Delta University Scientific Journal
Volume 2 Issue September (2019)

DELTA UNIVERSITY
SCIENTIFIC JOURNAL
Journal home page: www.deltauniv.edu.eg/dusj

Squamous Cell Carcinoma of the Oropharynx and the Effect of Botanicals

Mohammed E. Grawish
Faculty of Oral and Dental Medicine, Delta University for Science and Technology, Mansoura, Egypt.

Abstract
Context: Complementary and alternative medicines are currently being investigated for their usefulness in preventing, inhibiting, and reversing the progression of oropharyngeal squamous cell carcinoma (OSCC). Botanicals have great potential in cancer prevention because of their safety, low cost, and oral bioavailability.
Objective: In this review, potential natural OSCCs' preventive botanicals and their mechanisms of action will be discussed.
Methods: A brief bibliometric overview was conducted to obtain the available information of possible relevance to the issue. To this end, PubMed, Google and Google Scholar were interrogated for articles published in English between January 1, 2000, and December 31, 2010, that discuss botanicals and which could possibly be used in treating OSCC. The search was done to identify reports of botanicals' chemoprevention of OSCC. The study outcomes were evaluated and mechanisms of action were identified whenever possible.
Results: A wide range of such botanicals had been shown to prevent 7, 12-dimethylbenz[a]anthracene or 4-nitroquinoline 1-oxide induced OSCC in animal model systems. However, only a few have been tested for their efficacy in humans. Animal model and cell culture studies have clarified that botanicals act by several mechanisms at various stages of OSCC.
Discussion and Conclusions: By utilizing botanicals demonstrating potential mechanisms for efficacy, it is possible to maximize the chances of favorable outcomes while minimizing discomfort associated with conventional therapies.
Keywords: Carcinogenesis; 7, 12-dimethylbenz[a]anthracene; 4-nitroquinoline 1-oxide; Squamous Cell Carcinoma; Oropharynx; Botanicals Extract; Traditional Chinese Medicine; Monomeric Compounds; Dosage Variation; Bibliometry.

Introduction

Squamous cell carcinoma of the oropharynx (OSCC) has been defined as the cancer of those parts of the human body that are covered by the classificators *C00-C10* (Sankaranarayanan et al., 2006; Wittekind et al., 2010). It is among the most common cancers worldwide, and continues to represent a public health problem (Warnakulasuriya, 2010). Despite advances in therapy, cure rates and survival remain poor (Silverman et al., 2010). OSCC often appears to be preventable and is likely to be related to behavioral and lifestyle factors. Prevention of OSCC therefore remains the goal to reduce the impact of this disease (Day et al., 2003; Saunders & Wallace, 2010).

The use of dietary supplements, especially botanicals, or parts of them such as extracts or seeds as medicines predates recorded history and may be seen as a forerunner to modern medicine (Nobili et al., 2009). Technological advancement has facilitated the delivery of breakthrough bioactive compounds of botanicals with potency more or less comparable to those of conventional drugs (Rosenbloom et al., 2011). Also their low cost, (per-) oral bioavailability, and assumed safety at pharmacologically relevant concentrations have tremendous appeal. As a result, some women for example use herbal remedies during pregnancy (Low Dog, 2009). Phytochemicals have been evaluated for cancer chemoprevention and anti-cancer

properties, increasingly throughout the course of the past decade (Khan et al., 2008; Baskar et al., 2010; Gullett et al., 2010; Syed & Mukhtar, 2011), and interestingly, some of these botanicals were among the top 10 ingredients in "anti-aging" creams (Cronin & Draelos, 2010). This and previous reports (Svendsen et al., 1994; Kiyono, 2007; Longo et al., 2008; Herranz et al., 2010; Donate & Blasco, 2011) suggest that cancer chemopreventive agents and/or anti-ageing drugs may have something in common.

Methods

Google (Giglia, 2008; Kingsley et al., 2011), *PubMed* (Roberts, 2001) and *Google Scholar* (Walters, 2009) were interrogated to identify scientific literature of relevance to this area of research. Information on the role of botanicals in chemoprevention of OSCC published between January 1, 2000, and December 31, 2010 were analysed.

Results

Searching the different databases revealed that there are certain parts of trees and shrubs have chemopreventive effect against OSCC such as olive tree leaves; neem tree leaves, flowers and fruits; seaside clerodendron shrub leaves; ashwaghanda shrub roots; portia tree barks and certain specific algae. Common foods, some Chinese medicinal plants and some monomeric compounds also have a beneficial effect against OSCC.

