Review Article

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CHEMOPREVENTION: A REVIEW

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ABSTRACT:

Oral cancer is one of the most common cancers worldwide which is associated with less than 50% of 5 year survival rate. Current treatment modalities available for cancer are surgery, radiotherapy and chemotherapy. These curative therapies affect the quality of life of a patient by affecting speech, swallowing, breathing and also the appearance. Hence preventive modality like chemoprevention can be bought into broader light. Chemoprevention is done with use of natural, synthetic or biologic chemical substances which can prevent, suppress or reverse the process of carcinogenesis. Various chemopreventive agents have been evaluated such as vitamin A, vitamin E, beta carotene and many other dietary products. Newer agents such as cyclooxygenase-2 (COX-2) inhibitors, P^{53} gene have recently been used and proven effective. This article reviews these chemopreventive agents and their mechanism of action along with aspects of chemoprevention.

Key words: oral cancer, chemoprevention, vitamin A & E, COX-2 inhibitors, P^{53}.

INTRODUCTION:

Cancer is a growing health problem worldwide, with a steady rise in life expectancy. It is a multistage, multi-mechanism carcinogenesis process that involves mutagenic, cell death and epigenetic mechanisms, during the three distinguishable stages: initiation, promotion, and progression. As reducing the initiation phase to a zero level is impossible, the most effective intervention would be at the promotion phase to eliminate premalignant cells.[1]

Cancer chemoprevention was first defined in 1976 by Sporn.[2] as a pharmacologic modulation of regulatory pathways, over the effective use of drugs and micronutrients which block the mutagenic damage to DNA, and helps in prevention of cancer.[3]

It is said “prevention is better than cure” which holds true for oral cancer as the therapeutic measures may cause some severe complications; so the chemoprevention will be beneficial in management of oral cancer.

MECHANISM OF ACTION

Mechanisms of cancer chemoprevention is divided into two types: antimutagic and antiproliferative. The mechanism includes induction of cell cycle arrest and apoptosis or inhibition of signal transduction pathways mainly the mitogen-activated protein kinases (MAPK), glycogen synthase kinase (GSK),

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phosphoinositide 3-kinase (PI3K), protein kinases C (PKC) leading abnormal cyclooxygenase-2 (COX-2), and nuclear factor kappa-light chain-enhancer of activated B cells (NF-kB).[1]

The rationale of chemoprevention lies in the concept of field carcinogenesis which was first described in the early 1953 by Slaughter et al. They proposed that carcinogenic exposure of the oral mucosa is predisposing factor in the development of neoplasm at multiple sites in oral cavity.[2]

Multifocal areas of cancer develop from field carcinogenesis and lateral (intraepithelial) spread of genetically related pre invasive clones.[4]

A recent study by Sharma *et al*., (2001) shows that several agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), retinoids and SERMS have antiangiogenic activity.[5]

IV.CLASSIFICATION OF CHEMOPREVENTIVE AGENTS

Pharmacological and chemical structural classification of chemopreventive agents.[6]

1.Antimutagens/carcinogen blocking agents

Phase II metabolic enzyme inducers

N-acetyl-L-cysteine

Polyphenols

Curcumin, dehydroepiandrosterone (DHEA)

2. Antiproliferatives

Retinoids/Carotenoids: β-carotene, 13-cis-retinoic acid, vitamin A.

Glucose-6-phosphate dehydrogenase inhibitors

Aspirin

3. Antioxidants

COMMONLY TRIED CHEMOPREVENTIVE AGENTS IN ORAL CANCER

- Vitamin A and other retinoids
- Beta-carotene
- Vitamin E
- Dietary agents
- Newer agents

VITAMIN A AND OTHER RETINOIDS

Vitamin A (retinol) is effective in preventing or suppressing various forms of cancer. 13'-cis- retinoic acid induces protective effect in the development of secondary cancer in patients with epidermoid cancer of buccal cavity and the pharynx. The protective effects of retinoids such as retinol, retinal, retinoic acid, and retinal esters on AFB carcinogenicity are due to inhibition of AFB_1-DNA adduct formation resulting in less epoxide formation by affecting CYP450 systems.[7]

Vitamin A induces the activity of glutathione S-transferase and enhances the detoxification of AFB_1-epoxide. Retinoids have been used as chemopreventive agents in potentially malignant disorders like leukoplakia which usually develops in an invasive squamous cell carcinoma.

Retinoids also show transactivation activity, suppressing activity of other transcription factors, such as AP-1, which are critical mediators of transrepression activity. Retinoid transrepression activity

is linked to retinoid antiproliferative activity and also transactivation activity is linked to induction of differentiation.

BETA CAROTENE

In the late 1970s beta-carotene was discovered as a possible anticancer agent. Beta-carotene is known as a carotenoid, which apparentely acts as an antioxidant and has cancer protective ability.

It is one of the most efficient substances that quenches the excitation energy of singlet oxygen and traps organic free radicals.[8] The Beta-Carotene and Retinol Efficacy Trial (CARET) is one of several recent trials conducted to assess the chemopreventive efficacy and safety of beta carotene and related agents.[9] Beta carotene has been proven to be more effective in initiation phase than in promotional phase. It has an inhibitory action on lipid peroxidation in chemically induced neoplastic transformation.

Advantage of carotenoids is that they are nontoxic relatively with most common complication being yellow discoloration of skin.

VITAMIN E

The term vitamin E describes a family of light antioxidants. Alpha-tocopherol is the only form of vitamin E which is actively maintained in human body .Vitamin E (alpha-tocopherol) is a potent antioxidant; neutralizes free oxygen radicals and inhibits formation of carcinogenic nitrosamine.

