

REVIEW ARTICLE

Antioxidants: The counterstriking immunomodulators in therapeutics of oral lesions

Bharani Krishna Takkella^{1*}, Mulagolla Sirisha¹, Chukka Ram Sunil², Tejaswin Polepalle³, Katravath MadhuKiran Naik², Chaitanya Krishna Thakkella⁴, Varri Sujana², Bhavya Sri Sai Kandi⁵

¹ Department of Oral Medicine and Radiology, Dr.N.T.R University of Health Sciences, India. E-mail: bharanikrishna3@gmail.com

² Department of Conservative Dentistry and Endodontics, Dr.N.T.R University of Health Sciences, India. E-mail: drchrsunil@gmail.com

³ Department of Periodontics, Dr.N.T.R University of Health Sciences, India. E-mail: tejaswinpolepalle@gmail.com

⁴ Mechanical Engineering, Teesside University, UK. E-mail: chaitanyathakkella@gmail.com

⁵ Intern Dr.N.T.R University of Health Sciences, India. E-mail: kandibhavya9@gmail.com

ABSTRACT

Antioxidants are a group of natural phytochemicals found in dietary ingredients that can be utilised to treat oral lesions and diseases. They are employed as chemical compound alternatives since they have less adverse effects. The dietary antioxidants found in fruits and vegetables reduce the damage by modulating detoxification enzymes, increasing immune system, and hormone metabolism. Scientists were drawn to antioxidants because of their ability to modify cell cycle controls, apoptosis, invasion, angiogenesis, and metastasis. They have demonstrated significant success as single treatments or in combination with chemo-preventive medicines for oral lesions.

Inside this article, we will look at the immuno-modulating effects of antioxidants, which aid in the treatments and even sometimes avoidance of numerous oral and maxillofacial conditions that contribute to morbidity, such as autoimmune lesions, and death, such as oral cancer. Antioxidants are chemicals that considerably impede or decrease the degradation of a living matter and defend the organism from oxidative harm. As a result, the sickness will be significantly reduced.

Keywords: Antioxidants; Phytochemicals; Phenolics; Beta-carotene; Tocopherol; Cyanins; 13-Cis-retinoic Acid (Isotretinoin); Apoptosis; Autoschizis; EGCG (Epigallocatechin Gallate)

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1. Antioxidants classification: First classification

1.1 Antioxidants enzymatic

Superoxide dismutase, catalase, glutathione peroxidases, malonaldehyde, glutathione reductase, and glutathione transferase.

1.2 Antioxidants non-enzymatic

1) Nutrient—alpha tocopherol, vitamin A, beta carotene, vitamin E, ascorbate, glutathione, selenium.

2) Non-nutrient—ceruloplasmin, transferrin, uric acid, peptides, camosine.

2. Second classification

Antioxidants found in nature—can be distributed into the following categories:

1) Enzymes, such as superoxide, hydroxyl, and glutathione peroxidase.

2) Low molecular weight antioxidants—these are additionally classified as:

- a) Tocopherol, carotenoids, bilirubin, and certain polyphenyl antioxidants are examples of lipid-soluble antioxidants.
- b) Water-soluble antioxidants such as ascorbic acid, uric acid, and polyphenyls.

3. Phenolics

Phenolics occur by far the most abundant phytochemical class and are found throughout the plant world. Flavonoids, phenolic acids, and polyphenols are the three major classes of nutritional phenolics. These were all hydroxyl group (-OH) containing chemical substances in which the (-OH) is directly connected to an aromatic hydrocarbon chain. In the category of natural substances, phenol (C₆H₅OH) is considered a basic class. They are plant's secondary metabolites that play a vital function as defence chemicals. Phenols have various beneficial qualities for beings, and their antioxidant capabilities are significant in identifying their role as anti-free radical-mediated disease processes. Flavonoids are the most well-known and biggest category of plant phenols. Phenolics are also classified as a broad category that includes the commonly utilized hydroxyl-benzoic and hydroxyl-cinnamic acids. Phenolic polymers, often referred as tannins, are high-molecular-weight substances classified in two main types: hydrolysable tannins and condensed tannins.

