



Role of Free Radicals and Common Antioxidants in Oral Health, an Update

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This work was carried out in collaboration between all authors. Author AKN reviewed the manuscript. Author DP wrote the manuscript. Author Sreedevi managed the literature searches. Author KSR reviewed the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Free radicals have been implicated in the etiology of large number of major diseases. They can adversely alter many crucial biological molecules leading to loss of form and function. Such undesirable changes in the body can lead to diseased conditions. Antioxidants are compounds which destroy the free radicals in the body, thereby preventing against harmful oxidation- reduction reactions. Antioxidants are critical for maintaining optimum health and wellbeing. The best sources are fruits and vegetables which provide a variety of antioxidants like Vitamins A, C, E & carotenoids. As in every medical field, the usage of antioxidants is becoming more frequent in dentistry also. It can help adjunct treating the progress of oral problems such as periodontitis or gingivitis or progression of potentially malignant disorders to malignancy. Thus, a greater consumption of fruits and vegetables should be encouraged as they are the natural sources of these chemopreventive antioxidant along with other protective factors packaged by nature. This review focuses on commonly used effective antioxidants in different oral and dental pathologies as a new generation adjunctive remedy.

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1. INTRODUCTION

Oxygen is an ubiquitous element and a vitally important substance for life on earth especially for human life and it can both be beneficial and harmful to life [1]. High and soaring concentration of oxygen are found to be toxic, and can damage tissues [2]. The process of oxidation is a natural phenomenon of energy generation system and its by-product called "Free Radicals" which can damage healthy cells of the body [3]. These by-products are generally reactive oxygen species¹ and reactive nitrogen species [4]. They play a dual role as both toxic and beneficial compounds. The delicate balance between their two antagonistic effects is clearly an important aspect of life [5]. In a normal cell there is a balance between formation and removal of free radicals. However this balance can be shifted towards more formation of free radicals or when levels of antioxidants are diminished. This state is called "Oxidative Stress" and can result in serious cell damage if the stress is massive and prolonged [6].

Living cells are constantly exposed to oxidants from a variety of sources that can be exogenous and endogenous [7]. Fortunately free radical formation is controlled by various beneficial compounds known as "Antioxidants". Antioxidants are capable of stabilizing or deactivating, free radicals before they attack cells. They are absolutely critical for maintaining optimal cellular and systemic health and well-being [8].

Oxidative stress plays a major part in development of chronic and degenerative ailments such as cancer, arthritis, ageing, autoimmune disorders, cardiovascular disorders, neurodegenerative disorders, pulmonary disorders, ocular diseases, AIDS, psychological stress, in fetus, diabetes, male infertility [5]. Antioxidants can also be enzymatic or nonenzymatic which work synergistically and in combination with each other to protect cells or organs against free radicals [9]. Endogenous and exogenous antioxidants act as "Free radical scavengers" by preventing and repairing damages caused by reactive oxygen and nitrogen species and therefore can enhance the immune defense and lower the risk of cancer and degenerative diseases [5]. Thus, a greater consumption of fruits and vegetables should be encouraged as they are the natural sources of

these antioxidants [2]. Antioxidants are available from different sources including vitamins, minerals, enzymes and hormones as well as food and herbal supplements [10].

Free radicals and antioxidant therapy have attracted a great deal of attention in recent years [11]. Antioxidants are being widely used in routine general practice. There is an increased interest in the role of free radical oxidative damage in human diseases along with an upsurge in research implies its potential in dental practice too [12].

Oral cavity is exposed to lot of carcinogens and is prone to develop precancerous lesions and conditions which may turn to oral cancer. Dietary substitute play a vital role in prevention of oral cancer, potentially malignant disorders like leukoplakia, lichen planus, oral submucous fibrosis, burning mouth syndrome, dental caries, strengthening the bond strength of orthodontic brackets, aids in bone healing and treating peri implantitis [9]. These dietary substitutes are beta-carotene, provitamin A, vitamin A, C and E, polyphenols, curcumin [13]. Recently, it has been claimed that the imbalances in the levels of free radicals and antioxidants in saliva may play an important role in the onset of periodontal diseases [6]. Dental research in this area is still unfocused due to limited number of studies/ randomized controlled trials, definitive conclusions on their safety and efficacy cannot be commented upon. A need for confirmatory evidence and addressing the safety issues with a focus on oral health care seems to be an important requirement [12].

