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Citrus Flavonoids as Promising Agents in the Prognosis of Oral Squamous Cell Carcinoma and Other Cancers

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Abstract

Cancer as a disease is among the greatest killers across the globe. On a cellular scale it is a set of complex disorders involving uncontrolled cell division and proliferation induced by changed genetic composition or altered gene expression. Cancer is often triggered by the exposure of environmental carcinogens. Among the many forms of cancer affecting various body parts, the incidence of oral squamous cell carcinoma (OSCC) is quite high in human societies. The cases of mouth cancer are increasing in India owing to multiple risk factors like tobacco chewing, alcohols abuse and viral infection. The molecules implicated in mouth cancer comprise of oncogenes, second messengers, tumor suppressor genes, transcription factors, growth factors and hormone receptors. The prognosis of cancer is usually based on chemotherapy and radiotherapy which comes with a host of untoward reactions necessitating search for safer alternatives. In this quest plants appear promising because herbal extracts have traditionally been used to cure different diseases since ancient times. The extracts of plants usually contain phytochemicals like flavonoids, carotenoids, vitamins and fibres. Citrus plant extracts and flavonoids have been shown to possess high therapeutic potential in several diseases including cancers. Plant-based flavonoids include compounds such as hesperetin, naringenin, quercetin and kaempferol. This paper explores the efficacy of herbal extracts and their derivatives in the treatment of cancer.

Key words: oral squamous cell carcinoma, tobacco, oncogene, flavonoids, citrus plants, tumor suppressor gene.

1. Introduction:

Cancer is a complex cellular disorder characterized by uncontrolled division and proliferation. This is induced by changes in genetic composition, altered regulation of gene expression and exposure of environmental carcinogens. Oral squamous cell carcinoma is a highly fatal malignancy that spreads in the regions of head and neck. It is ranked fifth in the global rating of diseases that cause most human deaths (Sheth *et al*., 2015). An approximate estimation revealed that around 211,000 death and 405,000 new patients were reported annually worldwide (Christopher *et al*., 2016). According to international classification of diseases oral cancer or oral squamous cell carcinoma (OSCC) affected the oral cavity and pharynx that covers tumor of lips, tongue, salivary glands, gums, oropharynx, nasopharynx, hypopharynx, pharynx and other buccal areas (Silverman *et al*., 1990; Bagan *et al*.,

2010). The cause of mouth cancer considered modern lifestyle, environmental factors and viral factors, tobacco chewing and smoking, intake of alcohols are the major factors (Shenoi *et al*., 2012; Scully *et al*., 1993). Head and neck squamous cell carcinoma (HNSCC) and OSCC spread in regions of upper alimentary canal and respiratory system such as oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses. The OSCC is supposed to be a solid tumor which represents 6% of all solid tumors (Parkin *et al.,* 2005) and is ranked sixth among the cancers that influence human beings worldwide. Its incidence is especially high among Southeast Asian people mostly due to habits of chewing betel leaves, tobacco smoking and consumption of alcohols (Kumar *et al*., 2016).

Plants have traditionally been considered as the source of potent chemicals equipped with diverse medicinal effects. These phytochemicals are synthesized by plants and are categorized on the basis of their chemical composition, colour, odour and reactivity and are classified into several categories such as phenols, alkaloids, carotenoids, organosulphurs and phytoesterols (Saxena *et al*., 2013). Flavonoids are a class of phytochemicals characterized by 2 phenyl rings connected through an oxygen-containing heterocyclic ring which imparts their 15-carbon skeleton a characteristic C6-C3-C6 configuration. Flavonoids are abundant in plants abundant in plants where there are produced through various metabolic activities and have key roles in their growth and development. A number of recent studies have attempted to explore the therapeutic effects of flavonoids which appear to be quite promising. What is perhaps more exciting is that flavonoids have been implicated in the treatment of various cancers including OSCC.

Molecules associated with OSCC:

The etiology of cancer usually comprises of gene changes and therefore, the transformation of normal cells into malignant cells is often the result of chromosomal alterations (Boveri *et al*., 1914). Chromosomal aberrations involving deletions, duplications, translocations, or inversions are known to be associated with many specific forms of cancers occurring in humans and other mammals such as the head and neck or oral cancer. Chromosomal dysfunction may involve a host of destabilising conditions such as telomerase instability, disruption of chromosomal segregation, loss of cell cycle regulation, DNA damage (Reshmi *et al.*, 2005). The oral cancer is frequently associated with deletion of segments from 9^{th},13^{th},18^{th} and Y chromosomes. An estimation suggested that nearly two third cases of the cancer of head and neck arise due to translocation 9p21-22 (Ah-See *et al*., 1994). Thus, a number of molecules associated with chromosomal dynamics and cell cycle regulation can be implicated in progression of a particular variant of cancer. An exploration of such molecules may provide us with potential targets for plant based anticancer treatment. There are several citrus flavonoids that modulate intracellular molecular cascades and may have important role in treating cancer because of their antioxidant and antiproliferative effects. Here is a brief description of molecules that play critical roles in cancer.

