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PERSPECTIVE

Cranberry: Effects on Oral Health

Sujata M[1], Gurpreet K [2], Argha R[3]

1. MDS, Reader, Department of Periodontics and Oral Implantology, National Dental College & Hospital, Dera Bassi
2. MDS, Reader, Department of Periodontics and Oral Implantology, National Dental College & Hospital, Dera Bassi
3. MDS, Assitant Professor, Department of Dentistry, R G Kar Medical College & Hopsital, Kolkata

Corresponding Author: Department of Periodontics & Oral Implantology, National Dental College & Hospital, Dera Bassi; E-mail: malik_sujata@rediffmail.com

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ABSTRACT

Diets high in fruits, vegetables and grains contribute to improving health status in a number of ways. Cranberry appears to be a relatively unique fruit in that it may provide benefits of reducing oral diseases both through microbial anti-adhesion and possibly through antioxidant mechanisms. A non-dialysable cranberry fraction enriched in high molecular weight polyphenols has promising properties with respect to cariogenic and periodontopathogenic bacteria, as well as to the host inflammatory response and enzymes that degrade the extracellular matrix. Cranberry components are potential anti-caries agents since they inhibit acid production, attachment, and biofilm formation by Streptococcus mutans. Elucan-binding proteins, extracellular enzymes, carbohydrate production, and bacterial hydrophobicity, are all affected by cranberry components. Regarding periodontal diseases the same cranberry fraction inhibits host inflammatory responses, production and activity of enzymes that cause the destruction of the extracellular matrix, biofilm formation, and adherence of porphyromonas gingivalis, and proteolytic activities and co-aggregation of periodontopathogens. These effects suggest that cranberry components, especially those with high molecular weight, could serve as bioactive molecules for the production and/ or treatment of oral diseases.

Keywords: Cranberry, oral health, periodontal health

1. INTRODUCTION

The cranberry vaccinium macrocapon is one of native North American fruits that grow in the wild from the Carolinas to Canada. The fruit of cranberry is widely consumed in various fruit products, including fresh and dried fruits, sauces, and juices as well as in powder form in capsules and tablets. Cranberry extracts are rich source of flavonoids and especially of the flavonols myricetin and quercetin, and possess biological properties that may provide human health benefits. Traditional medicinal use of cranberry fruit by Native Americans was primarily for the

treatment of bladder and kidney ailments (Boon et al., 2004). There has also been a relatively long history of scientific research on this herbal remedy, dating back to its chemical characterization in the late 19th century (Raz et al., 2004). Therapeutic applications of cranberries documented during the 17th century include the relief of blood disorders, stomach ailments, liver problems, vomiting, appetite loss, scurvy and cancer (Siciliano et al., 1996). Recently, cranberry extracts have been receiving the increasing attention in various areas of the health research including infectious and non- infectious diseases.

Proanthocyanidins (condensed tannins) from cranberry juice inhibit the adhesion of uro-pathogenic fibrinated Escherichia coli to uroepitheial cells in the urinary tract (Howell et al., 2005). A high molecular weight cranberry fraction has also been reported to inhibit the adherence of P-fimbriated uro-pathogenic E.coli as well as sialic acid- specific adherence of Helicobacter pylori to human gastric mucosa, a critical step in gastric ulcer development (Burger et al., 2000). These in vitro observations have been supported by clinical studies showing that regular consumption of cranberry juice can suppress urinary tract infection in women (Stothers et al., 2002) and H.pylori infections in endemically affected populations (Zhang et al., 2005).

Cranberry extracts also exhibit an inhibitory effect on influenza virus adhesion and infectivity (Weiss et al., 2005) and exert a fungistatic effect on dermatophytic and other fungi, although they have no effect on the oral pathogenic fungus candida albicans (Swartz et al., 1968). Compounds that prevent this adhesion represent an alternative therapy to the use of antibiotics, since the anti - adhesion molecules do not kill or impair the growth of bacteria, yet they are able to prevent infection from developing.

An infection that develops following adhesion of bacteria is related to periodontitis, an inflammatory disorder of tooth supporting tissues. Gram negative bacteria, such as Porphyromonas gingivalis can colonize teeth, gingival epithelial cells and red blood cells or interact with other oral bacteria and proteins in the mouth trough receptors on their surfaces (Labrecque et al., 2006). In each of these infections, cranberry compounds have been implicated in preventing the bacterial adhesion process thus presenting a complementary or alternative methodology to prevent urinary tract infections, H.pylori infections and periodontitis.