2. OXIDATIVE STRESS AND FREE RADICALS

Free radicals are chemically active atoms that have charge due to an excess or deficient number of electrons [14]. It is a molecule with one or more unpaired electron in its outer shell [5]. Initial attack causes the free radical to become neutralized, another free radical is formed in the process, causing a chain reaction to occur [8]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are well recognized for playing a dual role as both deleterious and beneficial species. At low or moderate levels of concentration, ROS participate in the biosynthesis of molecules such as thyroxine, prostaglandin and enhances the

immune system. Macrophages and neutrophils generate ROS in order to kill the bacteria that may engulf by phagocytosis. At high concentrations, they generate oxidative stress and nitrosative stress, that can damage all cell structures [1]. In a normal cell there is a balance between formation and removal of free radicals. However this balance can be shifted towards more formation of free radicals or when levels of antioxidants are diminished. This state is called Oxidative stress and can result in serious cell damage, if the stress is massive and prolonged [14].

2.1 Generation of Free Radicals and Oxidants

Formation of ROS and RNS can occur by enzymatic and non-enzymatic reactions. Enzymatic reactions include those involved in the respiratory chain, the phagocytosis, the prostaglandin synthesis and cytochrome P450 system. Once formed, it yields various ROS and RNS such as hydrogen peroxide, hydroxyl radical (OH[•]), peroxynitrite (ONOO⁻), hypochlorous acid (HOCl) etc. [3] Free radicals can be produced from non-enzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing radiations [5].

2.2 Mechanism of Action of Free Radicals

1. DNA damage
2. Lipid peroxidation (through activation of cyclooxygenase and lipo oxygenase pathway)
3. Protein damage including gingival hyaluronic acid and proteoglycans.
4. Oxidation of important enzymes.
5. Stimulation of pro inflammatory cytokine release by monocytes and macrophages by depleting intracellular thiol compounds and activating nuclear factor kappa beta [1].

Free radical cause oxidative damage to nucleic acids, proteins and lipids, it produces damages of clinical importance and severity. One of the most crucial concerns is the mutation- induced carcinogenesis, the damage to cellular membrane lipoproteins and lipid- mediated oxidative damage leading to tegument ageing evolution. It represents the main threat for the genome integrity in the greater part of living organisms [7]

2.3 Role of Oxidative Stress and Free Radicals in Oral Cavity

The diseases associated with oxidative stress in oral cavity includes periodontitis, oral submucous fibrosis, oral lichen planus, oral cancers, dental caries, burning mouth syndrome, peri implantitis etc. The involvement of ROS and antioxidant defense mechanisms in human saliva has been demonstrated in various processes of oral cavity like healing periodontal disease, preventing oral carcinogenesis, reducing oral mucosa inflammatory reactions and ameliorating metal-based restoration reactions. In potentially malignant disorders as well as in malignancy dietary factors and environmental sources are responsible for generating oxidants. Many commonly used dental materials may form free radicals which includes bleaching agents, composite fillings, dental cements, ceramic restorations, metals in restorations, dental implants, intracanal medicament, [14] dentin bonding agents [14-16].

3. ANTIOXIDANTS

Today, the entire world is witnessing an upsurge in chronic health complications. Diets rich in fruits and vegetables have been reported to exert a protective effect against a variety of diseases. The primary nutrients thought to provide protection afforded by fruit and vegetables are the "Antioxidants" [17]. Antioxidants are substances which slow down the rate at which something decays because of oxidization [7]. Antioxidants acts as radical scavengers that helps in converting the radicals to less reactive species [18]. Antioxidants block the process of oxidation by neutralizing free radicals, in doing so the antioxidants themselves become oxidized. Because of this, there is a constant need to replenish our antioxidant resources [11].

