

Therapeutic Role of Phytochemicals in the Prevention of Oral Potentially Malignant Disorders and Oral Cancer – A Review

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ABSTRACT

BACKGROUND

Medicinal plants and their extracts have been found to possess potent anti-inflammatory, antioxidant and anti-cancer properties that slow down the cellular proliferation and malignant transformation rate of orally potential malignant disorders such as oral leukoplakia, oral submucous fibrosis and oral lichen planus. They are a potential source of antioxidants such as vitamin A, E, and C that neutralize the free radicals produced in various oral mucosal lesions thereby preventing the mucosal damage. They have been found to modulate cellular signalling pathways and, this activation influences the cellular defence mechanisms that protect the normal cells against reactive oxygen species or reactive metabolites and induces apoptotic death of cancerous cells, thus chemoprevention ensues to prevent, reverse or delay carcinogenesis. They have been studied to enhance tumour cell killing and inhibition of metastasis by increasing number of immunocompetent cells such as macrophages, cytotoxic T lymphocytes, natural killer cells and by recruitment of antibodies at the tumour site. Now a days, natural herbs or phytochemicals are gaining attention due to side effects and increased antimicrobial resistance that often occur with prolonged use of chemotherapeutic agents. Therapeutic effect of phytochemicals in oral PMDs is very promising as they prevent the progression of dysplasia from mild to severe. Literature has revealed significant reduction in burning sensation, difficulty in swallowing and speech, and pain associated with the oral mucosal lesion. However, more research should be conducted in future to establish their use as an adjunctive therapy in oral potentially malignant disorders. By this review, an attempt has been made to highlight therapeutic potential of diverse herbs such as aloe vera, tulsi, neem, curcumin, lycopene, green and black tea, peppermint etc. in the reduction of clinical symptoms of burning sensation and pain associated with the oral mucosal lesions, and discusses their indispensable role in prevention of oral cancer.

KEY WORDS

Antioxidants, Chemoprevention, Phytochemicals, Oral Cancer

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BACKGROUND

Oral mucosal lesions (OMLs) have been defined as an abnormal change in oral mucosa, and diverse clinical presentations of OMLs are red and white patches, ulcerations, swellings or growth, pigmentations or as normal variants are commonly encountered by the oral physicians in their daily clinical practice.¹ They can occur as solitary isolated lesions or in association with dermatological diseases, and present a diagnostic challenge to clinicians. Oral potentially malignant disorders (PMDs) such as leukoplakia, erythroplakia, etc present as white or red patches or as chronic non healing ulcer and require early diagnosis, prompt treatment to prevent malignant transformation. OML may be asymptomatic or symptomatic with pain / discomfort that may interfere with mastication or swallowing, besides this burning sensation to spicy foods, taste alterations, xerostomia, etc. are some common symptoms that affect the daily functional activities of patient. Therefore, clinicians should have adequate knowledge about the likely differential diagnosis of similar appearing lesions and emerging treatment options for their proper diagnosis and management.²

Literature revealed that most of the chemotherapeutic agents have significant adverse effects and cause antimicrobial resistance on prolonged use.^{3,4} Due to potential benefits of diverse herbs such as aloe vera, curcumin, tulsi, lycopene, green tea etc. researchers are moving towards botanical based medicines or plant derived derivatives, known as phytochemicals.^{4,5,6} Clinical trials have shown that therapeutic effect of phytochemicals in oral PMDs is very promising as they prevent the progression of dysplasia from mild to severe.^{1,4,5}

OXIDATIVE STRESS AND ORAL POTENTIALLY MALIGNANT DISORDERS

Several studies elucidating the association of oxidative stress as a contributing etiological factor in wide variety of oral diseases has been documented in the literature.^{7,8} Oxidative stress potentiates the release of highly reactive free radicals or reactive oxygen species (ROS) such as superoxide (O_2^-), hydroxyl (OH) and nitric oxide (NO).⁷ Cigarette smoke produces ROS mainly in form NO, and chronic alcohol consumption leads to production of ROS, and DNA adducts which are established risk factors for oral cancer.⁸ Oxidative stress damages the cellular protein by increasing its cross linkage, and fragmentation and affects DNA repair mechanisms, thereby resulting in increased DNA mutations [Figure 1].^{8,9}

ROLE OF PHYTOCHEMICALS IN FIGHTING OXIDATIVE STRESS

Studies have shown that phytochemical compounds present in natural herbs such as beta-carotene, lycopene, neem, aloe vera, tulsi, curcumin, etc. and their extracts have wide range of biological activity that include antibacterial, anti-inflammatory, anti-oxidant, anti-proliferative properties and suggested them to play key role in chemoprevention.^{10,11} Upon

entry into cells, phytochemicals are able to scavenge the free radicals immediately, and modulate cellular signalling pathways. Consequently, this activation influences the cellular defence mechanisms that protects the normal cells against ROS or reactive metabolites and induces apoptotic death of cancerous cells, thus chemoprevention ensues to prevent, reverse or delay carcinogenesis. Table 1 illustrates molecular targets of phytochemicals.

PHYTOCHEMICALS AND THEIR MECHANISM OF ACTION

Lycopene

Lycopene belongs to genus lycopersicum, is a bright red carotenoid pigment extracted from red fruits and vegetables chiefly tomato, red carrots, red bell peppers, watermelons, and papayas.¹¹

Phytochemical Action	Increases	Decreases
Cell proliferation	P53, p16, p27 cyclins D1, E, B1	CDK - 1, 2, 4 CDC - 2
Apoptosis	Bax, cyt C, caspase activation, PARP cleavage	Bcl 2, Bcl-xL, survivin, TRAF 1
Transcription factors	Nrf 2	NFκB, AP-1, STAT, MPAK, PI3K, Akt, βcatenin
Antioxidant-oxidative system	SOD, GSH	O_2^- , OH $^-$, NO, COX 2, LOX, NOS,
Tumour angiogenesis	-----	VEGF, EGF, TGF α, PDGF, VEGFR
Tumour invasion	MMP	ICAM, VCAM, ELAM, TIMP

