Inhibitory effect of cranberry extract on periodontopathogenic biofilm: An integrative review

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Abstract:
Background: Combating biofilm-dependent oral infections involves the use of synthetic antibiotics, which are often associated with bacterial resistance and adverse effects. As a result, herbs such as cranberry have emerged as an alternative treatment. The aim of this study was to evaluate, through an integrative literature review, the effectiveness of cranberry extract on cultures and biofilms of periodontopathogenic bacteria. Materials and Methods: in vitro and in vivo studies evaluating the action of cranberry extract on the growth, coaggregation and formation of periodontopathogenic bacteria and periodontal biofilm were identified. Searches were carried out in the “Cochrane Library,” “MEDLINE,” “Web of Science,” “Scopus,” “LILACS,” “Scielo,” and “Google Scholar” databases, using the terms: “vaccinium macrocarpon;” “cranberries;” “biofilms;” “periodontitis;” “aggressive periodontitis;” “periodontal diseases;” and “periodont.” Results: a low number of studies evaluating the effectiveness of cranberry extract on periodontal disease were found, and no human studies were identified. In general, the eight studies included in the revision found that the compounds effectively inhibited the formation of a biofilm of Porphyromonas gingivalis and Fusobacterium nucleatum at concentrations equal or superior to 62.5 µg/ml, but did not significantly inhibit bacterial growth or promote the breakdown of preformed biofilm. Conclusions: while most of the studies presented certain methodological limitations, they did identify an inhibiting effect of cranberry on periodontal bacteria. These results serve as support for the development of further studies evaluating the most effective vehicle and ideal concentration that can be used without causing adverse effects on oral tissues.

Key words: Biofilm, cranberry extract, Fusobacterium nucleatum, Porphyromonas gingivalis

INTRODUCTION

Over the past decade, cranberry extract and its molecular components have received increasing attention from researchers due to their general health benefits.[1] In particular, the properties of cranberry display potential for the prevention of microbial adhesion, especially with regard to controlling urinary tract infections.[2] Cranberry, which is present in a wide variety of products (sauce, jam, biscuits, and syrup), is consumed mainly in the form of juices and dried fruit.[3]

In terms of oral health, recent studies have indicated that cranberry extract, in various vehicles, has antimicrobial properties that can be used for the treatment of oral infections such as tooth decay. The inhibition of the production of organic acids produced by bacteria and the formation of dental biofilm justifies the use of such properties for the treatment and prevention of biofilm-dependent oral infections.[4]

For prevention/treatment of periodontal disease, the molecular components of cranberry also play an important role. The growth of two species of bacteria, Porphyromonas gingivalis and Fusobacterium nucleatum, associated with chronic periodontitis, is inhibited by cranberry extract.[5] Cranberry can also inhibit the adhesion of P. gingivalis to various proteins, including type I collagen, resulting in a further reduction of bacterial coaggregation in periodontopathogenic biofilms.[5]

Furthermore, Bodet et al. reported that cranberry components, specifically polyphenols, inhibited the proteolytic activity of red-complex bacteria.
These bacteria, *P. gingivalis*, *Treponema denticola*, and *Tannerella forsythia*, play an important role in the destruction of periodontal tissues. These observations suggest that the polyphenols present in cranberry have the potential to suppress the proliferation of these species of bacteria in periodontal pockets by limiting the availability of amino acids and peptides, on which their growth depends.

Considering that bacteria are the primary factors in the etiology of periodontal disease and that an uncontrolled immune response in the host can lead to the destruction of soft tissue and alveolar bone resorption, a study presenting scientific evidence supporting the effectiveness of cranberry extract in combating periodontal disease is of great significance. In addition, determining which components are associated with this action, as well as the main components of the extract that act on periodontopathogenic biofilms, is of paramount importance in understanding its clinical application. Therefore, the aim of the present study was to evaluate, through an integrative literature review, the effectiveness of cranberry extract on periodontopathogenic biofilm.