Flavonoids are polyphenolic chemicals found throughout ecosystems. Over 4,000 flavonoids have been identified, several of which are found in veggies, fruits, and consumables such as teas, coffee, and juice drinks. Those seems to have played a great effect in medical achievements from ancient times. They can be found in vascular vegetation as glycones, glucosides, and methylated compounds. Additionally, 4,000 flavonoids have been encountered in plant components ingested by mankind, with roughly 1,030 flavanols and 650 flavones being widely recognised. Flavanoids like as luteolin and catechins are more powerful antioxidants than nu-

trients such as vitamin C, vitamin E, and beta-carotene^[1].

Many therapeutic qualities have been claimed for them, including enzyme inhibition, anti-inflammatory activities, antimicrobial activities, anti-allergic activities, estrogenic action, powerful antioxidant action, vascular function, and cytotoxic anticancer activity. They are a diverse group of chemicals that play a crucial role in shielding raw mechanisms against the damaging effects of oxidation process on critical supermolecules such as carbs, proteins, lipids, and Genetic material.

4. Terpenoids (Terpenes)

Terpenes, commonly referred as isoprenoids, are the most abundant phytonutrient class in plant foods, soy plants, and grain. The significance of such terpenes to plants derives to their need for carbon via photosynthetic activity involving photosensitizing compounds. They are oligomers and polymers centered on photo-reactive chemistry. Terpenes were indeed tanins with just a heterogeneous group of high molecular mass polyphenolic molecules and the ability to form mutable and irrevocable developments with proteins (primarily), polysaccharides (cellulose, hemicellulose, pectin, etc.), alkaloids, nucleic acids, and natural resources, among other things. Based on its structural and chemical properties, tannins may be classified into four distinct categories: gallo tannins, ellagitannins, complicated tannins, and condensed tannins. Tannin-containing plants are often used as astringents, diuretics, and stomach and duodenal remedies.

5. Beta-carotene

Spinach, carrot, sweet potato, mangoes, papaya, and oranges are high in beta-carotene, a natural vitamin A precursor.

Beta-carotene's actions include:

- Antioxidant free radical reduction/elimination.
- Immuno-modulation-promotion of a rise in cell-reconciled immune reaction (T-helper, NK cells, and cells with IL-2 receptors) as a result of enhanced monocytes expression and tumour necrosis

factor-alpha activity.

- Mutagenesis inhibition.
- Cancer cell growth inhibition^[2].

In places with low oxygen concentrations, beta-carotene is also employed to scavenge able radicals like peroxy and hydroxyl radicals. Serum beta-carotene concentrations have been demonstrated to decline in several oral premalignant lesions and disorders, and due to its supplementation (30 mg/day) has resulted in lesions reduction. As per Liede *et al.*^[3], a beta-carotene-enriched diet can help avoid alterations in the oral mucosa, particularly in smokers, who have lower blood amount of vitamin C and beta-carotene than non-smokers. In one trial, 23 individuals with oral leukoplakia have been given beta-carotene in oral dosages of 90 mg/day for three months. A third of the 18 individuals who finished the research had a full clinical recovery. No details or clinical signs of poisonousness were observed in several of the patients.

5.1 Adverse effects

Portion of the beta-carotene stored in fatty tissue serves as the reserve form of vitamin A and can be split into this vitamin in the event of a deficiency. To maximise benefits and minimise damage, dose evaluation in future research must be based on known knowledge. Two large-scale trials found deleterious effects when beta-carotene dosages exceeded 20 mg/day. The content of many other antioxidant in the organism is likewise affected by selective carotene supplementation. High dosages of carotene increase plasma concentrations of beta-carotene, lycopene, and vitamin E while decreasing lutein and zeaxanthin levels.

6. Retinoic acid (vitamin A)

Retinoic acid is found in carotene and poultry meat, milk, and eggs. Furthermore, retinoic acid is processed into retinal in the gut, and retinol and hypervitaminosis develop while ingestion surpasses the liver's capacity to retain retinoids. Vitamin A is essential for the correct differentiation of epithelial cells. Retinoids' impacts on gene expression have been shown to alter the proliferation and development of normal cells and cancer cells *in vitro*.

Because retinoids promote apoptosis, which leads to proper cell maturation, and prevent carcinogenesis, they have been studied in the regulation and control of carcinogenesis. It has also been shown that epithelial cells grow slower after being exposed to retinoids^[1].

