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*Review Article*

# Oral Oncoprevention by Phytochemicals - A Systematic Review Disclosing the Therapeutic Dilemma

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**Abstract**

The aim of this article is to emphasize and focus on the preclinical and clinical update on phytochemicals and their role in prevention of oral carcinogenesis. Accordingly, the literature search was made following database: Embase, Medline, Science Citation index, NIH public access, pubmed and Cochrane Database of systematic reviews. Several internet websites were also searched to access publications from major phytochemical research sites and relevant information was obtained with regards to each plant chemical. The authors also spotted different list servers through wignet.com, Stanford cancer research etc:

The data base search was made from the inception to 1988 and updated till 2013. A systematic method was obtained for literature search and data collection was critiqued. 60 articles were searched, among which there were only 6 systematic reviews on phytochemicals regarding oral carcinogenesis. Additional articles were obtained on phytochemicals and their mechanism of action in other cancers, which were regarded as background material. The studies done by various authors on each phytochemical has been briefly emphasized.

## Introduction

Oral carcinomas are one of the most prevalent carcinomas representing 10 most common causes of death.[1] It is said to be a major health problem in most of the developing countries attributing to the present life style. The age related incidence rates of oral cancer vary from 20 per 100,000 populations in India.[2] Also approximately 95% of oral squamous cell carcinomas occur in people older than 40 yrs, with diagnosis at an average age of 60yrs as per se.[3] It is assumed that gradually increasing proportion of elderly people in the world will result in 50% of increased new cancer cases over the next 20yrs.[4] There are wide etiological factors of oral cancer which can be internal or external with external factors being tobacco, chemicals, radiation and infectious organisms and the internal factors include inherited mutations, hormones and immune status causing cancers.[5] The understanding of molecular mechanisms of oral cancer should be given more attention rather.

Phytochemicals have been attracting scientists due to their property in altering cell cycle control, apoptosis evasion, angiogenesis and metastases. They have proved their efficacy in mono treatments or in association with other chemo preventive agents. Phytochemicals can be broadly classified into vitamins carotenoids and food polyphenols phenols like flavonoids, phylotaxeins, sulfur rich compounds and phenolic acid indoles.[6] Phytochemicals are new alternatives and upcoming stratagem with reduced toxic effects. These agents can be topical and systemic although many of them have been contributed for the studies of skin and mammary carcinogenesis, only few studies have been conducted in prevention of oral carcinogenesis. Early diagnosis and prompt preventive strategies should therefore be contributed to improve the quality of life of patient. Despite the abundant literature on molecular mechanisms of phytochemicals very few of them have been put down in clinical trials. The present article is an attempt to focus on the systematic studies taking the data of preclinical and clinical trials employing phytochemicals and compiling them with few novel agents which update the review of literature.

### *Phytochemicals and their various mechanisms of actions*

Practically saying fruits and vegetables can be consumed easily, but the significance of phytochemicals and their beneficial effects in diet should be elaborated to the community. Several non nutritional compounds are ought to prevent cancer, and these heterogeneous group of molecules are named to be Phytochemicals.[7] It has been estimated that there are more than 5000 phytochemicals in the world out of which only 150 to 200 plants are consumed by humans.[8,9]

They can be basically categorized into vitamins and food polyphenols.[6] Moreover, they are pertinent in synergizing cytotoxic drugs by increasing their efficacy and reducing toxic effects on normal cells.[7] Therefore,

