CRANBERRY (VACCINIUM MACROCARPON) – A PHYTOMEDICINE WITH POTENTIAL IN THE MANAGEMENT OF PERIODONTITIS

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Abstract: Cranberry (*Vaccinium macrocarpon*) is known to have a therapeutic potential on human health. Several phytochemicals found in cranberry namely flavonol glysodies, proanthocyanidins and phenolic acids are known to contribute to its anti-microbial, anti-oxidant, and anti-inflammatory properties. In vitro studies have shown that cranberry may be potential therapeutic agents for the prevention and management of periodontal disease. This review focused on the beneficial effect of cranberry on oral and periodontal health and three possible mechanisms of action of cranberry on inhibiting the periodontal tissue destruction. Three possible targets of cranberry PACs include (i) periodontopathogens, (ii) host inflammatory immune response, and (iii) osteoclast differentiation and activity. Given that cranberry and its phytochemical constituents have shown beneficial effects in vitro, clinical trials are warranted to better evaluate the potential of these constituents for controlling and prevention of periodontal tissue destruction.

Keywords: Cranberry, Periodontitis, Host modulation, Anti-microbial, Phytochemicals, Proanthocyanidins.

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INTRODUCTION

Periodontitis is a destructive disease caused by host microbial interaction. Hence two major factors contribute to the pathogenesis of periodontitis [1]. First, invading bacteria cause direct damage to periodontal tissues through the secretion of toxic products [2]. Second, the host immune responses to those bacteria, which results in release of pro-inflammatory mediators are also involved in the progression of periodontitis [3].

Recently researchers have focused on developing risk-free adjuncts for standard periodontal disease treatment, such as use of nutritional support for their antimicrobial, anti-adhesive, immunomodulatory, and antioxidative properties. One of the well-researched phytomedicine in this field is cranberry and its extracts [4].

Cranberry (Vaccinium macrocarpon) is the fruit of a shrub of peat bogs located in the

colder regions of North America belonging to Ericaceae family. With its rich source of several classes of bioactive flavonoids including flavonols, anthocyanins, and proanthocyanidins (PACs) (Type A), it has considerable therapeutic potential [5]. In the last decade, studies have focused on general and oral health benefits of cranberry extract and its molecular components [6,7].

In terms of oral health, recent studies have indicated that cranberry extract has antimicrobial and anti-inflammatory properties that can be used for the management of oral infections, periodontal infection and dental caries [8,9,10].

In this review, the effect of cranberry and its active components for the oral, and periodontal health will be discussed. Possible mechanism of action of cranberry for inhibition and prevention of periodontal tissue destruction will be discussed.

Phytochemicals in Cranberry

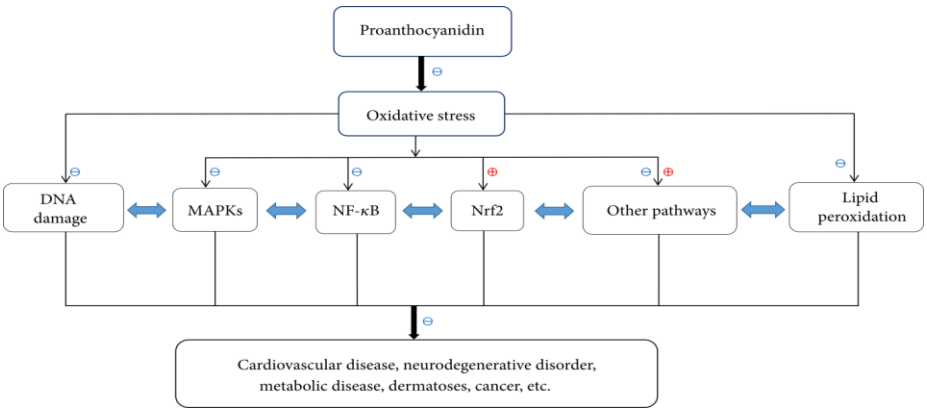
The word "phyto" is a Greek word that means "plant." Certain organic plant substances known as phytonutrients are suggested to improve human health. The phytonutrient content of fruits, vegetables, cereals, legumes, nuts, and teas is high [11].