Table 1. Illustrates Molecular Targets of Phytochemicals

Chemical Structure and Composition

It is a carotenoid, acyclic, lacks β-ionone ring; structure needed to form vitamin A therefore has no pro vitamin A activity that distinguishes its biochemistry from carotenes, α and β carotene.¹¹ Lycopene extract is produced from tomatoes with high concentration of lycopene approximately 150 - 250 mg / kg. Lycopene is a 40-carbon acyclic carotenoid containing 11 conjugated double bonds, contributing to its red colour. It exists as all trans isomer in natural form, is an unsaturated acyclic hydrocarbon with chemical formula C₄₀H₅₆ and molecular mass of 536.85 atomic mass unit (amu).^{11,12}

Mechanism of Action

It has been reported to be effective quencher of singlet oxygen (O_2^1), and free radicals such as hydroxyl, OH and peroxy radicals, and has been hypothesized to prevent carcinogenesis by inhibition of proliferation of killer B-1 (KB-1) cells, by upregulation of gap junction protein, connexin 43 expression, and enhances gap junctional communication. Its other beneficial effects are due to their ability to arrest cell cycle progression from G₀ / G₁ to S phase, interference with growth factor stimulation, regulation of transcription, increase of p53 protein levels and induction of phase II enzymes (Figure 2).^{12, 13,14}

Dosage and Clinical Trials

Regarding the dosage of lycopene, the daily intake of lycopene has been suggested to be 3.7 mg. Studies have shown that, lycopene when given in a dosage of 4 - 8 mg / day orally for three months in case of oral leukoplakia, and 16 mg / day for oral submucous fibrosis could prevent the risk of malignant

transformation. These studies have emphasized that daily oral dose of 8 mg is more efficacious than 4 mg a day in clinical improvement of oral leukoplakia, and has been found to prevent the oxidative damage in atrophic and erosive OLP.^{11,13} Gowda et al. observed the clinical improvement of oral submucous fibrosis patients after treatment with lycopene, 2000 µg, twice daily, for three months, with no significant toxicity.¹⁴ Kushwaha et al. found complete remission of atrophic and erosive oral lichen planus (OLP) after 8 weeks of treatment of lycopene. They concluded that lycopene is an effective therapeutic option for reversal of dysplastic changes in oral potentially malignant disorders (OPMDs) due to its antioxidant and anti-inflammatory activity.¹⁵

Brand Available

Lycopene is available in the market under different brand names as Lycored, Lynet, Lyconex (gennext), Lycobin etc.

Beta-Carotene

Beta carotene (β carotene) is a precursor to vitamin A and dark green, orange and yellowish fruits and vegetables are rich source of β carotene.¹⁶

Chemical Structure and Composition

β carotene belongs to the family of carotenoids which are terpenoids / isoprenoids. Basic structure is made up of 8 isoprene units, joined end to end to form an unconjugated chain and have β rings at both the ends, long conjugated chain imparts orange colour to β carotene.^{16,17}

Mechanism of Action

Carotenoids are scavenger of free radicals, they produce genetic and molecular responses such as overexpression of p53, reduction in neovascularization of tumour cells and induction of apoptosis. Their other actions are i) immunomodulation, stimulation of cell mediated immune response by increasing the activity of T lymphocytes; helper CD₄ lymphocytes, monocytes, cells with interleukin 2 (IL 2), tumour necrosis factor alpha (TNF α), and natural killer (NK) cells ii) inhibition of mutagenesis, and iii) inhibition of cancer cell growth, iv) reduces progression of dysplasia in oral PMDs, and v) reduce the expression of growth factors and immune regulatory factors (Figure 3).^{4,16,17}

Dosage

Physicians usually recommend β carotene from the food rather than as dietary supplements, limited trials have been conducted to establish the minimum level of β carotene required for the human health. As a dietary supplement, it is available in form of capsules and chewable tablets; 6 to 15 mg of β carotene per day and 3 to 6 mg of β carotene per day has been recommended for adults and children, respectively.¹⁶

Brand Available

It is marketed under brand names: Lumitene, A-Caro-25, Solatene, Centrum, Singles β carotene in form of capsules or chewable tablets.

Clinical Trials

Studies have suggested that serum carotene levels are decreased in oral PMDs and 30 mg / day β carotene capsules twice daily for 12 weeks result in increase in mouth opening,

reduction in burning sensation, and thickness of collagen bundles in oral submucous fibrosis (OSMF) patients.^{16,17} Randomised controlled trials reported that clinical improvement of oral PMDs with β carotene ranged from 14.8 % to 71 % with no significant side effects, only yellow discoloration of skin was seen in few patients.¹⁶ Garewal et al.¹⁷ showed a complete and partial response rate of 71 % in oral leukoplakia patients treated with a regimen; β carotene 30 mg / day for 3 months, followed by additional 3 months for responding patients, with no observable side effects.

Curcumin

Curcuma longa L. well known as turmeric or curcumin isolated from the root rhizomes of the plant Zingiberaceae, is one of the widely used herb in Unani, Ayurveda, Siddha and Chinese medicinal systems for the management of various ailments such as dermatological diseases, infections and stress.¹⁸

Chemical Structure and Composition

Curcumin is the main chemical constituent of turmeric with formula C₂₁H₂₀O₆ and molecular weight 368.38 amu. Curcuminoids such as curcumin, desmethoxycurcumin, bisdemethoxycurcumin are natural polyphenols and are the major phytochemicals known for their antioxidant, anti-inflammatory and anticancer potential.^{18,19}