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these Phytochemicals can be combined with chemo preventive agents with superior clinical applications in preventing oral cancer. Chemoprevention is a valuable and promising strategy in preventing the incidence of oral carcinogenesis by using specific natural and synthetic agents. The term "Chemoprevention" was coined by Michael B.Sporn in 1976.[10] They can be broadly classified into three categories namely blocking agents, suppressing agents and agents that reduce venerability to carcinogenesis.[11] Nevertheless these agents act through various mechanisms like antioxidant properties, anti lipid peroxidative activity, anti proliferative activity, free radical scavenging properties, anti tumor initiative property etc: Medicinal plants rich in bioactive phytochemicals and antioxidants have been in rise over the past few years as prospective chemo preventive agents. The dietary compounds and bioactive constituents like spirulina, curcumin, beta-carotene, dietary flavonoids, chalcone, green tea, garlic, black raspberries, piperine and dietary turmeric etc: have shown their chemo preventive potential in oral carcinogenesis.[5] These studies provide a basis for clinical evaluation of new phytochemicals for prevention of cancer stem cells. They may also facilitate us to discover new preventive strategies for cancer management and aid in improvising patients continued existence. Hereby we summarize some of the known agents with update of review of literature.

### *Preclinical and clinical data of phytochemicals for prevention of oral carcinogenesis*

The transformation of normal cell to cancer cell occurs through three distinct phases namely: Initiation, Promotion and Progression. Initiation of cancer is due to exposure of normal cells to carcinogenic and mutagenic agents. These initiated cells are irreversibly altered hence are prone to greater risk of neoplastic transformation. However initiation alone is not sufficient for tumor formation.[12] Likewise in promotion phase tumor promoters convert the initiated cells into neoplastic cells. Progression involves a stepwise evolution of neoplastic cells into higher degree of malignancy.[13-15] In general chemoprevention consists the use of phytochemicals for reversal and prevention of premalignant cells into malignant geno/phenotype.

Many preclinical studies have been done on various phytochemical agents

Garlic is a dietary phytochemical. The main components of fresh garlic are carbohydrates protein fiber and water. It contains essential amino acids, vitamins and minerals.[16] Meng etal conducted studies on DMBA induced buccal pouch carcinogenesis in Hamsters using different fractions of garlic extracts were taken with various measurements from (AtoE) where Garlic C showed immense reduction of tumor without effect on blood chemistry and body weight attributing to its antiproliferative activity.[17] Dorant etal carried out extensive studies on garlic extracts in humans and concluded that it has excellent anti carcinogenic property.[18] Desai etal and Kandil et al concluded that the natural killer cell activity can be attained by eating garlic (0.5g $kg^{-1}$daily) or taking garlic capsules of dose 1800mg daily for 3 weeks has been proved in several epidemiological studies.[19,20]

Flavonoids are group of more than 4000 polyphenolic compounds that occur naturally in foods of plant origin.[21] They are seen practically in all dietary plants, like fruits and vegetables (Figure 1). Flavonoids have been confirmed to inhibit carcinogenesis in vitro and considerable evidence indicates that they can also do so in vivo. Makita etal performed studies with dietary flavonoids namely chalcone, 2-hydroxychalcone and quercetin which showed chemo preventive action in 4-nitroquinolone 1- Oxide induced carcinoma formation in tongue.[22] Similiarly Hayashi et al used modified citrus pectin and quercetin chalcone on colon-25 tumors implanted in balb-c mice which resulted in decreased tumor size.[23] Shi et al, Fukai et al, Sakagami et al, Elattar et al conducted in vitro studies on cell systems like HSC-2, HSG, SCC-25 using flavonoids like Flavanones, isoflavans, EGC, chalcones, EGCG, curcumin, genistein, ECG, quercetin, cisplatin in oral cancer confirming its antiproliferative activity.[24-28] Recently it was proved that flavonoids are also effective in inhibiting signal transduction enzymes like protein tyrosine kinase(PTK), protein kinase C (PKC) and phosphoinositide 3-kinases which are involved in the regulation of cell proliferation.[29,30]