Additional to their effects on infectious agents, cranberry extracts inhibit the proliferation of human oral, colon, prostate and breast cancer cells lines (Seeram et al., 2004). In addition, cranberry extracts have potential beneficial effects on cardiovascular diseases (Chu et al., 2005). The potential benefits of cranberry juice constituents in reducing oral diseases are discussed.

Constituents of cranberry

The fruit contains following compounds-fructose and proanthocyanidins, triterpenoids, lactins, ascorbic acid, benzoic acid, quinic acid, oxalic acid, citric acid and malic acid.

Chemical composition of High molecular weight constituents of cranberry:

Zafriri et al (1989), using 12-14kDa molecular weight cut off dialysis membranes, first reported that most of the anti-adhesion activity in cranberry juice is in the form of high molecular weight, non-dialysable material (NDM). Other studies showed that oligomeric proanthocyanidins (PACs) inhibit the adhesion of P-fimbriated E.coli (Howell et al., 2005). Cranberry PACs are unique because the oligomeric molecules are of A type, whereas the PACs of most other fruits are of B type, type which is devoid of antiadhesion activity. NDM is a molecular species distinct from PAC, as reflected by differences in solubility in various solvents, in molecular weight, and in mass spectroscopic and nuclear magnetic resonance (NMR) spectra.

Potential benefits

Diets high in fruits vegetables and grains contribute to improving health status in a number of ways. Oxidative stress may play a role in development of many chronic diseases, including cardiovascular diseases. Ex vivo testing indicates that cranberry flavonoids inhibit the oxidation of human LDL cholesterol, with proanthocyanidins the most active flavonoid fraction.

Anti-adhesion: other potential body benefits

Cranberrie's adhesion inhibitors appear to act against a number of types of bacteria, potentially providing additional health benefits. Cranberries may be helpful in maintaining urinary tract health and gastrointestinal health.

Cranberry's potential antioxidant benefits

Oxidative stress is believed to play a role in normal aging and in development of many chronic diseases. All fruits, including cranberries, contain a variety of phytochemcials that may contribute to inhibit oxidative reactions. Cranberries and related fruits contain many flavonoids and phenolic acids with anti oxidant or other physiologically benefical activities. Cranberry flavonoids include anthocyanins (responsible for their red pigment), flavonols, flavan-3-ols, and proanthocyanidins. Recently, cranberries were identified as having among the highest amount of phenolic compunds of 20 common fruits tested on a fresh weight basis (Vinson et al., 2001). Phenolic compounds exhibit antioxidant effects in vitro. Many researchers believe that prevention of low - density lipoprotein (LDL) oxidation may protect against plaque formation in blood vessels.

2. POTENTIAL BENEFITS IN ORAL CAVITY

Cranberry NDM and dental caries

Oral biofilms (dental plaque) harboring bacteria are the major contributing virulent factors associated with diseases of the oral cavity such as caries, gingivitis and periodontitis (Steinberg et al., 2000). Oral biofilms, coating hard surfaces as well as soft tissues, are composed of bacteria,

cells, proteins and enzymes, embedded in an extracellular matrix (Marsh et al., 2005). The preliminary stage is the formation of an acquired pellicle.

Important constituents of the acquired pellicle are the glucosyltranferases (GTF) and fructosyltransferase (FTF). These polysaccharides play a pivotal role in adhesion of bacteria to the surface and in the maturation of the biolfilm. Bacteria from saliva attached to the acquired pellicle, proliferate on the surface, giving rise to microcolonies, of which mutans streptococci are frequently associated with a carious lesions. Cell- to-cell interactions, a phenomenon known as co-aggregration occurs.

There is convincing evidence that the formation of biofilm on tooth surfaces is a prerequisite for dental caries. Dental caries is the direct result of enamel dissolution by acids. Cariogenic bacteria embedded in the dental biofilm are highly aciduric and acidogenic. Reduction in pH occurs within minutes after exposure to dietary carbohydrates, especially when the biofilm reaches a critical bacterial mass due to poor oral hygiene. It is broadly accepted that regular oral hygiene reduces total bacterial mass and significantly diminishes the severity and frequency of dental caries.

The cranberry NDM appears to inhibit mutans streptococci adhesion and biofilm formation as well as coaggregation of considerable number of oral streptococcal species. Moreover, salivary counts of mutans streptococci are reduced significantly in volunteers using mouthwash supplemented with NDM from cranberry juice. (Yamanaka et al., 2004) tested the effect of 25% cranberry juice on the adhesion of oral streptococci to saliva - coated hydroxyapatite surfaces, they reported a significant inhibitory effect ranging from 80-95% on biofilm formation by S.sobrinus, S.mutans, S.criceti, S.sanguinis, S.oralis and S.mitis.