Changes in enzyme activities and DNA alterations caused by free radical reactions increase the chance of establishing cancerous cell lines. Reducing free radicals with antioxidants like vitamin A may help to avoid such cellular alterations. A link has been shown between vitamin A deficiency and an increased susceptibility to carcinogenesis, with an increased chance of developing various epithelial carcinomas of the lungs, colon, pharynx, larynx, and oesophagus. Isotretinoin (13-cis retinoic acid) may inhibit the formation of leading squamous cell carcinoma. Treatment with 13-cis retinoic acid (Isotrenitin) can restore the production of retinoic acid receptors (RAR) mRNA, which itself is lost in pre-malignancy, indicating a hopeful response to the treatment^[2].

- Inhibits keratinization and epidermal cell terminal differentiation; improves cellular immunity.
- Stops or slows the development of leukoplakia.
- Causes cancer cells to be cytotoxic and cytostatic.
- Has an impact on DNA, RNA, and gene function^[3].

It was recommended that individuals with a large premalignant oral lesion start with 50 mg of 13 RA/d. Shah *et al.*^[4] cured 16 affected individuals having oral leukoplakia given topical dosages of 13-cis retinoic acid (Isotrenitin) ranging from 3 to 10 mg/day administered as lozenges for six months. 5 (31.2%) of the individuals discontinued participation due to adverse effects, while two of the three patients who demonstrated complete clinical remission experienced relapses within 5 weeks after stopping the drug. In oral leukoplakia, Stich *et al.*^[5] investigated combination beta carotene and retinol, beta-carotene alone, and palliative, yielding full response rates of 27.5 percent, 14.8 percent, and 3.0 percent, respectively.

6.1 Adverse effects

Toxicities at preventive dosages include skin rash, nasal mucosal dryness and bleeding, conjunctivitis, oral mucositis, cheilitis, hyper-tri-glycerinemia, and teratogenic consequences. Topical treatment provides the potential benefit of delivering a high local dosage with less systemic exposure, reducing the risk of systemic adverse effects. The topical treatment, on the other hand, necessitates patient motivation and the capability to cooperate with repetitive local applications. Furthermore, topical administration may be problematic in some areas, and the drug may well be weakened by saliva. Because of the acid medium of the topical preparations or the base in which the drug is put, local tissue irritation in the form of tissue sensitivities and burning may occur with current topical administrations^[2].

7. Lycopene

It is a red, fat-soluble pigment produced by plants and microbes. Millard found it in 1876 and extracted it from other red fruits and vegetables, such as rose grapefruits, melons, pink guavas, and apricots. Apart from these, it is found in fungi and algae. It is the non-cyclic isomer of beta-carotene, which is essentially a carotenoid. It is among the most powerful antioxidants available. Lycopene, unlike most of the other carotenoids, does not exhibit pro-vitamin A activity. In a three-month double-blind, placebo-controlled randomised controlled experiment undertaken by Singh *et al.*^[6], lycopene supplementation at 4 mg and/or 8 mg per day reduced hyperkeratosis in 80 percent of patients. Complete clearance of the lesions was observed in 55% of individuals receiving 8 mg/day and 25% of those receiving 4 mg/day. Lycopene was identified as a viable therapy option in a comprehensive evaluation of antioxidants in the cure of different leukoplakia. Gupta *et al.*^[7] discovered that eating tomato—the primary source of lycopene—has a preventive effect on oral leukoplakia when researching the link of certain nutrients and dietary products with oral precancerous lesions. It has happened proven to limit the growth of KB-1 human being oral tumour cells by regulating connex-

in-43 (gap junction proteins) levels, resulting in increased gap-junctional communication. The average daily consumption of lycopene is calculated to be 3.7 mg^[1].

A three-month randomised controlled experiment done by Zakrzewska *et al.*^[8] indicated clinical and functional improvement in individuals with oral leukoplakia treated with 4 mg and/or 8 mg lycopene per day. Positive histological alterations were also seen in individuals receiving 8 mg of lycopene per day^[8].

7.1 Adverse effects

Large amounts of dietetic consumption have no negative impact on an individual's wellbeing. To present, there is no evidence of lycopene treatment-related adverse effects or systemic toxicity. According to numerous safety investigations, no negative effects were observed at the greatest consumption amount, 5 g/kg/day^[8].

