Cardiovascular Benefits Of OPC

Free radicals and oxidative stress play a crucial role in the pathophysiology of a broad spectrum of cardiovascular diseases, including congestive heart failure, vascular heart disease, cardiomyopathy, hypertrophy, atherosclerosis, and ischemic heart disease. Cardio-protective properties and mode of action of PCs are varied. PC supplementation has shown significant reduction in oxidized LDL, another important biomarker of cardiovascular diseases. PC have also been found to inhibit inducible endothelial CD36 expression, a novel cardio-regulatory gene[27] .

CONCLUSION

PC exhibits protective and therapeutic effect and it appears to have significant protection against inflammatory diseases and could be developed as a safe drug for the same

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