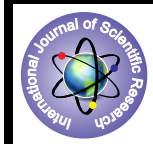


Cranberry : a Boon to Periodontium



Medical Science

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Dr. Babita Pawar	Professor, Department Of Periodontics, Rural Dental College, Loni, Maharashtra
Dr. P. P. Marawar	Professor And H.O.D, Department Of Periodontics, Rural Dental College, Loni, Maharashtra
Dr. Richa Patel	Post Graduate Student, Department Of Periodontics, Rural Dental College, Loni, Tal. Rahata, District Ahmednagar, 413736.
Dr. Tushar Bhople	Post Graduate Student, Dept. Of Periodontics, Loni, Maharashtra

ABSTRACT

Over the past decade, cranberries and their molecular components have received increasing attention from researchers in human health. A non-dialysable cranberry fraction enriched in high molecular weight polyphenols has very 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-carries agents since they inhibit acid production, attachment, and biofilm formation by Streptococcus mutans. Glucan-binding proteins, extracellular enzymes, carbohydrate production, and bacterial hydrophobicity, are affected by cranberry components. Cranberry polyphenols may reduce the inflammatory response, as well as the production and activity of proteolytic enzymes contributing to the destruction of the extracellular matrix in periodontal disease. The polyphenols of cranberries also interfere with various activities of Porphyromonas gingivalis, the main etiologic agent in chronic periodontitis. The unique combination of phytochemicals found in cranberry fruit may produce synergistic health benefits. Possible chemopreventive mechanisms of action by cranberry phytochemicals include induction of apoptosis in tumor cells, reduced ornithine decarboxylase activity, decreased expression of matrix metalloproteinases. This article summarizes the scientific evidence supporting the potential of cranberry polyphenols to prevent and/or treat diseases of oral diseases.

INTRODUCTION

The cranberry *Vaccinium macrocarpon* is one of three native North American fruits, the others being concord grapes and blueberries, that grow in the wild from the Carolinas to Canada. The fruit of the cranberry is widely consumed in various food products, including fresh and dried fruits, sauces, and juices, as well as in powder form in capsules and tablets. Cranberry extracts are a rich source of flavonoids and especially of the flavonols myricetin and quercetin, and possess biological properties that may provide human health benefits. Cranberry (*Vaccinium macrocarpon*) is a particularly rich source of (poly)phenols, which have been associated in vitro with antibacterial, antiviral, antimutagenic, anticarcinogenic, antitumorogenic, antiangiogenic, anti-inflammatory, and antioxidant properties (1,2,3).

and has positive effects on periodontal health. The effect of cranberry components on cariogenic and periodontopathogenic bacteria, and on host inflammatory responses is reviewed and potential benefits of cranberry juice constituents in reducing oral diseases are discussed.

Chemical Composition of Cranberry Extract

Several of the studies conducted to date have used a fraction of cranberries called the nondialyzable material (NDM), which is obtained by dialysis of concentrated cranberry juice. Chemical analysis of the NDM fraction has revealed that it contains about 65% proanthocyanidins, along with (0.35%) of anthocyanins. (4) These oligomeric proanthocyanidins are unique in that they have a double linkage between the epicatechin units (A type), whereas the majority of oligomeric proanthocyanidins in other fruits have a single linkage (B type). (5,6)

Effects On Periodontopathogens

The colonization of subgingival sites by periodontopathogens is a critical step in the initiation of periodontal disease. The capacity of periodontopathogens to form biofilms and to express adhesins, which allow them to adhere to host cells, tooth surfaces, basement membrane components, and oral bacteria, plays a major role in periodontitis (Rosan and Lamont, 2000). *P. gingivalis* is the key pathogen in chronic periodontitis (Hafjajee and Socransky, 1994). The cranberry NDM fraction is a potent inhibitor of biofilm formation by *P. gingivalis*, but does not affect the growth or viability of the bacteria (Labrecque et

al., 2006). It inhibits the attachment of *P. gingivalis* to various proteins such as type I collagen and fibrinogen (Labrecque et al., 2006) and the coaggregation of bacteria (Weiss et al., 1998, 2002). These findings suggest that cranberry may reduce the capacity of periodontopathogens to colonize subgingival sites. It acts by preventing bacterial adhesion rather than by inhibiting growth may be an advantage in that it reduces the development of resistant bacteria.

Inhibition of Intergeneric Bacterial Coaggregation

The stability of dental plaque relies on bacterial adhesion to an acquired proteinaceous pellicle covering the tooth surface and on interspecies adhesion known as coaggregation. Coaggregation interactions are probably the most important factor allowing bacteria to withstand both (i) cheek and tongue muscle, mechanical forces, and (ii) salivary flow, which tend to dislodge and wash away dental plaque. Weiss et al. (1998) reported that NDM reversed the coaggregation 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). (10)

Effect on Proteolytic Enzymes

Members of the red complex are closely linked to clinical measures of periodontitis, particularly pocket depth and bleeding on probing (Kasuga et al., 2000; Socransky et al., 1998). The strong proteolytic activities of bacteria of the red complex are important factors that contribute to periodontal tissue destruction through a variety of mechanisms, including direct tissue degradation and host inflammatory response modulation (Eley and Cox, 2003; Grenier, 1996; Holt and Ebersole, 2005; Imamura, 2003). The cranberry NDM fraction affects periodontopathogen proteinases 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., 2006b). (11) It blocks the ability of *P. gingivalis* to degrade native proteins, including type I collagen and transferring (Bodet et al., 2006b). 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. NDM also reduces the tissue destruction mediated by proteinases produced by these bacterial species. Yamanaka et al. (2006) reported the inhibitory effect on periodontopathogen proteinases by showing that cranberry polyphenol fractions have an inhibitory effect on *P. gingivalis* gingipain and *T. denticola* chymotrypsin-like activity. (12) 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; Kadowaki et al., 2004; Song et al., 2003). Thus, cranberry components exhibit promising properties against periodontopathogen proteinases.