Mechanism of Action

Its therapeutic effect in oral PMDs is explained by its potential to affect biological pathways that promote carcinogenesis. It inhibits the activity of nuclear factor -κB (NF-κB) transcription factor and genes involved in cellular proliferation such as cyclooxygenase (COX-2), TNF-α, cyclin D1, ICAM-1, c-myc, Bcl-2, matrix metallo-proteinases (MMP-9), inducible nitric oxide synthase (iNOS), and IL-6, IL-8. Moreover, curcumin acts at different stages of carcinogenesis process, causes cell cycle arrest, promotes apoptosis by up regulation of p16 and p53, and activation of p53 decreases expression of anti-apoptotic protein bcl 2. It inhibits tumour angiogenesis and metastasis by its inhibitory effect on VEGF, ICAM 1, MMP-9 and COX-2, acts as a scavenger of ROS and reactive nitrogen species generated by the oxidative stress mechanisms in PMDs and results in dose dependent reduction in cell adhesion molecules especially E cadherin involved in tumour growth.^{4,19} The anticancer effects of curcumin are mainly attributed by alteration of multiple cellular signalling pathways involved in cellular growth, apoptosis, invasion and metastasis which eventually result in activation of caspase 3 and concomitant PARP cleavage, and induces caspase dependent apoptotic pathway (Figure 5).²⁰

Dosage

Turmeric is available in both topical and oral formulation. Most common therapeutic regimen is 400 - 600 mg of turmeric capsules thrice a day for 8 weeks. It can be used as 5 % curcumin oral paste thrice a day for four weeks for symptomatic relief in oral lichen planus and oral submucous fibrosis lesions.^{18,19}

Brands Available

Tablets Turmix (300 mg curcumin and 5 mg piperine), 50 g curcumin cure next oral gel.

Clinical Trials

Studies have used turmeric in various formulations as capsules, oil or 1 % curcumin mucoadhesive gel and found it as an effective agent in reducing burning sensation in oral PMDs due to its anti-inflammatory action, Nigam et al.¹⁹ found significant reduction in visual analog scale (VAS) score from 6.91 to 3.98. In another study on OLP patients, significant improvement in burning sensation, ulceration and striae was noted after local application of turmeric extract twice daily for 3 months, Srivastava et al.²¹ in his study observed significant improvement in burning sensation and mouth opening in OSMF patients ($P < 0.01$). Due to lack of systemic toxicity and potent anti-tumour properties it could be used as an adjuvant therapy to treat PMDs resistant to currently available therapies. Studies have revealed that low solubility, high rate of metabolism, and low bioavailability of curcumin has become a challenge to effectively treat oral PMDs. To overcome this, nano formulation of curcumin has been introduced that enhances the bioavailability of curcumin, increases efficacy of topical corticosteroid triamcinolone acetonide, and reduces the need of prolonged administration of corticosteroids for the treatment of precancerous lesions.²²

Green Tea

Green tea and black tea made from young leaves and leaf buds of tea plant *Camellia sinensis* have been studied for their chemo preventive potential and green tea has shown greater efficacy against multiple cancers.²³

Chemical Structure and Composition

It contains four major polyphenols: epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin 3-gallate (EGCG), comprising 1 - 3 %, 3 - 6 %, 3 - 6 % and 7 - 13 % respectively of the fresh green tea leaf dry weight.^{23,24}

Mechanism of Action

Green tea exerts its action in different ways (Figure 4):²³⁻²⁵

1. Its antioxidant potential is attributed to neutralisation of free radicals by the hydroxyl groups,
2. EGCG is most active catechin, it inhibits tumour proliferation, induces apoptosis, arrests cells in G0 - G1 phase, down regulates cyclin D1 levels, increases p14 and p16 protein levels thus stabilize p53, and blocks angiogenesis by inhibition of vascular endothelial growth factor (VEGF) secretion by tumour cells.
3. EGCG acts on proteins and genes involved in development and progression of head and neck cancers, that include NF- κ B, EGFR, STAT3, Activator protein 1 (AP-1), Mitogen activated protein kinases (MAPK), TNF.

Dosage

Ingestion of 3 - 5 cups / day (up to 1200 ml / day) provides minimum of 250 mg / day catechins. For oral lesions, oral intake of 3 g of green tea has been found to be adequate.

Brands Available

Various green tea brands are available in market: Tetley green tea, Tazo green tea, twinning jasmine green tea, etc., and chewing gums containing green tea extract 120 mg; e.g. Xyloburst chewing gum (100 ct) are also available.

Clinical Trials

Hsu et al.²⁵ showed that EGCG was able to effectively inhibit the growth and invasion of tumour cells. For PMDs, oral green tea extract dose of 1 gm / cm² thrice daily for at least 6 months was found effective.²⁶ Schwartz et al.²⁷ performed a pilot study in which green tea extract (2000 - 2500 mg / day) given to smokers for four weeks showed reduction of smoking induced DNA damage and inhibition of tumour cell growth. Besides this, overexpression of HER-2 (neu / erbB2) has been found to contribute towards progression of oral cancer.^{28,29}

Aloe Vera (*Aloe barbadensis*)

Aloe vera is jelly like fleshy plant of the genus aloe, the inside of which contains liquid jelly that has soothing effect and is widely accepted species for medicinal and pharmaceutical purpose in many countries.³⁰

Chemical Structure and Composition

Aloe leaf has two major parts; i) the outer green rind including vascular bundles, and ii) the inner colourless parenchyma or pulp containing aloe gel. Aloe vera pulp is made up of three structural components: cell wall, the degenerated organelles and the viscous mucinous liquid gel within the cell. Aloe gel comprises of 99.5 % water and remaining 0.5 - 1 % of water soluble and fat-soluble vitamins, salicylic acid, minerals, sugars, enzymes, lignin, saponins, and amino acids.³⁰⁻³²

Mechanism of Action

The primary therapeutic effect of aloe vera is attributed to the polysaccharides contained in the gel of the leaves. It has excellent wound healing properties, some researchers have hypothesized that it increases both collagen synthesis and its cross linkage at the site of wound, which may be due to presence of acemannan, component of aloe vera composed of long chain of acetylated mannose, a muco-polysaccharide. Its macrophage activating potential stimulates the release of fibrogenic cytokines and its direct binding to growth factors stimulates the granulation tissue. Its anti-inflammatory effect is due to inhibition of COX, thereby reduces production of PGE₂, Lupeol is the most potent anti-inflammatory sterol of aloe vera that reduces inflammation in dose dependent manner. Aloe vera emodin, an anthraquinone, has the ability to inhibit apoptosis, growth and proliferation of cancerous cells (Figure 6)

Dosage

Aloe vera is available in form of gels, toothpastes, capsules and juice. It is recommended to take 200 - 300 mg of capsules per day, about 2 - 3 tablespoons (50 ml) of aloe vera juice per day, and 0.5 % aloe vera oral gel.^{29,30}

Clinical Trials

Sudarshan et al.³² found statistically significant reduction in burning sensation ($P = 0.008$), improvement in mouth opening ($P = 0.02$), and cheek flexibility ($P = 0.01$) in OSMF patients. Ali et al.³³ found weak evidence of aloe vera in management of symptomatic OLP patients, they concluded that aloe vera is more efficient and has comparable effect to triamcinolone acetonide.