The considerable antioxidant properties of cranberries are due in large part to their rich phytochemical profile, which includes three classes of flavonoids (flavonols, anthocyanins, and proanthocyanidins (PACs), catechins, hydroxycinnamic and other phenolic acids, and triterpenoids. They are rich in antioxidants called anthocyanins and proanthocyanins, as well as salicylic acid and vitamin C [12].

Mechanism of Action of Cranberry

New research suggests that cranberries have unique phytochemicals that set them apart from other fruits and may account for some of their health advantages. In the phenylpropanol metabolism, anthocyanins are produced by the polymerization of flavan-3-ol units into PACs, which are distinguished by epicatechin tetra- and pentamers. By preventing pathogens and combating inflammatory immune responses, PACs have the ability to guard against bacterial infection, hence lowering chronic destructive diseases including diabetes, cancer, and periodontal disorders [13].

Figure 1. Mechanism of action of proanthocyanidin (Picture adapted from Yang L *et al.*, 2018 [13])



Beneficial Effects of Cranberry and its Extracts on Systemic Conditions:

Urinary Tract Infection

Several theories have been put out to explain how cranberries work to prevent UTIs, including the inhibition of bacterial growth brought on by the presence of different acids in cranberries or the prevention of type 1 and p-fimbriae strains (especially from Escherichia coli) adhering to the urothelium [14]. Although cranberry components have been shown to inhibit bacterial adhesion in in vitro studies, results from clinical trials in humans have been inconsistent due to differences in study designs, conditions, end points or effect markers, study populations, and the use of non-standardized or dissimilar products.

Recent randomised trials (using various placebos and cranberry products) to assess the effects of cranberries in young women with recurrent UTIs produced mixed results, with one trial showing a significant reduction in UTI incidence as compared to placebo; three trials didn't show any significant difference between the two groups in reducing UTIs [15,16,17,18] and conflicting results were found in clinical trials in the paediatric population [14]. In individuals receiving radiotherapy, chemotherapy, or being pregnant, there is no conclusive data to support the usefulness of cranberries in preventing UTIs.

Cardiovascular Diseases

The impact of cranberries on CVDs has been linked to a number of different pathways. As well as other antithrombotic and anti-inflammatory mechanisms, it may affect cardiovascular risk factors like dyslipidemia, diabetes, hypertension, oxidative stress, endothelial dysfunction, arterial stiffness, and platelet function. It may also increase LDL's resistance to oxidation, inhibit platelet aggregation, lower blood pressure, and increase LDL's resistance to other antithrombotic and anti-inflammatory mechanisms [19].

Gastrointestinal Health Benefits

Numerous in vitro studies found that cranberry exhibit anti-adhesive activity against H. pylori bacteria, thereby preventing *H. pylori* infections [20].

Cancer

Cranberry anthocyanins and flavonoids have anti-proliferative or growth-inhibitory effects. Because of the compounds quercetin and ursolic acid, cranberries also exhibit anti-tumor action.[21] The first study to evaluate the possible anti-cancer properties of cranberries was published in 1996 by the University of Illinois [12]. Since then, various in-vitro and animal studies have been carried out to evaluate the anti-cancer abilities of cranberry components, with encouraging outcomes [22,23,24,25]. Therefore, these results point to the amazing potential of cranberries as a fruit that can prevent cancer through diet.

Neurological Disorders

For the treatment of neurological diseases like Alzheimer's, cranberry may be useful. In Alzheimer's disease model cells treated with dopamine and amyloid, a cranberry extract has been shown to lessen a Ca^{2+} homeostasis deficit. It has also been shown to improve brain function, neuroprotective responses, and some motor abilities in old rats [18]. However, no human clinical trials have been conducted to verify the cranberry's neuroprotective properties.

Cranberry extracts can protect the body, first of all, from intense harmful reactions and free radicals. Flavonoids and other phytochemicals present in cranberry extract can provide numerous health benefits.