Antioxidants are available from different sources, including vitamins, minerals, enzymes and hormones, as well as food and herbal supplements. These supplements may be in bar, gel, capsule, drops and tablet forms. Most recently, dental manufacturers and distributors have incorporated antioxidant supplements into toothpastes, mouth rinses/mouthwashes, lozenges, fluoride gels and dentifrices, oral sprays, breath fresheners and other dental products for the control of gingival and periodontal diseases. Topical antioxidants may also have an effect on oral cells [10].

Antioxidants help in:

1. Destroying the free radicals that damage cells.
2. Promoting the growth of healthy cells.
3. Protecting cells against premature, abnormal ageing.
4. Help fight age-related macular degeneration.
5. Provide excellent support for the body's immune system [3].

3.1 Deleterious Effects of Antioxidants

Antioxidant therapy in human reproductive medicine is controversial [19]. High doses of vitamin A may have embryotoxic and teratogenic effects including neural crest, musculoskeletal and urogenital anomalies [12]. High dose supplements of vitamin E and beta carotene may pose a health risk. Beta-carotene increased the risk of polyp recurrence in women [20]. Heavy consumption of carotene containing vegetables may cause amenorrhoea. Large doses of ascorbic acid may be associated with inhibition of ovarian steroidogenesis and increased probability of abortion [12].

3.2 Therapeutic Use of Antioxidants for Oral Lesions

1. Prevention of lesions in high risk individuals with mucosa that clinically appears normal with no history of either potentially malignant disorders or malignant lesions.
2. The treatment of potentially malignant disorders.
3. In patients who have had either potentially malignant disorders or malignant oral lesions that have been successfully treated, in order to prevent recurrence of treated initial lesion or to prevent development of a second or a separate primary [11].

4. BETA- CAROTENE

It is the most active carotenoid [13]. One of the major carotenoids in our diet and in human blood and tissues and its color varies from yellow to orange [21]. It has an important nutritional role as the principal precursor of vitamin A [22]. It is found in vegetables and fruits such as [13] beet root, apricots, carrots, pumpkin, sweet potato, tomatoes, watermelon, mango, papaya,

peaches, oranges, green beans, broccoli and spinach [21].

4.1 Main Actions of Beta Carotene Include

1. Anti-oxidant and free radical scavenging.
2. Immunomodulation, stimulation of increase in the numbers of T-helper and NK cells as well as cells with IL-2 receptors.
3. Inhibition of mutagenesis.
4. Inhibition of cancer cell growth [10].

4.2 Pathogenesis

Carotenoids have the capacity to trap peroxy radicals and quench singlet oxygen. β -Carotene is a scavenger of peroxy radicals, especially at low oxygen tension [21]. The electron rich conjugated double bond structure is primarily responsible for the excellent ability of beta-carotene to physically quench singlet oxygen without degradation and for the chemical reactivity of beta-carotene with free radicals and for its instability toward oxidation. The maximum protection to quench singlet oxygen is given by those carotenoids having nine or more double bonds [22]. The interaction of carotenoids with peroxy radicals may proceed via an unstable β -carotene radical adduct. Carotenoid adduct radicals have been shown to be highly resonance stabilized and are predicted to be relatively unreactive. They may further undergo decay to generate non radical products and may terminate radical reactions by binding to the attacking free radicals. Carotenoids act as antioxidants by reacting more rapidly with peroxy radicals than unsaturated acyl chains [21].

The use of beta-carotene has been recommended in order to prevent oral leukoplakia and possibly oral cancer. A diet supplemented with beta-carotene can prevent changes in oral mucosa especially in smoker patient who present low serum levels of vitamin C and beta-carotene when compared to non smokers. It has better therapeutic clinic response in the prevention of oral leukoplakia lesions in smoker patients than in non smokers [23]. It stimulates the activity of immune cells against tumor cells. Beta-carotene inhibits the initiation of cancer, decreasing the amount of damage free radicals do to DNA. High doses of beta-carotene even over long periods of time are not associated with serious toxicity. Cancer risk increases when our dietary intake of carotene is low. It increases the number of receptors on WBC for molecules

known as major histocompatibility complex II (MHC II) which help in monocyte action and direct killer T cells to cancerous cell [24]. Beta-carotene is available in synthetic and natural forms. Synthetic forms of beta-carotene have shown to increase the expression of connexin gene which codes for the gap junction protein. Synthetic beta-carotene has been used in the treatment of oral leukoplakia in humans and a marked regression was reported [25].