1. Trees and Shrubs

1.1. Olive Tree Leaves

The leaves of the olive tree (*Olea europaea L*; *NCBI Taxonomy ID*: *4146*) are well known for their traditional anti-diabetic and anti-hypertensive herbal drug (Sato et al., 2007). Extracts rich in oleuropein (*CAS no*: *32619-42-4*, 3 mg/kg body weight; bw) inhibited–carcinogenesis in the oropharynx of rattus norvegicus (*NCBI Taxonomy ID: 10116*), type Fischer (F344), after inductive treatment with 4-NQO (*CAS no*: *56-57-5*) (Grawish et al., 2010).

1.2. Neem Tree Leaves, Flowers and Fruits

Neem (*Azadirachta indica*; *NCBI Taxonomy ID*: *124943*) is a versatile tree of the Meliaceae family (*NCBI Taxonomy ID*: *43707*). The antiproliferative activity of neem tree flowers against some cancer cell lines has been established (Roy et al., 2007). Ethanol neem leaf extract (200 mg/kg bw) and neem leaf fractions (1, 10, 100 mg/kg bw, in a dose dependent manner, ddm) have been reported to inhibit the development of OSCC in the buccal pouch of hamsters (*NCBI Taxonomy ID*: *10036*) after application of DMBA (*CAS no: 57-97-6*) (Subapriya et al., 2005; Manikandan et al., 2008). Apoptosis of neem treated hamsters was mediated by the expression of Bim, Bcl-2 (*UniProt*: *Q687E0***),** caspase 3 (*UniProt*: *Q60431***),** and caspase 8 (Subapriya et al., 2005). The neem fruit limonoids azadirachtin (*CAS no*: *11141-17-6*; 10, 100 µg/kg bw) and neem flower nimbolide (*CAS no*: *25990-37-8*; 10, 100 µg/kg bw) appeared to block cell proliferative activity and induce apoptosis. Comparatively, nimbolide is a more potent antioxidant and cancer chemopreventive agent (Priyadarsini et al., 2009; Harish Kumar et al., 2010).

1.3. Seaside Clerodendron Shrub Leaves

Seaside Clerodendron (*Clerodendrum inerme*; *NCBI Taxonomy ID*: *49994*) is an evergreen sprawling shrub 1-1.8 m tall, which has two sterol constituents (Pandey et al., 2003). It was found that peroral administration of *Clerodendron inerme* aqueous leaf extract (500 mg/kg bw) reduced the incidence and size of DMBA-induced OSCC in the HBP (Manoharan et al., 2006).

1.4. Ashwaghanda Shrub Roots

Ashwaghanda (*Withania somnifera*; *NCBI Taxonomy ID*: *126910*) root extracts are commonly used in the Indian (Hindu) traditional medicine practice Ayurveda as a general tonic for overall health and as a remedy for a variety of ailments (Kataria et al., 2011). Withaferin-A (*CAS no*: *5119-48-2*; 20 mg/kg bw), a steroidal lactone isolated from *Withania somnifera*, appeared to

prevent alterations of both p53 (*UniProt*: *Q00366***)** and Bcl-2 and decreases micronucleus formation in the bone marrow when administered to DMBA-painted hamsters (Bargagna-Mohan et al., 2007; Panjamurthy et al., 2008). Withaferin-A prevented tumor formation and helped maintain erythrocyte integrity during DMBA induction of OSCC (Manoharan et al., 2008).

1.5. Portia Tree Barks

The Portia tree or *Thespesia populnea Soland ex Correa* (*NCBI Taxonomy ID*: *3638*; Family: *Malvaceae*; *NCBI Taxonomy ID*: *3629*) is a large tropical tree found in coastal forests and is native to India (Ilavarasan et al., 2003). The extract from the *Thespesia populnea* bark (300 mg/kg bw) has been reported to demonstrate cancer preventive efficacy in HBP contaminated with DMBA (Dhanarasu et al., 2010).

1.6. Algae

Spirulina (*NCBI Taxonomy ID*: *1154*) is a blue-green filamentous alga (*NCBI Taxonomy ID*; *1117*) (Hayashi et al., 1996). *Spirulina platensis* (*Arthrospira platensis*; *NCBI Taxonomy ID*: *118562*; 10 mg/day) inhibited dysplastic changes occurring in the HBP mucosa and had a long-term cancer regression role on DMBA-induced OSCC (Grawish, 2008; Grawish et al., 2010).