Naturally Occurring Phytochemical	Plant Source	Preventive Actions
Apigenin	<i>Moringa peregrina</i> , chamomile	Induces apoptosis
Colchicine*	<i>Colchicum autumnale</i>	Anti-mitotic
Curcumin	<i>Curcuma longa</i>	Induces apoptosis in cancerous cells Inhibits growth of tumour cells by reduction of COX 2, MMP 2, and EGFR expression
Cyanidin*	Berries, plums, red cabbage and red onions	Inhibits tumour cell growth, <i>COX 2</i> gene expression, and promotes the activation of AP-1 and NF - κB
3, 3' - Diindolylmethane (DIM)	Brassica sps. that includes vegetables such as broccoli, cauliflower, and collard greens	DIM modulates key CYP enzymes Inhibits angiogenesis, metastasis, and invasion of cancer cells
Epigallocatechin gallate (EGCG)	Green tea	Inhibits apoptosis and reduces expression of EGFR
Etoposide*	<i>Podophyllum peltatum</i>	Mitotic block
Genistein*	<i>Vicia faba</i> Soya beans <i>Flemingia vestita</i> (coffee)	Inhibits angiogenesis and tumour cell proliferation
Gingerol*	<i>Zingiber officinale</i> (ginger)	Decreases iNOS and TNF-alpha expression and induces apoptosis
Lycopene	Tomato, red carrot, watermelon and red papaya	Inhibits tumour cell proliferation, upregulates gap junction protein, i.e. connexin 43 expression, and enhances gap junctional communication.
Phenyl isothiocyanates (PEITC)*	Broccoli, cabbage (cruciferous vegetables)	Induces cell cycle arrest at G2 / M phase, Akt inactivation, and downregulates ERK 1 / 2 and MEK phosphorylation
Resveratrol*	Grapes and peanuts	Anti-inflammatory action, inhibits COX 2, MMP expression, tumour invasion and metastasis
Vitamin D3*	Mushroom	Vitamin D receptors (VDR)
Vitamin E (tocopherol)*	Sunflower oil	Inhibit NF-κB, STAT-3 and COX 2 Supresses cell proliferation, activity of NF κB, and inhibits activation of ERK MAP kinase
Vindesine*	Vinca roseus	Mitotic block
Vinorelbine*	Vinca roseus	Mitotic block

Table 2. Phytochemicals from Medicinal Herbs, Their Sources, and Anticancer Actions

*Therapeutic Role in oral potentially malignant disorders, and oral carcinogenesis is limited and demands future clinical trials

Author (Year)	Intervention	Herbal Agent Used	Outcome
Garewal et al. (1990) ¹⁷	To evaluate response of oral leukoplakia to β carotene	B carotene 30 mg / day for 3 months to 24 oral leukoplakia patients	71 % response rate observed.
Singh et al. (2004) ¹³	Efficacy of lycopene in the treatment of oral leukoplakia	20 patient's lycopene 8 mg / day, 20 patients lycopene 4 mg / day	Mean response of 80 %, 66.25 % and 12.5 % was seen with 8 mg, 4 mg lycopene and placebo, respectively
Schwartz et al. (2005) ²⁷	Molecular and cellular effects of green tea on oral cells of smokers	Green tea total extract (2000 – 2500 mg / day) was given to smokers for four weeks	Cell growth was reduced, and markers of apoptosis were upregulated.
Sudarshan et al. (2012)	To compare the efficacy of <i>Aloe vera</i> with antioxidants in the treatment for OSMF.	Group A: Topical application of 5 mg of <i>Aloe vera</i> gel three times daily for 3 months Group B: Antioxidant capsules twice daily for 3 months	<i>Aloe vera</i> showed a statistically significant reduction in burning sensation (P = 0.008), improvement in mouth opening (P = 0.02), and cheek flexibility (P = 0.01)
Srivastava et al. (2015) ²¹	To investigate the clinical efficacy of herbal medicines for the treatment of OSMF	Topical application of 1 gm tulsi and 1 gm turmeric mixed in glycerine base 3 - 4 times / day	Mean burning sensation was 6.07 ± 1.75 before the treatment and 2.22 ± 1.41 after the treatment (P < 0.001). Mean mouth opening was 24.46 ± 4.0 mm before the treatment and 27.85 ± 3.39 mm after the treatment (P < 0.001)
Nigam et al. (2017) ¹⁹	To evaluate the efficacy of curcumin in reducing the burning sensation in potentially malignant disorders of oral cavity.	Tab Turmix twice daily 15 days along with the topical application of turmeric and honey in a paste form by cotton applicator 2 – 3 times daily	VAS score decreased from 6.91 to 3.98 after 15 days.
Piyush et al. (2019) ¹¹	To evaluate and compare the therapeutic response of lycopene and curcumin with placebo in OSMF patients	Lycopene capsules 8mg twice daily Curcumin tablets 300 mg twice daily	Improvement in mouth opening, burning sensation, tongue protrusion, and cheek flexibility was 3.9 ± 4.9 mm, 4.8 ± 2.6, 5.0 ± 7.2 mm, & 0.36 ± 0.71 mm, respectively, for curcumin and 4.1 ± 4.2 mm, 5.0 ± 2.3, 2.4 ± 3.5 mm, & 0.66 ± 0.80 mm, respectively, for lycopene (P < 0.05).
Kushwaha et al. (2019) ¹⁵	To evaluate response of atrophic and erosive OLP to lycopene	Capsule lycopene 4 mg / day orally for 8 consecutive weeks to 13 OLP patients	Mean Thongprasom clinical sign score reduced by 60 %.
Bakshi M et al. (2020) ²²	To evaluate the efficacy of a combination of 1 % nanocurcumin gel with 0.1 % triamcinolone acetonide mouth rinse for OLP	31 patients with erosive or ulcerative OLP received 0.1 % triamcinolone mouth rinse and were then randomly divided into two groups; Group 1: Combination therapy with 1% nanocurcumin gel or Group 2: Placebo gel	A significantly higher decrease in the mean REU score was observed with nanocurcumin (P < 0.001).