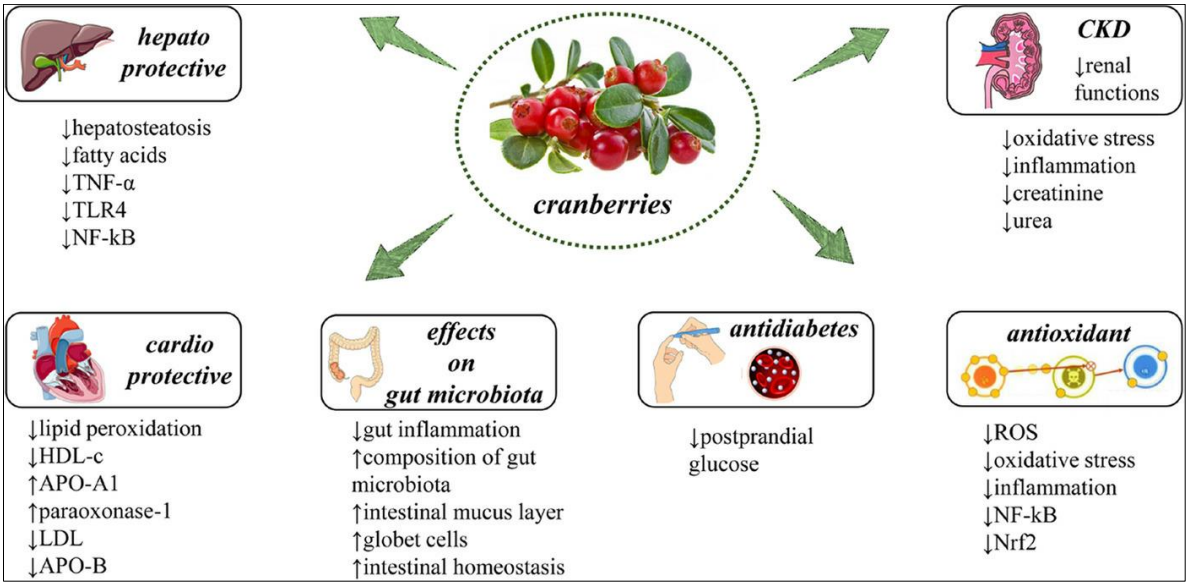


Figure 2. Therapeutic potential of cranberry (picture adapted from Amin, R., (2022) [6]

Oral Health Benefits of Cranberry

Dental Caries

The impact of cranberry fractions containing PAC on dental bio-film growth, persistence, and formation has been thoroughly studied. Cranberry PACs' capacity to suppress the activity and production of fructosyltransferase (FTF) and glucosyltransferase (GTF), which are involved in the creation of exopolysaccharides by *S. mutans*, has been attributed to their ability to stop the formation of sucrose-dependent bio-film [19]. In addition, the capacity of cranberry PACs to inhibit bacterial co-aggregation, lessen bacterial hydrophobicity, and modify cell surface molecules has been linked to the prevention of the non-sucrose-dependent bio-film development [26].

Oral Cancer

Supplementing with cranberries can have various effects depending on the stage of carcinogenesis and tumour development rates. Despite the data, there are few studies that support the use of these fruits for treating and preventing oral cancer. They should be avoided until more study is conducted, especially in metastasizing oral tumour conditions where the consequences are still unknown [27].