8. L-ascorbic acid (vitamin C)

Citrus fruits including kiwi, strawberries, papayas, and mangoes contain L-ascorbic acid (L-AA), often recognized as vitamin C. Adults in the United States should consume about 100 and 120 milligrammes of ascorbic acid per day. In the event of smokers, a daily consumption of almost 140 mg/day may lower L-AA concentrations in serum white cells. L-AA has had an anti-oxidizing function and interacts with superoxide generated by the cells' regular metabolic activities; this superoxide inactivation reduces the synthesis of nitrosamines throughout protein breakdown and helps to avoid damage to cellular DNA and cellular proteins. Other than being an antioxidant, L-AA does have the following influences:

- Slows the deterioration of vitamin E.
- Increases the activity of chemotaxis, phagocytosis, and collagen formation.
- Prevents the production of nitrosamines.
- Improves detoxifying via cytochrome P450.
- Prevents the production of fecal mutagens.
- Lowers oncogene expression^[4].

9. Alpha-tocopherol

Vitamin E refers to a trio of organic compounds that are substantially linked to alpha-tocopherol. Natural forms of vitamin E include four tocopherols, alpha, beta, gamma, and delta tocopherols, and four tocotrienols, alpha-, beta-, gamma-, and delta- tocotrienols. The most prevalent and effective form of vitamin E is alpha-tocopherol (AT). It can be found in vegetable oil, margarine, and green plants. The daily advised limit rates for male adults are 10.00 mg/day and 8.00 mg/day for grownup females^[4].

Ribeiro *et al.*^[9] investigated the toxicity and effectiveness of vitamin E in 43 individuals with OL using 400 IU twice each day for 6 months and discovered that ten patients (23%) had detailed clinical remission of lesion and 10 patients (23%) had a moderate clinical response. Tocopherol is an efficient antioxidant at elevated oxygen levels, shielding cellular membranes from lipid peroxidation. A dose of 800 IU/day for 6 to 9 months was regarded acceptable for chemoprevention of oral leukoplakia. AT's primary actions are as follows:

- Scavenging of free radicals.
- Membrane integrity and immune function regulation.
- Cancer cell progression/differentiation inhibition.
- Cytotoxic activity.
- Preventing mutagenicity and the generation of nitrosamines.
- Preventing the synthesis of DNA, RNA, and proteins in cancer cells.

Vitamin E has been recommended as an antioxidant in oral lesions by Chandra Mouli *et al.*^[10] Tobacco-specific nitrosamine (carcinogens) undergo an unique activation and detoxifying mechanism, which vitamin E can block. It has the potential to avoid oral cancer at an experimental stage, in premalignant lesions and premalignant situations. Many previous research show that antioxidants (vitamin E) can be used to treat oral mucosal diseases such as oral leukoplakia, oral lichen planus, oral submucous fibrosis, and oral cancer. In animal models, vitamin E shows synergistic inhibitory action against carcinogenesis and may have some

therapeutic benefits in humans. Many research employing vitamin E in oral leukoplakia found a good clinical response in 46% of 43 patients after 24 weeks, as well as a histological response with no major side effects. Another study discovered a substantial reduction for oral leukoplakia after combining vitamin E, retinol, and beta-carotene therapy^[8]. As a result, it shows promise for the treatment of leukoplakia.

9.1 Adverse effects

Synthetic vitamin E dosages utilised in antioxidant treatment may raise legitimate concerns, because in the United States, for example, 300 mg/d is the highest acceptable daily dosage of this supplement, and 2 g/d is already deemed hazardous. In comparison to vitamins A and D, vitamin E is only ostensibly harmless, i.e. somewhat non-toxic. When used in high doses, it can cause adverse effects (most notably during injections) by inhibiting 5-lipoxygenase in blood platelets and leucocytes (resulting in inadequate synthesis of thromboxane and leukotrienes), diminished blood coagulability (due to excessive suppression of platelet activation), and interruption of granulocyte and phagocyte anti-infective function relying on responsive oxidants.

10. Vitamin K

It is a fat-soluble 2-methyl-1, 4-naphthoquinone family that includes phyloquinone (K1), menaquinones (K2), and menadione (K3). One study discovered that vit K1 doses of 100–300 ng/ml inhibited cell proliferation. Vitamin K2 has been demonstrated to function at the cell cycle level, inhibiting the cell growth and initiating differentiation by acting on cyclins. The cytotoxic activity of vitamins C and K3 is characterised by autschizis, a cell death that is anatomically different from apoptosis and necrosis.