Table 3. Summary of Clinical Trials Conducted to Evaluate the Effectiveness of Herbs and Their Extracts in the Treatment of Oral PMDs

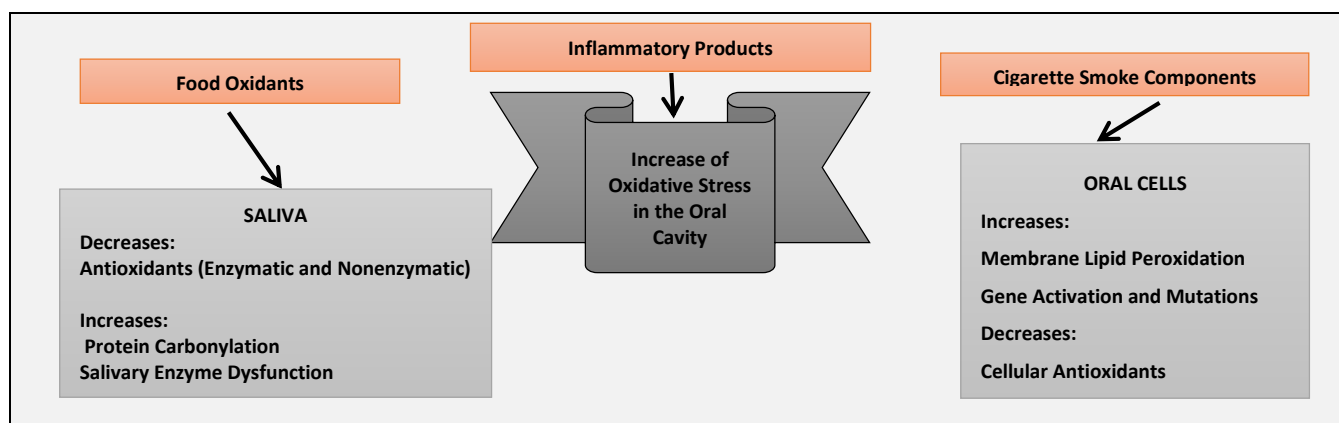


Figure 1. Shows Effect of Increased Oxidative Stress on Saliva and Oral Cells

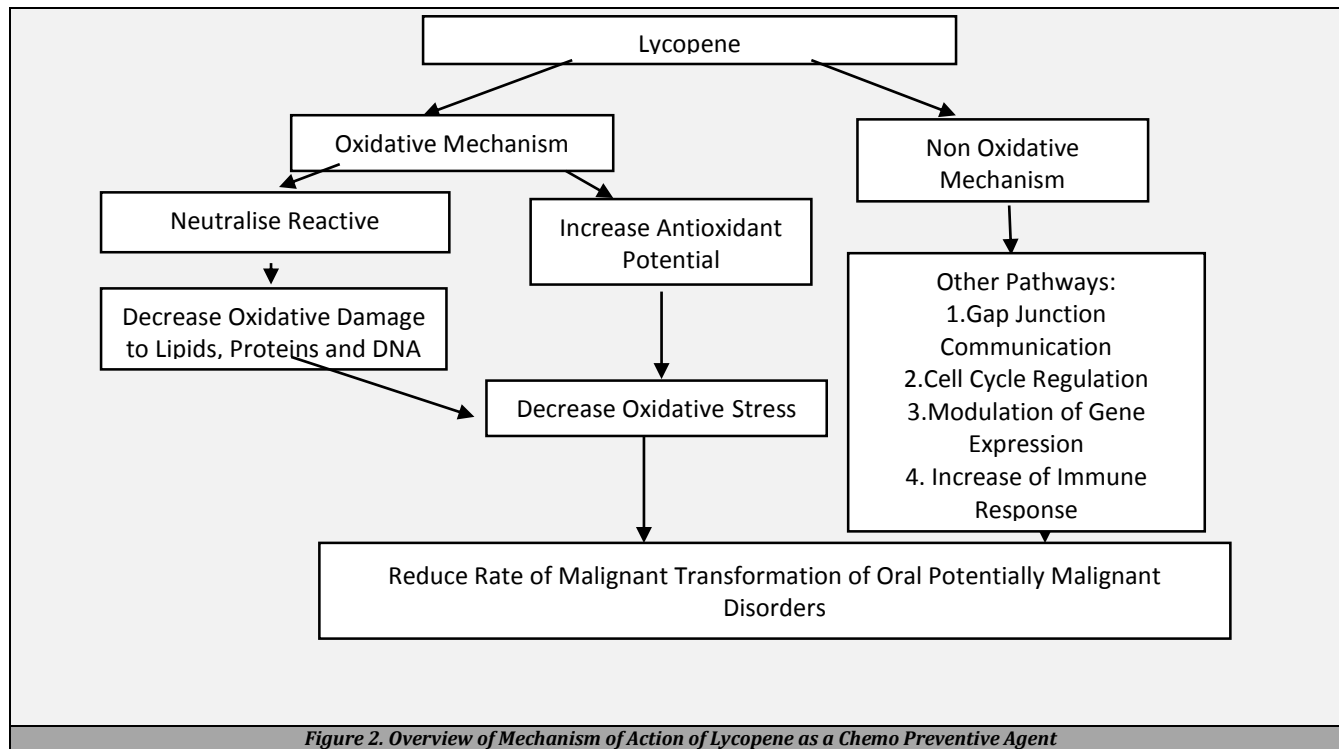


Figure 2. Overview of Mechanism of Action of Lycopene as a Chemo Preventive Agent