EFFECTS ON HOST RESPONSES

Anti-Inflammatory Properties:

Cranberry polyphenols reduce TNF- α -induced up-regulation of various inflammatory mediator production by human microvascular endothelial cells (Youdim et al., 2002). Bodet et al. (2006a) reported that the cranberry NDM fraction inhibits the production of pro-inflammatory cytokines (IL-1 β , IL-6, and TNF- α) and chemokines (IL-8 and RANTES) by macrophages stimulated with lipopolysaccharides (LPS) from periodontopathogens. (13)

Protoanthocyanidins may be responsible for this effect since they were 125-times more concentrated in the NDM fraction than in whole cranberry juice, which exhibited no significant anti-inflammatory properties. NDM may diminish the release of free toxic radicals associated with periodontal tissue destruction decreases nitric oxide and reactive oxygen species production as well as inducible nitric oxide synthase expression by LPS-stimulated macrophages (Chandad et al., unpublished data). The LPS-induced IL-6, IL-8, and prostaglandin E2 (PGE2) 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-inflammatory genes. The above findings indicate that cranberry may limit the inflammatory responses of both gingival fibroblasts and macrophages elicited by periodontopathogens. Cranberry constituents appear thus to have a high potential for the development of a new anti-inflammatory therapeutic approach.

Inhibition of Host Tissue-Degrading Enzymes

Host-derived matrix metalloproteinases (MMPs) is a key destructive enzymes in periodontal disease (Kinane, 2000). Excessive MMP activity is a hallmark of human periodontal disease leading to gingival collagen loss, periodontal ligament degradation, and alveolar bone resorption. Cranberry NDM inhibits LPS-induced MMP-3 and MMP-9 production by both gingival fibroblasts and macrophages (Bodet et al., 2007), and affect the phosphorylation and expression of various intracellular fibroblast proteins implicated in MMP production. (14) The NDM fraction acts by reducing AP-1 activity, which regulates MMP gene expression. The activity of MMP-3, MMP-9 and elastase, which are enzymes involved in extracellular matrix destruction, are efficiently inhibited by low concentrations of cranberry NDM. Cranberry NDM, by inhibiting both the production and activity of MMPs, may be a novel potential therapeutic option for treating periodontitis.

Antioxidant properties of cranberry fruit

Cranberry ranks high among fruit in both antioxidant quality and quantity (15) because of its substantial flavonoid content and a wealth of phenolic acids. Cranberry extracts rich in these compounds reportedly inhibit oxidative processes including oxidation of low-density lipoproteins (16,17). The antioxidant properties of the phenolic compounds in cranberry fruit may

contribute to the observed antitumor activities of cranberry extracts.

Cranberry phytochemicals and chemoprevention

Cranberry fruit has a diverse phytochemical profile that includes 3 classes of flavonoids (flavonols, anthocyanins, and proanthocyanidins), catechins, hydroxycinnamic and other phenolic acids, and triterpenoids. Several groups of researchers examined activity of whole polyphenolic extracts of the fruit or spray-dried juice. Mechanism of action supported by in vitro evidence include induction of apoptosis in cancer cells, decreased invasion and metastasis as a result of inhibition of MMPs, inhibition of ornithine decarboxylase expression and activity, and inhibition of inflammatory processes including cyclooxygenase (COX) activity.

Cranberry anthocyanins

The major anthocyanins in cranberry are galactosides and arabinosides of cyanidin and peonidin (18). Vaccinium fruits are among the most plentiful food sources of anthocyanin. cultivars (19). Because of superior antioxidant efficacy, cranberry anthocyanins may be expected to inhibit oxidative processes linked to tumorigenesis. Anthocyanin-rich extracts inhibited the induction of vascular endothelial growth factor by both hydrogen peroxide and tumor necrosis factor (TNF- α) and resulted in decreased hemangioma formation and tumor growth (20). This suggests that the antioxidant and anti-inflammatory properties of these compounds may limit angiogenesis.

Inhibition of cyclooxygenase activity

COX-2 overexpression plays important role in promoting certain cancers; thus, inhibition of COX-2 activity or expression presents another potential route to chemoprevention. Inhibition of cyclooxygenase activity by cranberry extracts was reported by Seeram et al. (21) in which anthocyanin fractions isolated from cherries and berries were evaluated for COX-1 and COX-2 inhibitory activity using an assay measuring oxygen uptake on conversion of arachidonic acid in microsomal preparations by either isoform. Cranberry anthocyanins inhibited COX-1 and COX-2 activity.

CONCLUSIONS

The polyphenols of cranberries, specifically the proanthocyanidins in the NDM fraction isolated from cranberry juice, has potential to prevent and treat dental caries and periodontal disease. These molecules can be integrated into oral hygiene products, which could be tested for their potential benefits in preventing oral diseases. Localized application of these bioactive substances to diseased periodontal sites, through irrigation or insertion of a resorbable fibre, can allow for modulation of the host response through inhibition of the enzymes that destroy the extracellular matrix and attenuation of the virulence of the periodontopathogens. Thus cranberry polyphenols can allow reductions in the use of antibiotics, thereby preventing the development of bacterial resistance. COX-2 inhibition by cranberry phytochemicals, particularly anthocyanins, may contribute to a decreased risk of the development of cancer. It will be important to continue to examine the roles of cranberry phytochemicals in regulating cellular processes related to apoptosis, inflammation, and proliferation, including the expression of key genes in these pathways, so that we may begin to understand how this unique blend of phytochemicals may best work.

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