Weiss et al (2004) reported that NDM has a significant inhibitory effect on biofilm formation by S.sobrinus, which is more prominent in the presence of sucrose. The reduction in biofilm mass and bacterial adhesion reported in these studies was not due to an antibacterial effect since at the concentrations used, there was no significant effect on bacterial viability (Duarte et al 2006). The ability to shift bacterial population towards a less pathogenic one is unique to cranberry.

Glucans formed by cell free GTF immobilized act as bacterial binding sites. The adhesion of streptococci to glucans via glucan- binding-proteins (GBP) present on streptococcal membranes is one of the mechanisms by which bacteria attach to the biofilm. Cranberry juice blocks bacterial adherence to glucan- binding sites in the salivary pellicle coating the tooth enamel by 40-85% and reduces the mass of the biofilm.

Cranberry juice significantly reduces the hydrophobicity (other mechanism of oral bacteria) of oral streptococci (Yamanaka et al., 2004). It may be concluded that NDM reduces bacterial adhesion to biofilms, lowers the mass of biofilms, and decreases polysaccharide production. This result in deformed biofilms that are thinner and less dense than biofilms not exposed to NDM (Steinberg et al., 2005). It may be assumed that those biofilms are less virulent.

Durate et al. (2006) observed that cranberry extract and PAC inhibit acid production by S.mutans. As summarized in Fig. 1, cranberry components may affect supragingival biofilm formation and influence tooth decay and ability to decrease acid production is yet another means by which it may act as an anti-caries agent.

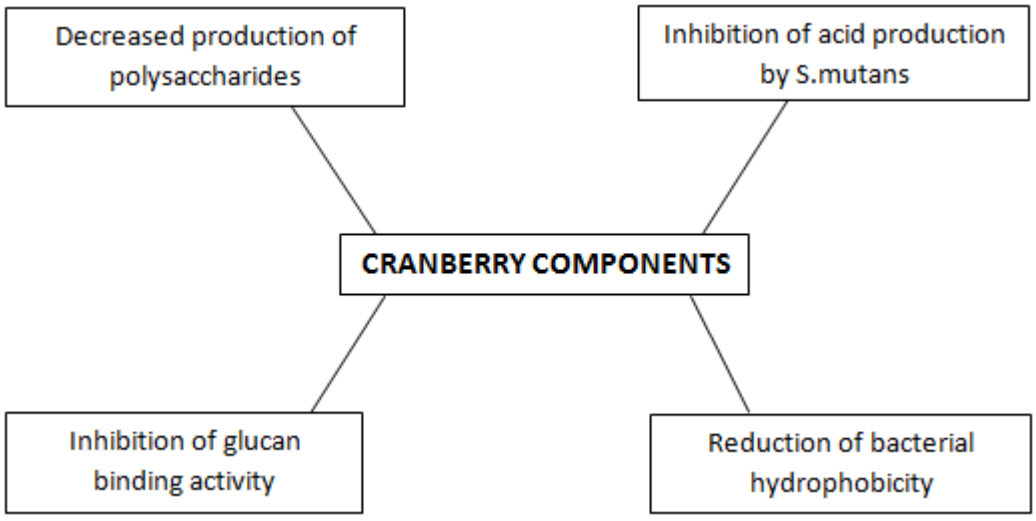

Figure 1
Properties supporting the anti-caries effect of cranberry

Inhibition of Intergeneric Bacterial Coaggregation

The stability of dental plaque relies on bacterial adhesion to an acquired proteinous pellicle covering the tooth surface and on interspecies adhesion known as co-aggregation. Coaggregation interactions are probably the most important factor allowing bacteria to withstand both (i) cheek and tongue muscles, meachanical forces, and (ii) salivary flow, which tend to dislodge and wash away dental plaque.

Weiss et al. (1998) reported that NDM reversed the co-aggregation of 49 out of 84 coaggregating bacterial pairs tested. It acted preferentially on pairs in which one or both members were Gram- negative anaerobes, frequently involved in periodontal diseases. Thus NDM has the potential to alter the subgingival microbiota and to enable the control of biofilm- related oral infections.