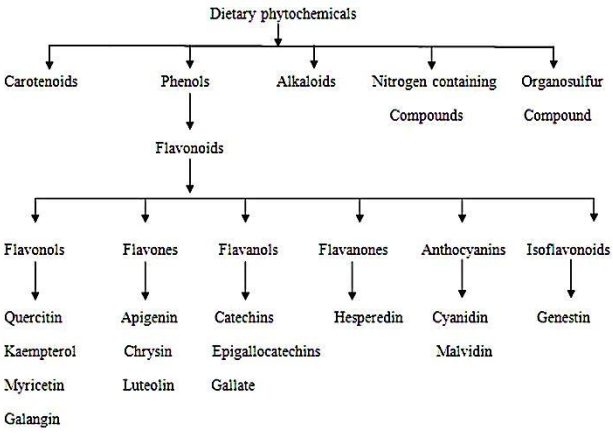


**Figure 1.** Flow chart representing Dietary flavonoids in oral cancer prevention.

Despite the presence of 40 or more naturally occurring carotenoids in the human diet, only a handful of carotenoids are commonly detected in human plasma and tissues.[31] The most common dietary carotenoids ,their isomers and various metabolites are carotenoids with 3 hydrocarbon carotenoids (carotenes): alpha-carotene, beta-carotene and lycopene, and three oxycarotenoids (xanthophylls): lutein, zeaxanthin and cryptoxanthin.[32] Astaxanthin has exhibited potent antioxidant, immunomodulating and enzyme-inducing properties, all of which suggest a potential role for this carotenoid in preventing cancer. Tanaka et al carried out studies on

rats with oral carcinogenesis attributing to the anti carcinogenic properties of xanthophylls. Moreover, its unique structural properties and its lack of pro-oxidant activity makes it a prime candidate for further investigation in this area of human health.[33] Dore J.E carried out in vitro studies in humans and concluded that more research is needed on the absorption and metabolism of these promising anticancer agents and on its interaction with other carotenoids and vitamins in the human system.[34]

Limonoids are naturally occurring compounds found in citrus fruit. They are described as modified triterpenes having 4,4,8 trimethyl1-17 furanyl steroid skeleton. The characteristic uses of limonoids include insecticidal, growth regulation, insect anti feedant and medicinal effects to plants and animals such as antiviral, antibacterial and antifungal properties.[35] The greatest attention is now towards anti carcinogenic and anti mutagenic effects of them. Hasegawa etal used topical application of limonoids which were found to inhibit both initiation and promotion phases of carcinogenesis in skin of mice.[36] In addition these compounds have shown anti neoplastic activity against chemically induced cancers of colon, stomach, and buccal pouch cancers. Studies done by Miller et al, Jacobi etal ,Ozaki et al has revealed that topical application of limonin glucoside showed 60% reduction in tumor burden.

Schwartz etal conducted preliminary studies on Spirulina fusiformis which is known to inhibit buccal cancers and prevent tumor development in hamsters.[37] Mathew et al conducted studies on spirulina in reversing oral leukoplakia in pan and tobacco chewers in kerala. They were administered spirulina fusiformis in the form of lyophilized powder (1gm/day).[38] The excellent properties of spirulina with its rich constituents like carotenoids, beta-carotene and crude protein have shown promising results in chemo preventive mechanisms. Bhavana et al compared spirulina fusiformis with pentoxyfilline in 40 patients with 20 in each group. Parameters like burning sensation, mouth opening, and tongue protrusion were taken and the results were significant in both groups although decreased burning sensation was more with spirulina.[39]

Azadirachta indica commonly known as neem. The abundant pharmacological actions of neem preclude antihelminthic, antibacterial, antifungal, anti hyperglycemic, anti-inflammatory, antiviral, anti tumor properties.[40] Nagini et al has shown the chemo preventive potential of neem and turmeric attributing to its anti lipido peroxidative and antioxidant properties in preventing oral carcinogenesis similarly, subapriya et al suggested the chemo preventive potential of neem leaf extracts in DMBA induced oral carcinogenesis due to their modulating effects on xenobiotics metabolizing enzymes during carcinogenesis.[5,41] Manoharan et al recommended that the antioxidant property of neem leaf can be used as chemopreventive agent in cancer.[41] Manikandan et al has shown the chemo preventive potential of Azadirachta indica leaf in DMBA induced oral carcinogenesis with its additive antilipidoperoxidative potential.[42] Hashmat et al elaborated the antioxidant and antitumor property of neem which could aid in prevention of cancer.[5]

