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Viral origin of oral cancer: its remediation by phytochemicals

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A B S T R A C T

Oral cancer, a type of head and neck cancer may be a result of human papillomavirus infection, particularly HPV16. Survival rate of oral cancer is poor and the death rate is quite high. An early detection could yield a better outcome, but normally these are diagnosed late due to lack of awareness. The existing treatment modalities are not free from side effects. Therefore adoption of natural means may be a rescue to the problem. Many phytochemicals are known to show their effects on oral cancer, among these many are known modulators of HPVs. Phytochemicals target a chain of cell signalling pathways that lead to carcinogenicity, but they show little toxicity. Phytochemicals in combination with other prophylactic measures may facilitate to develop effective preventive strategies. Therefore a good diet rich in fruits, vegetables and herbs may confer a protective role against cancer.

Introduction

Oral cancer is one of the leading forms of malignancies and the burden is expected to increase in coming years. The most predominant form of oral cancer is oral squamous cell carcinoma (Jordan and Daley, 1997). Incidences of oral cancer are found in Melanesia, South-Central Asia, Central and Eastern Europe, Africa, Central America, Eastern Asia, Taiwan and so on (Song *et al.*, 2014). Occurrence of oral cancer related to HPV infections are on the rise in the United States and in some countries in Europe. It is a potent problem in the Indian subcontinent as well (Coelho, 2012). The five year survival rate for this form of cancer is low thereby worsening prognosis (Jafari *et al.*, 2013). Incidences of oral cancer among other causative factors are dependent on geographical location, age, sex and habit (Coelho, 2012).

Viral infection is listed in the etiology of this cancer. Viruses sustain their existence by inserting their nucleotides into the host

system and this may be responsible for the development of carcinogenesis, though the disease may appear later. But, all viruses do not cause cancer; only some coined as onco-viruses are responsible for the malignant transformation. Human Papilloma Viruses (HPV), Epstein–Barr virus (EBV), Human T-lymphotropic virus (HTLV), Kaposi's sarcoma-associated herpes virus (HHV-8), Merkel cell polyomavirus, Hepatitis B virus (HBV) and Hepatitis C virus (HCV) are notable among these (Schiller and Lowy, 2010).

Among all the viruses, HPV is the notorious DNA virus, persistent infection of which causes a number of human cancers like cervical, oral, anal, vulval, vaginal, penile, laryngeal, oro-pharyngeal (middle part of throat, pallet, tongue, tonsil) and others (Giuliano *et al.,* 2008). Apart from causing cancer, HPV can cause serious health problems like oral lesions, plane warts, genital warts and is responsible for epidermodysplasia verruciformis (EV), which is a rare autosomal recessive disorder (Lipke, 2006; Münger *et al.,* 2004). HPV, which is mostly transmitted through sexual means, often gets cleared on its own. Nearly 200 types of HPVs have been identified and characterized and the list is gradually on the rise. They cause infections in skin keratinocytes and mucous membranes. All the 200 types of HPVs discovered so far, all are not potentially at high risk. HPV types 16, 18, 13, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82 and so on which are categorized as high risk types are known to cause cancers (Mannarini*et al.,* 2009). HPV16 and 18 are highly implicated in cervical carcinoma (Braaten *et al.,* 2008). A morphological similarity between genital and oropharyngeal epithelial cells have been documented. Epithelial cells are susceptible to HPV attack; therefore a probable link with oral cancer was established (Mannarini *et al.,* 2009). In addition to other causative factors like alcohol consumption, smoking, betel leaf and areca nut chewing etc, HPV16 contributes to the development of oral cancer. This is not only a disease of the elderly, even the younger generations are at risk.

A number of HPV strains are known to cause cancers of the genital organs. HPV is normally transmitted through skin-skin contact. Therefore it is interesting to know how HPV gets into the oral cavity. Adoption of certain forms of sexual practices like oral sex often contributes to the virus reaching the oral cavity and leading to carcinogenic transformation in the oropharyngeal region. Incidence of HPV infection is more among the youth who because of their fast lifestyle encounters sex at an early age and have multiple sex partners (Remschmidt *et al.,* 2014). It has been reported that HPV induced carcinogenesis is higher in people infected with Human Immunodeficiency Virus (HIV) (Stier, 2008). There may be two reasons: firstly HIV is immunosuppressive and secondly both the viruses are transmitted through unprotected sex (Gaester *et al.,* 2014).