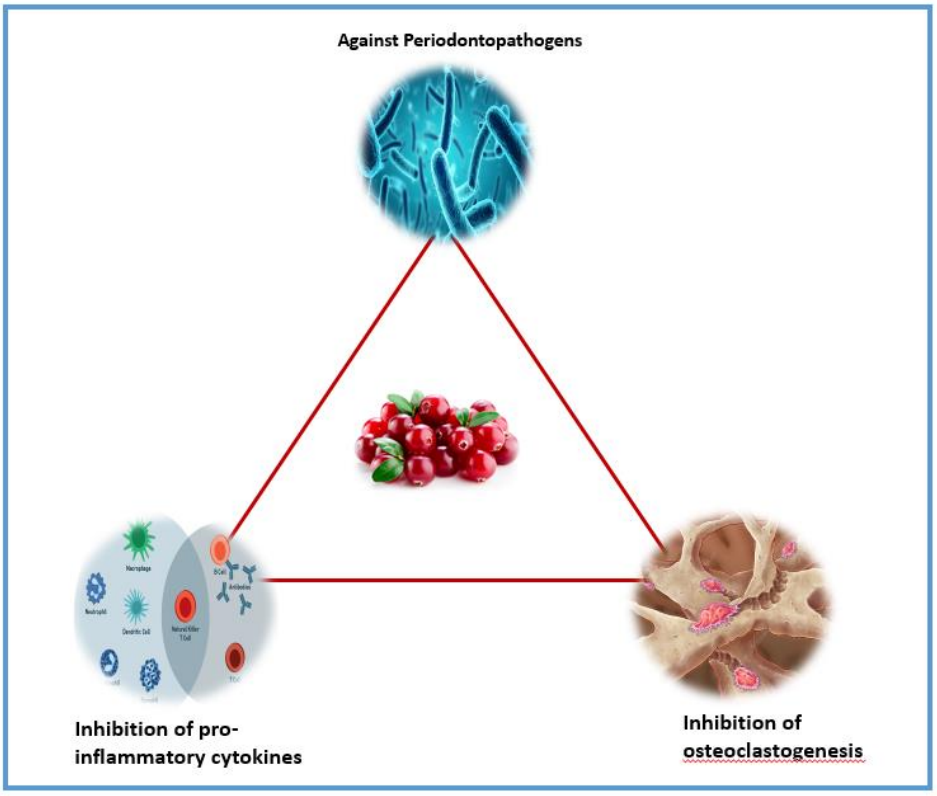
Role of Cranberry in Management of Periodontal Disease

Periodontitis is an inflammatory disorder leading to destruction of tooth supporting tissues including periodontal ligament and alveolar bone and is caused by gram negative anaerobic bacteria [28]. The continuous challenge to host immune systems is induced by host mediated destructive processes [29].

Targets for cranberry to prevent the initiation and progression of periodontal disease.[30]

TARGET 1: Inhibit the bacteria-mediated periodontal connective tissue destruction
TARGET 2: Inhibit the host-mediated periodontal connective tissue destruction
TARGET 3: Inhibit the alveolar bone destruction

Figure 3. Effect of cranberry for prevention of periodontal disease



Target 1: Inhibit The Bacteria-Mediated Periodontal Connective Tissue Destruction

Porphyromonas gingivalis is the key pathogen in chronic periodontitis. In order to promote its adherence to tooth surfaces, gingival epithelial cells, basement membrane components, erythrocytes, and oral bacteria, *P. gingivalis* is known to express a range of adhesins linked to either outer membrane or fimbria. At concentrations of 62.5 g/ml and higher, Labrecque *et al.* demonstrated that cranberry NDM (non-dialyzable material) might inhibit the development of *P. gingivalis* biofilm. However, cranberry fraction did not demonstrate any ability to desorb a *P. gingivalis* biofilm that had already developed [8].

Table 1. Studies on the effect of cranberry extracts on periodontopathogens

Author and year	Study design	Aim of the study	Targeted microorganism	Main results and conclusion
Weiss *et al.*, 1988 [31]	*In vitro* study	The ability of the high-molecular weight constituent derived from	● Actinobacillus actinomycetocomitans ● Actinomyces israeli	● A high-molecular-weight cranberry constituent at 0.6 to 2.5 milligrams per milliliter reversed

