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Proanthocyanidins and Dental Health: Uncovering the Benefits

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Proanthocyanidins (PAs) are a subclass of flavonoids that are widely distributed in different plant sources and have attracted interest due to their potential health advantages, especially in maintaining dental health. The purpose of this review is to better understand the properties and applications of proanthocyanidins in maintaining dental health. Proanthocyanidins have excellent antibacterial, anti-inflammatory, and antioxidant qualities that are vital for preventing oral illnesses such oral cancer, periodontal disorders, and dental caries. Furthermore, PAs have demonstrated efficacy in augmenting salivary flow, and encouraging tooth enamel remineralization. Moreover, proanthocyanidins are low in toxicity and have good biocompatibility, which makes them good choices for adding to a variety of mouthwash, toothpaste, and dental materials. Their minimal side effects and natural source make them even more desirable for use in oral health interventions. However, Further research is needed to fully investigate their therapeutic potential and optimize their use in preventive and treatment methods for oral diseases.

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Keywords: Proanthocyanidins; remineralization; oral health; dental caries; grape seed extract.

1. INTRODUCTION

Oral disorders have been the most prevalent medical condition worldwide since 1990 [1]. Exposure to fluoride and various antibacterial agents has reduced the prevalence of dental caries and periodontal infections globally [2]. However, the use of fluoride and antibacterial agents can lead to adverse effects such as fluoride toxicity and antimicrobial resistance [3]. Hence, there is a growing interest in researching plant-derived substances for the prevention of dental caries and the maintenance of oral health. In the course of this extensive search, the plant-derived polyphenolic substance proanthocyanidins (PAs), prevalent in various plants, have emerged as a potential agent in enhancing oral health.

The oral cavity consists of a complex ecosystem including microorganisms, saliva, teeth, and tissues. Any disturbance in this ecosystem can lead to oral health disorders such as tooth decay, periodontal diseases, inflammatory diseases, and oral cancer [4]. Conventional oral hygiene approaches utilize various chemical substances to promote oral health, often leading to adverse effects [5]. In contrast, the emergence of natural substances like PAs, which have fewer toxic effects, provides an innovative approach to maintaining dental health and treating various oral health issues.

PAs are polyphenol flavonoid substances obtained from plants. They are also known as condensed tannins, which are oligomers or polymers of flavan-3-ols (e.g., (−)-epicatechin or (+)-catechin) linked through interflavan bonds [6]. PAs from various sources have been reported to possess a variety of properties, including antioxidant activity, anti-inflammatory effects, antimicrobial properties, improvement of vascular function, anti-cancer properties, and remineralization properties, thus enhancing dental health [7].

The aim of this narrative review was to explore the sources, biochemistry, pharmacokinetics, properties, mechanisms of action in the prevention of oral health diseases, safety of plant-derived proanthocyanidins, and their potential applications in preventive dentistry, adjunctive therapy, and oral care regimens.

2. DIETARY SOURCES OF PROANTHOCYANIDINS

PAs exhibit a bitter taste available in various plant fruits, barks, leaves, seeds and nuts. The richest source of PAs is cocoa beans (9481.75 mg/100 g). Other dietary plant products such as cinnamon (8108.14 mg/100 g), Cranberries (Vaccinium oxycoccos) (418.77 mg/100 g), Red kidney bean, raw (Phaseolus vulgaris) (510.25 mg/100 g) Hazelnuts (Corylus avellana) (500.66 mg/100 g), Pecan nuts (Carya illinoinensis) (494.05 mg/100 g), Grape seed raw (Vitis vinifera) (373.4 mg/100 g), Plums (Prunus domestica) (247.27 mg/100 g), Currants, black (Ribes nigrum) (200 mg/100 g) and Almonds (Prunus dulcis) (184.02 mg/100 g). Most foods contain exclusively B-type PAs. A small number of foods, such as cranberries, plum, and peanuts, contain A-type PAs [8].

3. BIOCHEMISTRY

Proanthocyanidin are oligomeric compounds, formed from monomeric catechin and epicatechin molecules. These monomeric units are characterized by a C6-C3-C6 carbon skeleton, consisting of two aromatic rings (A and B) linked by a heterocyclic ring (C) with a hydroxyl group at C3(Fig. 1) [9]. The molecular weight of PAs is 594.5 g/mol. PAs are of two types – A type PAs and B type PAs (Fig. 2) depending upon the stero configuration and linkage between monomers [10]. B-type procyanidins are the most abundant, with procyanidins B1, B2, B3 and B4 occurring most frequently. B-type procyanidins are characterized by a single interflavan bond between carbon-4 of the B-ring and either carbon-8 or carbon-6 of the C-ring. A-type procyanidins have not only an interflavan bond but also a second ether linkage between the A-ring hydroxyl group and carbon-2 of the A-ring. The most common A-type compounds are A1 and A2. These linkages give rise to different types of PAs with varying degrees of polymerization and structural complexities.

PAs show a broad range of polymerization patterns, from dimers (two units) to polymers with high polymerization degrees (more than ten units). Enzymes like polyphenol oxidases or peroxidases catalyse the oxidative coupling of flavan-3-ol monomers. Interflavan linkage within proanthocyanidin polymers determine the

structural integrity and molecular stability. The most common linkages between the flavan-3-ol units are C4→C8 and/or C4→C6 bonds, produce branching or linear polymer structures. The proanthocyanidin oligomers and polymers exhibit variability that is attributable to the distribution of these linkages [11].