Beta-carotene can protect phagocytic cells from autooxidative damage, enhance T and B lymphocyte proliferative responses, stimulate effector T cell functions and enhance macrophage, cytotoxic T cell and NK cell tumoricidal capacities. A recent study in HIV-infected women reported lower serum concentrations of lycopene, alpha-carotene and beta-carotene especially in those with low counts of CD-4 helper cells [21]. It plays an important role in the pathogenesis of OSMF (oral submucous fibrosis) and that its level decreases with disease progression. The degree of oxidative damage in OSMF can be assessed by estimation of serum beta carotene levels in affected patients, and that the underlying deficiency of antioxidants can be corrected by dietary supplementation of beta carotene. This may be helpful for successful management of this condition and for avoiding the consequences of malignancy [26].

Therapeutic dose:

25,000 to 100,000 IU/day [24].

Epidemiological studies have suggested that beta-carotene is associated with an increased risk of lung cancer [27].

Commercial preparation:

Lutivit (L-arginine, vit E, beta carotene, lycopene, leutin), Luvion intra (leutin, beta carotene), Betared inversion (beta carotene, vitamin C) [28] (Table 1).

5. LYCOPENE

Red fruits and vegetables including tomatoes processed tomato products such as juice, ketchup, paste, sauce and soup, watermelons, pink-grapefruits, apricots and pink-guavas all are good sources of lycopene. Average daily dietary lycopene intake is to be 25-30 mg/day with processed tomato products accounting for 50%

of total intake [29]. Bioavailability improves with cooking [30].

5.1 Pathogenesis

It is a highly unsaturated straight chain hydrocarbon with total of 13 double bonds, 11 of which are conjugated. This unique nature of lycopene molecule makes it a very potent antioxidant [30]. The reactivity of lycopene, in biological systems depends on their molecular and physical structure, location or site of action within the cells, ability to interact with other antioxidants, concentration and the partial pressure of oxygen. Biologically lycopene tends to act as singlet oxygen and peroxy radical scavenger. The highly conjugated double bonds of lycopene play the most important role in energy transfer reactions. Lycopene has quenching ability towards singlet oxygen, based on the excited energy state and is greatly related to the length of the conjugated double bond system [31].

Among the carotenoids, lycopene is the most efficient singlet oxygen quencher. The physical quenching rate of lycopene was two times higher than β -carotene and 10 times higher than α -tocopherol [31]. Lycopene causes up regulation of antioxidant response element leading to synthesis of cytoprotective enzymes, the enhancement of intercellular gap junctions communication, the modulation of hormonal, inflammatory and immune system. Several studies in vitro showed that lycopene can promote apoptosis in human cancer tissue [32,33] with anti invasion and anti metastatic activity too. Lycopene has been reported to increase p53 protein levels in cancer cells [32]. Lycopene has shown significant improvement in leukoplakia, tomato consumption has the most protective effect on oral leukoplakia [32,30].

Several studies explained marked improvement in mouth opening and noticeable reduction of burning sensation on OSMF patients with the lycopene treatment than patients treated with placebo. This curative effect is due to inhibition of abnormal fibroblasts, up regulation of lymphocyte resistance to stress and suppression of inflammatory response. It is also found to be effective in reducing signs and symptoms of oral lichen planus. Lycored is a drug containing vitamin A, alpha-tocopherol, zinc and selenium with antioxidant properties and adds synergistically to the positive effects of lycopene [34,30].

High intakes of lycopene rich foods or supplements may result in a deep orange discoloration of skin known as lycopenodermia [30].

Lycopene is formulated along with multivitamins, formulated as capsules. There are many lycopene products available in the day to day market in the form of syrups and capsules [16].

