Literature Review Article

Polyphenols and oral health

Nikita Lolayekar[1]
Chaitanya Shanbhag[2]

Corresponding author:
Nikita Lolayekar
Department of Pedodontics and Preventive Dentistry
A.B. Shetty Memorial Institute of Dental Sciences
Mangalore – Karnataka – India
E-mail: drnikitashanbhag@gmail.com

[1] Department of Pedodontics and Preventive Dentistry, A.B. Shetty Memorial Institute of Dental Sciences – Mangalore – Karnataka – India.
[2] Department of Periodontics, A. J. Institute of Dental Sciences – Mangalore – Karnataka – India.

Abstract

Introduction: Polyphenols (PPs) are reactive metabolites abundant in plant derived foods, especially fruits, seeds and leaves. Polyphenols exert preventive activity against infectious and degenerative diseases including oral diseases. **Objective:** This non-systematic review discusses the preventive activity of PPs in the diet against oral diseases as well as their limitations. **Literature review:** Relevant references have been used to summarize the beneficial effects of PPs in our diet and to understand why they are receiving increasing interest from health professionals for potential clinical use, as well as food manufacturers and consumers alike. **Conclusion:** Better knowledge of dietary polyphenols could offer a very economical public health intervention in maintaining oral health.

Introduction

Polyphenols (PPs) exert preventive activity against infectious and degenerative diseases and may also help prevent oral diseases via various mechanisms [58]. These PPs are reactive metabolites abundant in plant derived foods, particularly fruits, seeds and leaves and are characterized by the presence of several phenol groups, which derive from L-phenylalanine [8, 37, 4]. Polyphenols are receiving increasing interest from consumers and food manufacturers as they are reducing agents, and together with other dietary reducing agents, such as vitamin C, vitamin E and carotenoids, they protect the body's tissues against oxidative stress [68].

Mechanism of action

Polyphenols are antibacterial and anti-oxidative natural agents [28]. Antioxidants are substances that scavenge free radicals-damaging compounds in the body that alter cells, tamper with DNA and even cause cell death. Antioxidants such as polyphenols

can neutralize free radicals and may reduce or even help prevent some of the damage they cause [14]. Since considerable evidence indicates that increased oxidative damage is associated with the development of most major age-related degenerative diseases, it has been speculated that PPs may have protective effects against such conditions [58]. According to a hypothesis, polyphenol (PP) activity against several forms of cancer, proliferative diseases, inflammation and neurodegeneration is mainly exerted through the inhibiting and modulating activities against a wide range of receptors, enzymes and transcription molecules [88].

Polyphenols in human diet

PPs are common in all human diets wherever fruit and vegetables are consumed [58]. Cereals, chocolate and dry legumes also contribute to the total polyphenol intake [67]. Their main dietary sources are fruits and plant-derived beverages such as fruit juices, tea, coffee and red wine. However, available information on quantitative PP intake is incomplete and comprehensive reference food composition tables are not available, because of the wide range of PPs and the considerable number of factors that modify their concentration in foods [58].

There is increasing interest in the effect of natural compounds, especially food extracts, on the resident oral microflora, both in terms of their ability to promote the growth of beneficial organisms and by their inhibition of the growth and metabolism of species associated with disease [60]. Of particular interest to us are PPs which may complement each other in bolstering the body's defense against various ailments as well help maintain a healthy oral environment.

Literature review

Polyphenols in food

Cocoa

Chocolate is very rich in PPs, and a minor consumption of chocolate may significantly contribute to total polyphenol intake [68]. Cocoa polyphenols tend to reduce inflammation by regulating proinflammatory mediators and controlling processes that oxidize low density lipids (LDL) in the development of atherosclerosis [73].

The possible protective effect of cocoa on dental caries is receiving increasing attention, but previously published data concerning the anticariogenic effects of constituents of chocolate are conflicting. An early study indicated that a high sucrose diet was equally cariogenic in the presence or absence of cocoa bean ash [90], while the incorporation of cocoa powder or chocolate into hamster diets was reported to reduce caries [78]. Later studies showed that caries scores [24] and the cariogenic potential indices (CPI) of chocolate were lower than sucrose in rat models; chocolate diets also resulted in lower recoverable viable counts of *Streptococcus sorbinus* [49]. Similarly, it has been shown *in vivo* [85] that the CPI of chocolate with high cocoa levels was less than 40% that of sucrose (10% w/v) and also lower than chocolates containing low cocoa levels.

More recent studies have focused on the biological activity of various extracts of cocoa or of waste materials from the chocolate industry, such as cocoa bean husk, which is known to contain high concentrations of polyphenols. Whilst cocoa mass extracts did not inhibit the growth of oral streptococci or reduce caries incidence or plaque accumulation in a rat model [55], cocoa bean husk extract was effective at reducing the growth rates and cariogenicity of *S. mutans* and *S. sorbinus* [56]. The possible mechanisms underlying these observations are not fully understood, but some relevant inhibitory effects on bacterial metabolism (e.g. acid production, insoluble glucan synthesis) have been reported [56, 59, 57].

Tea

Tea, made from the leaves of *Camellia sinensis* (fam. *Theaceae*), is one of the most popular beverages worldwide [40]. Tea polyphenols, particularly green tea catechins, are potent antioxidants and fight inflammation, DNA damage, and LDL oxidation [82].