**MATERIALS AND METHODS**

An integrative review of all *in vitro* and *in vivo* laboratory and clinical studies published in literature was conducted to assess the effectiveness of cranberry extract against periodontal biofilm. The inclusion criteria were: *in vitro* and *in vivo* laboratory studies which evaluated the effect of cranberry extract on the growth, coaggregation and formation of periodontal biofilm, and which involved the application of cranberry extract and/or juice on planktonic and biofilm cultures of periodontal bacteria. No date or language restrictions were applied. Laboratory studies that evaluated the action of cranberry extract on pro-inflammatory chemical mediators such as interleukins and prostaglandins were excluded, along with studies that evaluated the effect of cranberry extract combined with another substance, herbal or otherwise, and studies that did not have a control group.

The electronic search strategies were performed independently by three researchers, from March to August 2015, on the following databases: Cochrane Library, MEDLINE, Web of Science, Scopus, LILACS, Scielo and Google Scholar, using the following descriptors and/or keywords: “Aggressive Periodontitis”[Mesh], “Biofilms”[Mesh], “Chronic Periodontitis”[Mesh], “cranberries”, “cranberry”, “periodont*”. The search strategies used for each data base are described in Chart 1, “Periodontal Diseases”[Mesh], “Periodontitis”[Mesh], “Vaccinium macrocarpon”[Mesh].

After the database searches, the titles and abstracts were listed using a standardized form. The three researchers, using the same eligibility criteria, then selected the studies with the potential to be read in full and included in the review.

The data from the studies that were read in full and included in the review were recorded in a data extraction sheet by three authors who, independently and in a group of three, recorded the relevant data of the study (sample, country where the study was performed), methodological characteristics, details of extracts used, concentrations, and outcomes.

In the event of disagreement, the authors consulted the fourth author and through consensus, reached a joint decision.

**RESULTS**

The electronic and manual search strategy found 197 titles and abstracts. Of these, 15 were selected in accordance with the inclusion and exclusion criteria and read in their entirety. Finally, eight studies were selected for inclusion in the review [Figure 1 and Chart 2].

The majority of studies selected featured *in vitro* analyses. In these, high molecular weight components of cranberry extract (nondialyzable materials [NDM]), polyphenol fractions, and A-type cranberry proanthocyanidins (AC-PAC) in different concentrations (from 1.56 µg/ml to 10 mg/ml) were used. Their effects were mostly analyzed on planktonic cultures and periodontopathogenic bacteria biofilms [Table 1].

**Chart 1: Search strategies used for each database**

| Base       | Strategy                                                                 |
|------------|---------------------------------------------------------------------------|
| PubMedMed  | (((“Vaccinium macrocarpon”[Mesh] OR “cranberries” OR “cranberry”) AND “Biofilms”[Mesh] OR “Periodontitis”[Mesh] OR “Aggressive Periodontitis”[Mesh] OR “Periodontal Diseases”[Mesh] OR “periodont*”)) ANDTITLE-ABS-KEY(“Vaccinium macrocarpon” OR “cranberries” OR “cranberry”)) |
| Web of science | Topic: (“Vaccinium macrocarpon” or “cranberries” or “cranberry”) AND Topic: (“Biofilms” OR “Periodontitis” OR “Chronic Periodontitis” OR “Aggressive Periodontitis” OR “Periodontal Diseases”) |
| Scopus     | (TITLE-ABS-KEY(“vaccinium macrocarpon” OR “cranberries” OR “cranberry”) ANDTITLE-ABS-KEY(“Biofilms” OR “Periodontitis” OR “Chronic Periodontitis” OR “Aggressive Periodontitis” OR “Periodontal Diseases”)) |
| Cochrane   | “vaccinium macrocarpon” OR “cranberries” OR “cranberry” AND “Biofilms” OR “Periodontitis” OR “Chronic Periodontitis” OR “Aggressive Periodontitis” OR “Periodontal Diseases” |
| Lilacs     | “VACCINIUM macrocarpon” OR “cranberries” OR “cranberry” [Words] and “Biofilms” OR “Periodontitis” OR “Chronic Periodontitis” OR “Aggressive Periodontitis” OR “Periodontal Diseases”[Words] |
| Scielo     | (“VACCINIUM macrocarpon” OR “cranberries” OR “cranberry”) AND (“Biofilms” OR “Periodontitis” OR “Chronic Periodontitis” OR “Aggressive Periodontitis” OR “Periodontal Diseases”[Words]) |
| Google scholar | “VACCINIUM macrocarpon” + “cranberries” + “cranberry” + “periodontal diseases” + “periodontitis” |