11. Green tea

Green tea polyphenols' anti-carcinogenic properties, primarily EGCG (epigallocatechin-3-gallate), the most biologically active catechin, are likely inhibiting the activity of tumor for-

mation and advancement, induced apoptosis, and inhibition of cell reproduction rates, all of which slow tumour growth and development. Green tea polyphenols' antioxidant capacity is directly tied to the aromatic rings and hydroxyl molecules that comprise their structure, and is a result of the hydroxyl groups' binding and neutralisation of free radicals. Epigallocatechin-3-gallate arrests cells in the G0-G1 stage, downregulates cyclin D1, increases p14ARF and/or p16 protein content, therefore stabilising p53 and regulating apoptosis, and inhibits angiogenesis by lowering VEGF phosphorylation and inhibiting VEGF release by tumour cells. Green tea extract used topically has been demonstrated to diminish the severity of oral leukoplakia^[4].

11.1 Adverse effects

Green tea has positive effects, however, excessive use of green tea has been linked to possible negative effects. Caffeine is a primary component, and consuming over than 5 cups of green tea per day may result in sleeplessness, restlessness, and stomach distress. It has been noticed that green tea is used for weight loss, therefore high quantities of caffeine may induce significant negative effects. Green tea should be used with caution for this purpose. Tannins found in green tea, such as catechin and epicatechin, bond with non-heme iron in human blood. This inhibits absorption of iron, which can result in iron deficiency anaemia. Iron deficiency anaemia can induce fatigue, breathlessness, irritability, headaches, and irregular heartbeat. It also includes vitamin K, which is why excessive use of green tea is discouraged, and individuals on warfarin, aspirin, or anticoagulants may prevent blood clotting^[11].

12. Neem

Gallic acids, catechin, and epicatechin are phytochemicals linked to oral cancer that include glutathione, a carcinogen-detoxifying enzyme. Catechin can block the formation of metalloproteinases, limiting cancerous cells invasion and migration and triggering death. It has anti-inflammatory properties by inhibiting the activity of nuclear factor-b

(NF-b), which causes tumor cells to die. It is antibiotic, antifungal, antihelminthic, anticancer, anti-inflammatory, and neuroprotective. It is used in mouthwashes to treat aphthous ulcers. Neem leaf extract has been linked to the treatment of oral cancer. It is available in both dry and oil forms^[12].

13. Curcumin

Curcumin is a bright yellow phenolic compound derived from turmeric. It is a perennial herb of the Zingiberaceae family. It has been utilised for generations in Indian conventional medical treatment for its anti-inflammatory properties. Its principal ingredients are three curcuminoids, including curcumin (the vital element and the one accountable for its yellow coloring and anti-inflammatory properties due to the compounds demethoxycurcumin and bis demethoxycurcumin). It is well-known for its anti-carcinogenic as well as other curative potential. Turmeric's active ingredients are the flavonoid curcumin (diferuloylmethane) and several volatile oils such as tumerone, atlantone, and zingiberone. Sweeteners, proteins, and resins are some of the other components.

Curcumin, which makes about 0.3–5.4 percent of raw turmeric, is the most well explored active ingredient. It has anticancer effect in the oral cavity, inhibiting cell proliferation and induction of apoptosis in oral tumor cells. It is also linked to notch-1, nuclear factor b (NF-b), and cyclooxygenase-2 (COX2), liquid oxygen (LOX), iNOS (inhibitory nitric oxide synthase), matrices metalloproteinase 9 (MMP-9), tumour necrosis response (TNF), chemokines, various cell-surface adhesion molecules, and cyclin D1 expression. It can boost the effectiveness of cancer therapy with cancer necrotic factor apoptosis-inducing ligand (TRAIL). Curcumin applied twice weekly towards the buccal pouches of Syrian golden hamsters inhibits DMBA-induced oral carcinogenesis. A daily dosage of up to 10 g is indicated to decrease tumour development, progression, and metastasis. Because oxidative stress can play a role in the pathophysiology of Oral Lichen Planus, and Oral Lichen Planus is a chronic inflammatory illness, herbs with both anti-inflammatory and antioxidants qualities may be

effective in controlling Oral Lichen Planus^[13].