A number of beneficial effects have been attributed to tea consumption, including the prevention of oral cancer and tooth decay [27, 94]. Japanese folklore has it that drinking green tea 'makes the mouth clean' [65] and more specifically that 'there is an old tradition that those who drink a large amount of green tea have less tooth decay' [50]. In several animal experiments and human trials, green tea and black tea have been shown to significantly reduce plaque scores and caries index [51, 63, 16, 53, 35].

Tea infusions contain various amount of fluoride but the cariostatic effects could also be attributed to other components, such as the polyphenol moieties. Studies have indicated that tea polyphenols inhibit the glucosyltransferase of *mutans streptococci*

and also exert antibacterial activity against oral microorganisms. Green tea polyphenols have been claimed to exhibit antimicrobial effects against *mutans streptococci*, but only at relatively high levels. On the other hand, polymerized polyphenols, which are rich in oolong tea extracts (OTE), show very strong inhibitory activities. Furthermore, polymerized tea polyphenols decrease the cell surface hydrophobicity of oral streptococci including *mutans streptococci*, and inhibit cellular adhesion to the tooth surface. These effects collectively may contribute to the reduction of dental caries development in humans [52].

Although tea polyphenols have been shown to have anticancer activity *in vitro* and oral cancer preventive activity in animal models [42, 15] epidemiological evidence for oral cancer prevention has been sparse and inconclusive. For example, a population-based, case– control study in Denmark has found no association between tea consumption and the development of oral squamous cell cancer [6]. On the other hand, preliminary results from an intervention study have shown that oral and topical administration of a tea preparation significantly reduced the size of oral lesions and the incidence of micronucleated oral mucosa cells in leukoplakia patients compared with a nontreated group [43]. Because of the worldwide popularity of tea and because of the absence of toxicity as a natural dietary agent, tea is an excellent candidate for dietary cancer prevention [10] and at the same time could be seen as a dietary preventive measure against dental caries and periodontal diseases.

Cranberry

In the past decade, cranberry extracts have been attracting ever-growing attention by dental researchers [3]. The American cranberry is a member of the heath family native to North America, and it is known in the USA as a healthy drink containing a lot of vitamin C [91]. Cranberry polyphenol fraction has been shown to inhibit adhesion by various bacteria such as infectious pathogens of the urinary tract, *Helicobacter pylori* and pathogens of oral disease [13, 23, 39, 62, 72, 87]. 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-caries agents since they inhibit acid production, attachment and biofilm formation by *Streptococcus mutans*. Glucan-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 coaggregation of periodontopathogens [3]. Gregoire *et al.* [23] suggested that the biological activity of cranberry extracts resulted from the complex mixture of flavonoids rather than a single active compound.

Grape

Raisins contain polyphenols, flavonoids, and high levels of iron that may benefit human health. However, their oral health benefits are less well understood. It has been hypothesized that raisins contain antimicrobial phytochemicals capable of suppressing oral pathogens associated with caries or periodontal diseases and thus benefit oral health. Oleanolic acid has been shown to suppress *in vitro* adherence of cariogenic *Streptococcus mutans* biofilm. Grape seed extract, high in proanthocyanidins, has shown to positively affect the in vitro demineralization and/or remineralization processes of artificial root caries lesions, suggesting its potential as a promising natural agent for noninvasive root caries therapy [89].

Apple

Apples contain many types of phenolic derivates and flavonoids. Apple pulp contains catechin, procyanidin, caffeic acid and chlorogenic acid among other components. The skin contains all the aforementioned substances as well as flavonoids, not present in pulp, such as quercetin glycosides and cyanidin glycosides [2]. Studies show that the anti-inflammatory and antioxidant qualities of apple polyphenols have a wide range of health benefits, including protection of colon cells against free-radical damage that could cause cancer [70], prevention of bone loss in an experimental model of menopausal osteoporosis [61], decreased lipid oxidation, and cholesterol reduction. Population studies have linked increased consumption of apples with lower risk of some cancers, cardiovascular disease, asthma, and diabetes [5].

Applephenon is apple polyphenol extract produced commercially from unripe apples, and

has been used as food additive in order to prevent oxidation of components in foods and its application in functional foods is expected. In a lipid metabolism regulation study, administration of applephenon had the potential to exert strong anti-oxidative activity and to inhibit consumption of vitamin E and anti-oxidative enzymes [1].

Yanagida et al. [92] in an in vitro study, found that apple polyphenols (APP) markedly inhibited the activity of glucosyltransferases (GTF) purified from the cariogenic bacterial cells but showed no significant effect on the growth of the cariogenic bacteria. The strongest GTF inhibitors in APP were apple condensed tannins (ACT), a mixture of procyanidins. This means that APP and ACT might selectively inhibit the bacterial GTF activity under oral conditions.

Wine

Moderate wine consumption is known to have beneficial effects on human health [12]. The antioxidant and antiradical properties, particularly of red wine, attributed mainly to high polyphenol content [20, 64, 21], appear to protect against the risk of coronary heart disease and cancer. Wine also possesses antimicrobial properties. Sugita-Konishi et al. [79] showed the in vitro antibacterial activity of red and white wines against three potential enteropathogenic bacteria; the activity was exerted by polyphenol free fractions and was lost after the evaporation of small molecules, particularly acetic acid, suggesting that this small molecule could be responsible for the antibacterial activity. Findings in a study showed that wine is active against oral streptococci and S. pyogenes and suggest that it enhances oral health [12] although it may not be entirely attributed to the polyphenol content.