The effect of a mouthwash supplemented with NDM on oral bacterial levels was assessed. Following six weeks of daily usage of cranberry containing mouthwash by 29 volunteers, (experimental group) the salivary mutans streptococci count and the total bacterial count were reduced significantly(ANOVA, $P<0.01$) compared with the control group (30 subjects) who used a placebo mouthwash (Weiss et al. 2004).

Cranberry NDM and Periodontal diseases

Periodontal diseases are multifactorial infections that are caused by a specific group of Gram-negative anaerobic bacteria and that lead to the destruction of tooth supporting tissues. Two major factors are involved in the pathogenesis of periodontitis. The first is the microbial factor, which damage periodontal tissue via the molecules they produce, including proteolytic enzymes. The second is the host response to periodontal pathogens, notably the over- production of inflammatory mediators and matrix metalloproteinases, which are critical for the initiation and progession of periodontitis. Cranberry fractions have been reported to have beneficial inhibitory effects on these two factors.

Effects on Periodontopathogens

The cranberry NDM fraction is a potent inhibitor of biofilm formation by P.gingivalis,(key pathogen in chronic periodontitis) but does not effect the growth or viability of the bacteria (Labrecque et al., 2006). This cranberry fraction also inhibits the attachment of P.gingivalis to various proteins such as type I collagen and fibrinogen (Labrecque et al., 2006). In addition, as discussed above, cranberry NDM inhibits the coaggregation of bacterial pairs. These findings suggest that cranberry may reduce the capacity of periodontopathogens to colonize subgingival sites. In addition, the fact that cranberry NDM acts by preventing bacterial adhesion rather than by inhibiting growth may be an advantage in that it reduces the development of resistant bacteria.

The strong proteolytic activities of bacteria of the red complex(which includes P.gingivalis, T.forsythia, and T.denticola) are an important factor that contributes to periodontal tissue destruction through a variety of mechanisms, including direct tissue degradation and host inflammatory response modulation (Eley et al., 2003). The cranberry NDM fraction affects periodontopathogen preoteinases by dose - dependently inhibiting the gingipain(both Arg- and Lys-gingipain) and dipeptidyl peptidase IV activities of P.gingivalis, the trypsin-like activity of T.forsythia, and the chymotrypsin-like activity of T.denticola (Bodet et al., 2006 b). It also blocks the ability of P.gingivalis to degrade native proteins including type I collagen and transferring (Bodet et al., 2006 b). This suggests that NDM has the potential to reduce the multiplication of P.gingivalis, T.forsythia, and T.denticola in periodontal pockets, since their growth relies on the availability of amino acids and peptides. In addition, NDM may reduce the tissue destruction mediated by preoteinases produced by these bacterial species.

Of the three fractions tested (anthocyanin), proanthocyanidin, and flavonol), the proanthocyanidin fraction was the most effective whereas the anthocyanin fraction was the least. It has been suggested that inhibitors of periodontopathogen proteinases may reduce bacterial pathogenicity and therefore could be considered new therapeutic agents for periodontal diseases (Grenier et al., 2002).

3. EFFECTS ON HOST RESPONSES

Anti-Inflammatory Properties

The continuous high production of cytokines, including interleukin-1β(IL-1β),IL-6,IL-8 and tumour necrosis factor alpha(TNF-α), by host cells triggered by periodontopathogens, is thought to be responsible for the periodontitis - associated destruction of tooth- supporting tissues. It has been reported that cranberry contains molecules with anti-inflammatory properties. For instance, cranberry polyphenols reduce tumour necrosis factor- alpha (TNF-α) induced up-regulation of various inflammatory mediator production by human microvascular endothelial cells (Youdim et al., 2002).

It was recently reported (Bodet et al., 2006 a) that the cranberry NDM fraction inhibits the production of pro-inflammatory cytokines(IL-1β,IL-6,TNF-α) and chemokines (IL-8 and RANTES)by macrophages stimulated with lipoplysaccharides (LPS) from E.coli and major periodontopathogens, including A.actinomycetemcomitans, F.nucleatum, P.gingivalis, T.denticola and T.forsythia. Protoanthocyanidins may be responsible for the effect. NDM may diminish the release of free toxic radicals associated with the periodontal tissue destruction. Indeed, NDM decreases nitric oxide and reactive oxygen species production as well as inducible nitric oxide synthase expression by LPS-stimulated macrophages. The LPS-induced IL-6, IL-8 and prostaglandin E_2(PGE_2) responses of gingival fibroblasts are inhibited by cranberry NDM, which appears to act by inhibiting gingival fibroblast intracellular signalling proteins,leading to downregulation of activating protein-1(AP-1), a major transcriptional factor of pro-inflamamtory genes. Cranberry can also reduce the expression of cyclooxygenase 2, an enzyme involved in PGE_2 production.