13.1 Adverse effects

Researchers have identified unfavourable side effects connected with this polyphenol. Lao *et al.*^[14] performed a dose-escalation research in 34 healthy volunteers to establish the maximum tolerated dosage and tolerability of a sole oral dose of curcumin. The participants were given escalating dosages of curcumin varying from 500 to 12,000 mg, and their safety was evaluated 72 hours later. The experiment had twenty-four participants, seven of whom had mild toxicities that did not show up to be dose-related. These seven subjects particularly reported diarrhea, headache, rashes, and yellow stool. Curcumin at dosages varying from 0.45 to 3.6 g/day for 1 to 4 months was related with nausea and diarrhea, as well as an increase in blood alkaline phosphatase and lactate dehydrogenase levels in humans, according to another research. Curcumin dosages more than 8 g/day were unacceptably high in individuals with higher or premalignant lesions due to the bulky size of the pills. As a result, further research is needed to assess the long-term toxicity of curcumin before it could be licenced for human usage. It is generally regarded as harmless, however it may induce gastric irritation, stomach discomfort, nausea, diarrhea, allergic skin response, and anti-thrombosis activity that interferes with blood clot formation.

14. Cyanidins from grapes

Cyanidin is a pigment extract found in red berries such grapes, blackberries, cranberries, raspberry, apple, plum, red cabbage, and red onion. It has antioxidants and radical scavenging properties that may lessen the risk of cancer. It has been shown to decrease cell growth as well as the expression of the iNOS and COX-2 genes in colon carcinoma cells. Another research confirms this. According to Elattar *et al.*^[15], resveratrol in concentrations comparable to those found in red wines is an efficient regulator of oral squamous cell cancer cell growth and proliferation, hence contributing to its anti-tumor impact. Casto *et al.*^[16] investigated the efficacy of berry extracts to suppress the reproduction of

human tumour cells. According to research done by Selvendiran *et al.*, piperine has greatly extended its chemopreventive action by modifying lipid peroxidation and increasing antioxidant defence^[17].

15. Gingerol from gingers

Gingerol is the essential constituent of fresh ginger that gives it its characteristic spiciness. Ginger contains 1%–4% essential oils and an oleoresin, as well as zingiberene, curcumin, sesquiphellandrene, bisabolene, monoterpenoid aldehydes, and alcohols. It is antibacterial, anti-inflammatory, and analgesic. It has been examined for its anti-cancer properties in tumours of the colon, breast, ovary, and pancreas. Oyagbemi *et al.*^[18] have outlined the processes behind gingerol's medicinal actions. It reduces iNOS and TNF-alpha production by inhibiting I κ B α phosphorylation and NF- κ B nuclear translocation. When K562 and MOLT4 cells were treated with gingerol, the levels of ROS were much greater than in the control groups, triggering leukaemia cell death via the mitochondrial route. Gingerol and 6-shogaol were discovered to have anti-invasive effect against hepatoma cells by control of MMP-9 and TIMP-1, and 6-shogaol also controlled urokinase-type plasminogen activity in human hepatocarcinoma cells. Single dose of 6-shogaol, other active component of ginger, is more efficient than 6-gingerol and curcumin in suppressing TPA-induced expression of iNOS and COX-2 transcriptional activity in mouse skin, suggesting that additional *in vitro* and *in vivo* research is required. It is used to treat oral thrush as a sialogogue and to reduce toothache. Ginger may lessen the chemotherapeutic agent's toxicity^[13].

15.1 Adverse effects

Although the plant extracts seem to be quite safe, the most common adverse effects that have been recorded include headache, dizzy, agitation, nauseous, vomiting, diarrhoea, and cutaneous sensitivity. Ginkgo has been shown to suppress platelet-activating factors and to shorten bleeding times. As a result, caution was suggested among persons or individuals on anticoagulant treatment. This should not be taken during pregnancy or in

people suffering from biliary illness. Since ginger can interact with blood coagulation, it should be taken with caution in individuals taking anticoagulants like Coumadin or heparin^[12].