2. Common Food

2.1. Black Raspberries

Black raspberries (*Rubus occidentalis*; *NCBI Taxonomy ID*: *75079*) contain many compounds with both *in vitro* and *in vivo* preventive properties (Rodrigo et al., 2006). The lyophilized black raspberries (5% and 10%) have preventive properties and have been found to inhibit tumor formation in the oral cavity (Casto et al., 2002). The growth inhibitory effects on dysplastic human cells from the oropharynx were attributed to certain components in black raspberries that target specific signaling pathways regulating the progression of the cell cycle (Han et al., 2005). Ethanol extract (10, 50, 100 µg/ml, ddm) of freeze-dried black raspberries was a promising agent for prevention of oropharyngeal epithelial dysphasia (Rodrigo et al., 2006). Application of black raspberry bioadhesive gel (10% w/w gel or 0.5 g of 10% gel) containing anthocyanins (*CAS no*: *15067-77-7*) represented a promising strategy for human OSCC chemoprevention by modulation of gene expression and reduction of cyclooxygenase 2 (*UniProt*: *Q9NNY7***)** protein (Mallery et al., 2007; Mallery et al., 2008).

2.2. Cranberry and Grape Seeds

Cranberries (*Vaccinium macrocarpon*; *NCBI Taxonomy ID*: *13750*) are the fruit from the evergreen dwarf shrubs which can be used by pregnant or breastfeeding women as a preventive agent of urinary tract infections (Dugoua et al., 2008). Grapes (Vitis *vinifera*; *NCBI Taxonomy ID*: *29760*) are considered the world's largest fruit crops, with an approximate annual production of 58 million metric tons (Li et al., 2004). Grape seeds are rich sources of monomeric phenolic compounds, such as catechins (*CAS no: 7295-85-4*), epicatechin (*CAS no: 490-46-0*) and epicatechin-3-O-gallate (CAS no: *1257-08-5*) and dimeric, trimeric and tetrameric procyanidins (*CAS no: 4852-22-6*) which act as antimutagenic and antiviral agents (Stanković et al., 2008). Grape seed proanthocyanidins (*CAS no: 84929-27-1*) differ from cranberry proanthocyanidins in that they are more likely to contain galloylated flavan-3-ols, and the monomers are primarily B linked (Hayasaka et al., 2003). Extracts of grape seed were more cytotoxic than grape peel extracts and 70% methanol extracts of grape seed selectively killed two human oropharyngeal tumor cell lines (Shirataki et al., 2000). Cranberry and grape seed extracts (both 10 to 80 µg/ml, ddm) inhibited the proliferation of OSCC cell lines (CAL27 and SCC25) in a dose-dependent manner (Chatelain et al., 2010).

2.3. Tomato

The tomato is the edible fruit of the plant *Solanum lycopersicum* (*NCBI Taxonomy ID*: *4081*) (Luengwilai et al., 2010). Combined administration of tomato (0.25 mg lycopene/ml; *CAS no*: *502-65-8* ;) and garlic

(*NCBI Taxonomy ID*: *4682*; 12.5 mg/ ml) inhibited the development of OSCC in the HBP by downregulation of Bcl-2 and upregulation of Bax, Bim, P53 and the caspases 3 and 8 (Bhuvaneswari et al., 2004). They modulated xenobiotic-metabolizing enzymes mitigating the mutagenic and carcinogenic effects of DMBA (Bhuvaneswari et al., 2005). Lycopene (2.5 mg/kg, bw) exerts its preventive effects by modulating lipid peroxidation and enhancing the activities of the enzymes in the glutathione redox cycle as it reduced glutathione (GSH; *CAS no: 70-18-8*), glutathione peroxidase (GPx; *UniProt*: *P86215*), glutathione *S*-transferase (GST; *UniProt*: *P30116*) and glutathione reductase as biomarkers of cancer chemoprevention (Bhuvaneswari et al., 2001). Lycopene (3 and 7 mol/L) inhibited proliferation and enhanced gap-junction communication of KB-1 tumor cells from the human oropharynx (Livny et al., 2002). The observed effect of lycopene (4 or 8 mg/day) suggested that it can be effectively and safely used for the management of oropharyngeal leukoplakia (OLP) (Singh et al., 2004). Tomato paste containing lycopene (5 mg/kg bw reduced the incidence of OSCC in the HBP (Bhuvaneswari et al., 2004).