4. PHARMACOKINETICS

The interaction of the body to the PAs can be studied by understanding the mechanism of hydrolysis, absorption, metabolism, distribution, and excretion of Pas [12].

4.1 Hydrolysis

After oral consumption of oligomeric PAs, the PAs are hydrolysed by enzymes in the gastrointestinal tract into dimers and monomers. This process was mediated by the intestinal enzyme lactase phlorizin hydrolase (LPH) and the acidic pH in the stomach. The pH of the stomach is the critical factor in degradation of the oligomeric PAs. PAs cannot hydrolyse at pH above 7 [13].

4.2 Absorption

Following hydrolysis of the PAs, the monomeric units are absorbed via the gastrointestinal epithelium to reach the bloodstream by passive diffusion, facilitated transport, and active transport [14]. This is completely dependent on the chemical structure and physiochemical nature of the PAs. PAs with higher degree of polymerization have poor permeability and absorption owing to their higher molecular weight and presence of increased number of hydroxyl groups. PAs when taken as a solid food matrix are not readily absorbed. PAs when solubilized and available in an aqueous phase are bioavailable to the enterocyte surface of the small intestine. They are transported only via passive diffusion because the PAs having large number of hydroxyl groups are unlikely to cross the lipid bilayer via the transcellular pathway. After consumption of oligomeric PAs methylated metabolites of epicatechin were detected in the plasma within 8 hours, however, polymeric PAs weren't identified indicating that polymeric PAs on the whole cannot be absorbed directly by humans [15].

4.3 Metabolism

PAs are distributed in conjugated forms. Conjugation mechanisms help the body eliminate metabolites and increase solubility in water. The liver and small intestine are the primary sites of glucuronidation and methylation. Glucuronidation, which takes place in the luminal region of the endoplasmic reticulum via UGTs, primarily occurs in the small intestine. Catechol-O-methyltransferase (COMT) and cytosol sulfotransferases (SULT) are the primary enzymes in the liver responsible for sulfation and methylation. A fraction of the monomeric or dimeric flavan-3-ols are absorbed in the small intestine, while the remainder are transported to the liver for further processing [16]. Phenolic compounds undergo significant metabolism in the liver through phase I and II biotransformation pathways after ingestion. Intermittent metabolites with modified chemical structures are produced during phase I metabolism, which is comprised of oxidation, reduction, and hydrolysis processes mediated by cytochrome P450 enzymes (e.g., CYP1A2, CYP2C9, CYP3A4). In Phase II metabolism, enzymes such glutathione S-transferases (GSTs), sulfotransferases (SULTs), and UDP-glucuronosyltransferases (UGTs) catalyse the conjugation of the metabolites with endogenous substances like glucuronic acid, sulphate, and glutathione which are excreted via the bile [17]. The majority (more than 90%) of dietary polyphenols remain in the colon, with only 5% being absorbed in the small intestine. The PAs are broken down by the intestinal flora. Metabolite production results from the breakdown of PAs by bacteria. These metabolites, which include valerolactones and phenolic acids, may be advantageous to health. The kind of PA and the degree of polymerization can affect the kind and number of metabolites that are produced [18].

4.4 Distribution

The metabolites from the colon travel throughout the circulation and distribute to various organs. An animal study revealed PA metabolites, such as those generated from cocoa or hazelnut extract, have been found in tissues, including the thymus, liver, spleen, and testicles [19]. Elevated levels of PA metabolites are involved in immune function regulation and oxidative protection. Certain metabolites can enter the brain and cross the blood-brain barrier [20]. This suggests that they could be able to provide neuroprotection. The varied metabolites identified in blood and tissues may be due to variable intracellular metabolism or different absorption or elimination pathways in various organs.