**Chart 2: Articles excluded following complete reading and reasons for exclusion**

- Did not evaluate the effect of cranberry extract on periodontopathogenic bacteria and biofilm (7)
  - Sethi and Govila, 2011
  - O’May and Tufenkji, 2011
  - Palaska et al., 2013
  - Feghali et al., 2012
  - Steinberg et al., 2004
  - Yamanaka et al., 2013
  - Feghali et al., 2012
- Review did not discuss compounds obtained from cranberry (1)
  - Signoretto et al., 2012
Weiss et al., 1998, performed in vitro analysis of the effect of a cranberry juice concentrate on bacterial coaggregation and disaggregation. This was characterized as an NDM of high molecular weight derived from American cranberries. The authors added 0.05 ml of the concentrate (NDM) to preformed aggregates of two bacterial strains in mixtures of equal volume (0.05 ml). The results showed that coaggregation in 49 (58%) of the 84 pairs tested was completely reversed with NDM concentrations equal to or <2.5 mg/ml. The study also showed that the NDM preferably acted on pairs where one or both members were Gram-Negative bacteria. In addition, it was found that the NDM was more effective at inhibiting coaggregation, than at disaggregating preformed coaggregates. For example, only 0.25 mg/ml of NDM was needed to completely inhibit coaggregation of a tested bacterial pair, while a higher concentration of 1 mg/ml NDM was needed to reverse the coaggregation of the same pair. In another study by the same authors, in 2002, the concentration of NDM was increased to 10 mg/ml. In this study, around 90% of the coaggregation pairs tested were completely reversed, demonstrating that, in this case, a higher concentration resulted in greater inhibition of bacterial aggregation.

Labrecque et al., in 2006, evaluated the effect of concentrated cranberry juice on the growth, adhesion and biofilm formation of P. gingivalis. The juice concentrate was obtained from Ocean Spray Cranberries, Inc (Lakeville-Middleboro, MA, USA). It was dialyzed, lyophilized and dissolved in distilled water before use. Samples containing 50 µL of the solution were applied to the bacterial cultures. The effect of cranberry on bacterial growth was visually evaluated through comparison with the control group, which consisted of a saline solution of phosphate buffer and bacterial strains (pH 7.2). Biofilm formation was assessed by absorbance at 550 nm (A550). The results of the study revealed that cranberry was effective at inhibiting biofilm formation when compared to the control group when the concentration was <62.5 µg/ml. However, the effect on preformed biofilm was limited, with even higher concentrations proving ineffective.

Yamanaka et al., 2007, in an in vitro study, obtained polyphenol fractions from cranberry juice, in concentrations of 250 and 500 µg/ml. This resulted in a significant inhibition of biofilm formation when used on P. gingivalis and F. nucleatum, in concentrations of both 250 µg/mL and 500 µg/ml, when compared with the controls (P < 0.01), in which no concentration of the vehicle was used.

La et al., 2010 and Feldman, 2012 analyzed the effect of AC-PACs on the growth and biofilm formation of P. gingivalis (ATCC 33277). Growth was assessed by a reading of the optical density with a microplate reader. Biofilm formation was assessed by absorbance at 550 nm (A550) after the cultures had been stained with crystal violet for 15 min. In both studies, biofilm formation was inhibited at concentrations equal to or >50 µg/ml. However, bacterial growth was not affected.
**Table 1: Characteristics and summary of results of studies included in the review**