Along with the potential value for medicine, the discovery that the waste products of wine making such as fermented seeds and skins cast away after grapes are pressed, interfere with the ability of bacteria to contribute to tooth decay may be useful in drug-making and has economic implications.

Polyphenols in the oral cavity

Oral mucosa, where PPs reach highest concentration with respect to all other tissues is constantly exposed to oxidative stress from environment and diet [25, 34]. Proline-rich proteins (PRPs) and histatins together with PPs form stable complexes in the oral cavity which remain stable throughout the whole gastrointestinal tract [48, 75]. The hypothesis of direct anti-oxidant activity of PPs is potentially valid in explaining their preventive effect against diseases of the oral cavity, where PPs come into direct contact with tissues before being absorbed and metabolized [26] and are activated into aglycones by human and bacterial enzymes [86].

Some PP hydroxyls are very reactive but there are other important defensive functions with respect to their effect on dental diseases such as plant defense against pathogenic micro-organisms: Phenolic acids are antimicrobials and are directly involved in the response to micro-organisms [58]. Mechanisms well documented are hydrogen peroxide production, bacterial protein or enzyme inhibition and disinfectant activity of phenolic acids [11].

The activity of PPs against microbial enzymes and proteins is concentration dependent: at low concentration, PPs interfere with specific sites, whereas at high concentrations they cause denaturation [18]. PPs interact with microbial membrane proteins, enzymes and lipids, thereby altering cell permeability and permitting the loss of protons, ions and macromolecules [18, 33, 80]. In addition, micro-organisms stressed by exposure to PPs upregulate proteins related to defensive mechanisms, which protect cells or help cells survive, while simultaneously they down regulate various metabolic and biosynthetic proteins involved [9].

Oral cancer

The anticancer activity of several PPs is due to their ability to inhibit enzymes in carcinogenesis and tumor development [88, 19]. Catechins from tea inhibit the production of important metalloproteinases, thus potentially reducing invasion and migration [31], inducing apoptosis [32, 45] and growth arrest in both oral cancer [45] and oral leukoplakia cell lines [36]. Prevention of oxidative stress, modulation of carcinogen metabolism and prevention of DNA damage have been suggested as possible cancer preventive mechanisms for tea and tea polyphenols [93]. Other PPs inhibit DNA adduct formation and reduce cell proliferation in human oral cancer cells infected by human papillomavirus, implicated in the development of some oral cancers, inhibit proliferation in non-infected cells, show cytotoxic activity and induce apoptosis and cell differentiation [58].

Periodontal disease

PPs may also contribute to increase the anti-oxidant activity of oral fluids. When there is disequilibrium between oxidative stress and anti-oxidant activity, periodontal tissue destruction may appear. This suggests that antioxidant rich diets

might inhibit periodontal disease development and progression, particularly in subjects exposed to environmental and dietary sources of oxidative stress [58].

Lee *et al*. [40] showed that delivery of tea PPs by holding green or black tea in the mouth for 2-5 minutes increases the anti-oxidant capacity of saliva. Staudte *et al*. [77] said daily consumption of two fresh grapefruits for 2 weeks increases phagocytic activity of polymorphonuclear leucocytes in gingival crevicular fluid. PPs are also known to have antibacterial activity against periodontal pathogens, prevent biofilm formation and even decrease pocket depth with local application. He *et al*. [29] in their study showed that tea polyphenol had an effect in promoting the proliferation of human periodontal ligament fibroblasts. Sakanaka [66] *et al*. studied the inhibitory effects of green tea polyphenols on the production of a virulence factor of the periodontal-disease-causing anaerobic bacterium *Porphyromonas gingivalis* and showed that continuous application of tea polyphenols on a daily basis can be considered as a useful and practical method for the prevention of periodontal diseases.

Dental caries

The effect of PPs against dental caries has been generally investigated indirectly. PPs act against *mutans streptococci* by inhibiting glucosyltransferase (GTF) activity and insoluble glucan synthesis, adherence inhibition on hard surfaces, inhibiting acid production from sucrose or glucose, bacteriostatic activity against *mutans streptococci* and down regulation of essential enzymes for *streptococcus mutans* metabolism. Smullen *et al*. [76] in their study reported that commercially available and 70% aqueous propanone (P70) of unfermented cocoa, epicatechin polymer fraction, green tea and red grape seed were bacteriostatic and prevented acid production when added at the minimum inhibitory concentrations to cultures of *S. mutans* grown in a chemically defined medium supplemented with either glucose or sucrose. The extracts also reduced adherence of *S. mutans* to glass.

In vitro studies investigating the effect of specific PPs against *mutans streptococci* showed that tannins inhibit human salivary alpha-amylase which catalyzes hydrolysis of starch to oligosaccharides and binds to *viridans streptococci* and enamel, which in turn provide an acidogenic food source for cariogenic micro-organisms on the tooth surface

[69]. Cocoa flavonols stimulate peripheral blood mononuclear cells to secrete interleukin 5, which in turn, stimulates IgA production, thus possibly protecting against *mutans streptococci* [44].

Matsumoto *et al*. [46] in an *in vivo* study showed that administration of the oolong tea extract and its chromatographically isolated polyphenol compound into diet and drinking water resulted in significant reductions in caries development and plaque accumulation in rats infected with *mutans streptococci*.