Manoharan et al demonstrated the chemo preventive potential of curcumin and piperine in DMBA induced buccal pouch carcinogenesis with its anti lipido peroxidative and antioxidant activity.[43] Garg et al reported the chemo preventive potential of dietary turmeric with its property of augmenting apoptosis of initiated cells and inhibiting cell proliferation.[44] Tanaka et al resoluted the potential use of curcumin, beta-carotene and hesperdin with anti tumor initiating and promoting properties with its pronounced effects in oral cancer.[45]

Green tea is derived from Camellia sinensis and represents the most consumed beverages in the world, next to water. It contains poly phenols, glycosides, leuco-anthocyanins, and phenol acid with the polyphenols constituting 36% of the fresh green tea leaf dry weight.[46] Wide-ranging studies have been done on tea phenols. Srinivas et al conducted studies on 4-nitroquinoline 1-oxide induced oral cancer using green tea phenols with its stimulated detoxification mechanism. Chandra mohan et al used green and black tea phenols with its enhanced antioxidant effect in experimental oral carcinogenesis. Letchoumy etal used black tea phenols with its marked effects of stimulated detoxification cascade and its ability to prevent DNA damage.[47] Khafif et al used green tea extracts in reversing leukoplakia with anti proliferative efficacy.[48] Hsu et al, chen et al, kato etal concluded that green tea phenols reduce the invasion and migration of human oral cancer cells.[5] Lee et al delivered poly phenolic tea compounds like catechins and theoflavins by asking the subjects to have green and black tea resulting with slow release of these phenols which rally round in cancer prevention.[46]

Ferulic acid is hydroxycinnamic acid, found in the seeds of coffee, apple, peanut and orange. This phenolic phyto chemical is also found in rice, wheat, oats and pineapple.[49] It possesses multiple pharmacological and biological effects including anti-inflammatory, hepato protective, anticancer and antioxidant properties.[50] Balakrishnan et al carried out studies on 7,12-dimethyl benz[a]anthracene induced hamster buccal pouch carcinogenesis using ferulic acid with its efficacy of scavenging free radicals and antioxidant property. [51] Invitro studies has been done by Gupta S et al, Toda S et al, they concluded that scavenging effect of ferulic acid has been reported to be similar to that of superoxide dismutase which can prevent oral cancer.[5]

The new preventive strategies for cancer prevention also have been studied recently like black raspberries which are alleged to be given in diet in lyophilized form as it has effective in preventing esophageal and colon cancers. Casto et al studied the berry extracts and their ability to inhibit replication of human tumor cells.[52] Piperine has immensely resulted in extending its chemo preventive effect by modulating lipid peroxidation and augmenting

the antioxidant defense in accordance with studies done by selvendiran et al.[53] Reservatrol in concentration to that present in red wines has been effective inhibitor of oral squamous cell carcinoma cell growth and proliferation attributing to its anti tumor effect as studies done by Elattar et al.[54]

Procatechuic acid and costunolid are phenolic compounds which is a common component of human diet, such as brown rice (Oryza sativa). It has anti oxidant property and hence scavenges free radicals. Suzuki etal recommended the action of Procatechuic acid which prevents the progression of 4-nitroquinoline-oxide induced carcinogenesis.[55]

The other reported chemo preventive agents of oral carcinogenesis include ocimum sanctum which has excellent antitumor initiative property as described by karthikeyan et al.[5] S-allyl cysteine as described by Balasenthil etal showed protective effects in DMBA induced hamster buccal pouch carcinogenesis attributing to the elevation of hepatic glutathione and glutathione dependent enzymes which might play a key role in cancer prevention.[56] Mohan KV et al used bovine milk Lactoferin (BLF) in inhibiting DMBA induced genotoxicity.[57] (Table 1)