Lycopene intake in various diseases:

- 8 mg/day for treatment of oral leukoplakia
- 6.5 mg/day for treatment of lung cancer in non smoking women.
- 12 mg/day for treatment of lung cancer in non smoking men [30].

Commercial preparation:

Lycored, L-bex forte (lycopene 4000 IU, lutein, beta carotene 10 mg), Lyco-first (lycopene, vitamin A palmitate, vitamin E acetate) [28] (Table 1).

6. RETINOIDS

Retinoids are a class comprising natural derivatives and synthetic analogues of Vitamin A [35]. Its metabolically active form is Retinol.¹³ Retinoids are among the best studied micronutrients used today for human chemoprevention [35]. Dietary sources of retinol are primarily animal products and include milk, butter, egg, liver and fish. The clinical effects of vitamin A deficiency are related to keratinization of epithelia throughout the body with metaplasia of epithelium [13]. Important vitamin A derivatives to show antimutagenic activities include all-trans retinoic acid, 13-cisretinoic acid, 9-cis retinoic acid and retinyl palmitate [36]. Among all, 13-cisretinoic acid is more efficient [13].

6.1 Pathogenesis

The mechanism of action of the retinoids probably is linked to different nuclear RARs (retinoic acid receptors). The availability of RARs and retinoids is involved in the regulation of cell growth. After binding to the receptors, transcription factors (heterodimers or homodimers) are formed that bind to specific DNA sequences, leading to an up-regulation or down-regulation that ultimately affects gene transcription. It is believed that retinoids act by regulating gene expression through RAR nuclear receptors [37]. A relationship between the p53

pattern of expression and a lack of retinoic acid receptor-beta up regulation in oral premalignancy has also been suggested [35]. In prophylactic doses, the toxicities include mainly skin rash, dryness and bleeding of the nasal mucosa, conjunctivitis, oral mucositis, chelitis, hyper triglycerinemia, teratogenic effects [37]. The range of 0.5 to 1 mg/Kg/d of 13-cisretinoic acid as a starting dose is used for the treatment of premalignant oral lesions. 13-cisretinoic acid is supplied in 10, 20 and 40 mg capsules [13]. It is relatively not indicated in leukopenic, hypothyroid patients, people with high levels of cholesterol and triglycerides, hepatic and renal malfunction [23]. Antioxidant combinations (vitamin A,E,C) had proved to be most effective with maximal clinical resolution [38]. Lower concentrations of retinoids combined with other antioxidant agents could be alternatives with less adverse effects but same chemopreventive action [39].

Commercial preparation:

Acitretin 50, A-Ret-HC (tretinoin), Retino-A [28] (Table 1).

7. ASCORBATE

Vitamin C is mainly found in citrus fruits. The current recommended daily allowance for ascorbic acid ranges between 100-120 mg/per day for adults. It has been suggested that a daily intake of at least 140 mg/day is required for smokers because they usually present a reduction of L-Ascorbic acid (L-AA) concentration in serum leukocytes [23].

7.1 Pathogenesis

Vitamin C is a potent reducing agent and scavenger of free radicals in biological systems. Mono-anion form (ascorbate) is the predominant chemical species at physiological pH. Ascorbate readily undergoes two consecutive, yet reversible, one-electron oxidations to generate dehydroascorbate (DHA) and an intermediate, the ascorbate free radical (AFR). AFR is, however, a relatively unreactive free radical, with a reduction potential considerably low compared to the α -tocopherol radical, the glutathione radical and virtually all reactive oxygen and nitrogen species that are thought to be involved in human disease (e.g. superoxide anion, hydroxyl radical, hydroperoxyl radicals, singlet oxygen, nitrogen dioxide, nitroxide radicals and hypochlorous acid) [40].

The current recommended dietary daily allowances for vitamin C are 90 mg for men and 75 mg for women. From a toxicological standpoint, vitamin C supplementation is relatively safe, even in megadose levels (1-4g/day) [40]. Vitamin C is essential for collagen, [5] therefore, its deficiency results in disease of skin, gums and other tissues with high collagen content, [41] carnitine and neurotransmitter biosynthesis. Health benefits of vitamin C are antioxidant, anti-atherogenic, anti-carcinogenic, immunomodulator [5,40].