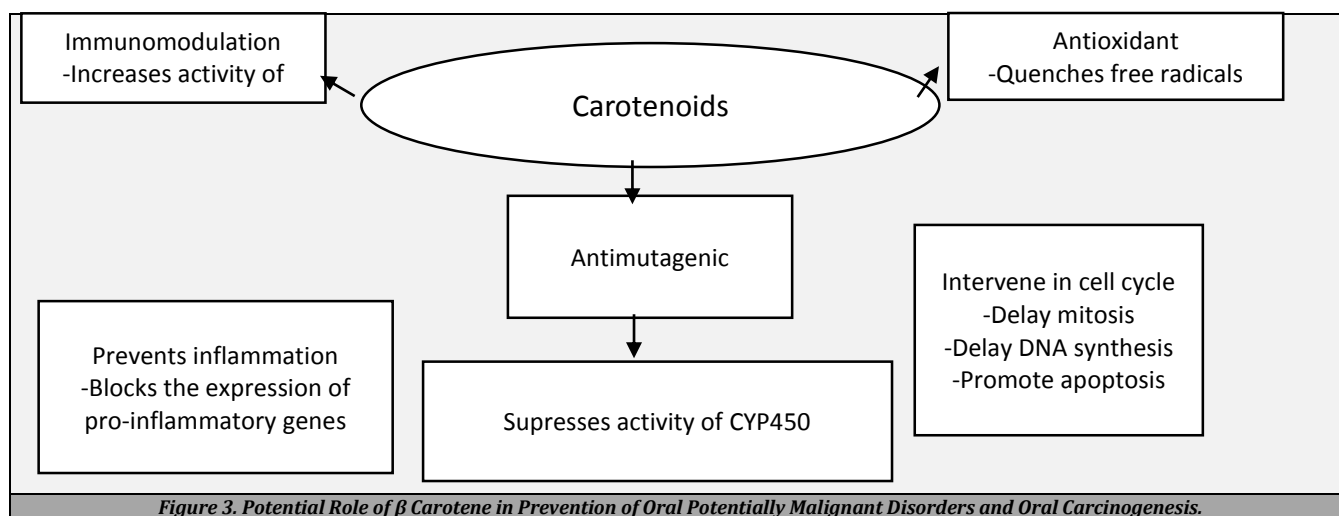


Figure 3. Potential Role of β Carotene in Prevention of Oral Potentially Malignant Disorders and Oral Carcinogenesis.

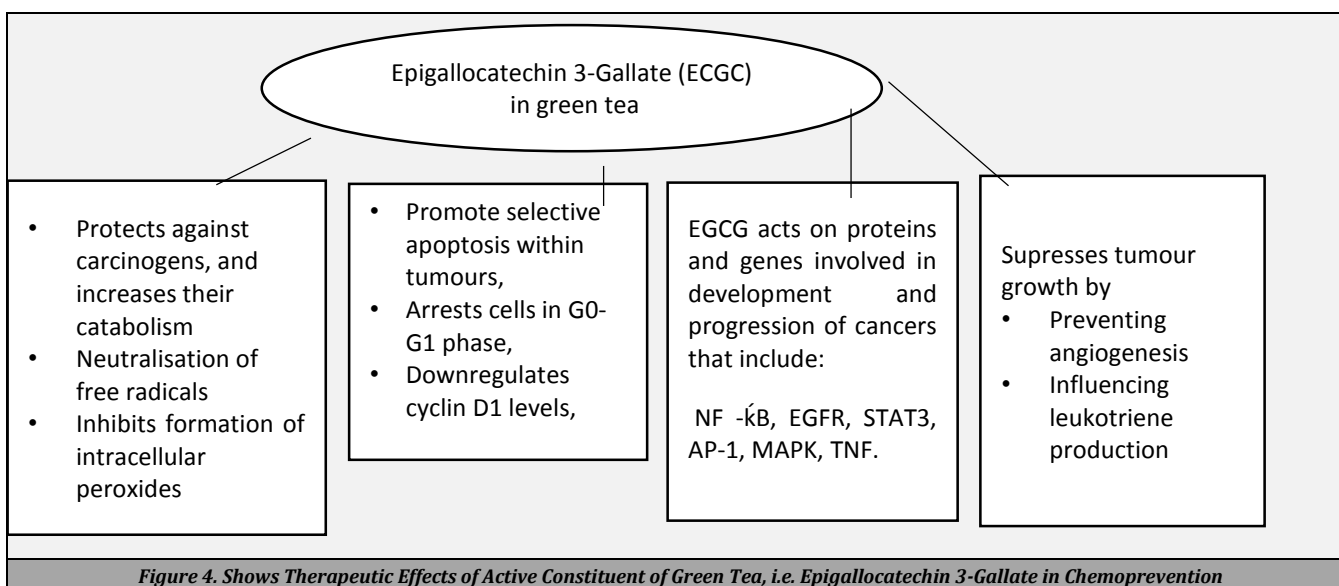


Figure 4. Shows Therapeutic Effects of Active Constituent of Green Tea, i.e. Epigallocatechin 3-Gallate in Chemoprevention