		cranberry juice to inhibit coaggregation of selected bacterial strains inhabiting the mouth	● Actinomyces Naeslundi ● Capnocytophaga sputigena ● Fusobacteriun nucleatum ● Porphyromonas gingivalis ● Prevotella denticola ● Prevotella intermedia ● Rothia dentocariosa ● Streptococcus oralis	the coaggregation of 49 (58 percent) of 84 coaggregating bacterial pairs tested. It acted preferentially on pairs in which one or both members are gram-negative anaerobes frequently involved in periodontal diseases. ● Anti-coaggregating cranberry constituent has the potential for altering the subgingival microbiota, resulting in conservative control of gingival and periodontal diseases
Weiss et al., 2002 [32]	*In vitro* study	The effect of cranberry juice on the co-aggregation of oral bacteria	● Actinobacillus actinomycetocomitans ● Actinomyces israeli ● Actinomyces Naeslundi ● Capnocytophaga sputigena ● Fusobacteriun nucleatum ● Porphyromonas gingivalis ● Prevotella denticola ● Prevotella intermedia ● Rothia dentocariosa ● Streptococcus oralis	●Coaggregation of representative pairs, A. naeslundii PK984 and F. nucleaum PK 1909 or A. israelii PK 14 and C. sputigena ATCC33612, was completely inhibited by NDM at concentration as low as 0.04 mg/ml. ●Coaggregation of 49 out of the 84 pairs tested was completely reversed by 2.5 mg/ml of NDM, whereas that of the remaining pairs could be only

				partially reversed. Nearly 90 % of all tested coaggregation pairs were completely reversed when NDM concentration was raised to 10 mg/ml. ● NDM acted preferentially on pairs in which either one or both members were Gram-negative (G+/G- or G-/G-, respectively). The coaggregation of 40 out of the 57 (70%) pairs in which at least one of the partners is Gram-negative was inhibited by 2.5 mg/ml and lower when compared with 9 out of the 27 (33%) Gram-positive pairs.
Labreque *et al.*, 2006 [8]	*In vitro* study	Effect of non-dialysable material (NDM) prepared from cranberry juice concentrate on growth, biofilm formation and adherence properties of P. gingivalis (Concentration of cranberry NDM at 250, 125, 50, 12.5, 2.5 or 0.5 mg/mL)	Porphyromonas gingivalis	A significant inhibition ($P < 0.05$) was observed when cranberry NDM was used at a concentration of 62.5 mg/mL and higher. Cranberry NDM is a potent inhibitor of biofilm formation by P. gingivalis. However, it has no effect on growth and viability of bacteria. Cranberry NDM also prevented

				significantly the attachment of P. gingivalis to surfaces coated with type I collagen, fibrinogen or human serum.
Yamanaka *et al.*, 2007 [33]	*In vitro* study (synergestic biofilm model- P.g and F. n)	Effect of cranberry polyphenol concentration at 250 and 500 μg/ml on the biofilm formation and activities of Arg-gingipain and Lys-gingipain in P. gingivalis	*P. gingivalis* ATCC 33277 and FDC 381, and F. nucleatum ATCC 25586, TDC 2 and TDC 20	At a dosage of 250 lg/mL, the polyphenol fraction significantly prevented the synergistic biofilm formation by P. gingivalis and Fusobacterium nucleatum when compared to untreated controls (p 0.01). At a polyphenol fraction concentration of greater than 1 lg/mL, arg-gingipain and lys-gingipain activities in P. gingivalis ATCC 33277 and FDC 381 were considerably reduced (p 0.05).
La VD *et al*., 2010 [10]	*In vitro* study	The effects of AC-PACs on *P. gingivalis* growth and biofilm formation, adherence to human oral epithelial cells and protein-coated surfaces, collagenase activity, and invasiveness. They also investigated the	Porphyromonas gingivalis	The pathogenicity of P. gingivalis was completely neutralized by AC-PACs in a dose-dependent manner; however, growth was unaffected. Additionally, they reduced the release of chemokine (C-C motif) ligand 5 (CCL5) and interleukin-8 (IL-8) by epithelial