Commercial preparation:

Limcee tablet 500 mg -1 gm, Chew-Cee 500 mg [28] (Table 1).

8. TOCOPHEROL

Vitamin E is a fat soluble vitamin with high antioxidant potency. The dietary sources of vitamin E are vegetable oils, wheat, germ oil, whole grains, nuts, cereals, fruits, soyabean, eggs, poultry, meat [5] the recommended daily limit rates are 10 mg/day for adult men and 8 mg/day for adult women [23].

Main actions includes:

1. Free radical scavenging
2. Maintenance of membrane integrity, immune function.
3. Inhibition of cancer cell growth/differentiation
4. Inhibits mutagenicity and nitrosamine formation
5. Inhibition of DNA and RNA, protein synthesis in cancer cells [42].

Therapeutic Dose:- 400-800 IU a day [24].

Commercial preparation:

Evion 200 mg, Ephyral 200 mg, Viteolin 200 mg [28] (Table 1).

9. POLYPHENOLS/ FLAVONOIDS

Because extensive and expensive testing of food additives is required to meet safety standards, synthetic antioxidants have generally been eliminated from many food applications. The increasing interest in the search for natural replacements for synthetic antioxidants has led to the antioxidant evaluation of a number of plant sources [43]. Catechins from tea inhibit the production of important metalloproteases, thus

potentially reducing invasion and migration, inducing apoptosis and growth arrest in both oral cancer and leukoplakia cell lines. Methoxylated flavonoids, present in citrus fruits, inhibit DNA adduct formation promoted by known carcinogens, such as tobacco nitrosamines. Proanthocyanidins, highly concentrated in red wine, pigmented fruits, nuts and chocolate, 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 [44].

9.1 Pathogenesis

PPs (polyphenols) have powerful antioxidant activity in vitro being capable of scavenging a wide range of reactive oxygen, nitrogen, and chlorine species, such as superoxide anion, hydroxyl radical, peroxy radicals, hypochlorous acid and peroxyxynitrous acid. They also chelate metal ions, thus decreasing their pro oxidant activity [44].

The anticancer activity of several polyphenols is due to their ability to inhibit enzymes in carcinogenesis and tumor development. 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 [45]. Antioxidant rich diets might inhibit periodontal disease development and progression, particularly in subjects exposed to environmental and dietary sources of oxidative stress. 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. Results of another study indicate that cariostatic activity of oolong tea extract was effective even after the establishment of streptococcus sorbinus in the oral cavity [45]. Average intake should be approximately 150-200 mg per day [36].

Commercial preparations:

Revistal 500, Biocare flavonoid complex [28]. (Table 1).

10. CURCUMIN

The polyphenol curcumin is the active ingredient in the herbal remedy and dietary spice turmeric [46].

10.1 Pathogenesis

In vitro studies have shown that curcumin inhibits lipo-oxygenase and cyclo-oxygenase activities, xanthine oxygenase activities, nitric oxide production and reactive oxygen species (ROS) generation. Curcumin also inhibits the production of pro-inflammatory monocyte/macrophage-derived cytokines [interleukin-8] (IL-8), monocyte inflammatory protein-1 (MIP-1), monocyte chemoattractant protein-1 (MCP-1), interleukin-1b (IL-1b), and tumor necrosis factor- α (TNF- α) or peripheral blood monocytes and alveolar macrophages. A recent study revealed that oxidative stimulation of G proteins in human brain membranes by metabolic prooxidants, homocysteine and hydrogen peroxide, can be significantly depressed by curcumin. It was shown to inhibit lipid peroxidation and exhibited more potent antioxidant activity than α -tocopherol [46].

