ISSN 2347-5579

Unique Journal of Medical and Dental Sciences

Available online: www.ujconline.net

Review Article

ANTIOXIDANTS- A BRIEF SYNOPSIS

Ranjit Kumar J[1*], Uma Maheswari S[2], Priyanka[3], Silpiranjan Mishra[4]

[1]MDS (Periodontics and implantology), Senior Lecturer, SRM Dental College and Hospital, Ramapuram, Chennai, Tamilnadu, India
[2]MDS (Oral Medicine and Radiology), Chennai, Tamilnadu, India
[3]MDS (Periodontics and implantology), Senior Lecturer, SRM Dental College and Hospital, Ramapuram, Chennai, Tamilnadu, India
[4]MDS (Oral Medicine and Radiology), Senior Lecturer, Kalinga Institute of Dental Sciences, KIIT University, Patia, Bhubaneswar, Odisha, India

Received: 16-07-2015; Revised: 14-08-2015; Accepted: 12-09-2015

*Corresponding Author: **Dr. J. Ranjit Kumar**
MDS (Periodontics and implantology), Senior Lecturer, SRM Dental College and Hospital, Ramapuram, Chennai, Tamilnadu, India

ABSTRACT

Free radicals are produced in our body by various physiological and pathological conditions. Free radical acts like a double edged sword with both favourable and unfavourable consequences. The body also has natural counter mechanisms to protect against the dangerous effects of free radicals. This article discusses the effects of free radicals, types of antioxidants, mechanism of action of antioxidants and the effects of antioxidants in dentistry.

Keywords: Antioxidants, Free radicals, Oxidative stress, Reactive oxygen species.

INTRODUCTION

Cells use oxygen to produce energy required for day to day life. Free radicals and oxidant byproducts are produced during the formation of ATP by mitochondria. These free radicals have dual role, i.e., in low quantities exerts beneficial effects and in higher quantities wields toxic effects. Oxygen paradox portrays the fact that survival of aerobic organism is not possible without oxygen; nevertheless oxygen is fundamentally dangerous to their presence.

Radicals are molecules that possess an unpaired electron in their outer orbital. They are generally unstable, highly reactive and cause extensive damage to DNA, protein and lipid, leading to oxidative stress and impaired cellular function. Oxidative stress occurs when there is an imbalance between oxidant production and the antioxidant capacity of the cell.

Natural counter mechanisms exist within the body to protect these cells against the oxidant injury. The various reactive oxygen species and metabolites are simultaneously removed by a complex network of antioxidants. The protective mechanism of anti-oxidants takes place in both enzymatic and non-enzymatic reactions. Moreover, the endogenous antioxidants also work along with exogenous antioxidants to combat the ROS. This review discusses the veracities about free radicals and the anti-oxidants.

FREE RADICALS AND OXYGEN

Free radicals are defined as molecules with an unpaired electron in the outer orbit[1]. They are generally unstable and highly reactive. ROS (reactive oxygen species) are formed from oxygen and RNS (Reactive nitrogen species) are formed from nitrogen by various endogenous systems under physiological or pathological conditions. ROS and RNS are the terms collectively defining free radicals and other non-radical reactive derivatives also termed oxidants.

Examples of oxygen free radicals:

Hydroxyl (OH•), Superoxide (O_2 •$^-$), Nitric oxide (NO•), Nitrogen dioxide (NO_2 •), Peroxyl (ROO•) and Lipid peroxyl (LOO•), Alkoxyl (RO•), and Hydroperoxyl (HO_2 •) radicals.

Examples of nitrogen free radicals:

Nitric oxide and Nitrogen dioxide (•NO_2)

Oxidants:

Byproducts that are not free radicals and generally called oxidants, but can easily lead to free radical reactions in living organisms[2].

Examples: Hydrogen peroxide (H_2O_2), Ozone (O_3), Singlet oxygen ($^1O_2$), Hypochlorous acid (HOCl), Nitrous acid (HNO_2), Peroxynitrite ($ONOO^-$), Dinitrogen trioxide (N_2O_3), Lipid peroxide (LOOH)

GENERATION OF FREE RADICALS AND OXIDANTS

ROS, RNS, and reactive chlorine species are produced in animals and humans under physiologic and various pathologic conditions[3].Thus, ROS and RNS include radical and non-radical species. Normally, bonds do not split in a way that leaves a molecule with odd, unpaired electrons. But, free radicals are formed each time a weak bond splits. Since free-radicals are unstable, they gain stability by quickly reacting with other compounds, mostly by attacking the nearest stable molecules abstracting its electron. When the attacked

molecule loses its electron, it becomes a free-radical itself, these formations of free-radicals continue on and on and finally result in the disruption of the substances.

