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Potential of CPP-ACP and cranberry proantho-cyanidin chewing gum for remineralization of perimylolysis in eating disorders patients

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Abstract

Background: Eating disorder (ED) is characterized by abnormalities in the pattern, amount, and nature of food eaten. Recent studies confirm the high prevalence of ED worldwide, which has increased significantly from 3.5% to 7.8% in the last 18 years. One of the common symptoms of ED sufferers is intentional vomiting, which can lower the pH of the oral cavity and induce perimylolysis. A new challenge is finding an innovation to alleviate perimylolysis in ED patients regarding behavior and dental treatment.

Material and Methods: The literature review was carried out in PUBMED, ResearchGate, and ScienceDirect with the keywords: CPP-ACP, proanthocyanidin, chewing gum, eating disorder.

Conclusions: Chewing gum containing CPP-ACP and proanthocyanidins from cranberries has been shown to have remineralization potential to help relieve perimylolysis in ED patients from a behavioral and dental perspective.

Keywords: CPP-ACP; Proanthocyanidin; Remineralization; Chewing Gum; Eating Disorder

1 Introduction

Along with the development of the era in the digital age, humans are indirectly required always to appear perfect as they see on social media. One of these demands is related to body shape and weight, which can trigger extreme measures to maintain an ideal body. This can lead to eating disorders (ED). Recent research confirms the high prevalence of ED worldwide, which has increased significantly from 3.5% to 7.8% in the last 18 years [1]. Eating disorders are disorders that can include eating behavior, food intake, and types of food. Eating disorders include anorexia nervosa, bulimia nervosa, and ruminant syndrome [2]. In anorexia nervosa and bulimia nervosa, patients usually regurgitate swallowed food because of excessive fear of being overweight and of a body shape that they think is inappropriate [3]. In contrast, ruminant syndrome patients usually spit out food that has been swallowed to be chewed again [4]. This situation can cause the condition of the oral cavity to become acidic and induce a disease called perimylolysis [5].

Perimylolysis is enamel erosion that usually occurs on the palatal side of the mandible so that it can change the anatomical shape and interfere with tooth function [5,6]. There is a need for a material that can suppress demineralization and increase tooth remineralization in perimylolysis patients. Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) is a nano complex of milk protein (CPP) and hydroxyapatite precursor (ACP) which has been shown to suppress demineralization and increase tooth remineralization through its role as a calcium phosphate reservoir on the tooth surface which helps induce remineralization. CPP-ACP is combined with an ingredient isolated from cranberries to enhance its function. The material is proanthocyanidin, a polyphenol class compound that has a role as a tooth remineralization agent by inducing cross-linking formation [7,8]. The two ingredients are combined as

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chewing gum, which increases saliva's flow rate, which can trigger the remineralization of enamel and an increase in pH due to its buffer activity [9].

2 Material and methods

2.1 Search strategy

A literature search in English was performed, using the PUBMED, ResearchGate, and ScienceDirect base to identify research of the Potential of CPP-ACP and Cranberry Proanthocyanidin Chewing Gum for Remineralization of Perimylolysis in Eating disorders Patients. Research and literature reviews from 2013 to 2022 were included. The following keywords were searched: CPP-ACP, proanthocyanidin, chewing gum, and eating disorder.

3 Results and discussion

3.1 Eating Disorder and Perimylolysis

Abnormalities in food intake, type of food, and eating behavior characterize eating disorders. This behavior is determined by the patient's attitude to body weight and shape [10]. The initial features of ED are mainly found in or around the oral cavity. Oral signs and symptoms of ED are usually observed either because of a history of malnutrition or self-induced vomiting. There are three main types of oral pathology of ED: pathological tooth erosion or loss, caries, and chronic vomiting. Medical conditions accompanying dental erosion include anorexia nervosa, bulimia nervosa, GERD, rumination disorder, and xerostomia. Enamel erosion is the most common oral complication, caused by vomiting, and becomes apparent about six months after onset. Usually, enamel erosion is found on the palatal side of the upper anterior teeth because they are often exposed to acid. This type of enamel erosion, known as perimylolysis, has a smooth and shiny appearance. In more chronic cases, erosion occurs on the maxillary teeth' palatal margins and the mandibular molars' occlusal surfaces. Occasionally, perimylolysis is the only oral symptom observed in a patient who induces vomiting [11].

3.2 CPP-ACP and Remineralization

Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) is a nano complex patented by Reynolds at the University of Melbourne, Australia, in 1997. The CPP-ACP nano complex consists of the protein casein phosphopeptide (CPP) derived from milk and its products and composed of phosphorylated serine residues and the amino acid glutamate. The most studied casein phosphopeptide (CPP) is derived from αs1-casein and β-casein. These two CPPs [αs1-casein f(59–79)5P and β-casein f(1–25)4P] contain specific chain sequences known as 'acid motifs.' The 'acid motif' consists of 3 serine phosphate groups followed by two glutamic acid residues of the order Ser(P)-Ser(P)-Ser(P)-Glu-Glu. At neutral pH, the 'acid motif' is a highly charged region, and this condition is related to the ability of CPP to bind minerals because the serine-phosphate group is the primary binding site for calcium. The nano complex also contains dental hydroxyapatite precursors, amorphous calcium phosphate (ACP), whose ions are phosphorylated by CPP serine residues. CPP with a specific sequence of 'acid motif' in tryptic digestion has been reported to stabilize amorphous calcium phosphate. Based on preliminary research, this nanocomplex can suppress demineralization and improve tooth remineralization [12,13].

Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) in perimylolysis patients works as a remineralizing agent by creating an environment rich in calcium and phosphate on the enamel surface. Casein Phosphopeptide (CPP) can maintain high concentrations of calcium and phosphate ions in metastable solutions by forming CPP-ACP nano complexes. The formation of CPP-ACP nano complexes will increase the total surface area and interaction with biofilms and tooth structure. The continuous use of CPP-ACP products will increase the saturation of Ca^{2+} and PO_4^{3-} ions in saliva and biofilms so that CPP-ACP acts as a reservoir of calcium phosphate that can suppress demineralization and encourage tooth enamel remineralization. The desensitizing effect of teeth is also produced through the penetration of calcium phosphate ions into the peritubular dentin, creating deposits that block some external stimuli and reduce dentin hypersensitivity. However, the stability of CPP- ACP mineral deposits in exposed dentin can be affected by brushing, an acidic diet, and phosphatase production by oral bacteria. For this reason, continuous topical application is required to maintain significant precipitation formation of Ca^{2+} and PO_4^{3-} ions on the tooth surface [14].

3.3 Proanthocyanidin in Cranberry

Cranberries are known as a fruit with high levels of vitamin C and fiber. Apart from this, the health benefits of cranberries are mainly associated with the various types of polyphenol group compounds they contain. Polyphenols are plant metabolites of flavonoid and non-flavonoid compounds found in multiple food and beverages. The polyphenol content also provides unique organoleptic characteristics and properties for cranberries [15]. Some flavonoids, such as the flavan-3-ols catechin and epicatechin, polymerize to form tannins. Tannins are plant secondary metabolites that can be hydrolyzable or condensed. The condensed tannins are also known as proanthocyanidins. Proanthocyanidins are polymeric flavonoids with flavan-3-ol subunits linked via C4 or C6 positions. These flavan-3-ol polymers are often linked via C-C bonds (type B proanthocyanidins) or C-O-C bonds (type A proanthocyanidins). Oxidative condensation in type B occurs between the C4 carbon of the heterocycle and the C6 or C8 carbon. The four most common type B proanthocyanidin dimers such as B1, B2, B3, and B4, are linked via C4-C8 chemical bonds, whereas proanthocyanidins B5, B6, B7, and B8 contain interflavant C4-C6 bonds [15,16]. Meanwhile, type A proanthocyanidins are linked via a C2-O-C7 addition bond or a C2-O-C7 ether bond that produces a double-bond proanthocyanidin. Catechin and epicatechin are the building blocks in the formation of proanthocyanidin. The leukoanthocyanidin reductase enzyme will catalyze catechins synthesis, the first step in proanthocyanidin biosynthesis [17]. The proanthocyanidins in cranberries are unique because they are dominated by type A proanthocyanidins which are generally not found in most fruits (type B is commonly found). The proanthocyanidin contained in cranberry (type A) inhibits a-amylase more strongly than type B. The effect of additional ether binding can be attributed to its higher hydrophobicity. In addition, cranberry proanthocyanidins also have a higher degree of polymerization than grape proanthocyanidins, thereby increasing the strength of the polymer [18].

3.4 Proanthocyanidin and Remineralization

Cranberry is a phytotherapy agent containing proanthocyanidin (PA), a polyphenolic compound. Proanthocyanidins are metabolites of natural plants that are widely available, especially in fruits and vegetables, and have many therapeutic benefits. According to various journals, proanthocyanidins can affect tooth remineralization through two mechanisms. The first is to cause mineral deposition in the superficial area above the lesion by forming a complex that is not easily soluble. Furthermore, in the context of dentine erosion, proanthocyanidin can increase the percentage of microhardness recovery by reacting with the exposed organic matrix to stabilize collagen because it induces the formation of cross-links [18]. PA as a cross-linking agent, can strengthen collagen molecules so that they cannot be separated from each other due to mechanical strength. In addition, PA can also prevent the chelation of calcium and phosphate ions from dentine during acid challenge. PA also plays a role in binding calcium ions from the remineralization solution, causing calcification in the matrix [19]. PA formed stable interfibrillar bridges with collagen through hydrogen and covalent bonds, while the special triple helix conformation was preserved. The phenolic hydroxyl groups of proanthocyanidins can form hydrogen bonds with the amide carbonyl or hydroxyl groups of collagen fibrils, thereby increasing their mechanical properties. During the cross-linking processes, PA molecules changed the water dynamics by displacing the bound water of collagen, allowing more liquid-like particles to penetrate fibrils. PA is also a polyanionic molecule that can chelate charged ions and act as a ligand to bind calcium ions, thereby increasing the distribution of minerals to the collagen fibers. From molecular dynamics analysis, calcium ions exhibit more energetically favorable interactions with PA than natural collagen molecules' primary residues (Pro and Gly). It is conceivable that the presence of PA can enhance mineral ion association and promote nucleate heterogeneous calcium phosphates to facilitate collagen mineralization. This mechanism forms a stable collagen matrix that can function as a mechanical barrier, inhibiting the adverse effects of acids and further loss of minerals [20].