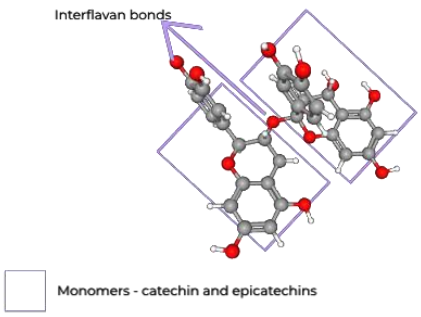

Fig. 1. Chemical structure of proanthocyanidin

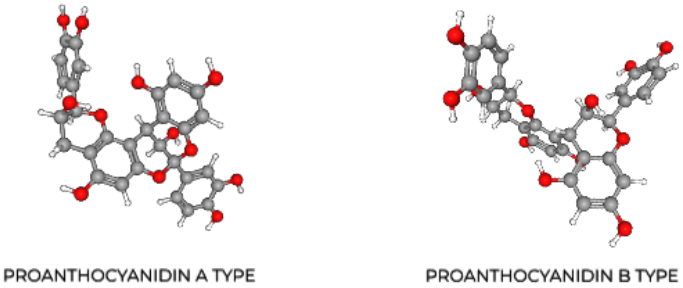

Fig. 2. Chemical structure of a type and b type proanthocyanidins

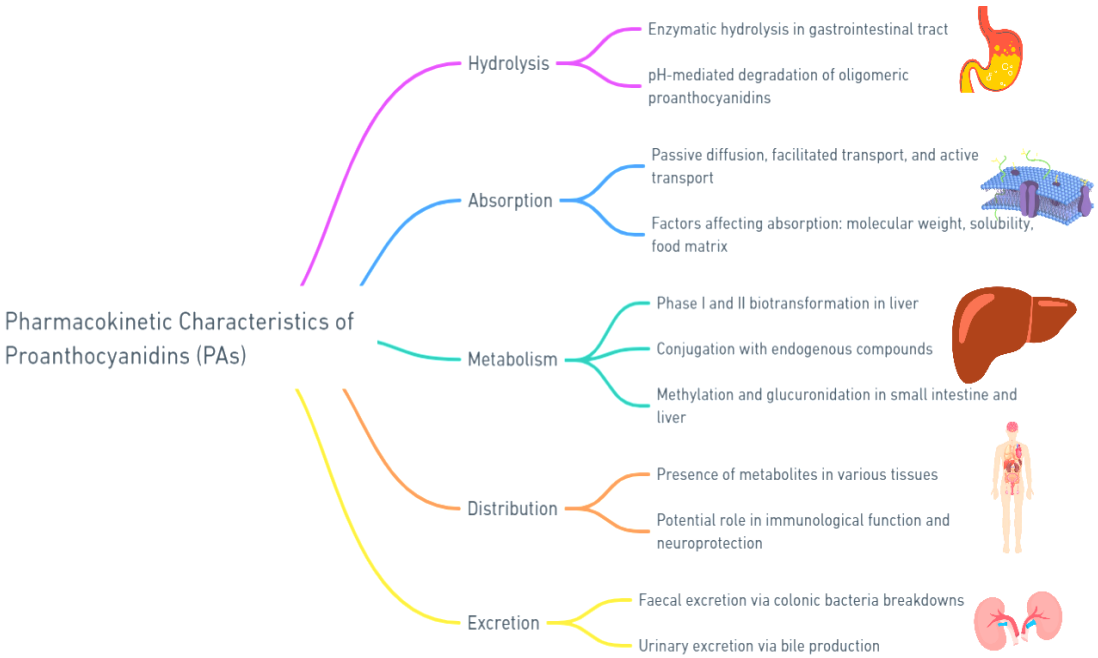

Fig. 3. Pharmacokinetic action of proanthocyanidins

4.5 Excretion

PAs are excreted mainly through urine and faeces in monomeric or dimeric forms. The liver produces bile to aid in fat digestion, which is another way the body eliminates these substances during metabolism [21].

5. PROPERTIES OF PROANTHOCYANIDINS

5.1 Antioxidant Properties

The antioxidant properties of PAs are based on the multifaceted mechanism of action including scavenging of free radicals, chelation of metal ions, enhancement of endogenous antioxidant defences, ant inflammatory effects, stabilization of the cell membrane, and modulation of the signalling pathway.

Scavenging of free radicals - Free radicals are highly reactive molecules that contain single electrons and can damage lipids, proteins, and DNA in biological systems. PAs are powerful antioxidants that can transfer electrons or hydrogen atoms to unstable free radicals, therefore stabilising them thus protect cells and tissues from oxidative injury [22].

Chelation of metal ions – Metal ions like copper, iron and zinc catalyse the production of highly reactive oxygen species (ROS) via mechanisms such as the Fenton reaction, resulting in oxidative stress. PAs chelate with these metal ions, preventing them from participating in hazardous processes and lowering ROS generation [23].

Regeneration of antioxidants - Superoxide dismutase (SOD), Catalase (CAT), and Glutathione peroxidase (GPx) are antioxidant enzymes occurring naturally in the body essential for neutralising ROS and protecting cells from oxidative stress. PAs may increase the expression of these enzymes such that strengthening the cellular antioxidant defence mechanism [24].

Inhibition of enzymes – Enzymes like NADPH oxidase and xanthine oxidase produce ROS as a consequence of their usual metabolic processes. PAs inhibits the activity of these enzymes which reduces ROS generation and oxidative stress [25].

Synergistic anti-inflammatory effects - Oxidative stress and inflammation are closely related phenomena, with one exacerbating the other. PAs have anti-inflammatory effects that supplement their antioxidant activity [26].

Stabilization of cell membrane - PAs can protect cellular membranes from oxidative damage by integrating into and stabilising the lipid bilayer. This contributes to the integrity and function of cell membranes, preventing cellular content leakage and ensuring cellular homeostasis [26].

Modulation of the signalling pathway – PAs modulate gene expression, stimulate nuclear factor erythroid 2-related factor 2 (Nrf2), and suppress pro-inflammatory mediators, thereby strengthening cellular antioxidant defence mechanisms [27].