Oncogenes: An oncogene is any altered gene that has potency to transform normal body cells into tumor cells by changing gene expression patterns. This altered regulation leads to abnormal translation of certain proteins in human or animals. The human cells possess two major classes of genes i.e., proto-oncogene and tumor-suppressor genes. They encode different types of proteins that regulate homeostasis of the cells like cell growth and proliferation but mutational irregularities in these genes results in cancer (Nelson *et al*., 2007). Proto-oncogenes are normal cellular genes but transformation of proto-oncogenes into oncogenes leads to their overexpression through gain of function (gof) mutations. There are three major mechanisms that mediate the transformation of proto-oncogenes into oncogenes i.e., point mutations in proto-oncogene, over-expression of proto-oncogene by localized DNA replication, or chromosomal translocation of the promoter of growth regulatory

gene. Some retroviral oncogenes (e.g., the *ras* genes) have been linked to oral squamous cell carcinoma (Field *et al*., 1992; Lodish *et al*., 2000). Some other proto-oncogenes that lead to abnormal gene expression comprise of epidermal growth factor receptor (EGFR), c-myc, int-2, hst, PRAD-1 and bcl, all of which have been linked to the development of oral malignancy.

Growth factors and cell surface receptors: Growth factors are usually circulating or local proteinaceous hormones which are necessary for normal growth of cells. Likewise, cell surface receptors are meant to bind ligands (e.g., peptide hormones) which cannot enter their target cells. This category of proteins comprises of signal transducers, transcription factors, pro or anti-apoptotic factors, cell cycle control proteins, DNA repair proteins, and growth factor receptors etc. Any kinds of mutations in such genes cause serious disorders and may result in development of cancers (Todd *et al*., 1997).

Transforming Growth Factors (TGF) are proteins which play potent role in cell growth and differentiation. One of their types is transforming growth factor alpha (TGFα) which was found over-expressed in oral malignancies. It was initially observed in hyperplastic epithelium and later in the inflammatory infiltrate basically involving the eosinophils that cover the epithelial lining of oral cancer cells. The second one is transforming growth factor beta (TGFβ) which acts as tumor suppressor as well as a tumor promoter (Todd *et al*., 1991; Nagaraj *et al*., 2010).

Cell surface receptors are the molecules that recognize specific ligands and bind them so that they may transmit signal to the interior of a cell which is a prerequisite for signal transduction cascade. Mutational changes in cell surface receptors can increase the number of receptors or production of ligand independent mitogenic signal (Aronson *et al*., 1991; Hunter *et al*., 1991). Signaling cascades initiated by cell surface receptors may be quite varied in nature. For instance, the epidermal growth factor receptor (EGFR) is a tyrosine kinase-mediated transmembrane receptor which is the member of the human EGFR (HER)-ErbB family (Ng *et al*., 2008; Grandis *et al*., 1993) of G-protein coupled receptors (GPCRs) (Dorsam *et al*., 2007).

Second messengers: The role of second messengers is to transmit the message carried by the first messengers (i.e., hormones or other chemical messengers). In case of hormones where the ligand binds to the outer cellular membrane, the second messenger carries the message initiated from the inner membrane side to the interior of cytoplasm. The activation of second messenger follows ligand binding at the receptor present on the cell surface. The activated second messenger targets cytosolic molecules or nucleus and promotes physiological activities like cellular proliferation, differentiation, migration, survival and apoptosis (Adjei *et. al*., 2005; Nelson *et. al*., 2007). The most frequent member of intracellular signaling pathways found in malignant cells is the *ras* gene family (H-ras, K-ras, N-ras) which has been reported in human mouth or oral cancer (Todd *et al*., 1997)

Transcription factors: There are some specific proteins that participate in transcription of RNA from DNA so as to regulate the activation of other genes and are hence called transcription factors. These transcriptional activities are altered in various cancers and many of the cancer-related genes are transcription factors. For instance, the c-myc gene is reported to exist in over-expressed form in oral cancer by gene amplification which promotes cellular proliferation (Riviere *et al*., 1990; Spandidos *et al*., 1985).

Tumor suppressor genes: The tumor suppressor genes control cell division and proliferation in normal cells and are essential for normal cellular function. However, mutational changes caused by deletion, point mutation and chromosomal rearrangement often result in inactivation of tumor

suppressor gene (TSGs) in both copies (Yokota *et al*., 1993). The genes *p53* and *rb* (*retinoblastoma*) are the two most famous TSGs. Of these, p53 is implicated in head and neck cancers where it is reported that smoking and tobacco chewing triggers the *p53* mutation (Brennan *et al*., 1995).