High consumers of coffee, barley coffee, tea and wine show lower lactobacilli and *mutans streptococci* levels in plaque and saliva and lower dental plaque scores than low/ non-consumers [74]. Results of another study indicate that cariostatic activity of oolong tea extract was effective even after the establishment of *S. sorbinus* in the oral cavity and was more effective in drinking water than in diet. Furthermore, OTE may contain some anticaries substances that affect the virulence of *S. sorbinus* other than glucosyltransferases [54].

In an *in vivo* study conducted to study the effect of mouth washes containing oolong tea extract on plaque deposition in human volunteers, the results showed that while OTE significantly inhibited plaque deposition it has no significant effect on *S. mutans*. It was concluded that OTE had strong antiplaque properties due to its ability to inhibit insoluble glucan synthesis [83].

Despite studies showing the preventive effect of polyphenols, the evidence that they are an active anti-caries measure is only classified as fair since they do not decrease caries incidence directly.

Food and nutritional supplements

The current evidence for protective effects of PPs against oral diseases should lead to dietary recommendations that maybe optimized for particular population groups as well as to the design of new food products that may satisfy future needs. There is already a gradual change taking place in food guide pyramids with polyphenol rich foods being a small but important part of the balanced diet. It has also generated new expectations for improvements in health, with great interest from the food and nutritional supplement industry regarding promotion and development of polyphenol-rich products [67]. PPs are already being incorporated into chocolates, chewing gums, mouth rinses and beverages in order to prevent dental diseases. But many of the products available today are yet to receive FDA approval even though they are already

being promoted as antioxidant and polyphenol rich products.

A study investigating the potential use of tea polyphenol extracts in jelly candies, its taste, color, consistency and general consumer's acceptance indicated that tea polyphenols extracts were accepted by consumers as food product constituents, and might be an interest of wider usage as food components [22].

Hannig *et al.* [28] in their study to investigate the effect of different polyphenolic beverages like black tea, green tea, grape juice, cistus tea or red wine on initial bacterial adherence to enamel in the oral cavity; showed that rinses with all beverages reduced the amount of detectable bacteria. They concluded that rinses with certain polyphenolic beverages as well as consumption of these foodstuffs may contribute to prevention of biofilm induced diseases in the oral cavity. The anti-cariogenic effects against alpha-haemolytic streptococci showed by polyphenols from cocoa, coffee, and tea in a study by Ferrazzano *et al.* [17] also suggest further studies to a possible application of these beverages in the prevention of pathogenesis of dental caries.

However, it is still impossible to evaluate the individual and societal benefits that increases in polyphenol intake could have for the general population or for particular groups at specific disease risk [67].

Discussion

Drawbacks/ limitations

The main factor that has delayed research on polyphenols is the considerable diverse and complexity of their chemical structures [67]. Polyphenols are not evenly distributed in plant tissues, and food fractionation during processing may result in a loss or enrichment of some phenolic compounds [68]. In apple, quercetin is found in the peel (1 mg/g fresh weight); the peeled fruit contains no other flavonols [7]. Similarly, polyphenols in wheat grain are principally contained in the outer layers (aleurone cells, seed coat) and are lost during the refining of flour [71]. Conversely, pressing may result in the solubilization of phenolic compounds in juices otherwise present in the unconsumed parts of the fruit [68]. For a number of reasons, including structural diversity, lack of standardized analytical methods and variation of content in a particular foodstuff, it is extremely difficult to estimate the average daily intake of polyphenols. Most authors refer to the data published 25 years ago. A daily intake of 1 g of total phenols was reported, but the methods used to obtain this result were not detailed [68, 38]. It appears that polyphenol intake depends to a large extent on dietary habits and preferences. This concerns not only the consumption of polyphenols as a whole or that of the different classes of polyphenols but also that of each individual phenolic compound. The evaluation of polyphenol dietary intake still lacks precision. Most of the data on polyphenol content in food originate from scattered sources. A more comprehensive and thorough survey of the occurrence in food of the various types of polyphenols must be undertaken using well-standardized methods [68]. Much of the evidence on the prevention of diseases by polyphenols is derived from in vitro or animal experiments, which are often performed with doses much higher than those to which humans are exposed through the diet [67]. At the same time, maintenance of a high concentration in plasma requires a repeated ingestion of the polyphenols over time, as has been observed with volunteers consuming tea every 2 hours [84].

However, the half-life of metabolites formed in the colonic microflora is longer due to the long residence time of polyphenols in the colon. Measurement of the plasma antioxidant capacity suggests that more phenolic compounds are present, largely in the form of unknown metabolites, produced either in our tissues or by the colonic microflora. It will be important to learn more about these metabolites, particularly because of their potent biological activity. We need to better assess the role of the microflora in the bioavailability of polyphenols and to determine the proportions of the plasma phenolic metabolites absorbed by the small intestine or by the colon after transformation by the micro-flora. Changes in the composition of the colonic microflora could explain the large interindividual variations in bioavailability [68].

We should not forget that many polyphenols have a taste and/or a color [41]; food must be not only good for health but also acceptable to consumers [67]. After the consumption of a given source of polyphenols or of a given diet, we should be able to evaluate the contribution to the prevention of oxidative stress with regard to other dietary antioxidants as well as be able to predict the tissue levels of specific metabolites that may bind to specific receptors and trigger the responses beneficial for our health [68]. The mechanism of action of PPs *in vivo* could be different from the in-vitro mechanism. In fact classical antioxidant activity is unlikely to be the principal explanation

for cellular effects in humans where non-specific protein or enzyme modulating mechanisms are primarily involved [58].