5.2 Antibacterial Properties

The antibacterial properties of PAs include, direct microbial inhibition, biofilm inhibition, quorum sensing inhibition, antibiotic synergy, and immunomodulatory effects. PAs have direct antibacterial activity against a variety of bacterial infections, including Gram-positive and Gram-negative bacteria. They damage bacterial cell membranes, impede enzyme activity, and prevent microbial adhesion and biofilm formation, resulting in bacterial growth suppression and cell death. PAs interrupt biofilm formation, which prevents bacterial colonisation and persistence, making them effective against chronic and recurring infections. It affects quorum sensing, reduces bacterial pathogenicity, and makes bacteria more susceptible to antimicrobial drugs such that reducing antimicrobial resistance [28].

5.3 Anti inflammatory properties

Downregulation of inflammatory mediators - PAs prevent the formation and release of pro-inflammatory mediators, including cytokines, chemokines, and prostaglandins thus inhibiting inflammation. PAs (extracts as well as monomers, dimers, or trimers) can downregulate the transcription and secretion of proinflammatory cytokines, including the interleukins (ILs) IL-1b, IL-2, Il-6, and IL-8, tumor necrosis factor-a (TNF-a) and interferon-c (INF-c), and can upregulate the secretion of anti-inflammatory cytokines such as IL-10, IL-4, or transforming growth factor-b (TGF-b) in peripheral blood mononuclear cells, macrophages, or lymphoid cell lines [26].

Inhibition of enzymes - PAs have the ability to inhibit enzymes involved in the arachidonic acid

(AA) pathway. This inhibitor targets important enzymes such as phospholipase A2, cyclooxygenases (COX), and lipoxygenases (LOX), decreasing the generation of pro-inflammatory mediators such prostaglandins (PGs) and leukotrienes (LTs). Procyanidins have been shown to suppress COX2 on various levels, including gene transcription, protein expression, and enzyme activity. They compete with arachidonic acid (AA) for binding to COX proteins, reducing the production of PGs. Furthermore, procyanidins have been demonstrated to decrease LOX action, notably the development of pro-inflammatory long-lasting tissues. While the specific interactions between PAs and LOXs are unknown, research indicates that the presence of galloyl moieties in PAs may improve their inhibitory efficacy [26].