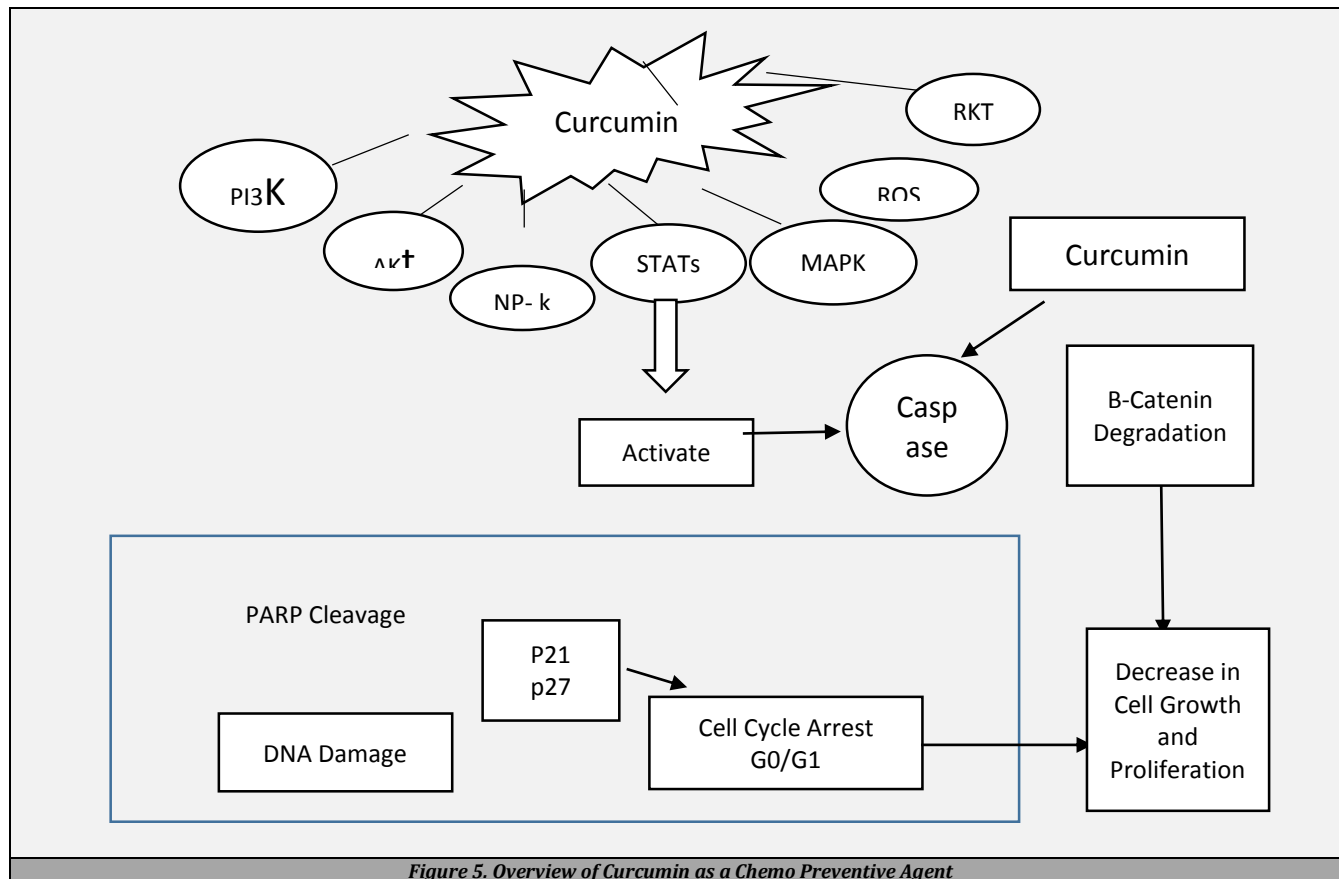


Figure 5. Overview of Curcumin as a Chemo Preventive Agent

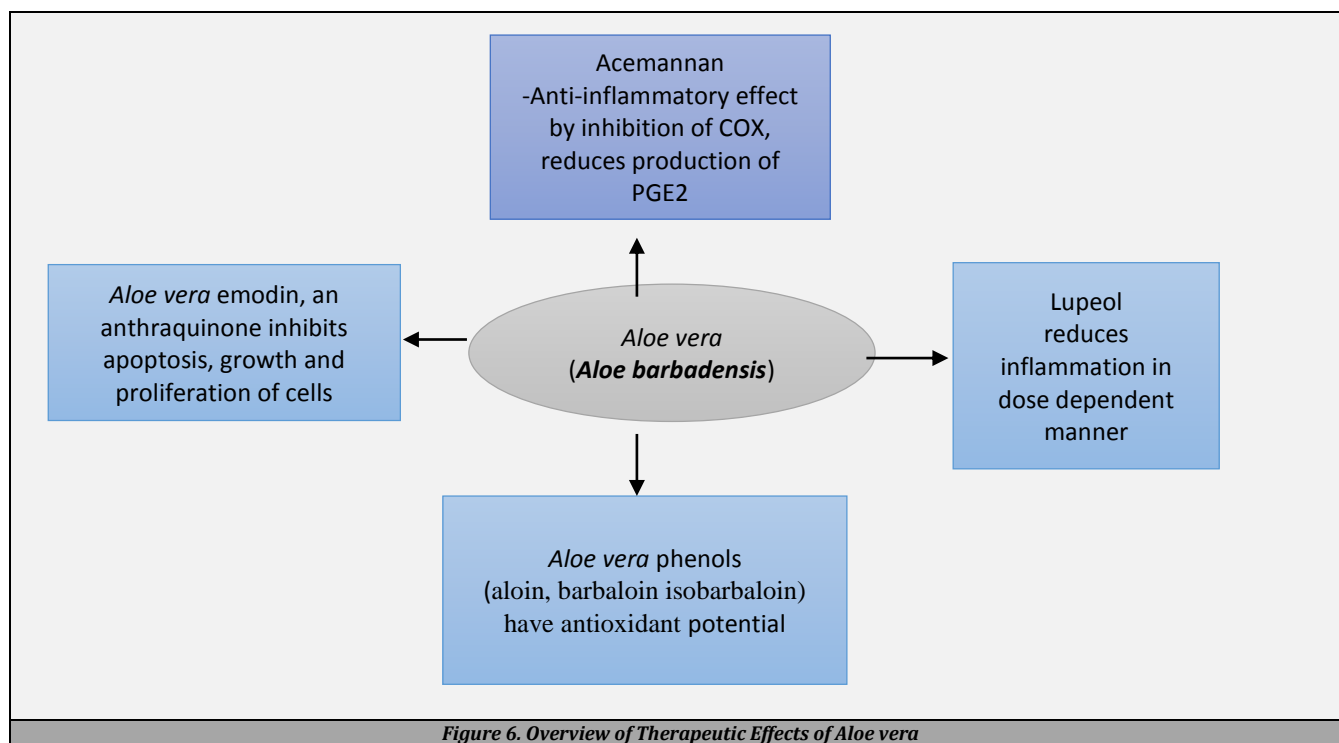


Figure 6. Overview of Therapeutic Effects of Aloe vera

Table 2 illustrates various phytochemical compounds present in natural herbs and their mechanism of action, and Table 3 summarizes preclinical and clinical data from literature pertaining to effectiveness of herbs and their extracts in the treatment of oral PMDs.