Neoplastic potential of HPV is due to two HPV genes encoding oncoproteins E6 and E7. Disruption of a viral protein E2 leads to synthesis of E6 and E7. E6 and E7 inactivates tumor suppressor genes p53 and pRb respectively, leading to increase in mitotc potential, instability of the genome, lack of DNA repair, deregulation of cell cycle and defects in programmed cell death or apoptosis (Mannarini *et al.,* 2009). The cell cycle regulatory protein p16 is found to be over-expressed in HPV related oral cancer and is responsible for poorer prognosis (Mannarini *et al.,* 2009). HPV contributes to malignancy by targeting Nuclear factor kappaB (NFκB) mediated

signaling pathways (Vandermark *et al.*, 2012). Alterations in the copy number of DNA, absence of functional splicing mechanism, chromosomal aberrations, chromosome rearrangements, changes in DNA methylation patterns are common manifestations of HPV induced carcinogenesis.

Oral cancer may mainly be divided into carcinomas of the oral cavity, lip vermilion and oropharynx (Wangmo *et al.*, 2010). The symptoms of oral cancer have resemblance with other non-malignant oral problems, therefore are very often ignored at the initial stage. Also, people are often unaware of the signs and symptoms of the disease and because of this lack of knowledge they visit the doctor when the disease has progressed. Some of the common symptoms include swelling or lumps in the oral cavity, white, red or speckled patches in the mouth, numbness, sores on the face that do not heal, difficulty in chewing and swallowing, hoarseness of voice, unexplained weight loss, obstruction in airway, chronic pain in ears and so on. Oral cancer shows a multitude of clearly defined and visible pre-cancer stages (Neville and Day, 2002). Leukoplakia (white patches), erythroplakia (red patches), erythroleukoplakia, lichen planus and oral submucous fibrosis are some of the pre cancerous stages of oral cancer. These lesions, commonly referred to as Oral Potentially Malignant Disorders (OPMD) may develop into malignancy if left untreated.

There are four main stages of oral carcinoma. Stage I signifies that the cancer has started its journey through the tissues spanning the mouth or oropharynx and the tumor is less than 2 cm. In stage II cancer, the tumor size ranges between 2 cm and 4 cm. If the tumour size exceeds 4 cm and may spread to the lymph nodes, it is a stage III cancer. In stage IV cancer, the cells spread from the oral cavity to various parts of the body like lungs or bones. There are four grades of oral cancer based on how the cells look under a microscope. In grade I cancer there is hardly any morphological difference between the normal and cancer cells; therefore it is a low grade cancer. Grade II is an intermediate stage, where slight changes are seen. Grades III and IV are categorised as the worse type, where abnormal cells are found in abundance. Cells are poorly differentiated and undifferentiated in grades III and IV respectively. Therefore, with the progression of carcinogenesis, well differentiated cells gradually drift towards undifferentiated cells.

Outcome of oral cancer is bad as it remains unnoticed, unless there is severe pain or other obvious symptoms, which normally creep in at a late stage. Therefore, the most important prognostic factor in oral cancer is the stage at which it is diagnosed. Very often oral cancer is diagnosed at relatively advanced stages. Surgery continues to be the mainstay of therapy for oral cancer. External beam radiation therapy and brachytherapy are commonly used to treat early stages of oral cancer or are used as an adjuvant therapy after surgery. Chemotherapy may also be employed along with surgery and radiation to reduce the degree of metastasis in oral cancer (Day *et al.*, 2003). Oral cancer treatment therefore involves a multi-disciplinary team comprising of surgeons, oncologists for radiotherapy and chemotherapy, dental surgeon. Role of nutritionists, rehabilitation and specialists are equally important in the process. However, existing treatment procedures show enormous adverse side effects like dry mouth, decay of tooth, ulcers, infections, stiffness of jaws, pain, numbness in mouth, bleeding from mouth, fatigue, taste disorder,

cavities in teeth, and so on. Therefore more emphasis needs to be given on alternative modes of treatment which might help to combat the disease with minimal side effects. Plant derived phytochemicals are a good option in this context. Abundant of phytochemicals are found in nature. Bioactive non-nutrient compounds found in fruits, vegetables, herbs and spices are known to possess a wide variety of disease fighting properties. They possess anti-inflammatory, anti-oxidant, anti-carcinogenic activities and control lipid peroxidation, proliferation and scavenges free radical (Bhavana and Lakshmi, 2014). They exert all these activities by targeting several cellular pathways involved in carcinogenesis. Phytochemicals are mainly categorized as carotenoids, phenolics, alkaloids, nitrogen-containing compounds, and organosulfur compounds (Chandra *et al.,* 2012). Phytochemicals are known to play a role in cancer prevention as well. Prevention of onset of carcinogenesis is always preferred rather than treating the offending growth. The term chemoprevention, coined by Michael B.Sporn in 1976, is a strategy to prevent cancer by blocking, suppressing and retarding the process of carcinogenesis (Bhavana and Lakshmi, 2014). It is well documented that a diet rich in fruits and vegetables can help fighting a wide range of chronic diseases including cancer (Chandra *et al.,* 2012). Phytochemicals provide an important area of research as they are active against all the stages of cancer and have well documented chemo-preventive properties. Moreover, these plant derived products are relatively non-toxic as they target the cancer cells without affecting the surrounding normal cells. This differential action of the plant derived products makes them unique as an anticancer agent (Gopalakrishnan and Tony Kong, 2008).