		anti-inflammatory effects of AC-PACs in oral epithelial cells stimulated by *P. gingivalis*.		cells treated with P. gingivalis, but they had no effect on the release of IL-6.
Feldman et al 2012 [34]	In Vitro study	To investigate whether two natural compounds, A-type cranber3ry proanthocyanidins (AC-PACs) and licochalcone A, act in synergy against Porphyromonas gingivalis and the host inflammatory response of a macrophage model.	Porphyromonas gingivalis	AC-PACs and licochalcone A were found to act in synergy to inhibit P. gingivalis growth and biofilm formation.
Polak et al 2013 [35]	*In vitro* and In Vivo-mice study	The effect of high molecular weight cranberry constituent (non-dialyzable material [NDM]) on the virulence of a mixed infection with Porphyromonas gingivalis and Fusobacterium nucleatum in mice	● Porphyromonas gingivalis ● Fusobacterium nucleatum	● The NDM component of cranberry juice prevents P. gingivalis or F. nucleatum from adhering to epithelial cells. ● In comparison to mixed infection without NDM, NDM to the mixed infection resulted in partial protection against disease severity and decreased alveolar bone loss by around 20%.
H R. Rajeshwari *et al.*,	*In vitro* study	The efficacy of thermoreversible	● S. mutans ● E. faecalis ● actinomycetemcom	Antimicrobial activity of CJC showed MIC value

2017 [36]		gel of cranberry juice concentrate (CJC) as local drug delivery for the treatment of periodontitis. Antimicrobial activities like MIC, MBC, antiadhesion, antibiofilm and time kill assay against the panel of organisms	itans ● P. gingivalis ● T. forsythia	of 50mg/ml and MBC value of 100mg/ml with desirable antiadhesion (83-90%) and antibiofilm activity (70-85%). CJC was evaluated for its biocompatibility using periodontal fibroblasts by cell based MTT assay and found to be nontoxic
Pellerin, Geneviève *et al.*, 2021 [37]	*In vitro* study	Deacidification (0%, 19%, 42%, 60%, and 79%) from cranberry juice by EDBM affects its antibacterial activity against major periodontopathogens as well as its anti-inflammatory properties in an oral epithelial cell model.	● Aggregatibacter actinomycetemcomitans ● Porphyromonas gingivalis ● Fusobacterium nucleatum	Porphyromonas gingivalis and Fusobacterium nucleatum were unaffected by a deacidification rate of 60%, while Aggregatibacter actinomycetemcomitans, which is planktonic and embedded in biofilms, was still susceptible to it. Regardless of the rate of deacidification, cranberry juice increased the adhesion of A. actinomycetemcomitans and P. gingivalis to oral epithelial cells but decreased the adhesion of F. nucleatum by half. When exposed to deacidified cranberry juice with a deacidification rate of 42% compared to the raw beverage, F. nucleatum produced more hydrogen

				sulfide.

In summary, Table 1 represents studies evaluating the effect of cranberry against Periodontopathogens. The literature search revealed most studies performed were of an in-vitro design and the results reported that proanthocyanins of cranberry have anti-microbial and anti-adhesive properties against common Periodontopathogens such as *P. gingivalis, T. forysthia, T. denticola, F. nucleatum,* and *A. actinomycetocomitans*.

Target 2: Inhibit the Host-Mediated Periodontal Connective Tissue Destruction

High production of cytokines by host cells triggered by periodontopathogens is responsible for destruction of tooth supporting tissues [38]. Bodet *et al.* (2006) researched at how red complex bacteria (*P.gingivalis, T. forsythia,* and *T. denticola*) responded when exposed to Non-Dialysable Material (NDM) made from concentrated cranberry juice. Using synthetic chromogenic peptides, the impact of NDM on *P. gingivalis* gingipain and dipeptidyl peptidase IV, *T. forsythia* trypsin-like activity, and *T. denticola* chymotrypsin activity was assessed. Authors have reported that the proliferation of *P. gingivalis, T. forsythia,* and *T. denticola* in periodontal pockets as well as their protease-mediated destructive processes that occur in periodontitis may be inhibited by NDM [9].

Same research group in 2006 investigated the effect of NDM from cranberry juice concentrate on macrophages' production of pro-inflammatory cytokines in response to *Actinobacillus actinomycetocomitans, Fusobacterium nucleatum* sub spp., *Porphyromonas gingivalis, Treponema denticola, Tanerella forsythia,* and E. coli lipopolysaccarides (LPS). Regulation of TNF-, IL-1, IL-6, IL-8, and IL-8 on Activation By using cranberry fraction to stimulate macrophages before being stimulated by lipopolysaccharides, RANTES generation was measured by ELISA. According to the findings, cranberry fraction was a potent inhibitor of the pro-inflammatory cytokine and chemokine response to LPS [39].