3.5 Combination of Proanthocyanidin and CPP-ACP on Remineralization

PA-modified collagen elicited more ACP nanoparticle deposition along the microfibrillar space. Therefore, mineral aggregation around collagen fibrils will increase with increasing PA concentration and achieve more satisfactory mineralization. Bridge-like bonds between PA molecules and collagen fibrils could facilitate further ACP nanoparticle infiltration and reduce the interfacial energy of collagen fibrils [20]. PA is acidic and can lower the pH of CPP-ACP. It will enhance remineralization by releasing more amorphous calcium phosphate ions into the tooth lesion. On the other hand, the calcium-binding effect of PA also allows more significant mineral deposition in the lesion. Using a combination of PA and CPP-ACP has a synergistic effect on remineralization and optimal interaction of minerals with the collagen matrix because it recovers some part of the mechanical characteristics of the collagen matrix [21]. Proanthocyanidins play a role in the remineralization process, especially by inducing cross-linking mechanisms of collagen fibers and increasing the distribution of minerals into them. Dentine is a mineralized collagen matrix containing approximately 35% organic matter; the remaining 65% is inorganic matter and water. Enamel comprises 96% inorganic matter with only about 4% organic matter and water [22]. Thus, PA plays a more significant role in remineralizing dentine due to the higher organic matter composition than enamel, whereas CPP-ACP has a more significant role in remineralizing enamel. Combining these two materials will increase the potential for tooth remineralization in patients with eating disorders with perimylolysis.

3.6 The Role Of Chewing Habits In Overcoming Eating Disorders

Eating disorders are characterized by abnormalities in eating behavior, food intake, and types of food. This behavior is primarily determined by the patient's attitude to body weight and body shape. This disorder has core psychopathological characteristics, which can be described as an overestimation of weight and body shape, in which patients assess self-esteem in terms of shape and weight and their ability to control it. Eating disorders are associated with several physical symptoms grouped under three behaviors, namely anorexia nervosa (loss of appetite), bulimia nervosa (extreme attempts to cope with weight gain), and ruminant syndrome (re-chewing and swallowing regurgitated food) [23]. Various behavioral strategies are carried out to overcome eating disorders, including chewing gum. Previous case reports found no regurgitation after the implementation of such treatment was found in patients, even after one to two years of follow-up. Chewing gum consumption has benefits related to the regulation of oral acidity. A recent study reported that mastication and chewing gum taste could increase the salivary flow rate. The increase in salivary flow rate is a response to gustatory (taste) and mechanical (mastication) stimuli. In addition to increasing salivary flow rate, gum mastication increases salivary pH and plaque (increased bicarbonate ions) and triggers enamel remineralization. However, unlike salivary flow, which only increases when given stimulation (mastication), saliva's pH will still increase after 15-20 minutes of stimulation. Concerning eating disorders, increased pH by saliva will reduce tooth erosion due to acid exposure from the vomit of people with eating disorders [24].

3.7 CPP-ACP vs Xylitol Chewing Gum

Both chewing gum containing CPP-ACP and xylitol can increase the salivary flow rate and pH. This is because chewing gum for a long time will increase the stimulated saliva, which ultimately causes an increase in salivary pH [25,26]. According to research by Prathima et al., there is no significant difference between the two types of chewing gum with its ability to increase the flow rate, pH, and salivary buffer capacity. However, chewing gum with CPP-ACP content showed better results than gum with xylitol content in increased buffer action [25]. Another study by Padminee et al. stated an increase in pH and salivary buffering ability after using gum with CPP-ACP content. The CPP-ACP nano complex serves as a reservoir of calcium and phosphate ions that help maintain pH and salivary buffers. This may be because the mineral ions in CPP-ACP gum are almost as many as those in a liter of remineralized solution or saliva. Thus, the increased availability of ions derived from CPP- ACP gum will offset the decrease in pH. Furthermore, neutral $CaHPO_4$ formed by ion pairs released from CPP-ACP takes a role in reducing most acids. CPP-ACP also has the credibility of promoting remineralization even in acidic environments [26].

4 Conclusion

From the analysis conducted on various kinds of literature, chewing gum containing CPP-ACP and proanthocyanidins (from cranberries) has the potential as a remineralizing agent regarding ingredients and preparation. The remineralizing potential of this chewing gum can help treat perimylolysis patients due to eating disorders. Further research is needed to prove the potential and effectiveness of using this chewing gum as an adjuvant treatment in treating patients with perimylolysis.

Compliance with ethical standards

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Disclosure of conflict of interest

We declare that there was no major conflict of this article

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