Curcumin inhibits cancer development and progression, targeting multiple steps in the pathway to malignancy. Curcumin has activity as both a blocking agent, inhibiting the initiation step of cancer by preventing carcinogen activation and as a suppressing agent, inhibiting malignant cell proliferation during promotion and progression of carcinogenesis. Curcumin has been shown to interfere with many processes involved in angiogenesis. Curcumin inhibits fibroblast growth factor induced neovascularization. The angiogenic ligands vascular endothelial growth factor and angiopoietin 1 and 2 which act in a coordinated fashion in angiogenesis are inhibited by curcumin. It can exert both radioprotective effects in normal cells and radiosensitizing effects in cancer cells. It has been suggested that curcumin's ability to reduce oxidative stress and inhibit transcription of genes related to oxidative stress and inflammatory responses may afford protection against the harmful effects of radiation where as the radiosensitizing activity might be due to the upregulation of genes responsible for cell death [46].

Curcumin-loaded nanospheres were able to exert a more pronounced effect on the cancer cells as compared to conventional curcumin thus indicating the potential of nanoparticle-based formulation as an adjuvant therapy for clinical application in prostate cancer. Curcumin lack of systemic toxicity and broad-reaching mechanism of action may make it best suited as an adjuvant therapy for head and neck cancers. Minor

adverse effects related to the use of curcumin include gastrointestinal adverse effects and haematological adverse effects [47].

Commercial preparations:

Turmeric curcumin 450, Turmeric Himalaya, Turmix tablets 300 mg (curcumin extract) [28] (Table 1).

11. ALOE VERA

The fresh gel or mucilage from *Aloe barbadensis* Mill otherwise known as aloe vera—is a handy homegrown remedy [48]. It has very strong antioxidant nutrients. Glutathione peroxidase activity, superoxide dismutase enzymes, and a phenolic antioxidant were found to be present in Aloe vera gel, which may be responsible for these antioxidant effects. Apart from these, it also contains A, C, and E vitamins. These free radical components get rid of the toxins and carcinogenic properties from the pollution and poor quality foods we eat. In oral cavity it is used for treatment of aphthous ulcers, gingivitis, lichen planus, alveolar osteitis, as a denture adhesive, Applications directly at sites of periodontal surgery, as an adjunct to scaling and root planning in periodontitis, chemical burns caused by accidents with aspirin, extraction sites respond comfortably, angular cheilitis, burning mouth syndrome, patients with sore gums and teeth with dentures maladaptive, around dental implants to control inflammation caused by bacterial contamination [49].

Commercial preparation:

Aloe-E, Nidwash forte (glycolic acid, salicylic acid, aloe vera extract) [28] (Table 1).

12. HONEY BEE

Propolis is a sticky, resinous substance collected by honey bees from the sap, leaves, and buds of plants, and then mixed with secreted beeswax. In dentistry, propolis has been used for the treatment of aphthous ulcers, candidiasis, acute necrotizing ulcerative gingivitis (ANUG), gingivitis, periodontitis and pulpitis. Studies on propolis applications have increased because of its therapeutic and biological properties [50].

12.1 Pathogenesis

Propolis can prevent tissue damage from oxidative stress by decreasing the

overproduction of superoxide anion and by restoring respiratory control ratio in mitochondrial tissue. According to an Italian Study, propolis extract with CAPE (caffeic acid phenethyl ester) and its active components showed a dose-dependent free radical scavenging effect, a significant inhibition of xanthine oxidase activity, and an antilipoperoxidative capacity. Propolis extract with CAPE was more active than propolis extract without CAPE. The experimental evidence, therefore, suggests that CAPE plays an important role in the antioxidant activity of propolis [50].

Current research involving propolis in dentistry spans many fields and highlights its antimicrobial and antiinflammatory activities, particularly in cariology, oral surgery, pathology, periodontics, endodontics and pedodontics. It may boost the effects of anticarcinogenic drugs, thus enabling a decrease in the administered dose and in turn

leading to reduction in side effects. Propolis has been reported to promote epithelial formation as well as vascular and fibroblastic neoformation of the connective tissue. Thus it can be hypothesized that the topical application of propolis on surgical wounds may promote faster epithelium and connective tissue healing [50]. It can be used in the treatment of dental caries, plaque, chronic periodontitis, oral candidiasis, pulp therapy in primary and permanent teeth, dental hypersensitivity, halitosis, lichen planus, recurrent aphthous stomatitis, denture stomatitis, radiation mucositis, new storage media following avulsion of tooth.