The above findings indicate that cranberry may limit the inflammatory responses of both gingival fibroblasts and macrophages elicited by periodontopathogens.

Cranberry constituent appear thus to have a high potential for the development of a new anti-inflammatory therapeutic approach. Cranberry NDM may also protect host cells from the toxicity of periodontopathogen components. It significantly enhances the viability of gingival fibroblasts cultivated for five days in the presence of A.actinomycetemcomitans LPS (Bodet et al., 2007; Bodet et al., 2007) and protects macrophages from the cell toxicity induced by cell envelope components of T.denticola and peptostreptococcus micros (Labrecque et al., 2007).

Inhibition of Host Tissue-Degrading Enzymes

Much evidence points to host-derived matrix metalloproteinases(MMPs) as destructive enzymes in periodontal disease (Kinane et al. , 2000). Cranberry NDM inhibits LPS-induced MMP-3 and MMP-9 production by both gingival fibroblasts and macrophages (Bodet et al., 2007; Bodet et al., 2007), and affect the phosphorylation and expression of various intracellular fibroblast proeteins implicated in MMP production. The NDM fraction appears to act by reducing AP-1 activity, which regulates MMP gene expression. In addition, the activity of MMP-3, MMP-9 and elastase, which are enzymes involved in extracellular matrix destruction, are also efficiently inhibited by low concentrations of cranberry NDM. Interestingly, sub-antimicrobial doses of doxycycline, which downregulates MMP activity, is indicated as an adjunctive treatment for periodontitis and confers clinical benefits to patients with periodontitis (Preshaw et al., 2004). Cranberry NDM, by inhibiting both the production and activity of MMPs, may be a novel potential therapeutic option for treating periodontitis (Weiss et al., 1999).

Potential for Periodontal Disease Treatment

To prevent the initiation and progression of periodontal disease, oral hygiene measures, mechanical debridement, surgery and antimicrobial pharmaceutical agents are used to reduce the subgingival biofilm accumulation, while these procedures are effective in managing the majority of patients with periodontitis, conventional therapy does not always achieve the desired clinical outcome. The chronic nature of periodontitis implies that clinicians should continuously monitor their patients and the preventive treatment approaches. The management or prevention of periodontal disease in high risk individuals (smokers, diabetics, individuals with a genetic predisposition) requires either strict bacterial control or combinations of bacterial control and adjunctive treatments, such as host modulators. Various approaches are envisaged to develop new adjunctive treatment for periodontitis including modulating MMPs, prostanoids,cytokines, and NOS activity and inhibiting periodontopathogen proteinases (Kornman et al., 1999). Cranberry components have interesting inhibitory properties against many pathogenic mechanisms involved in the initiation and development of periodontitis. Interestingly, combination therapy involving a subantimicrobial doxycycline dose with non-steroidal anti-inflammatory drugs synergistically suppresses enzymes involved in extracellular matrix destruction in the gingiva of chronic periodontitis patients (Lee et al., 2004). This suggests that treatments targeting multiple pathogenic mechanisms involved in periodontal diseases may be a successful therapeutic approach.

The development of strategies as adjuncts to conventional therapy for individuals with a substantially increased risk for periodontitis may involve local applications of NDM to modulate the host response, inhibit enzymes involved in extracellular matrix destruction, and attenuate periodontopathogen virulence. Cranberry components thus appear to be promising candidates for the development of novel adjunctive treatments for periodontal diseases.

4. CONCLUSION

While components isolated from cranberry juice may help fight oral diseases, the high dextrose and fructose content as well as the strong acidity of commercially available cranberry juice makes it unsuitable for oral hygiene use. On the other hand, recent research suggests that cranberry components possess a promising potential for use as supplements for improving oral health,Significantly,the cranberry NDM fraction disrupts the pathogenic mechanisms of dental caries and periodontal diseases. It may be incorporated into mouthrinses or toothpastes as well as to gels or strips to prevent/treat oral diseases, including dental caries and periodontal diseases. while such approach must be validated by clinical studies, the one clinical study (Weiss et al., 2004) performed with NDM-supplemented mouthwash which reduced the salivary S.mutans in healthy adult volunteers suggest that the anti-adhesion and anti-biofilm therapy by edible dietary constituents may probe to be the method of choice to improve oral health hygiene.

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