**Table 1.** Reported onco preventive agents in Oral carcinogenesis

| Phyto chemical | Mechanism of action | Preclinical studies | Clinical studies |
|---|---|---|---|
| Garlic | Anti proliferative<br>Anti carcinogenic<br>Natural killer cell activity | Meng et al[17] | Dorant et al[18]<br>Desai et al[19]<br>Kandil et al[20] |
| Flavonoids<br>(Quercetin,Chalcone) | Anti proliferative | Hayashi et al[23] | Shie et al[24]<br>Fukai et al[25]<br>Sakagani et al[26]<br>Elattar et al [27] |
| Xanthophylls<br>( Lutein, Zeaxanthin, Cryptoxanthin, Astaxanthin) | Anti oxidant<br>Immuno modulator | Tanaka et al[33] | Dore J.E [34] |
| Limonoids | Anti carcinogenic<br>Anti mutagenic | Hasegawa et al[36] | Miller et al [36]<br>Jacob et al [36]<br>Ozaki et al [36] |
| Spirulina fusiformis | Suppressed cell proliferation | Schwartz et al[37] | Mathew et al[38]<br>Bhavana et al[39] |
| Azadirachta indica | Ant lipidoperoxidative<br>Antioxidant<br>Antitumor activity | Subapriya et al[40]<br>Nagini et al[41]<br>Manikandan et al[42] | Hashmat et al[40]<br>Manoharan et al[43] |
| Curcumin<br>Piperine | Antilipidoproliferative<br>Antioxidant | Garg et al [44] | Tanaka et al[45] |
| Green tea | Antioxidant<br>Antilipidoproliferative<br>Stimulates detoxification cascade | Srinivas et al[46]<br>Lee et al[46] | Chandramohan et al[47]<br>Letchoumy et al[47]<br>Khafif et al[48]<br>Hsu et al[5]<br>Chen et al[47]<br>Kato et al[46] |
| Ferulic acid | Anticancer activity<br>Antioxidant | Zhao et al[49]<br>Balakrishnan et al[51] | Gupta et al[50]<br>Toda et al [5] |
| Black Raspberries | Inhibits replication of human tumor cells | | Casto et al[52] |
| Piperine | Modulates<br>lipid peroxidation and antioxidant defense | - | Selvendiran et al[53] |
| Reservatrol | Antitumor property | - | Elatter et al [54] |
| Oryza Sativa<br>(Procatechuic acid &Costunolid) | Antioxidant | - | Suzuki et al[55] |
| Ocimum Sanctum | Anti tumor property | - | Karthikeyan et al[40] |
| S-allyl Cysteine | Elevation of hepatic glutathione and glutathione dependent enzymes | Balasenthil et al[56] | - |
| Bovine milk Lactoferrin | Inhibits DMBA induced genotoxicity inturn prevents Oral Cancer | Mohan KV et al[57] | - |

## *Recent trends*

### *Nano Chemoprevention*

An advent in the field of research endowed the experts to take an innovative step in prevention of cancer with an avenue of introducing nanotechnology with chemoprevention and termed it as nano chemoprevention. In Toto it is an emerging branch which has been flourished extensively in the field of chemo preventive research, as it is inexpensive, tolerable and pertinent approach for cancer control and management.