Production of ROS and RNS can occur in the cells by two ways

Enzymatic reactions

Free radicals generated in respiratory chain, the cytochrome P450 system, the phagocytosis, and the prostaglandin synthesis are mainly due to enzymatic reactions[4].

Non-enzymatic reactions

Free radicals are formed due to non-enzymatic reactions of oxygen with organic compounds, ionizing radiations and the non-enzymatic process during oxidative phosphorylation (i.e. aerobic respiration) in the mitochondria[2,5,6]

Sources for ROS and RNS formation

ROS and RNS are generated from either endogenous or exogenous sources. Free radicals are formed endogenously by the body during infection, inflammation, immune cell activation, ischemia, excessive exercise, mental stress, cancer and aging.

Pollution, cigarette smoking, alcohol, cooking (smoked meat, used oil, fat), herbicides, certain drugs (cyclosporine, tacrolimus, gentamycin, bleomycin), heavy metals (Cd, Hg, Pb, Fe, As), radiation[5] are some of the sources of exogenously formed free radicals. After diffusion into the body by various routes, these exogenous compounds are decomposed or metabolized into free radicals.

BIOLOGICAL ROLES OF FREE RADICALS

There are "two faces" of free radicals i.e. they serve as signalling and regulatory molecules at physiologic levels, at the same time as highly deleterious and cytotoxic oxidants at pathologic levels[7].

Beneficial effects of free radicals

Free radicals may play an important role in the basis of life and biological growth, linking their beneficial effects on the organisms[8].

- Signal transduction[9], Gene transcription[9], Regulation of soluble guanylate cyclase activity in cells[9, 10], Relaxation and proliferation of vascular smooth muscle cells[11], Leukocyte adhesion[11], Platelet aggregation[11], Angiogenesis[11], Thrombosis[11], Vascular tone and Hemodynamics[11], Neurotransmitter[7], Mediator of the immune response[7].

Toxic effects of free radicals

Formation of free radicals and other reactive species can result in the oxidation of biomolecules, which in turn leads to cell injury and death. The cellular components which are highly susceptible to damage by free radicals[7] are

- Lipids - peroxidation of unsaturated fatty acids in membranes
- Proteins - denaturation and loss of enzymatic activity
- Carbohydrates – formation of carbon centered radical leading to chain breaks in important molecules.
- DNA- mutagenesis and carcinogenesis[7, 8]

OXIDATIVE STRESS

An imbalance between oxidants and antioxidants in favour of the oxidants, potentially leading to damage, is termed 'oxidative stress'[12] . Normally aerobic metabolism results in the formation of oxidants, but can be produced at higher rates during pathophysiological conditions. Generally, a complex network of antioxidants exists to protect the cells against oxidant injury. Several strategies are applied by both endogenous and exogenous antioxidants to protect against reactive oxygen species-mediated injury.

SCAVENGING OF FREE RADICALS BY ANTIOXIDANTS

'Antioxidants' are substances that nullify free radicals, or their actions. Molecules which can deactivate free radicals and prevent the oxidation of other molecules and protect them from damage are known as Antioxidants. The deactivation of free radicals or their action is completed by anti-oxidant defence mechanism.

Mechanism of action

An antioxidant is a molecule that has the capacity to slow down or prevent the oxidation of other molecules. During oxidation reactions free radicals are formed which in turn leads to chain reactions that damage the cells.

Antioxidant molecules halt these chain reactions by

- Eliminating the free radicals
- Converting highly active ROS into less active molecules (i.e. scavenging)
- Avoiding the conversion of the least ROS into more destructive forms.

Body's antioxidant system

Antioxidant system in our body can be divided into enzymatic and non-enzymatic groups.

The enzymatic antioxidants include superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase. The non-enzymatic antioxidants include the lipid soluble vitamins, vitamin E, vitamin A or beta-carotene and the water soluble vitamin C.