Finally, it must be pointed out that exposure levels depend on the mode of presentation of the polyphenols. The risk of consuming high doses of polyphenols from naturally polyphenol rich foods is low, but we must take into account the negative effects of other ingredients in these foods, such as cholesterol increasing fats in coffee, alcohol in wine, and fat in chocolate [47]. Pediatric dosages for polyphenol consumption have still not been determined.

Safety

At times there can be over-estimation of current knowledge regarding beneficial effects when we need to consider the safety. Companies selling various PP rich products give different dosages and recommendations, all which are commonly found on the internet. Furthermore, a significant increase in the consumption of polyphenols, as for many other phytomicronutrients, may not be without risks [47]. Some hazards associated with the consumption of polyphenols are documented, but evaluation among humans is still very limited [67].

People with heart problems, kidney disorders, stomach ulcers, and psychological disorders (particularly anxiety) should not take green tea. Pregnant and breast-feeding women should also avoid green tea [14]. The inhibition of non-heme iron absorption attributable to simultaneous tea consumption is well known; high consumption of polyphenols may increase the risk of iron depletion in populations of individuals with marginal iron status [81].

Intakes from habitual diets are usually lower than the doses used in these studies, and the food matrix may also influence the effects of polyphenols, which may explain why observational epidemiologic studies have not shown, for example, any carcinogenic effects of polyphenols to date [30]; although this is probably also attributable to lack of accurate exposure assessment and residual confounding [47].

Before human intervention trials are designed to confirm the effect of PPs on the oral cavity with use of fortified foods or supplements, a safety assessment of applied dose should be performed [41]. But the known effects mentioned make human trials with high doses of these PPs unethical. Before we reach that stage, however, we need to accumulate substantial data from *in vitro*, animal, and observational epidemiologic studies with only relevant forms and doses, to ascribe a potential beneficial effect to total or specific polyphenol intake.

In the 17th century, Paracelsus rightly said, "All substances are poisons; there is none which is not a poison. It is the dose that distinguishes a poison from a remedy". [47]

Conclusion

In summary, regular consumption of foods/beverages containing polyphenols may help prevent oral cancer effectively. With regard to dental diseases, studies on humans are needed to confirm the promising results provided by many experimental studies. Better knowledge of structure, dose and bioavailability of dietary polyphenols will be essential in the future to properly evaluate their role in the prevention of oral diseases. And if all this is substantiated, putting PPs on the menu could offer a very economical public health intervention in maintaining oral health.

References

1. Akazome Y. Characteristics and physiological functions of polyphenols from apples. Biofactors. 2004;22(1-4):311-4.

2. Alberto MR, Canavosio MAR, Manca de Nadra MC. Antimicrobial effect of polyphenols from apple skins on human bacterial pathogens. Electronic Journal of Biotechnology (Special Issue). 2006;9(3):205-9.

3. Bodet C, Grenier D, Chandad F, Ofek I, Steinberg D, Weiss EI. Potential oral health benefits of cranberry. Crit Rev Food Sci Nutr. 2008;48(7):672-80.

4. Boudet AM. Evolution and current status of research of phenolic compounds. Phytochemistry 2007;68:2722-35.

5. Boyer J, Liu RH. Apple phytochemicals and their health benefits. Nutr J. 2004;12(3):5.

6. Bundgaard T, Wildt J, Frydenberg M, Elbrond O, Nielsen JE. Case-control study of squamous cell cancer of the oral cavity in Denmark. Cancer Causes Control. 1995;6:57-67.

7. Burda S, Oleszek W, Lee CY. Phenolic compounds and their changes in apples during maturation and cold storage. J Agric Food Chem. 1990;38:945-8.

8. Chesson A, Russel WR, Provan GJ. Metabolites of the phenylpropanoid pathway-common origin common properties. In: Chesson A, Russel WR, Provan GJ, editors. Polyphenols in foods. Luxembourg: Office for Official Publications of the European Community; 1997. p. 17-23.

9. Cho YS, Schiller NL, Kahng HY, Oh KH. Cellular responses and proteomic analysis of Escherichia coli exposed to green tea polyphenols. Current Microbiology. 2007;55:501-6.

10. Chow HH, Cai Y, Hakim IA, Crowell JA, Shahi F, Brooks CA et al. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. Clin Cancer Res. 2003;9:3312-9.

11. Cushnie TPT, Lamb AJ. Antimicrobial activity of flavonoids. International Journal of Antimicrobial Agents. 2005;26:343-56.

12. Daglia M, Papetti A, Grisoli P, Aceti C, Dacarro C, Gazzani G. Antibacterial activity of red and white wine against oral streptococci. J Agric Food Chem. 2007;55:5038-42.

13. Duarte S, Gregoire S, Singh AP, Vorsa N, Schaich K, Bowen WH et al. Inhibitory effects of cranberry polyphenols on formation and acidogenecity of Streptococcus mutans biofilms. FEMS Microbiol Lett. 2006;257:50-6.

14. Ehrlich SD. University of Maryland Medical Center. Green tea [cited 2009 Nov 29]. Available from: URL: http://www.umm.edu/altmed/articles/green-tea-000255.htm.

