Review Article

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POTENTIAL SYSTEMIC AND ORAL HEALTH EFFECTS OF CRANBERRY: A REVIEW

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Received on: 11/07/16 Revised on: 30/07/16 Accepted on: 22/08/16

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DOI: 10.7897/2277-4343.074171

ABSTRACT

Past few decades have witnessed a drastic resurgence towards herbal medicines. Amongst them, cranberries have attracted numerous researchers owing to their phytochemical content. The unique combination of phytochemicals found in cranberry fruit may produce synergistic health benefits. Recent in vitro and animal studies have demonstrated potential health effects of cranberry consumption; however in vivo data only partially supports this. This mixed outcome may be the result of variations in forms, dosage, regimens, patient compliance, etc. The present article is an attempt to review the existing research on the health effects of cranberry.

Key-words: Anti-bacterial, anti-adhesive, anti-cancer, cranberry, oral health

INTRODUCTION

Cranberry (*Vaccinium macrocarpon*) grows in the cold regions of north-eastern North America. Though not usually consumed raw, its intake can be marked because of its presence in various food products like cereal bars, cheese, chocolates, dietary supplements and medicines. Cranberry contains abundant polyphenols, which have anti-bacterial, anti-viral, anti-mutagenic, anti-carcinogenic, anti-angiogenic, anti-inflammatory and anti-oxidant properties.[1,2] This review aims to highlight evidence suggesting the effect of cranberry on health. Literature was searched mainly through Medline. Other databases included: Web of Science, Google Scholar and Scopus. Search terms were cranberry, polyphenols, flavonols, anti-adhesive, antibacterial, oral health.

Table 1: Nutrient and anti-oxidant capacity of Raw Cranberry per 100gm (Source: USDA National Nutrient data base)

Energy	46 kcal
Fibre, total dietary	3.6 gm
Sugars total	4.04 gm
Calcium (Ca)	8 mg
Magnesium (Mg)	6 mg
Phosphorus (P)	11 mg
Potassium (K)	80 mg
Sodium (Na)	2 mg
Vitamin C, total ascorbic acid	14 mg
Vitamin A, IU	63 IU
Carotene, beta	36 Cg

Composition and bioactive components

Cranberries have moderate levels of vitamin C, dietary fibers, essential and non-essential micronutrients (Table 1).[3,4] American cranberry is rich in phytochemicals, particularly A type proanthocyanidins (PACs), flavonols, anthocyanins, benzoic acid, terpenes and ursolic acid which impart anti-adhesion, anti-oxidant properties to cranberry.

Health effects of cranberry

Urinary tract infections (UTIs)

UTIs are one of the most commonly acquired bacterial infections both in and outside the hospital setting. 40-50% of women suffer from at least one UTI during their lifetimes, whereas 20-30% of these women experience its recurrence.[5,6] Thus, UTIs are a public health concern. Focusing on UTI prevention is important because of their recurrent nature, antibiotic resistance and medical costs. The most widely used alternative is use of cranberry, which has proved efficacious in many clinical trials. Cranberry extract has been shown to be useful in preventing recurrent UTIs in women and children by inhibiting the adherence of *Escherichia coli* in the urinary tract mucosa through their high molecular weight tannins.[7-9]

Several mechanisms have been proposed to describe action of cranberry in UTI prevention such as preventing the adhesion of type 1 and p-fimbriae strains (particularly from *Escherichia coli*) to the urothelium or inhibition of the bacterial growth due to the presence of various acids in cranberries.[7-9] Though the effects of cranberry components on bacterial adhesion have been

demonstrated in in-vitro studies, there is inconsistency in the results of human clinical trials because of differences in study designs, conditions, end points or effect markers, study populations and use of unstandardized or dissimilar products.[10]

Women, at higher risk of developing UTI and recurrent UTIs, have been mostly studied using cranberry intervention. Recent randomized trials (using different placebos and cranberry products) conducted to evaluate effect of cranberry in young women with recurrent UTIs, showed mixed results, with one trial showing significant reduction in incidence of UTIs as compared to placebo;[11] whereas three trials didn't show any significant difference between two groups in reducing UTIs.[12-14] There is no clear evidence showing the effectiveness of cranberry in UTI prevention in patients undergoing radiotherapy or chemotherapy as well as in pregnant women; whereas contrasting results have been obtained in clinical trials conducted in pediatric population.[15-17]