CLASSIFICATION OF ANTIOXIDANTS

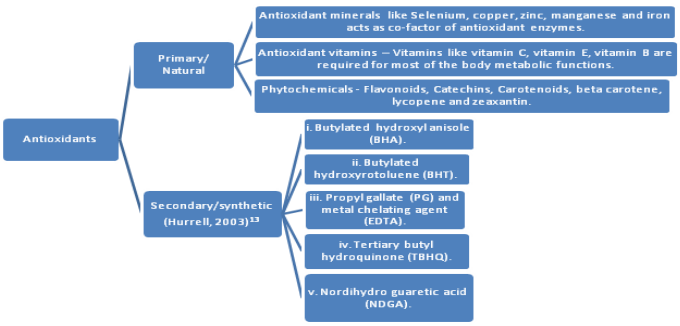

Figure I: Classification of antioxidants

TYPES OF ANTIOXIDANTS

The body has various mechanisms to neutralize oxidative stress by producing antioxidants, either naturally formed within the body (endogenous antioxidants), or externally supplied through foods (exogenous antioxidants).

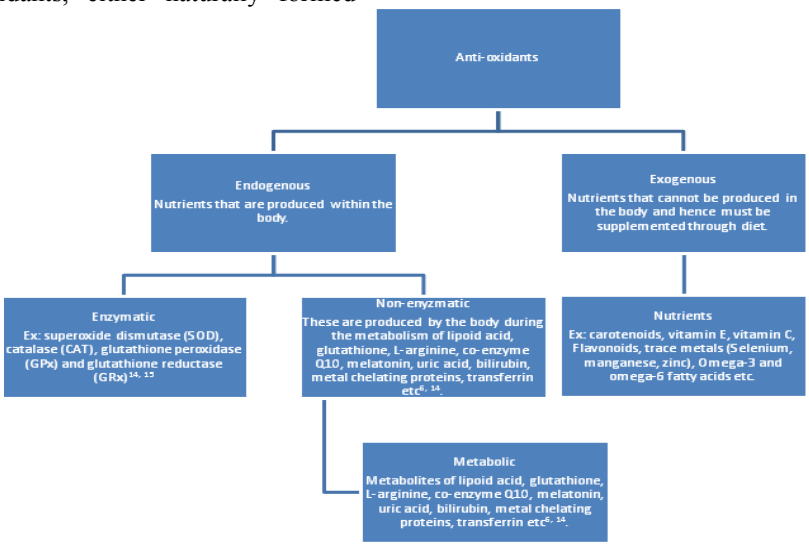

Figure II: Types of antioxidants

Nutrient antioxidants (Exogenous)

Vitamin E:

Vitamin E is a fat soluble vitamin and chiral compound with 8 stereoisomers. It has high antioxidant potency. In humans, α-tocopherol is the most bioactive form and safeguards cell membrane from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction. The dietary sources of vitamin E are vegetable oils, wheat germ oil, whole grains, nuts, cereals, fruits, eggs, poultry, meat[13].

Vitamin C (Ascorbic acid):

Ascorbic acid, is a water-soluble vitamin. Vitamin C works synergistically with vitamin E to reduce free radicals and also rejuvenates the reduced form of vitamin E. Natural sources of vitamin C are acid fruits, green vegetables, and tomatoes. Ascorbic acid is a labile molecule, therefore it may be lost during cooking[14].

Beta-carotene:

It acts as a powerful antioxidant and is the best quencher of singlet oxygen. Beta-carotene is present in many fruits, grains, oil and vegetables (carrots, green plants, squash, spinach)[13]

Lycopene:

Lycopene has strong antioxidant and anti-proliferative properties. The main exogenous source of lycopene is tomatoes, and the lycopene in cooked tomatoes, tomato juice and tomato sauce are more bioavailable than that in raw tomatoes[15].

Selenium (Se):

The health benefits of Se are antioxidant, anti-carcinogenic and immunomodulator[16]. The major sources of Se are water, garlic, onion, grains, nuts, soybean, meat, liver, yeast and seafood[13].

Flavonoids:

These are polyphenolic compounds mainly present in plants and have potent antioxidant activity[17]. The natural sources of flavonoids include fruit, vegetables, grains, bark roots, stems, flowers, tea and Wine. etc[18].