15. Elattar TM, Virji AS. Effect of tea polyphenols on growth of oral squamous carcinoma cells in vitro. Anticancer Res. 2000;20:3459-65.

16. Elvin-Lewis M, Steelman R. The anticariogenic effects of tea drinking among Dallas school children. J Dental Res. 1986;65:198.

17. Ferrazzano GF, Amato I, Ingenito A, De Natale A, Pollio A. Anti-cariogenic effects of polyphenols from plant stimulant beverages (cocoa, coffee, tea). Fitoterapia. 2009;80(5):255-62.

18. Fung DYC, Taylor S, Kahan J. Effects of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) on growth and aflatoxin production of Aspergillus flavus. Journal of Food Safety. 1977;1:39-51.

19. Galati G, O'Brien PJ. Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties. Free Radical Biology and Medicine. 2004;37:287-303.

20. German JB, Walzem RL. The health benefit of wine. Annu Rev Nutr. 2000;20:561-93.

21. Goldfinger TM. Beyond the French paradox: the impact of moderate beverage alcohol and wine consumption in the prevention of cardiovascular disease. Cardiol Clin. 2003;21:449-57.

22. Gramza-Michalowska A, Regula J. Use of tea extracts (Camelia sinensis) in jelly candies as polyphenols sources in human diet. Asia Pac J Clin Nutr. 2007;16(Suppl 1):43-6.

23. Gregoire S, Singh AP, Vorsa N, Koo H. Influence of cranberry phenolics on glucan synthesis by glucosyltransferases and Streptococcus mutans acidogenecity. J Appl Microbiol. 2007;103:1960-8.

24. Grenby TH, Mistry M. Precise control of the frequency and amount of food provided for small laboratory animals by a new electronic metering technique, used to evaluate the cariogenic potential of chocolate. Caries Res. 1995;29:418-23.

25. Halliwell B, Rafter J, Jenner A. Health promotion by flavonoids, tocopherols, tocotrienols, and other phenols: direct or indirect effects? Antioxidant or not? American Journal of Clinical Nutrition. 2005;81(Suppl):268S-76S.

26. Halliwell B, Zhao K, Whiteman ML. The gastrointestinal tract: a major site of antioxidant action? Free Radical Research. 2000;33:819-28.

27. Hamilton-Miller JM. Anti-cariogenic properties of tea (Camellia sinensis). J Med Microbiol. 2001;50:299-302.

28. Hannig C, Sorg J, Spitzmüller B, Hannig M, Al-Ahmad A. Polyphenolic beverages reduce initial bacterial adherence to enamel in situ. J Dent 2009;37(7):560-6.

29. He QM, Liu JG, Xu RZ, Zhang J, Fan Q, Jiang C. Effect of tea polyphenols on proliferation of human periodontal ligament fibroblasts. Nan Fang Yi Ke Da Xue Xue Bao. 2008;28(8):1409-11.

30. Hertog MGL, Hollman PCH, Katan MB, Kromhout D. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in the Netherlands. Nutr Cancer. 1993;20:21-9.

31. Ho YC, Yang SF, Peng CY, Chou MY, Chang YC. Epigallocatechin-3-gallate inhibits the invasion of human metalloproteinases and urokinase-plasminogen activator. Journal of Oral Pathology and Medicine. 2007;36:588-93.

32. Hsu S, Lewis JB, Borke JL, Singh B, Dickinson DP, Caughman GB et al. Chemopreventive effects of green tea polyphenols correlate with reversible induction of p57 expression. Anticancer Research. 2001;21:3743-8.

33. Ikigai H, Nakae T, Shimamura T. Bactericidal catechins damage the lipid bilayer. Biochimica et Biophysica Acta. 1993;1147:132-6.

34. Johnson IT. New approaches to the role of diet in the prevention of cancers of the alimentary tract. Mutation Research. 2004;551:9-28.

35. Kempler D, Anaise J, Westreich V, Gedalia I. Caries rate in hamsters given nonacidulated and acidulated tea. J Dent Res. 1977;56:89.

36. Khafif A, Schantz SP, Al-Rawi M, Edelstein D, Sacks PG. Green tea regulates cell cycle progression in oral leukoplakia. Head and Neck. 1998;20:528-34.

37. Knags AR. The biosynthesis of shikimate metabolites. Natural Product Reports. 2003;20:119-36.

38. Kuhnau J. The flavonoids: a class of semi-essential food components: their role in human nutrition. World Rev Nutr Diet. 1976;24:117-91.

39. Labrecque J, Bodet C, Chandad F, Grenier D. Effects of high molecular-weight cranberry fraction on growth, biofilm formation and adherence of Porphyromonas gingivalis. J Antimicrob Chemother. 2006;58:439-43.

40. Lee MJ, Lambert JD, Prabhu S, Meng X, Lu H, Malaikal P et al. Delivery of tea polyphenols to the oral cavity by green tea leaves and black tea extract. Cancer Epidemiology Biomarkers and Prevention. 2004;13:132-7.

41. Lesschaeve I, Noble AC. Polyphenols: factors influencing their sensory properties and their effects on food and beverage preferences. Am J Clin Nutr. 2005;81(suppl):330S-5S.

42. Li N, Han C, Chen J. Tea preparations protect against DMBA-induced oral carcinogenesis in hamsters. Nutr Cancer. 1999;35:73-9.