MISCELLANEOUS PLANT DERIVED PHYTOCHEMICALS

Black Tea

Black tea has high concentration of catechins and the flavins that delay tumourigenesis, induces apoptosis, scavenges ROS and downregulates cyclooxygenase 2 (COX2), NFkB, protein kinase B (Akt) and interferes with activity of carcinogen

metabolizing enzymes.³³ Debolina et al.³⁴ suggested that regular intake of black tea at least above four cups can reduce tobacco associated DNA damage.

Neem

Neem (*Azadirachta indica*), contains catechin which can inhibit the production of MMP, thereby reducing the invasion and migration of cancer cells. Its anti-inflammatory potential is explained by suppression of activation of NF- κ B which induces apoptosis of cancer cells.^{35,36}

Tulsi

Holy Basil, *Ocimum sanctum* Linn well known as tulsi in India, possess potent anticancer, anti-inflammatory and antioxidant properties. Tulsi due to its immunomodulating property can be used to relieve the symptoms of OLP and other precancerous lesions. Eugenol and linalool have been studied to enhance its antifungal activity against candida albicans and candida tropicalis, hence, could be used as an alternative treatment option for candidiasis.^{37,38} Srivastava et al.²¹ found local application of 1 gram of tulsi in glycerine 4 - 5 times / day for 15 mins resulted in reduction in burning sensation and increase of mouth opening in OSMF patients. In another comparative trial, Singh et al.³⁹ found it effective in reducing burning sensation, pain and white striae in OLP patients.

Ginger

Ginger (*Zingiber officinale* Roscoe) is well known condiments belonging to zingiberaceae family and consist of numerous active constituents. Gingerol, is a major component that decreases progression of dysplasia in oral PMDs by its unique antioxidant, anti-inflammatory, anti-angiogenesis and anti-cancer properties. It exerts anti-inflammatory effect by inhibition of arachidonic acid metabolism in both COX and LOX pathways, inhibits LPS induced activation of macrophages by decreasing proinflammatory cytokines and chemokines, decreases proliferation of T cells and release of IL-2 and IFN γ . Ginger extracts exerts dose dependent cytotoxicity on oral cancer cells by activation of caspase 3 mediated apoptosis, reduces expression of VEGF.³⁹

Peppermint

Peppermint (*Mentha piperita*) is a natural herb belonging to lamiaceae family and has stimulant, carminative properties. It has long history of safe use, both in medicinal preparations and as a flavouring agent. Mentha extract (ME) acts as a potential anticancer agent by induction of cellular apoptosis, up regulation of caspase 3 expression, causes G1 cell cycle arrest, up regulation of *bax* gene, and elevated expression of p53 and p21 induces proinflammatory cytokine response.^{4,40}

Chamomile

Chamomile, *Matricaria recutita*, L., syn. *Matricaria chamomilla* L is most ancient medicinal herb, member of Asteraceae family, dried flowers of chamomile contain terpenoids, flavanoids, 1 - 2 % volatile oils such as alpha-bisabolol, alpha-bisabolol oxides A & B, and matricin, that contribute to its

therapeutic benefits. Apigenin, chemical compound of chamomile is gaining interest due to its excellent antimutagenic and anticancer properties.³⁷ It regulates cell cycle at all stages; protects DNA from the genotoxic damage, slows down cell cycle progression, induces apoptosis and scavenges free radicals. It exhibits pro apoptotic activity by up regulation of p53 expression, increases expression of Bax and Bak apoptotic protein, caspase 3 and 9 expression, inhibits VEFF, MMP 9 and COX 2 expression thereby play a major role inhibition of tumour angiogenesis and metastasis. It has been found that 2.5 % chamomile infusion resulted in reduction of intensity of chemotherapy induced oral mucositis by decrease of pain score and fewer ulcerations than controls at day 22 after first cycle of chemotherapy.^{6,41}

Mushrooms

Mushrooms such as shitake, maitake, reishi and some agaricus species have emerged as a wonderful source of antioxidants. The active components of mushrooms are lentinan, krestin, hispolon, lectin, calcaelin, illudin S, psilocybin, Hericium polysaccharide A and B (HPA and HPB), ganoderic acid, schizophyllan, laccase, etc. Polysaccharides are most potent component of mushroom with anti-tumour and immunomodulating properties.^{4,6,42} They enhance tumour cell killing and inhibition of metastasis by increasing number of immunocompetent cells such as macrophages, cytotoxic T lymphocytes, NK cells and by recruitment of antibodies at the tumour site and prevents the malignant transformation of oral PMDs.⁴²

SAFETY OF PHYTOCHEMICALS

Plant based products, phytochemicals are generally considered safe; side effects have been reported to occur at larger doses or due to presence of certain impurities e.g. allergens, pollens etc.⁴⁰ Unlike allopathic medications, herbal products are not tested for the purity; therefore, physicians should be aware of various drug interactions and patients should take phytochemical supplementation only on physician's prescription.

CONCLUSIONS

Emerging antimicrobial resistance and side effects which, we are facing time to time with these allopathic medicines recapitulate the need of phytomedicine in the treatment of oral mucosal lesions. Many researchers have found absolute results i.e., clinical improvement in burning sensation, difficulty in swallowing and speech, and reduction in pain associated with the lesion with both topical and systemic formulations of herbs such as aloe vera, turmeric, lycopene, etc. More evidence-based trials should be carried out in future to establish phytochemicals as a reliable adjunctive therapy in the treatment of oral PMDs.

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