The generation of prostaglandin E (PGE) is cyclooxygenase-dependent, and cranberry has been demonstrated to lower its expression. Cranberry extract reduced the inflammatory reactions that periodontopathogens induced in gingival fibroblasts and macrophages [40]. A key factor in the degeneration of periodontal tissue is the production of matrix metalloproteinases (MMPs) by resident and inflammatory cells in response to periodontopathogens. By stimulating human monocyte-derived macrophages with *Aggregatibacter actinomycetocomitans,* La *et al.* (2009) examined the effects of A-type cranberry proanthocyanidins (AC-PACs) on the production of various MMPs as well as the catalytic activity of recombinant MMP-1 and MMP-9. The outcomes demonstrated that AC-PACs suppress MMP synthesis in a concentration-dependent manner as well as MMP-1 and MMP-9 catalytic activity [41].

Table 2. Studies evaluating the effect of cranberry extract on host immune inflammatory response

Author and	**Study design**	**Aim of the study**	**Method of the study**	**Results**

year				
Bodet et al 2006[9]	*In vitro* study	To investigate the effect of non-dialysable material (NDM) prepared from cranberry juice concentrate on the proteolytic activities of P. gingivalis, T. forsythia and T. denticola.	Using synthetic chromogenic peptides, it was determined how NDM affected the activities of P. gingivalis' gingipain and dipeptidyl peptidase IV (DPP IV), T. forsythia's trypsin-like activity, and T. denticola's chymotrypsin-like activity. Additionally, fluorometry was used to assess P. gingivalis' ability to break down fluorescein-labeled type I collagen and fluorescein-labeled transferrin in the presence of NDM.	NDM inhibited the proteinases of P. gingivalis, T. forsythia, and T. denticola as well as the degradation of type I collagen and transferrin by P. gingivalis in a dose-dependent manner.
Bodet et al 2006[39]	*In vitro* study	To determine the impact of cranberry juice concentrate-derived non-dialyzable material on the pro-inflammatory cytokine response of macrophages caused by lipopolysaccharides (LPS) from Actinobacillus actinomycetemcomitans, Fusobacterium nucleatum subsp. nucleatum, Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia	Interleukin-1 beta (IL-1beta), IL-6, IL-8, tumor necrosis factor alpha (TNF-alpha), and Regulated on Activation Normal T-cell Expressed and Secreted (RANTES) production by macrophages treated with the cranberry fraction prior to stimulation by LPS was evaluated by ELISA.	the cranberry fraction was a potent inhibitor of the pro-inflammatory cytokine and chemokine responses induced by LPS
Bodet et al 2007[42]	*In vitro* study	To investigate the effect of a proanthocyanidin-enriched cranberry fraction, prepared from cranberry juice concentrate, on inflammatory mediator	Interleukin (IL)-6, IL-8, and prostaglandin E(2) (PGE(2)) production by fibroblasts treated with the cranberry fraction and stimulated by A. actinomycetemcomitans	The LPS-induced IL-6, IL-8, and PGE(2) responses of gingival fibroblasts were

		production by gingival fibroblasts stimulated by the lipopolysaccharide (LPS) of Aggregatibacter actinomycetemcomitans.	LPS was evaluated by enzyme-linked immunosorbent assay. Changes induced by A. actinomycetemcomitans LPS and the cranberry fraction in the expression and phosphorylation state of fibroblast intracellular signaling proteins were characterized by antibody microarrays	inhibited by treatment with the cranberry fraction. This fraction was found to inhibit fibroblast intracellular signaling proteins, a phenomenon that may lead to a down-regulation of activating protein-1 activity. Cranberry components also reduced cyclooxygenase 2 expression
Tipton et al 2013[4] [3]	*In vitro* study	To determine the effects of IL-17 ± cranberry components on IL-6 and IL-8 production by human gingival epithelial cells and fibroblasts.	NDM (5-50 g/mL), IL-17 (0.5-100 ng/mL), or NDM + IL-17 were cultured with human gingival epithelial cells, normal human gingival fibroblasts, and serum-free media for 6 days. In culture supernatants, IL-6 and IL-8 levels were assessed using ELISA. Lactate dehydrogenase activity released into cell supernatants and activity of a mitochondrial enzyme, respectively, were used to measure membrane damage and viability. ANOVA and Scheffe's F were used to evaluate the data for post hoc comparisons.	Inhibition of gingival fibroblast and epithelial cell production of IL-6 and IL-8 by cranberry NDM and IL-17