16. Capsaicin

Other compounds obtained from plants for spices, in addition to curcumin, have anti-cancer properties. Capsaicin, a spicy ingredient of pepper plants, is widely acknowledged to have anti-cancer characteristics, reducing growth and induction of apoptosis in a broad variety of human tumor cell lines, however, its genotoxic and cancerous capabilities have also been described in multiple papers. Capsaicin has been shown to decrease TPA-induced NF-B activation by inhibiting IB breakdown and consequent nuclear translocation of NF-B/p65. It also inhibits TNF- and TPA-induced adherence of AP-1 and NF-B to DNA binding sites in sentient leukaemia cells and causes apoptosis in human mammary epithelial cells by inducing JNK1 and p38 and depressing ERK. Furthermore, capsaicin therapy inhibits VEGF-stimulated angiogenesis via inhibiting VEGF-induced p38 MAPK and Akt stimulation. In a rodent study, capsaicin administration significantly increases the activity of phase II enzymes such as glutathione S-transferase and quinone reductase in the liver and colon of experimental F344 rats and reduces the advancement of azoxymethane (AOM)-induced colon pre-malignant lesions, aberrant crypt foci (ACF), as well as adenocarcinoma. Tanaka *et al.*^[19] also demonstrated that capsaicin supplementation inhibits chemically induced tongue tumorigenesis in male F344 rats. Capsaicin is a painkiller used in topical application to treat neuropathic pain due to its analgesic action. Capsaicin thereby desensitises stimuli produced by heat, chemical, and mechanical sources. Capsaicin has been proven in studies to be beneficial in people suffering from burning mouth syndrome.

16.1 Adverse effects

Capsaicin has an impact on skin (irritant, sensitizer), eye (allergen), ingestion, and inhaling (lung irritant, lung sensitizer). In mice, the LD50 is 47.2 mg/kg. Painful capsaicin-containing pepper expo-

sure are one of the most regular plant-related exposures reported to poison control centres. They induce searing or stinging discomfort to the skin and can cause nausea, vomiting, stomach pain, and blistering diarrhoea if consumed in large doses by adults or tiny amounts by children. Excessive tears, discomfort, conjunctivitis, and blepharospasm result with eye exposure.

17. Garlic

Garlic is a biological active ingredient that is utilised in Ayurveda to treat a variety of ailments. Allicin, the main component of garlic, is thought to have anti-inflammatory and immunomodulatory activities. Allicin has been shown to significantly reduce inflammatory product release, neutrophil migration, and bacterial and viral inhibition. They also inhibit oxidation and play an important role in immunological regulation. According to one study, allicin can be an efficient pain reliever, promote ulcer healing, and prevent the relapse of recurrent aphthous stomatitis.

17.1 Adverse effects

It has been observed that garlic extract causes a burning feeling in the gastrointestinal system, nausea, diaphoresis, and light-headedness. These extracts may also induce contact dermatitis, and excessive garlic consumption has indeed been linked to severe spontaneous spinal epidural hematoma.

18. Aloe vera

For millennia, people have recognised and used the *A. vera* plant for its medical and cosmetic qualities. The term *A. vera* is derived from the Arabic term *alloe*, which means bright bitter material, and *vera*, which means truthful in Latin. *A. vera*, the wonder plant, has been shown to be advantageous in a variety of health functions. Vitamins, enzymes, minerals, carbohydrates, lignin, saponins, salicylic acids, and amino acids are among the 75 potentially active ingredients. Vitamins A (beta-carotene), C, and E are present and act as antioxidants, helping to neutralise free radicals.

18.1 Adverse effects

In sensitive people, the detrimental consequences of aloe on a topical treatment may produce redness, burning, stinging, and, in rare cases, widespread dermatitis. Anthrax quinones including such aloin and barbaloin cause the majority of allergic responses. It is important to try it on a tiny area initially to rule out any allergic responses. Abdominal pains, diarrhoea, crimson urine, hepatitis, dependence, or deepening of constipation result with systemic ingestion of aloe vera. Long-term usage has been linked to an increased risk of colorectal tumor. Electrolyte imbalances may occur as a result of the laxative impact (low potassium levels).

19. Conclusion

Antioxidants are crucial in the treatment of numerous oral lesions and disorders, acting as a key adjuvant in halting the malignant potential of these illnesses. Thorough understanding of these phytochemicals is essential for clinicians in order to avoid the chronicity of lesions and hence reduce morbidity and death in patients with any recognised oral illness.

Conflict of interest

The authors declare no potential conflicts of interest.

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