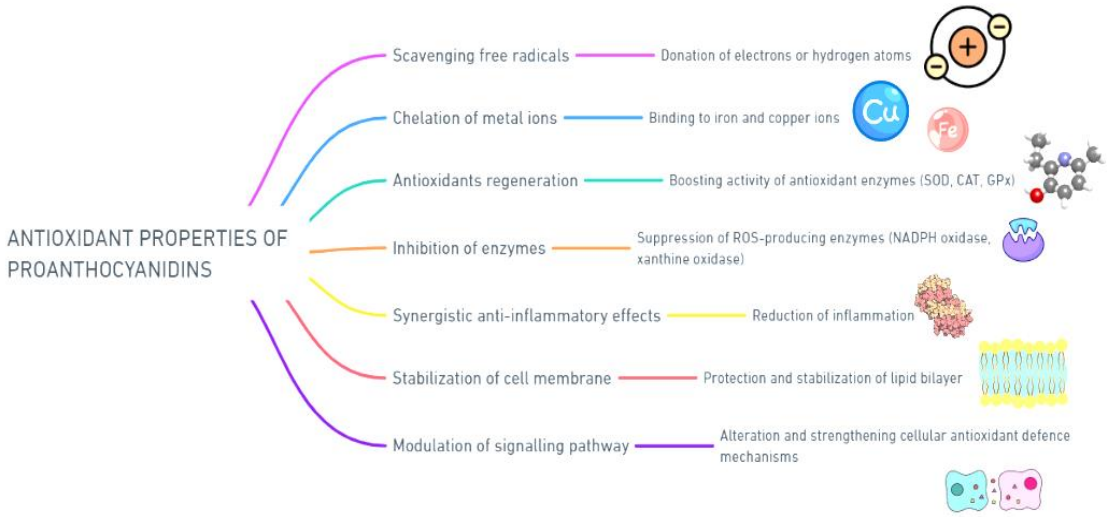

Fig. 4. Antioxidant properties of proanthocyanidins

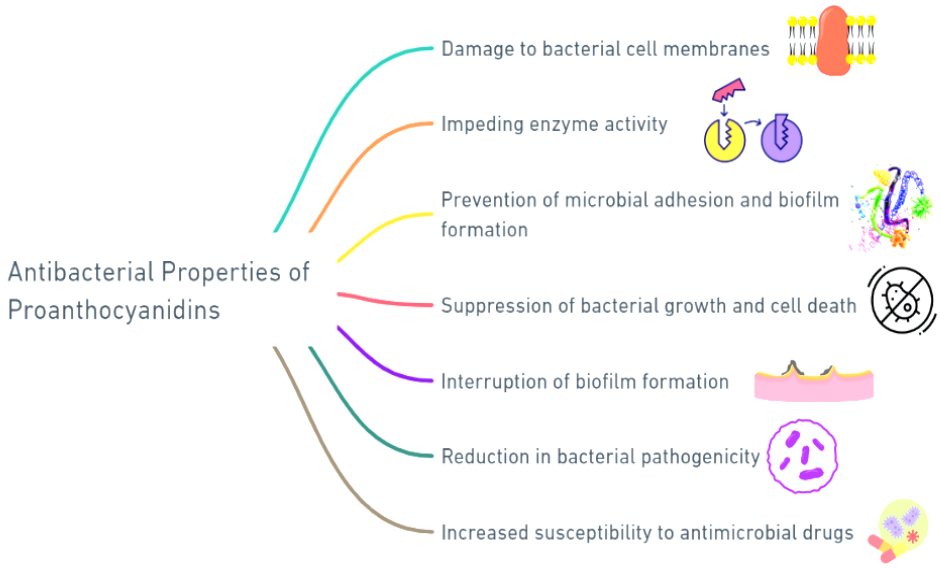

Fig. 5. Antibacterial properties of proanthocyanidins

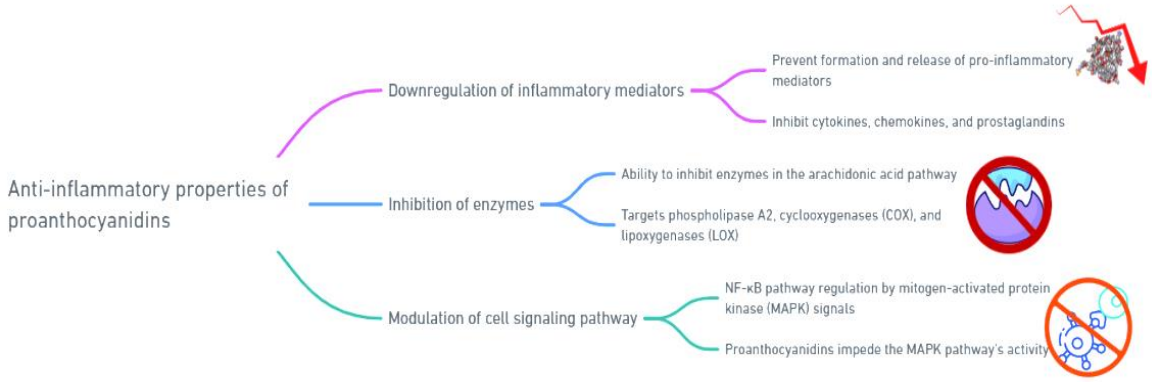

Fig. 6. Anti- Inflammatory properties of proanthocyanidins

Modulation of cell signalling pathway – The NF-κB pathway, a major proinflammatory signalling system that controls the expression of several proinflammatory genes, is largely regulated by mitogen-activated protein kinase (MAPK) signals. Proinflammatory cytokines like IL-6, TNF-α, and IL-1β, as well as inflammatory mediators like nitric oxide (NO), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and prostaglandin E2, are all transcriptionally regulated by MAPKs. Proanthocyanidins (PAs) directly impede the MAPK pathway's activity when under stress. Procyanidins (PCs) have shown anti-inflammatory characteristics in mouse brain cells by focusing on iNOS, COX-2, IL-6, IL-1β, and TNF-α [27].

6. MECHANISM OF ACTION ON ORAL HEALTH

6.1 Inhibition of Oral Pathogens

PAs inhibits various species of bacteria which are responsible oral health disorders such as dental caries, periodontal diseases and other oral conditions. Some of the known oral pathogens that PAs have shown to inhibit include:

Streptococci mutans – It is one of the primary causative agents of dental caries. The mutans strain of Streptococcus metabolises carbohydrates to generate acids, which can cause enamel demineralization and caries. PAs have been shown to limit the growth and acid production of Streptococcus mutans, lowering its cariogenic potential [29]. PAs inhibits the growth of Streptococcus mutans by destabilizing the bacterial cell membrane via inhibition of the ATPase enzyme [30]. PAs inhibit the acid production and glucosyltransferase activity such that inhibits the bacterial biofilm formation [31]. PAs plant extracts cause remarkable downregulation of the virulence genes responsible for the adherence, biofilm formation, extracellular polysaccharide synthesis and acid production [32]. PAs extracted from cranberry, grape seeds and Uvaria chamae inhibited S. mutans [31].

Periodontal pathogens - PAs containing extracts from green tea, blueberry, cranberry fruits, Rumex acetosa L, Pelargonium sidoides, grape seed, pomegranate fruit, and have shown to effectively inhibit porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, prevotella intermedia and Fusobacterium nucleatum which are responsible for gingival and periodontal infections [33].

6.2 Remineralization Action on Teeth

PAs have remineralization properties on teeth by following mechanisms:

Formation of hydroxyapatite crystals - The PA molecules contain a number of hydroxyphenyl groups, which may act as ligands to bind calcium ions. PAs have been shown to interact with calcium ions and phosphate ions present in saliva to form complexes. These complexes serve as precursors for the formation of hydroxyapatite crystals, which are the main mineral component of tooth enamel. These complexes are Spherical amorphous calcium

phosphate depositions. ACP clusters that form along the collagen fibrils may act as mineral precursors, delivering an additional external source of calcium and phosphate ions in a controlled manner for remineralization in deeper parts of the carious lesion [34]. Hydroxyapatite precipitate may occur via a metastable crystalline transition.

Formation of a protective barrier against mineral loss – PAs stabilizes the organic matrix of the demineralized teeth structure and form a protective layer to prevent the teeth on acidic conditions on further mineral loss. By forming a barrier against acids, PAs help prevent further demineralization and promote the remineralization of enamel lesions [35].