| Author(s) | Year of study | Type of study | Vehicle used for antimicrobial action | Concentration of vehicle used for antimicrobial action | Microorganisms of periodontopathogenic biofilm on which vehicle acted | Main results |
|-----------|---------------|---------------|----------------------------------------|-------------------------------------------------------|---------------------------------------------------------------|--------------|
| Weiss et al., 1998 | In vitro | High molecular weight cranberry component (NDM) | 0.6-2.5 mg/ml | F. nucleatum, S. oralis, A. israelii, P. gingivalis, A. naeslundii, A. actinomyctemcomitans | Coaggregation was inhibited in 49 of 84 coaggregated bacterial pairs tested (58%). The cranberry was more effective in pairs where one or both members were anaerobic gram-negative bacteria, frequently involved in periodontal disease. The coaggregation of 40 (70%) of 57 couples in which at least one member was gram-negative was inhibited by 2.5 mg/ml or less of NDM, compared to nine (33%) of 27 Gram-positive pairs. |
| Weiss et al., 2002 | In vitro | High molecular weight cranberry component (NDM) | 0.04 mg/ml, 2.5 mg/ml and 10 mg/ml | A. actinomyctemcomitans, A. israelii, A. naeslundii, C. sputigena, F. nucleatum, P. gingivalis, P. loescheii, P. denticola, P. intermedius, R. dentocariosa, S. gordonii, S. oralis | Disaggregation of A. naeslundii and F. nucleatum or A. israelii and C. sputigena was observed with a concentration of 0.04 mg/ml. At concentrations of 2.5 mg/ml, the coaggregation of 49 out of 84 pairs tested was completely reversed. When the concentration was increased to 10 mg/ml, the coaggregation of around 90% of the pairs tested was completely reversed. A much more effective action was observed in pairs where one or both members were anaerobic Gram-negative. |
| Labrecque et al., 2006 | In vitro | Juice concentrate free of sugars and acids characterized as an NDM of high molecular weight | Concentrations of 0, 15.63, 32.25, 62.5, 125, 250 and 500 µg/ml | P. gingivalis (ATCC 33277) | Significant inhibition of biofilm formation was observed ($P<0.05$) for concentrations ≥62.5 µg/ml. SEM showed that in comparison to the control group, there was little bacterial coaggregation. The action of cranberry on preformed biofilm was limited. Even at a concentration of 250 µg/ml, no bacterial breakdown occurred. |
| Yamanaka et al., 2007 | In vitro | Polyphenol fractions obtained from cranberry juice | 250 µg/ml and 500 µg/ml | P. gingivalis and F. nucleatum | Significant inhibition of biofilm formation was observed by P. gingivalis and F. nucleatum cell culture. Polyphenol fractions prepared in a solvent solution with a 70% ethanol base were added to this culture medium. Two concentrations were used, 250 µg/ml and 500 µg/ml. The formation of biofilm was significantly inhibited by the polyphenol fraction at concentrations of 250 µg/ml or 500 µg/ml when compared to the control groups ($P<0.01$), which did not receive any concentration of the vehicle. This suggests that cranberry polyphenols have the potential to prevent, or reduce the severity of periodontal disease. |
| La VD et al., 2010 | In vitro | AC-PACs were isolated | 0, 50, 100 and 200 µg/ml | P. gingivalis (ATCC 33277) | The formation of biofilm by P. gingivalis was significantly less with concentrations of 50 and 100 µg/ml of AC-PACs. The AC-PACs inhibited the formation of biofilm by 45%±6% and 60%±4% with concentrations of 50 and 100 µg/ml, respectively. There was no significant effect on the growth of cultures of P. gingivalis. |
| Feldman et al., 2012 | In vitro | AC-PACs were isolated | 50, 25, 12.5, 6.25, 3.12, 1.56 and 0 µg/ml | P. gingivalis | The AC-PACs inhibited the formation of biofilm at concentrations of 50 µg/ml. However, there was no effect on bacterial growth, even at the highest concentration tested (50 µg/ml). |

*Contd...*
Table 1: Contd...

| Author et al., 2013 | Type of study | Vehicle used for antimicrobial action | Concentration of vehicle used for antimicrobial action | Microorganisms of periodontopathogenic biofilm on which vehicle acted | Main results |
|-------------------|---------------|--------------------------------------|-----------------------------------------------------|--------------------------------------------------|--------------|
| Polak and in vivo | In vitro and in vivo | High molecular weight cranberry component (NDM) | 4 µg/ml | F. nucleatum and P. gingivalis | Periodontitis was induced in rats by a mixed infection of P. gingivalis and F. nucleatum. The consumption of NDM by the infected mice attenuated the severity of experimental periodontitis when compared with mice untreated with NDM (P < 0.05). The addition of NDM attenuated alveolar bone loss induced by mixed infection by approximately 20%. |

