Oral and Physiological Benefits of Cranberries

Running title: Periodontal disease and Cranberries

**Abstract**

Cranberries are known to prevent urinary tract infection and it is also helpful in maintaining the oral health. Cranberry juice is a widely consumed and recommended beverage for preventing urinary tract infection. Clinical studies in women have shown that cranberries help to prevent the recurrence of infection, as the evidence showed the presence of various extracts of cranberries in the patients’ urinary tracts, proving the effectiveness and the mechanism. The primary compound involved in fight against the infection is Proanthocyanidin A (PACs) that is now the focus of studies to treat common diseases such as dental caries and periodontal disease, from which it is speculated the mechanism to involve disrupting the bacterial adhesion.

Keywords: Periodontal disease; Cranberries; Biofilm; Dental caries; Dental plaque

**Introduction**

Cranberries are known to promote oral health, especially when the juice of cranberries is a popular beverage and a recommended dietary remedy for the prophylaxis of urinary tract infection (UTI). Clinical trials showed that cranberries did improve the condition of recurrent urinary tract infection in females[1]. Cranberry extracts in the urine samples could be inked to proanthocyanidins, which is now a hot compound for studies on its use in other common diseases, such as Helicobacter pyloric-associated gastritis, dental caries and periodontal disease, given that it is suspected to play a role in inhibiting the adhesion of bacteria on tissues or cells. Proanthocyanidins (PACs) [1], the most abundant flavonoid extracted from cranberries, have been reported to show antimicrobial, antioxidant and anti-inflammatory activities and prevent adhesion of microorganisms. Recent in vitro studies have shown that PACs may be a potential therapeutic agent for the prevention and management of periodontitis, an inflammatory disease of bacterial origin affecting the tooth-supporting tissues [2]. Since the phytochemicals in cranberries have been proven to benefit human health, this review would focus on the specific preventive effect of PACs on the breakdown of connective tissues and alveolar bone destruction, as well as their potential for controlling periodontal disease. Possible mechanisms may include inhibiting bacterial and host-derived proteolytic enzymes, inflammatory response in the host, and osteoclast differentiation and activities. With the interesting properties exhibited by PACs in these in vitro studies, the evidence does warrant further investigation by clinical trials to better evaluate the potential of the compound to control periodontal disease [2,3].

**The significance of oral diseases**

Oral diseases are a global public health problem, caused by a range of modifiable risk factors common to many noncommunicable diseases (NCDs), including sugar consumption, tobacco use, alcohol use and poor hygiene, and their underlying social and commercial determinants. It is with particular concern over their rising prevalence in many low-income and middle-income countries, linked to wider social, economic, and commercial changes(WHO, 2020). Oral diseases, while largely preventable, pose a major health burden for many countries and affect people throughout their lifetime, causing pain, discomfort, disfigurement and even death. It is estimated that oral diseases affect nearly 3.5 billion people (WHO, 2022). Normally the body's natural defenses and good oral health care, such as daily brushing and flossing, keep bacteria under control. However, without proper oral hygiene, bacteria can reach levels that might lead to oral infections, such as tooth decay and gum disease. he two are connected in many ways. Oral health is essential to general health and well-being at every stage of life. Oral conditions have an impact on overall health and disease. Bacteria from the mouth can cause infection in other parts of the body when the immune system has been compromised by disease or medical treatments. Neglecting this can cause infections in your teeth and gums that can lead to tooth decay, gum disease (periodontitis), tooth loss, dry mouth, mouth ulcers, and other problems that can create the climate for worsening dental health. If uncontrolled, bacteria in the mouth can multiply and enter the bloodstream, affecting other parts of the body. Gum disease, in particular, has been linked to heart disease, diabetes, respiratory ailments, and even Alzheimer's disease. Poor oral health is linked to diabetes, heart disease, adverse pregnancy outcomes, stroke and respiratory conditions. The main diseases that affect oral health are tooth decay, gum disease and oral cancers. These conditions are largely preventable.