2. Risk factors:

There is no single trigger for any kind of cancer and oral cancer is no exception. The risk of oral cancer is aggravated by a host of factors which are briefly summarized here:

Tobacco: Chewing or smoking of tobacco is the most dominant factor that promotes cellular malignancy and causes millions of deaths worldwide. It is involved in cancers of different parts of the body such as cancers of oral cavity, pharynx, larynx and oesophagus (Gupta *et al*., 1995). The prevalent carcinogens reported in tobacco include 4-(nitrosomethylaminno)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN) (Warnakulasuriya *et al*., 1999).

Betel leaf or 'paan' is consumed frequently in Southeast Asian countries mainly in the Indian subcontinent. It is usually chewed and is a combination of ingredients namely cloves, cardamom, betel leaf, tobacco, lime, areca and zarda. Various studies have reported that consumption of these ingredients was associated with initiation of oral cancer that appears in the form of pre-cancer symptoms such as erythroplakia, leukoplakia and oral submucous fibrosis (Axell *et al*., 1987).

Alcohol: Alcohol intake and its consumption with tobacco synergistically promotes the risk of oral cancer including the malignancies of oral cavity, pharynx, larynx and oesophagus (IARC, 1985). However, a study revealed that alcohol consumption were found to be an independent risk factor for leukoplakia in oral cavity (Jafarey *et al*., 1977).

Viral infection: Viruses are among the major risk factors that promote malignancy of different vital organs. Human papilloma virus (HPV), Epstein Barr Virus (EBV) and Herpes simplex virus were reported to induce oral malignancy in oral squamous epithelium (Negri *et al*., 2000).

Citrus flavonoids in management of oral cancer:

Citrus fruits are very common and have widespread distribution worldwide. Their consumption is considered very healthy due to the presence of highly beneficial nutrients in their juices and peels that promote human health (Wang *et al*., 2014). Among the chief bioactive components present in citrus plants are flavonoids, carotenoids, essential oils, phenols and vitamin-c (Li *et al*., 2014). Several previous studies and recent researches suggested that the extracts of citrus plants were effective against different diseases and disorders owing to active phytochemicals identified as flavonoids. Citrus flavonoids possess broad range of pharmacological activities that modulate molecular mechanisms especially in cancer cells.

Table 1: List of citrus flavonoids and their molecular response in different cancers.

Flavonoids	**Chemical name**	**Molecular response**
Naringenin	2,3-dihydro-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one (Wilcox et al.,1999).	Block the expression of HER-2TK activity and shows anti-proliferative activity in breast cancers (Chandrika et al., 2016). Increase ROS production and initiates apoptosis with increasing the ratio of Bax/Bcl-

		2 in prostate cancer (Lim et al., 2017).
Quercetin	3,3',4',5,7-pentahydroxyflavone (Lakhanpal and Rai, 2007).	Inhibits ROS production and MicroRNA-21 (miR-21) expression in chromium mediated malignance in colon cancer (Pratheeshkumar et al., 2016; Han et al., 2016).
Hesperetin	3',5,7-trihydroxy-4'-methoxyflavone (Parhiz et al., 2015).	Mediates apoptosis by via activation of Fas death receptor/extrinsic pathway that promotes expression of Bax, caspase-3,-9 in lung cancer (Elango et al., 2018).
Luteolin	3',4',5,7-tetrahydroxyflavone (Lin et al., 2008).	Caused G1 phase cell cycle arrest vai inhibition of CDK2 activity in melanoma cancer (Casagrande and Darbon, 2001).
Nobiletin	5,6,7,8,3',4'-hexamethoxyflavone (Huang et al., 2016).	Down regulates PRAP2 and upregulates AMPK cascades caused apoptosis in nasopharyngeal carcinoma (Zheng et al., 2019).
Kaempferol	3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one) (Alam et al., 2020).	Administration with cisplatin decrease the level of c-Myc mRNA level increase CDKN1A mRNA in ovarian carcinoma cells (Choi and Ahn, 2008).
Apigenin	4',5,7-trihydroxyflavone (DeRango-Adem and Blay, 2021).	Apigenin inhibits cancer cell invasion and migration in prostate cancer (Zhu et al., 2015).