Various *in vitro* and *in vivo* studies have been carried out to ascertain the role of phytochemicals in oral cancer. Anthocyanins abundant in black raspberries are reported to have chemopreventive action in oral cancer. Components present in black berries namely ellagic acid, ferulic acid and β-sitosterol are known to be effective in oral cancer owing to their ability to affect replication, cell cycle progression and growth of tumor cells (Casto *et al.,* 2002). Ellagic acid targets and inhibits molecules involved in various pathways leading to oral carcinogenesis (Srivastava *et al.,* 2015). It has been reported that strawberries are rich in vitamins, folic acid, calcium, selenium, β-sitosterol, ellagic acid, ferulic acid, kaempferol, quercetin etc. These components are reported to inhibit formation of tumor in animal models of oral cancer (Casto *et al.,* 2013). Genestein, obtained from soyabeans, reduces invasion of oral cancer cells and thus may be considered effective in oral squamous cell carcinoma (Myoung *et al.,* 2003). Genestein and biochanin A are known to reduce growth and proliferation of oral cancer cell lines by inhibiting phosphorylation of extracellular signal-regulated kinase (ERK) and Akt (Iriti and Varoni, 2013). The flavone baicalein induces cell cycle arrest in oral cancer cells by increasing CDK4 (cyclin-dependent kinase) and cyclin D1 degradation (Iriti and Varoni, 2013). Proliferation of oral cancer cells OSCC are reported to be inhibited by quercetin, a flavonol. This flavonol acts by causing cell cycle arrest at the G1 phase and induction of apoptosis. It also leads to decreased invasion and migration of cells (Iriti and Varoni, 2013). Vitexin, a flavone is known to induce programmed cell death in oral cancer cells via p53 dependant pathway (Iriti and Varoni, 2013). In Syrian hamsters oral carcinogenesis induced by 7,12-dimethylbenz(a)anthracene (DMBA) has been found to be prevented by the flavones

apigenin by reduction of oxidative stress and modulation of detoxification systems (Iriti and Varoni, 2013). Tea is a widely accepted beverage worldwide and shows potent anti-cancer properties. Epigallocatechin gallate (EGCG) present in green tea show chemopreventive activity in oral cancer cell lines as well as in models of OSCC in hamster buccal pouch induced by DMBA. EGCG has been shown to induce apoptosis, arrest cell cycle, modulate several transcription factors and decrease the migration and invasion of cells via modulation of matrix metalloproteinases. Tea polyphenols also show their efficacy against oral carcinogenesis by relieving oxidative stress and activities of phase I enzymes; at the same time they induce phase II detoxification enzymes to counter the elevated level of oxidative burden (Iriti and Varoni, 2013). A mixture consisting of green and black tea extracts and pigments when administered to patients resulted in a decrease in size of oral lesions (Iriti and Varoni, 2013). Lycopene are also known to be effective in premalignant lesion management in oral cancer (Lu *et al.*, 2011). Curcumin inhibits growth and proliferation of oral cancer cells and induces programmed cell death in these cells by acting via various signaling pathways involved in the malignant transformation (Liao *et al.*, 2011). Polyphenols resveratrol and quercetin have been reported to inhibit growth and proliferation of SCC-25, a human oral squamous carcinoma cells and thus may be considered as chemopreventive agents in oral cancer (ElAttar and Virji, 1999). A mixture of carotenoids in mineral water effectively inhibited tumorigenesis induced by by 7,12-dimethylbenz(a)anthracene in hamster buccal pouch (Schwartz *et al.*, 1989).