**Cranberry Extract**

In the past few years, cranberry extract has increasingly attracted more attention from dental researchers [4]. This paper would explore the potential benefits of the extract in oral diseases, such as dental caries and periodontal disease. Cranberries are rich in high-molecular-weight polyphenols and polyphenols exist in thousand different forms, all of which are very promising in reducing caries activity (dental plaques) and periodontal disease, as well as controlling the inflammatory responses and enzymes that break down the extracellular matrixes[3]. The cranberry extract is characterized as an anti-caries agent, for its ability to inhibit acid production, bacterial adhesion and biofilm formation, targeting specifically the *Streptococcus* strains, in which the production of glucan-binding protein, the activities of extracellular enzymes, the metabolism of carbohydrates and bacterial hydrophobicity are affected [5]. For periodontal disease, the cranberry extract acts to suppress the host’s inflammatory response, inhibit the production and destructive activities of bacterial enzymes in the plaques, and prevent the formation of biofilm for adhesion, proteolytic activities and aggregation of pathogens in the periodontium. These show that cranberries, especially its high-molecular weight ingredient, can be used as bioactive substance for the prevention and treatment of oral diseases. Substance with a high molecular weight represents how far the substance can stretch before rupturing. The higher degree of entanglement allows the material to be pulled further before the chains break. And high molecular weight increases the viscosity of the material - makes it harder to process the material using conventional methods [4]. The interaction between a large amount of cranberry extract and clinical oral drugs such as Midazolam, Amoxicillin , Ceflacor, Cyclosporine, Salicylate, flurbiprofen, warfarin, tizanidine [20-25], such as Warfarin (Coumadin) interacts with cranberry, and Nifedipine (Procardia) interacts with cranberry. Warfarin is used to slow blood clotting. Atorvastatin (Lipitor) also interacts with cranberry. So medications changed by the liver enzyme (Cytochrome P450 2C9 (CYP2C9) substrates) interacts with cranberry. Like aspirin, cranberries contain salicylic acid. If you take aspirin regularly, as a blood-thinner, for example, or if you are allergic to aspirin, you should not take cranberry supplements or drink a lot of juice.

**Composition of Cranberries**

Cranberries contain quite a variety of substances, such as Proanthocyanidins A (PACs), tannic acid, organic acids, catechins, iron, zinc and other trace elements. Studies have pointed out that the major antibacterial component is Proanthocyanidins A, which can prevent dental caries, periodontal disease or urinary tract infection [6,7]. Over the last decade, in vitro clinical studies have found that some raspberry extracts are involved in microbial infection and spreading, especially the proanthocyanidins, which have an inhibitory effect on the adhesion of *E. coli* to urothelial cells. According to research, high-molecular-weight extracts in cranberries also showed similar effect to prevent the adhesion of P-fimbriated *E. coli* to the mucosa of gastric wall in humans; thus, preventing the development of gastric ulcers. These in vitro observations are consistent with evidence of cranberry extracts inhibiting urinary tract infection and *E. coli* infection. There are also some evidence supporting its inhibitory effect on some skin pathogens, but it has no effect on the oral pathogen, *Candida albicans* [8-10].