Omega-3 and omega-6 fatty acids:

These fatty acids are polyunsaturated, which cannot be produced by human body, and therefore supplied to the body only by food supplements like fat fish (salmon, tuna, halibut, sardines, pollock), algae, walnut, nut oils and flaxseed.

Omega-3 fatty acids decreases the inflammation, while Omega-6 fatty acids tends to promote inflammation, hence it is important to maintain an appropriate balance of omega-3s and omega- 6s in the diet, as these two substances work together to promote health[19].

CLINICAL EFFECTS OF ANTIOXIDANTS

- Antiatherosclerotic effects[20, 21]
- Antiinflammatory effects[22, 23]
- Antitumor effects[24, 25]
- Antithrombogenic effects[26, 27]
- Antiosteoporotic effects[28]
- Antiviral effects[29, 30]

APPLICATION IN DENTISTRY

Salivary antioxidants:

Saliva contains antioxidant compounds like uric acid, ascorbic acid, salivary peroxidase, glutathione and antioxidant enzymes. Antioxidants support the body's defense mechanism by neutralizing free radicals and counteracting oxidative stress. In oral cavity, they play an important role in the maintaining the periodontal health, prevents dental caries, tissue damage and promotes wound healing.

Periodontology:

Imbalance between oxidants and antioxidants due to depleted antioxidants can result in oxidative stress leading to tissue damage. Many studies suggest that there is a significant relationship between oxidant status and periodontal status, the oxidative stress playing an important role in the pathology of periodontitis[31]. Deficiency of ascorbic acid, alpha tocopherol and beta carotene can result in gingivitis or periodontitis[32]. Hence, antioxidant can support the damaged periodontal tissues[33,34]. Antioxidants can reduce inflammation by breaking the free radical chain reaction and also by reducing

inflammatory molecular expressions in immune system within the gingival connective tissues[35]; therefore can be used for reducing periodontal inflammation of chronic periodontitis.

Restorative dentistry:

Salivary peroxidase controls the growth and metabolism of numerous microorganisms, thereby reducing the incidence of dental caries. Low levels of antioxidants in saliva, mostly salivary peroxidase system may result in onset and development of dental caries[36]. Cranberries were reported of having antibacterial activity against Streptococcus Mutans and halt dental caries[37]. Epigalloactechin-3-gallate in green tea can act as scavenger, thereby lowers the possibility of dental caries and plaque formation[38]. Eugenol present in clove acts as an enzyme activator for an antioxidant and also has scavenging effect[35]; effective in toothache. Grape seed or pine bark extract can be used to increase the bond strength values for restorative treatment after bleaching[39, 40].

Orthodontics:

Pine bark extract solution was used to increase bond strength of brackets[40, 41]. Altan et al study demonstrated that systemic propolis usage stimulated bone formation in the expanded suture area[42].

Oral and maxillofacial surgery:

Sheresta et al. stated that grape seed extract has a positive effect on treating peri-implantitis[43]. It was reported that caffeic acid phenethyl ester which can be found in Propolis have significantly improved bone healing in rat models[44]. Vitamin-E can decrease wound healing time since it is a powerful lipid soluble antioxidant.

Oral cancer:

Antioxidants have an ability to reduce cell growth and prevent proliferation of oral carcinomas[45, 46] through apoptosis, stimulation of cytokines, gene expression. Dietary antioxidants can protect against oxidative damage by interrupting oxidants before they try to destroy the tissues[47]. It also plays a role in chemoprevention by reversal of oral premalignant lesions like leukoplakia. Vitamins like vitamin A, vitamin E, vitamin- C α- carotene and minerals like zinc, copper, manganese and selenium acts as enzyme activators; cytotoxic in action and can be used in treating premalignant conditions[35]. Epigalloactechin-3-gallate in green tea has scavenging effect and are effective in the treatment of leukoplakia[35]. Spirulina fusiforms acts as effective quencher of highly reactive singlet oxygen and can be used effectively in the treatment of buccal squamous cell carcinoma[35]. Studies also show that the concurrent use of antioxidants like vitamins, selenium with radiation and chemotherapy increased the effectiveness[48].