Polak et al., 2013, carried out in vitro and in vivo analysis of the action of high molecular weight components of cranberry extract (NDM) at a concentration of 4 µg/ml in rats with periodontitis induced by a mixed infection of P. gingivalis and F. nucleatum. [20] NDM consumption by the infected mice reduced the severity of experimental periodontitis in comparison to mice untreated with NDM (P < 0.05), and adding NDM to the mixed infection attenuated alveolar bone loss by approximately 20%.

**DISCUSSION**

The present study aimed to gather scientific evidence to assess the effectiveness of cranberry extract on periodontal disease, through an integrative review. All types of studies that met the established inclusion criteria were included in this study. It was not possible to perform a systematic review of randomized controlled trials, which have a high level of scientific evidence, due to the absence of such studies in existing literature, as research involving cranberry extract is still at the laboratory level.

The results of the search strategy identified a small number of studies that evaluated the effect of cranberry extract on periodontal disease. No human study has found, indicating that the level of scientific evidence, in terms of meeting the objective of this study, was low.

In recent years, the use of cranberry to treat urinary tract infections, especially in women, has shown satisfactory results in randomized controlled clinical trials. [21] This herbal medicine is responsible for inhibiting the adherence of Escherichia coli and other pathogens to the epithelial cells and for selecting bacteria with lower adhesion potential in the gastrointestinal tract, thereby reducing the formation of biofilms. [22] Its potential action on Gram-negative bacteria, therefore, generates possible discussions about the existence of inhibitory effects on periodontal bacteria, which are also associated with peri-implant disease.

The studies included in this review used different types of vehicles to verify the antibacterial action of cranberry extract on periodontopathogenic biofilm. Among the microorganisms studied, P. gingivalis and F. nucleatum were the most studied, as these are the anaerobic bacteria most related to the biofilm in question, one of the main etiological factors of chronic periodontitis.[23,24] The vehicles consisted mainly of polyphenol fractions, high molecular weight components of cranberry (NDM) and AC-PAC. The concentrations also varied, indicating that research in this area has not reached a consensus on the ideal vehicle for cranberry, or the optimal concentrations for the greatest antimicrobial action on periodontopathogenic biofilm.

In general, the studies included in the review identified one limitation of cranberry compounds: that they failed to significantly inhibit bacterial growth or promote the breakdown of preformed biofilm. They did, however, effectively inhibit the formation of P. gingivalis and F. nucleatum biofilm at concentrations equal to or >62.5 µg/ml. [13,15-20] The mechanism of action involved in this inhibition is still controversial. Some believe that cranberry causes a modification of the hydrophobicity of the bacterial surface of bacteria; [13] Others, however, report that compounds derived from cranberry can cause the inhibition of cariogenic biofilm enzymes and proteases of periodontopathogenic biofilm. [2,18]

While this is not yet sufficiently clear, what is known is that irrespective of the fact that bacterial viability remains unchanged, if there is no biofilm formation, the chances of developing periodontal disease, and consequently peri-implant disease are lessened.

Although most of the studies presented certain methodological limitations (none compared the effectiveness of cranberry to an antimicrobial considered “gold standard” and there was no consensus on the optimal concentration of the vehicles used), the in vitro and in vivo laboratory studies performed until, nowadays, identify an inhibiting effect of cranberry on periodontal bacteria and serve as a support for the development of further studies assessing the most effective vehicle and the ideal concentration to be used, without causing adverse effects on oral tissues. From such studies, in the future, more accurate results will be obtained, which will, in turn, allow the application and clinical evaluation of cranberry extract on patients with the periodontal disease with greater safety. This is important as an alternative to the use of synthetic antibiotics, which are often associated with cases of bacterial resistance and numerous adverse effects.
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Conflicts of interest
There are no conflicts of interest.

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