Naringenin is a citrus flavonoid found in fruits, leaves and vegetables (Mbaveng et al., 2014; Jadeja et al., 2014). A study conducted with naringenin and myiricetin on oral squamous cell carcinoma cell lines such as SCC-25 and HaCaT cells validated that both these flavonoids affected the SCC-25 cells by its growth inhibition. The anti-proliferative activity of myricetin and naringenin is due to apoptosis mechanism which acts via cell cycle impairment such as G0/G1 and G2/M phase arrest following 24h treatment in SCC-25 and HaCaT cells respectively (Maggioni *et al*., 2014). Quercetin is a well-known flavonoid present in different parts of plants such as in leaves, fruits peels, seeds and stems. Quercetin possesses high potency against various neoplastic malignancies in different cancer cell lines. The anti-neoplastic activity of Quercetin has been observed in OSCC against various cell lines of tongue and pharynx. Quercetin induces several morphological changes in human oral cancer cells like cell shrinkage (Ma *et al*., 2018), cellular edema, necrosis or apoptosis (Haghiac *et al*., 2005). Kaempferol has been shown to possess various pharmacological properties and one of them is anti-neoplastic activity reported in various cancers including the head and neck cancer. The anti-neoplastic activity of kaempferol is reported in dose dependent manner while treating the SCC-1483 cells where it induces apoptosis. Furthermore, other cancer cell lines (SCC-25, SCC-QLL1) were also treated with kaempferol and found to induced apoptosis as well as caspase-3 activity (Kang *et al*., 2010). A citrus

flavonoid (3',5, 7-trihydroxy-4'-methoxyflavone) possesses wide range of pharmacological activities such as antioxidant and anti-inflammatory (Parhiz *et al*., 2015). It inhibits cellular malignancy via suppression of phosphatidylinositol 3-kinase (PI3K)/protein kinase-B activities (Li *et al*., 2017). Tangeretin is a potent natural citrus flavonoid known to produce anti-proliferative effects in many cancers like skin, blood, brain and ovarian carcinoma (Arafa *et al*., 2021). Tangeretin was found to be effective as it induced apoptosis by activating p53 protein level in rat's hepatocellular and breast cancer model (Krstic *et al*., 2018). Luteolin is a member of citrus flavonoids synthesized by metabolic activities of citrus plants. It has been shown to possess therapeutic potential against diseases such as cancer and many more (Yang *et al*., 2008). Luteolin blocks mRNA activation by suppression of mitogen activated protein kinase (MAPK) signaling and down regulates nuclear AP-1 and NF-kB (Jeon *et al*., 2015).

3. Discussion:

A series of previous studies as well as recent researches conducted have established cancer as a dreadful killer and a leading cause of death in human beings. Cancer may be defined as abnormal cellular proliferation that causes lack of contact inhibition leading to invasion of cells to adjacent tissues in a process called metastasis (Hanahan *et al*., 2000). There are several forms of cancers affecting human society including breast, prostate, head and neck or oral cancers and many more. Oral cancer or Oral squamous cell carcinoma (OSCC) affected the oral cavity and pharynx that covers the tumor of lips, tongue, salivary glands, gum, oropharynx, nasopharynx, hypopharynx, pharynx and other buccal areas (Silverman *et. al*., 1990; Bagan *et. al*., 2010). The chief causes of mouth cancer comprise of modern lifestyle, environmental factors, viral infections, tobacco chewing or smoking, and intake of alcohols (Shenoi *et al*., 2012; Scully *et al*., 1993). Carcinogenesis is accompanied with alterations of extracellular and intracellular molecules such as oncogenes, cell surface receptors, growth factor, second messengers, and transcription factors. Several types of modern treatments against cancer involve chemotherapy, radiation therapy and surgery but these are accompanied with undesirable side effects apart from being costly. The adverse effects of radiotherapy or chemotherapy result from the fact that the chemicals used in such therapies harm normal cells too. Hence, the pharmaceutical research is desperately seeking medications derived from approaches that rely on plant-based cures and alternative strategies. It is very exciting that herbal extracts containing active phytochemicals such as flavonoids, carotenoids etc are equipped with anti-tumour properties (Sultana *et al*., 2014). Citrus fruits are consumed worldwide for their healthy nutritious juice and antioxidant properties. Oranges, pomelos, lemons and grapefruits are common citrus fruits enriched in bioactive phytochemicals that elicit anti-inflammatory, antioxidant, neuroprotective and anti-cancer effects (Zhang *et al*., 2021). Citrus flavonoids including naringenin, hesperetin, quercetin & many more have been studied against various cancers through in-vitro and in-vivo studies and the existing evidence strongly indicates that plant-based natural active metabolites and phytochemicals can reduce the risk of cancers in future.

4. Conclusion:

The foregoing description presents a satisfactory account of the many studies that prove the efficacy of citrus fruits in treating cancer among other diseases. The anti-tumour effects of citrus fruits owe a lot to the presence of various flavonoids which might be of immense therapeutic significance. In the face of fresh evidence, there is increased interest in exploiting the pharmaceutical properties of citrus fruits. Therefore, citrus flavonoids are drawing the interest of scientists and are expected to play a significant role in cancer cure of the future.

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