CONCLUSION

Current research illustrates the beneficial effects of antioxidant therapy in dentistry. Even though few studies have reported the promising role of antioxidant therapy in medical and dental fields, still few issues are to be considered regarding the antioxidant supplementation in treating various diseases. The proper dose and duration of an antioxidant supplementation to exert beneficial effects is not yet established. As we know "Too much of anything could destroy. Too much darkness could kill, but too much light could blind." Similarly antioxidants when used excessively can produce toxic effects. For example, vitamin A in large dose may have toxic effects. Hence, large scale studies are necessary to determine the pharmacokinetics, pharmacodynamics and the pros and cons of antioxidants for successful antioxidant therapy.

REFERENCES

1. Gilbert DL. Fifty years of radical ideas. Annals of the New York Academy of Sciences 2000;899(1):1-14.
2. Genestra M. Oxyl radicals, redox-sensitive signalling cascades and antioxidants. Cell Signal 2007;19(9):1807-19.
3. Evans P, Halliwell B. Micronutrients: oxidant/antioxidant status. Br J Nutr 2001;85 Suppl 2:S67-74.
4. Halliwell B. Biochemistry of oxidative stress. Biochem Soc Trans 2007;35(Pt 5):1147-50.
5. Valko M, Leibfritz D, Moncol J, et al. Free radicals and antioxidants in normal physiological functions and human disease. The international journal of biochemistry & cell biology 2007;39(1):44-84.
6. Droge W. Free radicals in the physiological control of cell function. Physiol Rev 2002;82(1):47-95.
7. Fridovich I. Fundamental aspects of reactive oxygen species, or what's the matter with oxygen? Ann N Y Acad Sci 1999;893:13-8.
8. McCord JM. The evolution of free radicals and oxidative stress. Am J Med 2000;108(8):652-9.
9. Zheng M, Storz G. Redox sensing by prokaryotic transcription factors. Biochem Pharmacol 2000;59(1):1-6.
10. Lander HM. An essential role for free radicals and derived species in signal transduction. Faseb j 1997;11(2):118-24.
11. Ignarro LJ, Cirino G, Casini A, Napoli C. Nitric oxide as a signaling molecule in the vascular system: an overview. J Cardiovasc Pharmacol 1999;34(6):879-86.
12. Sies H, Cadenas E. Oxidative stress: damage to intact cells and organs. Philos Trans R Soc Lond B Biol Sci 1985;311(1152):617-31.
13. Willcox JK, Ash SL, Catignani GL. Antioxidants and prevention of chronic disease. Crit Rev Food Sci Nutr 2004;44(4):275-95.
14. Naidu KA. Vitamin C in human health and disease is still a mystery? An overview. Nutr J 2003;2:7.
15. Donaldson MS. Nutrition and cancer: a review of the evidence for an anti-cancer diet. Nutr J 2004;3:19.
16. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact 2006;160(1):1-40.
17. Korkina LG, Afanas'ev IB. Antioxidant and chelating properties of flavonoids. Adv Pharmacol 1997;38:151-63.
18. Middleton E, Jr. Effect of plant flavonoids on immune and inflammatory cell function. Adv Exp Med Biol 1998;439:175-82.