43. Li N, Sun Z, Han C, Chen J. The chemopreventive effects of tea on human oral precancerous mucosa lesions. Proc Soc Exp Biol Med. 1999;220:218-24.

44. Mao TK, Van De Water J, Keen CL, Schmitz HH, Gershwin ME. Effect of cocoa flavonols and their related oligomers on the secretion of interleukin-5 in peripheral blood mononuclear cells. Journal of Medicinal Food. 2002;5:17-22.

45. Masuda M, Suzui M, Weinstein IB. Effects of epigallocatechin-3-gallate on growth, epidermal growth factor receptor signaling pathways, gene expression, and chemosensitivity in human head and neck squamous cell carcinoma cell lines. Clinical Cancer Research. 2001;7:4220-9.

46. Matsumoto M, Minami T, Sasaki H, Sobue S, Hamada S, Ooshima T. Inhibitory effects of oolong tea extract on caries-inducing properties of mutans streptococci. Caries Res. 1999;33(6):441-5.

47. Mennen LI, Walker R, Bennetau-Pelissero C, Scalbert A. Risks and safety of polyphenol consumption. Am J Clin Nutr. 2005;81(suppl):326S-9S.

48. Mitaru BN, Reichert RD, Blair R. The binding of dietary protein by sorghum tannins in the digestive tract of pigs. Journal of Nutrition. 1984;114:1787-96.

49. Mundorff SA, Featherstone JDB, Bibby BG, Curzon MEJ, Eisenberg AD, Espeland MA. Cariogenic potential of foods. I. Caries in the rat model. Caries Res. 1990;24:344-55.

50. Nakahara K, Kawabata S, Ono H, Ogura K, Tanaka T, Ooshima T et al. Inhibitory effect of oolong tea polyphenols on glucosyltransferases of mutans streptococci. Appl Environ Microbiol. 1993;59:968-73.

51. Onisi M, Ozaki F, Yoshino F, Murakami Y. An experimental evidence of caries preventive activity of non-fluoride component in tea. Koku Eisei Gakkai Zasshi. 1981;31:158-62.

52. Ooshima T. Anti-caries activity of tea polyphenols foods food ingredients. J Jpn. 2005;210(4): summary.

53. Ooshima T, Minami T, Aono W, Tamura Y, Hamada S. Reduction of dental plaque deposition in humans by oolong tea extract. Caries Res. 1994;28:146-9.

54. Ooshima T, Minami T, Matsumoto M, Fujiwara T, Sobue S, Hamada S. Comparison of the cariostatic effects between regimens to administer oolong tea polyphenols in SPF rats. Caries Res. 1998;32(1):75-80.

55. Ooshima T, Osaka Y, Sasaki H, Osawa K, Yasuda H, Matsumoto M. Cariostatic activity of cacao mass extract. Arch Oral Biol. 2000;45:805-8.

56. Ooshima T, Osaka Y, Sasaki H, Osawa K, Yasuda H, Matsumura M et al. Caries inhibitory activity of cacao bean husk extract in *in vitro* and animal experiments. Arch Oral Biol. 2000;45:639-45.

57. Osawa K, Miyazaki K, Shimura S, Okuda J, Matsumoto M, Ooshima T. Identification of cariostatic substances in the cacao bean husk: their anti-glucosyltransferase and antibacterial activities. J Dent Res. 2001;80:2000-4.

58. Petti S, Scully C. Polyphenols, oral health and disease: a review. Journal of Dentistry. 2009;37:413-23.

59. Paolino VJ, Kashket S. Inhibition by cocoa extracts of biosynthesis of extracellular polysaccharide by human oral bacteria. Arch Oral Biol. 1985;30:359-63.

60. Percival RS, Devine DA, Duggal MS, Chartron S, Marsh PD. The effect of cocoa polyphenols on the growth, metabolism, and biofilm formation by Streptococcus mutans and Streptococcus sanguinis. Eur J Oral Sci. 2006;114:343-8.

61. Puel C, Quintin A, Mathey J, Obled MJ, Davicco P, Lebecque S et al. Prevention of bone loss by phloridzin, an apple polyphenol, in ovariectomized rats under inflammation conditions. Calcif Tissue Int. 2005;77(5):311-8.

62. Raz R, Chazan B, Dan M. Cranberry juice and urinary tract infection. Clin Infect Dis. 2004;38:1413-9.

63. Rosen S, Elvin-Lewis M, Beck FM, Beck EX. Anticariogenic effects of tea in rats. J Dent Res. 1984;63:658-60.

64. Ruf JC. Overview of epidemiological studies on wine, health and mortality. Drugs Exp Clin Res. 2003;29:173-9.

65. Sakanaka S, Kim M, Taniguchi M, Yamamoto T. Antibacterial substance in Japanese green tea extract against Streptococcus mutans, a cariogenic bacterium. Agr Biol Chem. 1989;53:2307-11.

66. Sakanaka S, Okada Y. Inhibitory effects of green tea polyphenols on the production of a virulence factor of the periodontal-disease-causing anaerobic bacterium Porphyromonas gingivalis. J Agric Food Chem. 2004;52(6):1688-92.

67. Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. Am J Clin Nutr. 2005;81(suppl):215S-7S.

68. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. American Society for Nutritional Science; 2000. p. 2073S-84S. Presented at the symposium "Chocolate: Modern Science Investigates an Ancient Medicine" held February 19, 2000 during the 2000 Annual Meeting and Science Innovation Exposition of the American Association for the Advancement of Science in Washington, D.C. Published as a supplement to The Journal of Nutrition.