The tunability and surface function of nano particulate system encapsulates single or multiple entities of chemo preventive drugs which has poor solubility, low bioavailability and which are undesirable solvents.[58] The nano carriers which are biocompatible and biodegradable allow the preparation of water soluble medications either polymers like Poly lactic acid (PLA), Poly (DL-lactide - co-glycolide acid) (PLGA), Starch and chitosan etc: which have been utilized for the delivery of various drugs.[59]

Initially natural agents like EGCG (Epigallocatechin-3-gallate), curcumin, resveratrol and combinations of curcumin and resveratrol, EGCG tannic acid and curcumin with nano particles like PLGA – DMAB, PEG, liposomes and gelatin have been tried in target organs of prostate cancers, pancreatic cancers, breast cancers and head and neck carcinomas.[58] The bioactive phyto chemicals like EGCG has immensely resulted in enhanced bioavailability and improved its therapeutic efficacy with nanoparticles.[60] Curcumin employed with nano particles showed reduced inflammatory induction and suppressed HNSCC growth in vivo and in vitro.

Similarly nano particles of resveratrol have enhanced its preventive and therapeutic effect.[2] Although several nano particles have been employed, chitosan has been a suitable nano material for oral route. The chemo preventive potential of narigenin loaded nano particles was described in DMBA induced experimental oral carcinogenesis of Syrian hamsters. Oral administration of narignen has prevented the tumor formation also reduced the degree of histological lesions.[12] Despite of advancements in the routes of drug administration, oral drug delivery is inevitable and preferred route. Although various routes of oral drug delivery have been described trans mucosal oral route is best formulated to treat both local and systemic conditions.

Regardless of many drugs formulated for oral administration nano chemoprevention in oral cancer has been tried out in dietary phytochemicals like carotenoids and flavonoids. Wang et al carried out liposome encapsulated curcumin releases for suppressing growth of head and neck squamous cell carcinoma.[61] Siddiqui et al used green tea polyphenol epigallocatechin-3-gallate by employing nanoparticles in head and neck cancers.[58] Similiarly Wu X et al used topical muco adhesive fenretinide patches for site-specific chemoprevention of oral cancer with nano particles of propylene glycol.[62] Topical application of anthocyanins like black raspberry gel (10%) is said to release flavonoids not only in saliva and oral tissues but also in plasma. Ling et al, Ugalde et al and Mallery et al has carried out extensive research on black raspberry gel and proved its efficacy in oral premalignant and malignant lesions with nano particles.[63] Lu X et al, Naraynan et al enlightened the use of resveratrol loaded polymeric micelles and its chemo preventive approach in oral cancer.[64]

The future prospectus of nano chemoprevention should be overwhelmed and explored further on other phytochemicals for its potential use in the chemoprevention of oral cancer. This advancement will facilitate us to achieve the physiological concentrations which may be unattainable when administered as a part of diet. The ultimate goal is to surpass and explore the phytochemicals which may be unachievable in the diet. Hence further preclinical, clinical chemo preventive studies on phytochemicals will help us to achieve a fruitful way for cancer prevention in human population. Keeping current studies in mind the encapsulated phytochemical can be administered once daily or once per week which may be effective in target organs.[54]

## Conclusion

At the end of this preventive strategy and extensive research engine, we summarize that research on phytochemicals is still fragmentary and uncertain, yet preclinical and clinical trials should be more promising and progressive.

The present article was anticipated and summarized on different phytochemicals taking into account the preclinical and clinical data, and the pleiotropic action of plant chemicals, which direct themselves to multiple intracellular targets affecting different cell signaling pathways and altering the cancer cells with limited toxicity.

Finally the dietary habits are at most important as we consume hundreds of bioactive phytochemicals in constituents of fruits and vegetables, the health promoting activities and specific biological activitiy of these phytochemicals should be realistic and emphasized. Significant emerging technologies like nano chemoprevention should be materialized with compilation of new phytochemicals that aid in prevention of oral cancer. Hence consumption of whole food should be given importance, rather than the consumption of mono plant chemical.

Furthermore the additive and synergic activities of phytochemicals can be combined with chemotherapy and radiotherapy, limiting the doses and trimming down the toxicity. The appraisal and broader work in phytochemicals needs to be executed with reference to oral cancer.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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