Studies show that beta-carotene and vitamin E causes regression of oral leukoplakia either alone or in combination, thus revealing their preventive role in oral cancer (Garewal, 1994). ZengShengPing (ZSP) consists of a mixture of six herbs having medicinal properties. It shows chemopreventive activity on animal models of oral cancer, and also in human patients suffering from oral leukoplakia (Sun *et al.*, 2010) *Azadirachta indica* (neem) possesses a wide variety of biological activity incliding anti tumor properties. Neem leaf extracts exhibit its anti lipid peroxidative and antioxidant properties, thereby preventing oral cancer (Bhavana and Lakshmi, 2014). Phytochemicals present in tulsi like eugenol, luteolin, apigenin, myretenal, β-sitosterol, rosmarinic acid, and carnosic acid are effective against oral cancer due to their ability to increase the anti-oxidant activity, alter expression of genes, induce apoptosis and inhibit the metastatic process (Baliga *et al.*, 2013). Garlic extracts are known to reduce tumor size and show anti-proliferative activity in animal models of oral cancer (Bhavana and Lakshmi, 2014). *Spirulina fusiformis* inhibits cancers of the oral cavity in hamsters (Bhavana and Lakshmi, 2014). Another study showed spirulina helps to revert oral leukoplakia in pan and tobacco chewers (Bhavana and Lakshmi, 2014). Avocados contain phytochemicals which perturb ROS levels in oral cancer cell lines and thus may serve as a chemo-preventive agent (Ding *et al.*, 2009). Safrole, a phenylpropene obtained from sassafras plants is known to possess anticarcinogenic effects on human oral squamous cell carcinoma HSC-3 cells because of its ability to induce apoptosis. It has been found that safrole diminishes the size and volume of tumor in mouse models as well (Yu *et al.*, 2011).

Neutraceuticals are helpful in oral cancer, where HPV plays a vital role. It is therefore

important to know the action of these phytochemicals on HPV mediated carcinogenesis. Genestein from soybean possess immunomodulatory effect and elicit its action against HPV associated cancer in a mouse model (Ghaemi *et al.,* 2012). Quercetin, a type of flavonols found in abundance in onions finds use in the cure of genital warts which are caused due to HPV infection (Petersen and Weismann, 1995). Vegetables like spinach and kale, rich in vitamins and minerals fight against HPV by boosting up immunity. Cruciferous vegetables like broccoli etc, squash, bell peppers are antioxidants and help neutralizing free radicals that damage tissue and make cells susceptible to infection. Pumpkins are rich in vitamin A and aid in enhancement of immunity by regulating cell to cell signaling. Vegetables like carrots, squash, tomatoes, sweet potatoes, lettuce contain high amounts of beta-carotene which helps to control HPV. Beta carotene is also known to reduce oral leukoplakia in patients (Garewal *et al.,* 1999). Folate is present in legumes, cereals, asparagus, oranges etc whose deficiency is well known to enhance the risk of various diseases including oral cancer (Piyathilake *et al.,* 2014). It is also related to the prevention of HPV16. Not only vegetables, fruits also find a place in a healthy diet. An association between intakes of fruits is inversely proportional to the risk of HPV-16 linked HNSCC (Meyer *et al.,* 2008). Fruits also add on immunity and combat warts. Berries particularly blue berries, cherries and many other fruits are rich source of antioxidants. Herbs add taste and flavor to the cooking. Many of the herbs are anticancer agents. Some of the active ingredients of herbs are of immense help in fighting diseases. Garlic, stud with antioxidant properties ward off viral infections by stalling their multiplication; they are also anti-bacterial and anti-parasitic. Flavonoids and phenolic acids present in oregano help fight infections. Other herbs that boost up immune potential are goldenseal, astragalus, Echinacea, bayberry, horehound, red clover, fenugreek and hawthorn (Balch, 2006). EGCG, polyphenols from the most popular beverage tea show a plethora of health benefits. They find use as an ointment in the treatment of genital warts and are anti-inflammatory and antiproliferative, which imparts the chemopreventive activity. Apart from these properties, anti-viral potential aid in the control of HPV infections. Green tea had shown its efficacy against external genital and anal warts (Scheinfeld, 2013).

In conclusion, oral cancer is a deadly disease with a low survival rate and high mortality rate. HPV, a DNA virus affecting epithelial cells, is one of the leading causes of cancers of the oral cavity. The main treatment modality involves surgery with radiotherapy or chemotherapy as adjuvants. However, these procedures pose several side effects. A diet rich in fruits and vegetables is a key to good health. Phytochemicals gained special importance because of their action against development of carcinogenesis. They aid in control of cell cycle, evasion of programmed cell death, angiogenesis and spread of cancer to distant body parts. It has been documented that phytochemicals prevent oral cancer. They also help control HPVs. Further studies and clinical trials are warranted to establish the potential of these molecules in control and therapy of HPV induced oral cancer.

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