Enhancement of Calcium and Phosphate Uptake – PAs when applied on demineralized teeth increases the uptake of calcium and phosphate ions. Diffusion of these calcium and phosphate into the demineralized enamel led to restoration of the lost minerals during the carious process. This eventually leads to enamel repair and strengthening [35].

Creation of favourable environment for remineralization – PAs possess synergistic antioxidant and anti-inflammatory properties. Oxidative stress and inflammation have been implicated in the pathogenesis of dental caries and enamel demineralization. By reducing oxidative damage and inflammation, PAs create a favorable environment for remineralization to occur [36].

7. APPLICATIONS OF PRO-ANTHOCYANIDINS IN DENTISTRY

7.1 Dental Caries

PAs are known to prevent dental caries by the following actions – 1. Reduction of caries causing pathogens Streptococcus mutans and inhibition of biofilm formation [29-32]. 2. Uptake of calcium and phosphate ions by the demineralized enamel [3]. Formation of amorphous calcium phosphate particles which are the precursors of hydroxyapatite crystals [34].

Xu L et al 2011, found that the PAs derived from Sorghum bicolor (B type PAs predominantly containing catechin monomers) showed preventive action against dental caries by inhibiting the production of acid from S. mutans and S. sobrinus in an invitro environment. It also had the properties of scavenging superoxide anion radicals [37]. Zagnat M et al 2017, found that the crude PAs extracted from grape seeds when applied topically on rat teeth in a experimentally modelled carious environment had significant anti carious properties. It had antibacterial and anti-adherence effects on the dental biofilm, anti-oxidant properties, and immunomodulatory actions which are important factors in the prevention and progression of dental caries [38]. Koo H et al 2010, found that there was a significant reduction in the severity of smooth surface caries on rat teeth on topical application of PAs from cranberry extract for 7 days [39]. This was attributed to the properties of type A PAs with predominant epicatechin monomers. This type of PAs binds irreversibly to the catalytic and glucan binding domains to form protein polyphenol complexes. Oligomeric A PAs has effects on the bacterial cell membrane thus inhibiting the glycolytic pathway and inhibition of glucosyltransferases. The inhibition of the acid production of the bacteria is attributed to the dimeric PAs mainly A2 [40].

The PAs derived from grape seed extract has shown to have good remineralization properties on the demineralized teeth comparative to that of the fluoride in the invitro carious environment [41]. Acil et al 2005, discovered that Type 1 collagen is deficient in enamel but Type X collagen is present in the enamel matrix that might be implicated in enamel mineralization by the PAs.

7.2 White Spot Lesions in Orthodontics

Randomized controlled trials on grape seed extract PAs hydrogel (containing 95% PAs) on application on white spot lesion following post orthodontic therapy was significantly reduced on application for 6 months. The reversal of white spot lesions was attributed to the mineral deposition on the demineralized subsurface enamel by formation of insoluble calcium phosphate complexes in the saliva making the Ca and PO3 ions bioavailable for remineralization [42]. PAs have both hydrophobic and hydrophilic properties, which enhances their capacity to attach to a wide range of substances, ions, minerals, proteins, and carbohydrates in an irreversible insoluble manner making it a strong remineralizing agent [43].

7.3 Gingival and Periodontal Disorders

PAs have significant antibacterial properties against periodontal pathogens such as Porphyromonas gingivalis, Aggregatibacter

actinomycetemcomitans, Fusobacterium nucleatum, Prevotella intermedia, Treponema denticola, Tannerella forsythia, Eikenella corrodens, and Peptostreptococcus micros [44]. The development of periodontitis is mainly because of the presence of the dental plaque on the teeth surface and the immune inflammatory response of the host. The periodontal pathogens activate both innate and adaptive immune responses releasing pro inflammatory cytokines such as IFNγ, IL-17, TNF-α, IL-1, and IL-6 and enzymes such as MMPs. The inflammatory response defends the body from microorganisms and their infiltration into deeper tissues (such as bone). However, if the inflammatory process persists and is poorly regulated by the host, it can produce the most serious adverse changes in periodontal tissue form and function, including as periodontal pockets, attachment loss, gingival recessions, tooth mobility, tooth migration, and tooth loss – periodontal infections [45].

MMPs are responsible for the breakdown of periodontal tissues leading to periodontal infections. These are calcium and zinc dependent enzymes which are responsible for the destruction of the extracellular matrix, collagen matrix, elastin, gelatin, matrix glycoproteins and proteoglycans. These MMPs are present predominantly in the fibroblast cells, neutrophils and macrophages that are activated by bacterial proteinases. Under normal conditions, MMPs offer protective properties in wound healing. In conditions of periodontal infections, the bacteria lead to the increased production of MMPs leading to the destruction of the periodontal tissues. MMPs also activate the inflammatory pathway by release of cytokines. PAs are known to have anti-inflammatory properties can inhibit the MMPs such that can be used as a potential therapeutic agent in periodontal infections [44,45].