**Pathophysiological Mechanism of Preventing Periodontal Disease**

Proanthocyanidins are extracted from cranberries the fruit and are the most abundant flavonoid among the ingredients. Recent experiments have all pointed to its therapeutic potential as an agent in the prevention and treatment of periodontitis, which is an inflammatory disease of bacterial origin affecting the tooth-supporting periodontium [11-14], beside its potential to prevent urinary tract infection and oral health, as well. It is speculated that it can: 1) inhibit bacterial and host-derived proteolytic enzyme activities; 2) inhibit the inflammatory response in host; and 3) prevent the differentiation and activities of osteoclasts. These were proven in animal experiments, but it will require more clinical trials (randomized and controlled) to better assess its potential in the prevention and treatment of periodontal disease [15,16]. Another studies have found that the flavonoids in cranberry extract can inhibit the Glucosyltransferase enzymes (GTF) required for the formation of dental plaque, and an average of 250 mg of flavonoids can effectively inhibit 50% of GTF activities, while the teeth are naturally built to resist the bacteria by as much as 40%. Furthermore, experimental data showed that the active substances of cranberries, specifically the flavonoids (including Quercetin and Myricetin) can resist some degree of acidification and control the bacterial strain, *S.mutans*, that causes tooth decay. By reducing the chance of forming dental plaque, it may possibly prevent the formation of caries. In addition, cranberries stop Haemophilus bacteria from adhering to the mucosal epithelial cells; hence, reducing the chance of urinary tract infection. Recently, it was confirmed that PACs can prevent periodontal disease and dental caries by inhibiting the proteolytic enzymes from bacteria and the host, or inhibiting the host's inflammatory response, as well as inhibiting the differentiation and activities of osteoclasts. For periodontal disease and the necrosis of the tissues that are induced by gram-negative bacteria, the cranberry extract is highly effective in inhibiting MMPs and elastase secreted by inflamed oral cells. Plus, it plays to stop the acid-producing enzyme B and C (GTF-B, GTF-C), as well as F-Type ATPase in bacterial mitochondria. Overall, the evidence showed the cranberry extract with function to prevent periodontal disease and tooth decay, in addition to the inhibition of plaque formation and bacterial adhesion [9,15,17].

**Drug interaction**

There are several medications reported to be interacted with cranberry extract, such as Midazolam, Amoxicillin , Ceflacor, Cyclosporine, Salicylate, flurbiprofen, warfarin, tizanidine [20-25]. The underlying mechanisms may be based on in vitro evidence cranberry juice is an inhibitor of cytochrome P450. Intake of cranberry juice may increase the concentration of some medications in the human body. However, only consumption of large quantities of cranberry juice (approximatley1-2 L per day) and for an extended period (more than 3-4 weeks) may affect the effect of some medications, such as warfarin [26]. Although the total avoidance of cranberry juice by warfarin users may not be necessary, however, in certain situations of higher intake of cranberry juice or concentrate, patients who are taking medications mentioned above should be warned and monitored. Another interesting report shows that subjects who consumed cranberry juice were found to show marked increase of salicylic and salicyluric acids in urine within 1 week of the intervention (https://pubmed.ncbi.nlm.nih.gov/15826036/), suggesting that cranberries may contain components similar to salicylic acid. Therefore, any subjects should be careful to take cranberries if they have any allergic history or sensitivity to salicylic acid [23-27].

**Conclusion**

Cranberries are rich in healthy ingredients with nutritional value. In recent years, there was an increase in the public’s attention to the use of cranberries (Vaccinium macrocarpon) in North America, specifically the phytochemicals, namely anthocyanins, flavonols, flavan-3-ols, phenolic acid derivatives, proanthocyanidines, etc. These chemicals are the main ingredient of the cranberries’ inhibitory effect on bacteria, helping to fight against urinary tract infection and childhood diseases [16-18]. They are anti-bacterial, anti-adhesion, antioxidant and anti-inflammatory. Studies have shown that PACs in cranberries will help the connective tissues such as the gums and alveolar bones to resist breakdown and destruction by bacteria. PACs are flavonoid-rich substances extracted from the cranberries, which are known to be anti-bacterial, anti-adhesion, antioxidant and anti-inflammatory. In recent years, more experiments have extracted PACs from cranberries as the potential agent to treat periodontitis[19]. Thus, it is expected for the cranberries to show therapeutic effects in oral health care in the future. Cranberry is considered safe with almost all medications. In medicinal doses it may increase the effect of anti-coagulation drugs like warfarin (Coumadin), causing bleeding. Cranberry pills are relatively safe but may cause stomach upset in some people. Anyone with a sensitivity or allergy to salicylates, a history of kidney stones or those taking the blood-thinning drug Warfarin may want to avoid cranberry supplements.

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