69. Scannapieco FA, Torres G, Levine MJ. Salivary alpha-amylase: role in dental plaque and caries formation. Critical Reviews in Oral Biology and Medicine. 1993;4:301-7.

70. Schaefer S, Baum M, Eisenbrand G, Janzowski C. Modulation of oxidative cell damage by reconstituted mixtures of phenolic apple juice extracts in human colon cell lines. Mol Nutr Food Res. 2006;50(4-5):413-7.

71. Shahidi F, Naczk M. Food phenolics: sources, chemistry, effects, applications. Lancaster: Technomic Publishing Co. Inc.; 1995.

72. Sharon N, Ofek I. Fighting infectious diseases with inhibitors of microbial adhesion to host tissues. Crit Rev Food Sci Nutr. 2002;42:267-72.

73. Sies H, Schewe T, Heiss C, Kelm M. Cocoa polyphenols and inflammatory mediators. Am J Clin Nutr. 2005 Jan;81(1 Suppl):304S-12S.

74. Signoretto C, Burlacchini G, Bianchi F, Cavalleri G, Canepari P. Differences in microbiological composition of saliva and dental plaque in subjects with different drinking habits. New Microbiol. 2006;29(4):293-302.

75. Skopec MM, Hagerman AE, Karasov WH. Do salivary proline-rich proteins counteract dietary hydrolysable tannin in laboratory rats? Journal of Chemical Ecology. 2004;30:1679-92.

76. Smullen J, Koutsou GA, Foster HA, Zumbé A, Storey DM. The antibacterial activity of plant extracts containing polyphenols against Streptococcus mutans. Caries Res. 2007;41(5):342-9.

77. Staudte H, Sigusch BW, Pfitzner A, Klinger G, Glockmann E. Grapefruit influence the clinical and paraclinical parameters in periodontitis patients. Journal of Dental Research. 2001;80:647.

78. Stralfors A. Inhibition of hamster caries by substances in chocolate. Arch Oral Biol. 1967;12:959-62.

79. Sugita-Konishi Y, Hara-Kudo Y, Iwamoto T, Kondo K. Wine has activity against entero-pathogenic bacteria in vitro but not in vivo. Biosci Biotechnol Biochem. 2001;65:954-7.

80. Tamba Y, Ohba S, Kubota M, Yoshioka H, Yamazaki M. Single GUV method reveals interaction of tea catechin (-)-epigallocatechin gallate with lipid membranes. Biophysical Journal. 2007;92(9):3178-94.

81. Temme EHM, van Hoydonck PG. Tea consumption and iron status. Eur J Clin Nutr. 2002;56:379-86.

82. Tipoe GL, Leung TM, Hung MW, Fung ML. Green tea polyphenols as an anti-oxidant and anti-inflammatory agent for cardiovascular protection. Cardiovasc Hematol Disord Drug Targets. 2007;7(2):135-44.

83. Turesky S, Gilmore ND, Glickman I. Reduced plaque formation by chromethyl analogue of vitamin C. J Periodontol. 1970;41:41-93.

84. van het Hof KH, Wiseman SA, Yang CS, Tijburg LB. Plasma and lipoprotein levels of tea catechins following repeated tea consumption. Proc Soc Exp Biol Med. 1999;220:203-9.

85. Verikaki E, Duggal MS. A comparison of different kinds of European chocolates on human plaque pH. Eur J Paed Dent. 2003;4:203-10.

86. Walle T, Browning AM, Steed LL, Reed SG, Walle UK. Flavonoid glucosides are hydrolysed and thus activated in the oral cavity in humans. Journal of Nutrition. 2005;135:48-52.

87. Weiss EI, Kozlovsky A, Steinberg D, Lev-Dor R, Bar Ness Greenstein R, Feldman M et al. A high molecular mass cranberry constituent reduces mutans streptococci level in saliva and inhibits in vitro adhesion to hydroxyapatite. FEMS Microbiol Lett. 2004;232:89-92.

88. Williams RJ, Spencer JPE, Rice-Evans C. Flavonoids: antioxidants or signaling molecules? Free Radical Biology and Medicine. 2004;36:838-49.

89. Wu CD. Grape products and oral health. J Nutr. 2009;139(9):1818S-23S.

90. Wynn W, Haldi J, Law ML. Influence of the ash of the cacao bean on the cariogenicity of a high-sucrose diet. J Dent Res. 1960;39:153-7.

91. Yamanaka-Okada A, Sato E, Kouchi T, Kimizuka R, Kato T, Okuda K. Inhibitory effect of cranberry polyphenol on cariogenic bacteria. Bull Tokyo Dent Coll. 2008;49(3):107-12.

92. Yanagida A, Kanda T, Tanabe M, Matsudaira F, Oliveira Cordeiro JG. Inhibitory effects of apple polyphenols and related compounds on cariogenic factors of mutans streptococci. J Agric Food Chem. 2000;48(11):5666-71.

93. Yang CS, Lambert JD, Sang S. Antioxidative and anti-carcinogenic activities of tea polyphenols. Arch Toxicol. 2009;83(1):11-21.

94. Yang CS, Maliakal P, Meng X. Inhibition of carcinogenesis by tea. Annu Rev Pharmacol Toxicol. 2002;42:25-54.