The PAs extracted from Ulmus macrocarpa Hance bark, tea leves (Camellia sinensis), cranberries (Vaccinium macrocarpon fruits), blueberries Vaccinium corymbosum, V. angustifolium inhibited (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, and MMP-13) involved in periodontitis [46]. Govindaraj J et al 2019, investigated the therapeutic effects of endotoxin induced experimental periodontitis on rats. On receiving PAs for 30 days, there was significant inhibition of reactive oxygen species, and lipid peroxidases. Thus, concluded that it can be used as a potential agent in the treatment of periodontal diseases [47] Díaz Sánchez RM et al 2017 in an RCT, found that the cranberry extract PAs in form of tablet enhanced the gingival and periodontal status [48].

7.4 Peri Implantitis

The PAs inhibits MMP- 9 gene expression in osteoblasts and osteoclast formation which can prevent the bone resorption. Periodontitis leads to osteoclast genesis because of inflammatory cytokines and osteoclasts proliferation. Osteoclasts produced from monocyte/macrophage progenitors stimulate alveolar bone degradation through RANKL and M-CSF. PAs were discovered to decrease RANKL-dependent osteoclast development and MMP secretion while enhancing IL-8 secretion, which suppresses osteoclast activity. It also affects bone regeneration by inhibiting the NF-κB signalling pathway. PAs at low doses reduced TNF-α-induced suppression of osteogenic differentiation via the NF-κB signalling pathway, limiting bone resorption and improving bone regeneration [49,50].