Cardiovascular diseases (CVDs)

Cranberries are rich source of phenolic phytochemicals, including phenolic acids (benzoic, hydroxycinnamic and ellagic acids) and flavonoids (anthocyanins andflavonols). A growing body of evidence suggests that polyphenols may contribute to reducing the risk of CVDs.[18] Various mechanisms have been proposed for effect of cranberry on CVDs. It may act by increasing the resistance of LDL to oxidation, inhibiting platelet aggregation, reducing blood pressure and via other antithrombotic and anti-inflammatory mechanisms or by affecting cardiovascular risk factors such as dyslipidemia, diabetes, hypertension, oxidative stress, endothelial dysfunction, arterial stiffness and platelet function.

Various studies suggest that cranberry anthocyanins lower LDL-C and increase HDL-C but the precise mechanism leading to this improved lipoprotein profile is incompletely understood. Also, the data supporting the effect of cranberry bioactives on CVD risk factors like diabetes mellitus and hypertension are frail. Several in-vitro and human trials suggest that cranberry bioactives have anti-inflammatory and oxidative stress-reducing actions and decrease concentrations of inflammatory cytokines.[19,20] Several animal and laboratory studies have shown favorable effects of cranberry bioactives on endothelial function and arterial stiffness.[21-23] In contrast, clinical studies of cranberry bioactives on endothelial vasodilator function have provided mixed results.[19,24] Although no clinical study has examined the effects of cranberry consumption on platelet aggregation responsible for acute cardiovascular events such as unstable angina and acute myocardial infarction; Yang et al. demonstrated that cranberry contains a compound called as delphinidin-3-glucoside an anthocyanin which significantly inhibited platelet activation and thrombosis.[25]

Despite of extensive research, unanswered questions regarding the role of cranberry in cardiovascular health include its desirable form, optimum amount, duration of consumption, the potential beneficiaries and their mechanisms of cardiovascular action.

Gastro-intestinal health

Helicobacter pylori are gram negative bacteria associated with gastrointestinal diseases such as gastric, duodenal and peptic ulcers, as well as gastric cancer and lymphoma. More than half of the world population is infected early in life (usually before the age of 10 years) and in the absence of antibiotic therapy, it generally persists for life. Numerous in vitro studies have shown cranberry components to have an anti-adhesion activity against *Helicobacter pylori*.[26-29]

Viral diseases [30,31]

Cranberry and its PAC and non-dialyzable material (NDM) fractions were found to inhibit the infectivity of many viruses in target cell lines or the interaction of the influenza virus with its receptor on erythrocytes (e.g. hemagglutination). Significantly, cranberry juice inhibited infectivity of *enteroviruses*; PAC inhibited surrogate *enteroviruses* and NDM inhibited influenza virus in cell cultures. Although these studies suggest that consumption of cranberry may prevent infections caused by these viruses, there is dearth of human trials to testify this.

Dental caries

Several researchers have recently demonstrated that bioactive components of cranberry may inhibit the activity of acidogenic bacteria, aid in inhibition of biofilm formation by *Streptococcus mutans* and *Streptococcus sobrinus*, ultimately inhibiting caries formation.[32] The high molecular weight NDM, an active ingredient of Cranberry, has shown to reverse the co-aggregation of majority of bacterial pairs. It exhibits tannin-like properties and is highly water-soluble. Pre-coating of the bacteria with NDM has shown to reduce their ability of biofilm formation.[33] Cranberry components inhibit the glucosyltransferase and F-ATPase activity, acid production and acid tolerance. The polyphenols in cranberries may limit dental caries initiation and progression by inhibiting the colonization of bacteria on teeth and acid production by cariogenic bacteria.

Several in-vitro studies have been carried out to assess whether cranberry components inhibit adhesion of oral bacteria to tooth surfaces and epithelial cells, as well as to each other, one of which demonstrated its anti-adhesion property.[33] Bacterial adhesion to the hydroxyapatite pellets, pretreated with saliva, decreased significantly after exposure to cranberry. Also NDM fraction of cranberry inhibited 80-95% of streptococcal biofilm formation. Other studies also confirmed the ability of cranberry extracts to prevent biofilm formation by cariogenic streptococci.[34-36]