Vitamin E and menadione (a water-soluble synthetic vitamin K) prevent AFB_1 -induced mutagenesis in the Ames bacterial system.[7]

Vitamin E inhibits cancer development via various mechanisms such as down regulation of p53, stimulation of wild type of p53, blockage of transforming GF-α causing anti-angiogenic effect, activation of heat shock proteins.

DIETARY AGENTS

Routine consumption of fruits and vegetables is strongly associated with reduced risk for many of the cancers. The strongest evidence pertains to reduced risk for cancers of the mouth and pharynx, esophagus, stomach and lungs.[10]

The NCI has identified about 35 plant-based foods that possess cancer-preventive properties such as garlic, soybeans, turmeric, tomatoes and cruciferous vegetables (for example, broccoli, cauliflower and Brussels sprouts).[11]

The recent search for anticarcinogenic substances in fruits and vegetables includes identification of anti inflammatory compounds which influence the generation of prostaglandins.[10]

LYCOPENE

Lycopene is a phytochemical, synthesized by plants and microorganisms. It is not synthesized by

animals.It is an acyclic isomer of beta-carotene.[12] Lycopene, gives the ripe tomato its bright red color and is a very effective natural antioxidant, quencher of free radicals and DNA protector.[13] Lycopene's bioprotective activity enables it to inactivate free radicals.[12] It protects DNA from the damage induced by 1-methyl-3-nitro-1-nitrosoguanideand H_2O_2.[13] Lycopene suppresses oral carcinogenesis induced by DMBA. Though it is known as an antioxidant, in bioprotective activity both oxidative and non oxidative mechanisms are involved.

CURCUMIN

Curcumin a yellow pigment present in the rhizome of turmeric (*Curcuma longa* L). It is species is one of the most extensively investigated phytochemicals, and has chemopreventive potential. Topical application of curcumin inhibits the catalytic activity of epidermalextracellular signal regulated kinase(Erk) ½ which has an ability to inactivate Nf-kB and COX2.[11] Curcumin binds directly to and activates VDR (the nuclear vitamin D receptor), inducing the VDR target genes CYP3A4, CYP24, p21 and TRPV6.[14]

CAPSAICIN

Capsaicin a pungent component of hot chilli pepper (*Capsicum annuum* L.) is suspected as a carcinogen or a co-carcinogen because of its irritant properties, but other studies indicate that the compound has chemopreventive and chemoprotective effects.[11] Some investigators suspect that capsaicin is a carcinogen or tumor promoter, others have reported that it has chemopreventive effects. Interestingly, capsaicin has been found to preferentially repress the growth of some transformed human cells.[15] Capsaicin inhibits constitutive and induces activation of NF-kB in human malignant melanoma cells and causes inhibition of melanoma cell proliferation.[11]

RESVERATROL

Resveratrol (3,4',5-trihydroxy-*trans*stilbene) is a phytoalexin present in grapes. It is an antioxidant ingredient of red wine. Resveratrol causes dose-dependent inhibition of recombinant human COX-2 enzyme activity, inhibits the redistribution of PKC activity induced by PMA, inhibits PMA-mediated induction of COX-2 transcription, suppresses PMA-mediated induction of COX-2 promoter activity, suppresses PMA-mediated increases in the production of PGE2 and suppresses PKC-a and ERK1-mediated induction of COX-2 promoter activity.[16]

Resveratrol suppresses TNF-α-induced phosphorylation and nuclear translocation of p65, and NF-κB-dependent reporter-gene transcription in myeloid leukaemia cells.[11]

GENISTEIN

Genistein a soy-derived isoflavone contributes to the cancer preventive activity of soya. PMA or TNF-α-induced NF-κB DNA binding and NF-κB-derived

COX2 promoter activity, were inhibited in human alveolar epithelial carcinoma cells by genistein treatment.[17] Genistein at the apoptogenic concentration inhibites the H2O2 or TNF-α-induced activation of NF-κB by reducing phosphorylation of IκBα and the nuclear translocation of NF-Kb.[11]

EPIGALLOCATECHIN 3 GALLATE (EGCG)

EGCG is chemopreventive polyphenol found in green tea. It is an antioxidant. Green tea contains higher amounts of catechin derivatives, like epigallocatechin (EGC), epicatechin (EC), and their gallates (ECG and EGCG). Some of the catechins are converted to theaflavins (TF) and thearubigins (TR) by enzymatic oxidation and coupling reactions during the production of black tea. The action of EGCG in the presence of EC, and that of whole green tea infusion shows a more efficient cancer preventive activity than EGCG alone. Green tea consumption enhances the antitumor activity of sulindac and tamoxifen.[18]

NEWER AGENTS

Potential new targets for chemoprevention are: p53 gene, H-ras gene, COX-2 inhibitors, epidermal growth factor receptor (EGFR) inhibitors, NF-KB.[14] Enhanced synthesis of COX-2 derived prostanoids influence several processes which are linked to carcinogenesis, including apoptosis, angiogenesis, cell proliferation, and invasiveness. Combined targeting of EGFR and COX-2 shows great promise for reducing the burden of cancer in many sites.[19]

The current generation of epigenetic drugs targets to inhibit the activity and expression of DNMTs and HDACs. Among the DNMT inhibitors, nucleic acid inhibitors like 5-azacytidine is the most widely studied epigenetic drug. Reevaluation of hypomethylating drugs *in vitro* and *in vivo*, approved by Food and Drug Administration are helping patients live longer with fewer side effects.[1]

CONCLUSION:

Since cancer is the sixth largest group of malignancy and spreads extensively hence it is best to destroy it before it spreads. Chemoprevention helps in achieving an aim of preventing, arresting or reversing the process before it gets converted into an extensive stage. Further studies in future based on understanding of mechanism of carcinogenesis will help in reducing the morbidity and mortality rates of oral cancer.

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