Dispensable forms for treatment in dentistry: Propolis mouthwash (0.5% aqueous alcohol solution), tooth paste, propolis ointment, propolis intracanal medicament, propolis extract, tablet form, propolis mouth spray [51].

Table 1. Common antioxidants with commercial preparations

S. no	Type of antioxidant	Pharmaceutical company
1.	Beta-Carotene	1) Lutivit (25 mg L-arginine, 25 mg Vitamin E, 10 mg beta carotene, 6% lycopene, 7 mg leutin) by Microvision 2) Luvion intra 25,50,75 mg (leutin, beta carotene) by Inventure 3) Betared inversion (10.33 mg beta carotene , 100 mg vitamin C, 75 mcg selenium, 25 IU vitamin E) by Invision
2.	Lycopene	1) Lycored (2000 mcg lycopene, 35 mcg selenium, 75 mg zinc) by Jagsonpal pharmaceuticals ltd 2) L-bex forte (4000 IU lycopene, leutin, 10 mg beta carotene) by Lincoln ltd 3) Lyco-first (lycopene, vitamin A palmitate, vitamin E acetate) by Invision
3.	Retinoids	1) Acitretin 50 by Stiefel lab 2) A-Ret-HC (tretinoin) by Menarini India Pvt ltd and Shalaks pharmaceuticals 3) Retino-A by Valeant pharmaceuticals
4.	Ascorbate	1) Limcee tablet 500 mg- 1 gm by Abbott healthcare 2) Chew-Cee 500 mg by Zifam pinnacle pvt ltd
5.	Tocopherol	1) Evion 200 mg by Merck India ltd 2) Ephynal 200 mg by Abott and Primal health care 3) Viteolin 200mg by Glaxo Smithkline pharmaceutical
6.	Polyphenols	1) Revistal 500 by Ranbaxy 2) Biocare flavonoid complex by Biocare
7.	Curcumin	1) Turmeric curcumin 450 by Nature's Bounty 2) Turmeric Himalaya by Himalaya 3) Turmix tablets 300 mg (curcumin extract) by Sanat products ltd
8.	Aloe vera	1) Aloe-E by Shaswat herbal helath care 2) Nidwash forte (glycolic acid, salicylic acid, aloe vera extract) by Nidus
9.	Honeybee	1) Bioglan propolis 1000 by Bioglan 2) Triple bee complex by YS organic beefarm

Commercial preparations:

Bioglan propolis 1000, Triple bee complex [28] (Table 1).

13. ENDOGENEOUS ANTIOXIDANTS ENZYMATIC

In addition to dietary antioxidants, the body relies on several endogenous defence mechanisms to help protect against free radical induced cell damage. The antioxidant enzymes – glutathione peroxidase, catalase, and superoxide dismutase (SOD) – metabolize oxidative toxic intermediates and require micronutrient cofactors such as selenium, iron, copper, zinc and manganese for optimum catalytic activity. It has been suggested that an inadequate dietary intake of these trace minerals may compromise the effectiveness of these antioxidant defense mechanisms. All these play very important role in saliva by keeping free radicals in check thus preventing various oral pathologies particularly periodontitis [8].

14. CONCLUSION

Antioxidants scavenge the free radicals which are increasing at a fast rate because of increasing pollution, smoking, stress and genetic disorders. Thus they are indispensable for a healthy and long life. They have proven to increase longevity, combat serious diseases like cancer and cure and prevent many chronic degenerative diseases. In dentistry, they have proven efficacy in preventing and curing periodontitis, dental caries, candidiasis, many potentially malignant disorders even oral cancers. The interdependence of systemic and oral health is well known, thus its probable that reducing oxidative stress in oral environment with antioxidants has the potential of improving well being of an individual. Thus if we increase the intake of antioxidants by consuming more of natural antioxidant containing foods like carotenoids, lycopene, retinoids, vitamins etc and synthetic supplements in case of deficiency, we can surely lead a long and disease free life. In this way we can secure a healthy life for our progeny by decreasing the incidence of genetic disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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