One study investigated the effect of a mouthwash containing NDM fraction of cranberries on oral health both in-vitro and in-vivo. Microflora of the oral cavity, particularly *Streptococcus mutans*, was significantly reduced after use of mouthwash for a period of 6 weeks. The in-vivo study conducted showed inhibition of *Streptococcus sobrinus* adhesion to hydroxyapatite surfaces pretreated with saliva due to use of NDM fractions.[37] Only two clinical trials in recent times have reported inhibitory effect of cranberry components on *Streptococcusmutans*.[38,39]

Periodontal diseases

Periodontal diseases are manifestations of colonization of subgingival sites by periodontal micro-organisms. It is the capacity of these bacteria to adhere to the host tissues to form a biofilm which influences periodontitis. NDM fraction of cranberry inhibits biofilm formation by *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, which are associated with chronic periodontitis.[40] Studies have reported the anti-adhesion activity of NDM fraction to type I collagen proteins on *Porphyromonas gingivalis* and inhibited subsequent biofilm formation.[41] It is suggested that cranberry phenols may be useful in regulating the host response and perhaps treating periodontitis in poorly controlled diabetics.[42] Though large-scale clinical

trials are recommended, these results suggest that cranberry can play a vital role in maintaining gingival health.

Anti-cancer activity

Cranberry has the highest anti-oxidant property amongst all the berries because of its rich flavonoid and phenolic acids content. It also has an anti-inflammatory action. These properties may play a role in its anti-tumour activities. Anthocyanins & flavonoids present in cranberry possess anti-proliferative or growth inhibitory properties.[43,44] Anti-tumour activity of cranberry can also be observed due to presence of quercetin and ursolic acid.[45]

The very first report on assessment of potential anti-cancer activity of cranberry appeared in a study conducted in University of Illinois in 1996.[46] Since then, numerous animal experiments and in-vitro studies have been conducted to assess anti-cancer properties of cranberry components, which have shown promising results.[45] Few studies involving human oral cancer cell lines have demonstrated the beneficial role of cranberry in controlling oral cancer.[47,48] Hence, these findings suggest the miraculous potential of cranberry as a dietary chemo-preventive fruit.

Anti-fungal activity

Candida albicans is a commensal micro-organism and major human fungal pathogen. Though it is rarely harmful, its overgrowth may result in candidiasis. Cranberry has been tried as an antifungal agent, but limited research is available to assess this effect. Numerous in-vitro studies have reported anti-adhesion and anti-biofilm formation activities of cranberry components against *Candida albicans*.[49-52]But reliable human studies are recommended in this area.

Drug interactions

Potential interactions of foods and beverages with medications are of deep concern in clinical practice; same holds true for herb-drug interactions. Therefore, an increasing number of case reports of life-threatening interactions between cranberry and warfarin have been reported.[53,54] But well-controlled, clinical pharmacokinetic and pharmacodynamic studies published in the scientific literature do not show a clinically relevant interaction between cranberry juice and either warfarin metabolism or International Normalized Ratio (INR) in subjects on warfarin.[55,56]

CONCLUSION

Till date, numerous studies have been conducted and many reviews published on potential health benefits of cranberry, cumulatively asserting the unique health-promoting role of cranberries. Though the use of cranberry for preventing a wide range of infections has great potential, clinical studies have focused mainly on UTIs because of antibiotic resistance to UTI specific *Escherichia coli* strains. Researchers should also focus on other areas of beneficial actions of cranberry. Unlike medicines or treatment, cranberries can be consumed regularly, apparently have a good track record of safety and are cost-effective. However, consuming cranberry is only an adjunct and cannot be a substitute to medical treatment or prevention of systemic or oral diseases. Further research should be directed to understand mechanism of action, to evaluate impact of dose, form and duration of cranberry consumption on physiological functions and health outcomes.

Cranberry, though not cultivated in India, is extensively marketed to India and is easily available in various forms like juice, gels, extract, chocolates and its potential health benefits need to be explored among Indian population. With minimal side effects & herbal medicines being part of India's traditional healthcare system, cranberries can become a cost-effective panacea.

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Cite this article as:

Mahesh R. Khairnar, Pranali V. Shimpi, Umesh Wadgave, Sandeep Patil, Manjiri A. Deshmukh. Potential systemic and oral health effects of cranberry: A review. Int. J. Res. Ayurveda Pharm. Jul - Aug 2016;7(Suppl 3):136-140 http://dx.doi.org /10.7897/2277-4343.074171

Source of support: Nil, Conflict of interest: None Declared