19. Logan AC. Omega-3 fatty acids and major depression: a primer for the mental health professional. Lipids Health Dis 2004;3:25.
20. Hertog MG, Kromhout D, Aravanis C, et al. Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. Arch Intern Med 1995;155(4):381-6.
21. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. Lancet 1993;342(8878):1007-11.
22. Ferrandiz ML, Nair AG, Alcaraz MJ. Inhibition of sheep platelet arachidonate metabolism by flavonoids from Spanish and Indian medicinal herbs. Pharmazie 1990;45(3):206-8.
23. Laughton MJ, Evans PJ, Moroney MA, Hoult JR, Halliwell B. Inhibition of mammalian 5-lipoxygenase and cyclo-oxygenase by flavonoids and phenolic dietary additives. Relationship to antioxidant activity and to iron ion-reducing ability. Biochem Pharmacol 1991;42(9):1673-81.
24. Stefani ED, Boffetta P, Deneo-Pellegrini H, et al. Dietary antioxidants and lung cancer risk: a case-control study in Uruguay. Nutr Cancer 1999;34(1):100-10.
25. Fotsis T, Pepper MS, Aktas E, et al. Flavonoids, dietary-derived inhibitors of cell proliferation and in vitro angiogenesis. Cancer Res 1997;57(14):2916-21.
26. Osman HE, Maalej N, Shanmuganayagam D, Folts JD. Grape juice but not orange or grapefruit juice inhibits platelet activity in dogs and monkeys. J Nutr 1998;128(12):2307-12.
27. Gryglewski RJ, Korbut R, Robak J, Swies J. On the mechanism of antithrombotic action of flavonoids. Biochem Pharmacol 1987;36(3):317-22.
28. Hegarty VM, May HM, Khaw KT. Tea drinking and bone mineral density in older women. Am J Clin Nutr 2000;71(4):1003-7.
29. Wang HK, Xia Y, Yang ZY, Natschke SL, Lee KH. Recent advances in the discovery and development of flavonoids and their analogues as antitumor and anti-HIV agents. Adv Exp Med Biol 1998;439:191-225.
30. Kaul TN, Middleton E, Jr., Ogra PL. Antiviral effect of flavonoids on human viruses. J Med Virol 1985;15(1):71-9.
31. Dahiya P, Kamal R, Gupta R, et al. Reactive oxygen species in periodontitis. J Indian Soc Periodontol 2013;17(4):411-6.
32. Labrecque J, Bodet C, Chandad F, Grenier D. Effects of a high-molecular-weight cranberry fraction on growth, biofilm formation and adherence of Porphyromonas gingivalis. J Antimicrob Chemother 2006;58(2):439-43.
33. Maxwell SR. Prospects for the use of antioxidant therapies. Drugs 1995;49(3):345-61.
34. Nakamoto T, McCroskey M, Mallek HM. The role of ascorbic acid deficiency in human gingivitis--a new hypothesis. J Theor Biol 1984;108(2):163-71.
35. Carnelio S, Khan SA, Rodrigues G. Definite, probable or dubious: antioxidants trilogy in clinical dentistry. Br Dent J 2008;204(1):29-32.
36. Tenovuo J, Lehtonen O, Aaltonen A, Vilja P, Tuohimaa P. Antimicrobial factors in whole saliva of human infants. Infection and immunity 1986;51(1):49-53.
37. Schmidt MA, Riley LW, Benz I. Sweet new world: glycoproteins in bacterial pathogens. Trends Microbiol 2003;11(12):554-61.
38. Aksakalli S. Antioxidants in Dentistry: Review of Literature. Dentistry 2013;4(181):2161-1122.1000181.
39. Berger SB, De Souza Carreira RP, Guiraldo RD, et al. Can green tea be used to reverse compromised bond strength after bleaching? Eur J Oral Sci 2013;121(4):377-81.
40. Vidhya S, Srinivasulu S, Sujatha M, Mahalaxmi S. Effect of grape seed extract on the bond strength of bleached enamel. Oper Dent 2011;36(4):433-8.
41. Aksakalli S, Ileri Z, Karacam N. Effect of pine bark extract on bond strength of brackets bonded to bleached human tooth enamel. Acta Odontol Scand 2013;71(6):1555-9.
42. Altan BA, Kara IM, Nalcaci R, et al. Systemic propolis stimulates new bone formation at the expanded suture: a histomorphometric study. Angle Orthod 2013;83(2):286-91.
43. Shrestha B, Theerathavaj ML, Thaweboon S, Thaweboon B. In vitro antimicrobial effects of grape seed extract on peri-implantitis microflora in craniofacial implants. Asian Pac J Trop Biomed 2012;2(10):822-5.
44. Ucan MC, Koparal M, Agacayak S, et al. Influence of caffeic acid phenethyl ester on bone healing in a rat model. J Int Med Res 2013;41(5):1648-54.
45. Shirataki Y, Kawase M, Saito S, et al. Selective cytotoxic activity of grape peel and seed extracts against oral tumor cell lines. Anticancer Res 2000;20(1a):423-6.
46. King M, Chatelain K, Farris D, et al. Oral squamous cell carcinoma proliferative phenotype is modulated by proanthocyanidins: a potential prevention and treatment alternative for oral cancer. BMC Complement Altern Med 2007;7:22.
47. Skibsted LH, Dragsted LO, Dyerberg J, et al. [Antioxidants and health]. Ugeskr Laeger 2006;168(34):2787-9.
48. Lamson DW, Brignall M. Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. Alternative Medicine Review 1999;4: 304-29.

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