In summary, Table 2 represents literature evaluating the effect of cranberry on host immune response. It can be inferred from the literature reviewed, that non dialyzable material (NDM) from cranberry extract has potent inhibitor effect on proteinases, pro-inflammatory

cytokines and chemokines.

Target 3: Inhibiting the Alveolar Bone Destruction

Typical hallmark of periodontitis is the loss of alveolar bone. Gram-negative anaerobic bacteria in dental plaque can trigger the human immune system, which can then result in an inflammatory process that is damaging. Proinflammatory mediators (cytokines and chemokines) are produced and released during inflammation, which spreads to the alveolar bone next to the gingival [44]. By either boosting osteoclast proliferation or encouraging the differentiation and maturation of progenitor cells, the buildup of inflammatory cytokines promotes osteoclastogenesis [45].

Tanabe *et al.* investigated impact of A-type cranberry proanthocyanidins (AC-PACs) on the activity of osteoclasts and bone resorption. Even in the presence of osteoclastogenesis mediators, cranberry PACs can suppress the development of pre-osteoclastic cells, indicating that PACs may either directly or indirectly interfere with osteoclastogenesis mediators [46].

According to research by Woniewicz, Magorzata, *et al.*, cranberry functional beverage (CFB) consumption for eight weeks reduces dental plaque, alters antioxidant status, and reduces systemic inflammation in gingivitis patients [47].

Table 3. Studies assessing the inhibitory effect of cranberry extract on alveolar bone destruction

Author and year	Study design	Aim	Main results
Tanabe *et al.*, 2011 [46]	*In vitro* study	The effect of A-type cranberry proanthocyanidins (AC-PACs) on osteoclast formation and bone resorption activity.	Even in the presence of osteoclastogenesis mediators, cranberry PACs can prevent preosteoclastic cells from maturing, indicating that PACs may directly or indirectly interfere with mediators that are involved in osteoclastogenesis.
Galarraga-Vinueza, Maria Elisa *et al.*, 2020 [48]	*In vitro* study	To evaluate cell viability, anti-inflammatory activity, and macrophage polarization properties of different cranberry concentrates	After 24 hours of exposure, cranberry concentrates (A-type PACs) had no effect on HGF, SAOS-2, or macrophage viability. Cranberry concentrates at 50 and 100 g/mL inhibited the expression of pro-inflammatory cytokines (IL-8 and IL-6) in macrophages activated by LPS. Cranberry concentrates at a concentration of 100 g/mL significantly increased the expression of the

			anti-inflammatory IL-10 in LPS-stimulated macrophages after 24 hours. When cranberry concentrates were given to LPS-stimulated macrophages, M1 polarization considerably diminished. In all of the untreated control groups, there were significant numbers of positive M1 macrophages. All LPS-stimulated macrophages treated to cranberry concentrates for 1 and 24 hours saw a significant increase in M2 polarization.

In summary, Table 3 represents *in vitro* studies assessing the effect of cranberry extract in inhibition of alveolar bone destruction. From the literature, it can be concluded that cranberry proanthocyanins component have inhibitory effect on osteoclastogenesis; thereby inhibit the alveolar bone destruction.

CONCLUSION

Phytochemicals with the potential to modulate bacterial virulence and host responses have evolved as novel therapeutic agents for managing periodontal infections. Cranberry derived PACs are promising candidates due to their ability to inhibit periodontopathogen virulence factors and MMPs and to modulate the activities of the cells making up the periodontium. However, the need of the hour are human clinical trials which will provide a higher level of evidence required to prove the beneficial effect of cranberry in successfully managing the periodontal disease.

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