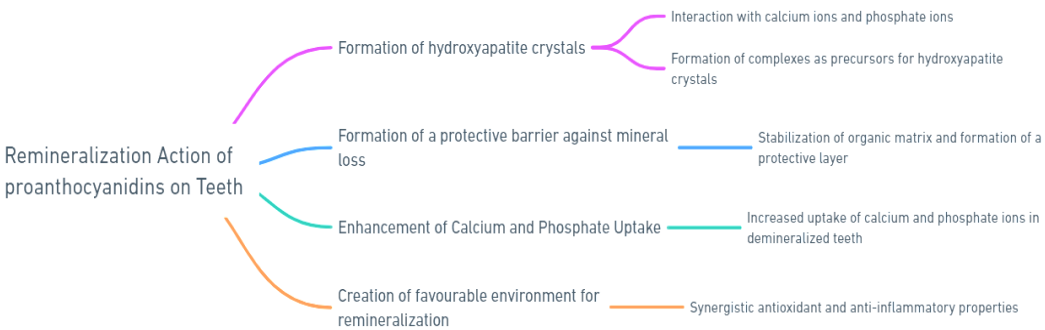

Fig. 7. Remineralization actions of proanthocyanidins on teeth

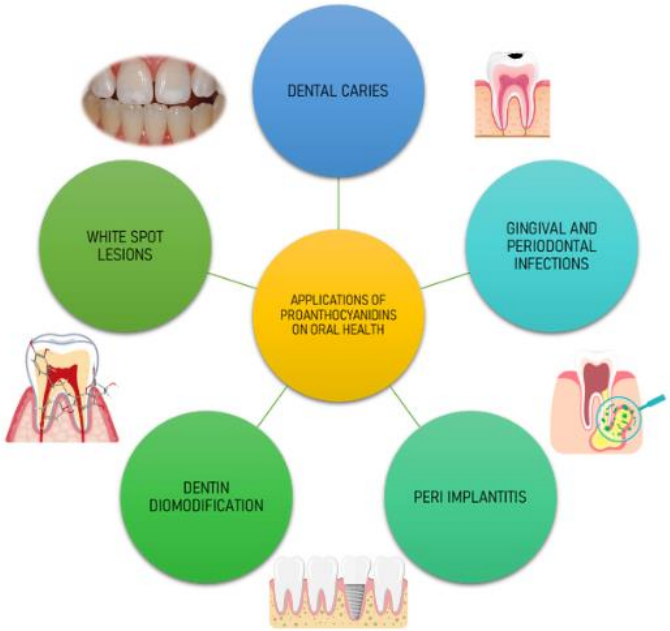

Fig. 8. Applications of proanthocyanidins on oral health

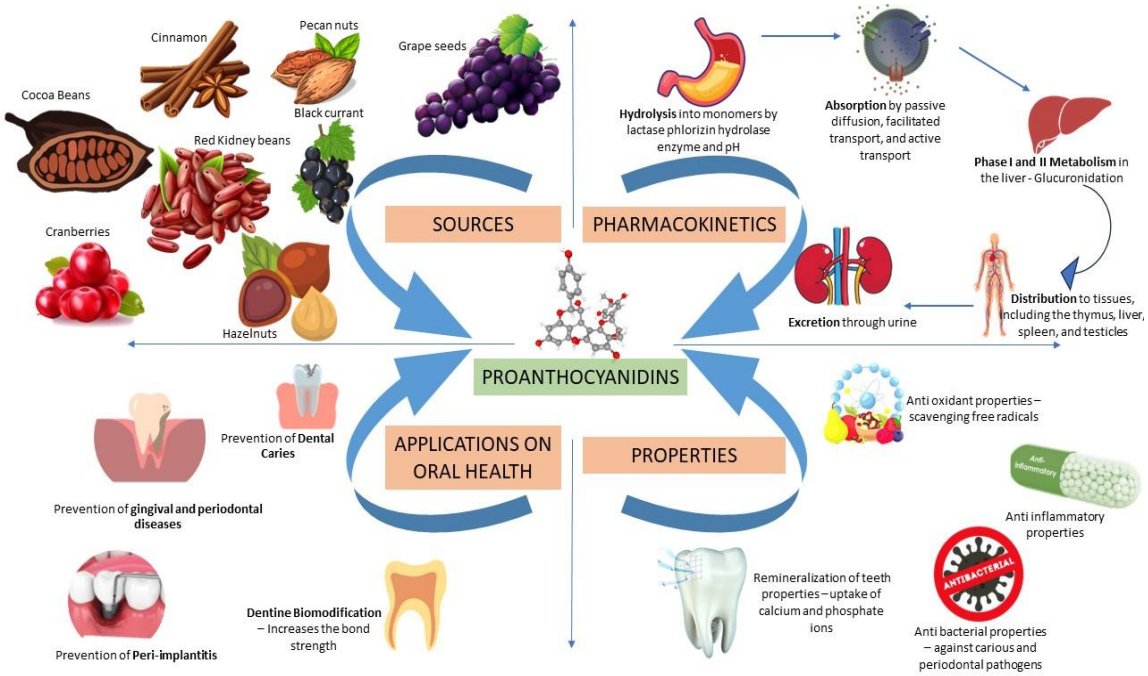

Fig. 9. Summary of sources, pharmacokinetics, properties and applications on oral health

Macrophages are an important mediator between tissue healing and alleviation of inflammation in the inflammatory response at the sites of periodontitis and peri-implantitis. Their dual pathways impact disease progression and tissue homeostasis by supporting both turnover and tissue repair. Macrophages take on an M1 phenotype when stimulated by bacterial byproducts such as lipopolysaccharides (LPS), which causes them to secrete pro-inflammatory cytokines and cause harmful osteolytic inflammation. On the other hand, alternative activation results in an M2 phenotype, which is linked to constructive inflammation and is

characterised by the release of growth factors that aid in tissue repair as well as anti-inflammatory cytokines. Macrophages are an important mediator between tissue healing and alleviation of inflammation in the inflammatory response at the sites of periodontitis and peri-implantitis. Their dual pathways impact disease progression and tissue homeostasis by supporting both turnover and tissue repair. Macrophages take on an M1 phenotype when stimulated by bacterial byproducts such as lipopolysaccharides (LPS), which causes them to secrete pro-inflammatory cytokines and cause harmful osteolytic inflammation. On the other hand, alternative activation results in an M2 phenotype, which is linked to constructive inflammation and is characterised by the release of growth factors that aid in tissue repair as well as anti-inflammatory cytokines [51].

7.5 Dentine Biomodification

PAs have the ability to bio modify demineralized dentin matrix, inhibit proteolytic activity, and stabilize the adhesive/dentin interface against enzymatic degradation. PA has been shown to improve the durability of adhesive restorations by inducing collagen cross-linking, increasing the resistance of collagen to degradation, and enhancing the mechanical properties of dentin matrix. Additionally, PA has been found to inhibit the biodegradation of collagen fibrils within the hybrid layer and increase the immediate and long-term adhesion of adhesive systems to demineralized dentin in in vitro methods.PA has been shown to protect collagen from degradation by inducing irreversible conformational changes in proteases, inhibiting the production of matrix metalloproteinases (MMPs), and increasing the density of the collagen network. Additionally, PA may interfere with protease production and activation by modulating host immune responses. PA also increases the resistance of the collagen matrix against enzymatic degradation by inducing exogenous cross-links and decreasing collagenase absorption. These mechanisms contribute to the stabilization and protection of collagen, making PA a potential natural [52,53].

8. SAFETY

PAs (PAs) produced from grape seeds have been extensively toxicologically tested, demonstrating their safety for usage in a variety of food supplements. Studies on rats revealed no immediate oral toxicity, even at high doses, and no indication of mutagenicity or teratogenicity. However, some caution is necessary because PAs from other sources, such as Hamamelis virginiana bark, caused minor DNA damage in human hepatoma cells. Nonetheless, a patented product including catechin-type monomers and PAs showed good safety in rats and healthy volunteers, with no side effects identified. PAs may also have an effect on macronutrient digestion and absorption, thus lowering protein consumption which could be advantageous in obesity prevention. They may, however, interact with metal ions, reducing the bioavailability of important minerals like as iron and zinc, necessitating precautions for their effective usage in extracts [54,55].

The summary of the sources, pharmacokinetics, properties, and applications of PAs on Oral health is given in Fig. 9.

9. CONCLUSION

To summarize, PAs extracted from natural sources have anti-inflammatory, antioxidant, anti-bacterial, anti-cariogenic and remineralizing properties with minimal adverse effects can be used in enhancing the overall oral health. The PAs can be incorporated into the oral care products and treatment strategies in the prevention and therapeutic management of dental caries, gingival, periodontal and overall oral health status of the individual. Many in vivo studies and clinical studies are required to explore and validate the use of PAs, their clinical applications and optimal formulations for use in dentistry.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc have been used during writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology.

Details of the AI usage are given below:

1. Whimsical's mind map maker for creation of flowcharts

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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