2.4. Garlic

Garlic (*Allium sativum L*. fam. *Allioideae; Taxonomy ID: 40553*) is one of the most commonly used herbal remedies and food spices. Alliinase (*UniProt*: *D2CXF2*), alliin (sulfur-containing compounds, *CAS no: 556-27-4***)**, and allicin (compounds produced enzymatically from alliin, *CAS no: 539-86-6*) are the main constituents of garlic (Aviello et al., 2009). Administration of S-allylcysteine (*CAS no*: *21593-77-1*; 200 mg/kg bw) or aqueous garlic extract (250 mg/kg bw) suppressed DMBA-induced oropharyngeal carcinogenesis as revealed by the absence of neoplasms, induction of *transglutaminase* and inhibition of Bcl-2 expression. It also restored retinoic acid receptor-beta mRNA (*UniProt*: *Q8VHB7*) expression to normal (Balasenthil & Nagini, 2000: Balasenthil et al., 2001; Balasenthil et al., 2002; Balasenthil et al., 2003). S-allylcysteine (0, 2, 5 10, 20 mM, ddm) effectively inhibited the proliferation, up-regulated the expression of E-cadherin (*UniProt*: *Q9UII7*) molecule and stabilized the E-cadherin/beta-catenin (*UniProt*: *P35222*) adherent junction complex in human OSCC cell lines (Tang et al., 2009). Altered cytokeratin expression and enhanced quantities of circulatory antioxidants were suggested to be associated with garlic-mediated cancer chemoprevention (250 mg/kg bw) of experimental OSCC in the HBP (Balasenthil et al., 2000; Balasenthil et al., 2002).

In 4NQO-induced rat tongue carcinogenesis, garlic (25 mg/ml) might execute its preventive effects by modulating lipid peroxidation and enhancing the levels of GSH, GPx (*UniProt*: *P04041*) and GST (*UniProt*: *Q6LDP3*) (Balasenthil et al., 2001).

2.5. Ginger

Ginger (*Zingiber officinale*; *NCBI Taxonomy ID*: *94328*) is one of the plants' family is from the plant family *Zingiberaceae* (*NCBI Taxonomy ID*: *4642*) which includes cardamom (*NCBI Taxonomy ID*: *105181*) and turmeric. The active constituent is gingerol (White, 2007). When 400 mg of ginger powder is added to laboratory chow it is presumed to have a preventive effect on oropharyngeal carcinogenesis through induction of apoptosis and suppression of tumor growth and proliferation (Khater, 2010).

2.6. Pepper

Pepper, contains Piperine and capsaicin and its biological activities especially anti-cancer activity is widely studied. Piperine (*CAS no*: *94-62-2*) extracted from *Piper longum* (long pepper; *NCBI Taxonomy ID*: *49511*) and *Piper nigrum* (black pepper; *NCBI Taxonomy ID*: *13216*) is an active alkaloid, consumed by a large number of individuals worldwide (Koul & Kapil, 1993). Piperine (50 mg/kg bw) had been suggested to execute Piperine (50 mg/kg bw) has been proposed to have a

chemopreventive effect on DMBA-mediated induction of OSCC in the HBP (Krishnakumar et al., 2009). The modifying effects of dietary *capsaicin* (*CAS no*: *404-86-4*; *ATC/DDD*: *N01BX04*; active component of chili peppers; *NCBI Taxonomy ID:* 4073; 500 ppm, w/w) and rotenone (*CAS no*: *83-79-4*; 500 ppm) on the initiation or promotion phase of 4-NQO-induced rat tongue carcinogenesis, reduced the frequency of OSCC (Tanaka et al., 2002).

2.7. Green, Black and Yerba Mate Tea

Tea, from the plant *Camellia sinensis L.* (*NCBI Taxonomy ID*: *4442*), is one of the most common beverages consumed worldwide and is generally consumed in its green, black, or oolong form. The main tea extract components are tea polyphenols and tea polysaccharides (Monobe et al., 2010). Green tea extract (GTE, 0.6% solution in tap water) and curcumin (*CAS no*: *458-37-7*; 10 µmol) (Li et al., 2002) had anticancerogenic effects by apoptosis induction, cell proliferation inhibition and angiogenesis. It has been proposed that green tea polyphenols (*CAS no*: *84650-60-2*; 200 mg /kg bw/day) may act as a detoxifying agent, altering the expression of glycoconjugates and immunological markers (Srinivasan et al., 2008), modulating lipid peroxidation and enhancing antioxidant ability in an OSCC model. The recent effect was also associated with black tea polyphenols (*BTP*, *CAS no*: *84650-60-2*; 0.05% Polyphenon) (Chandra Mohan et al., 2005).

Epigallocatechin-3-gallate (*CAS no*: *989-51-5*; 0 to 60 µM or 5, 10, 20, 50 µM, ddm) of green tea decreased the expression of matrix metalloproteinase (MMP) 2 (*UniProt*: *P08253*) and 9 (*UniProt*: *P14780***)**, urokinase plasminogen activator (*UPA*; *UniProt*: *P00749*) and inhibited the invasion and migration of carcinoma HSC-2 cells and normal HGF-2 fibroblasts cells (Babich et al., 2005; Ho et al., 2007; Kato et al., 2008). A phase II randomized, placebo-controlled trial of GTE (500, 750, or 1,000 mg/m^2, ddm) concluded that GTE may suppress oropharyngeal premalignant changes, in part through reducing angiogenic stimulus (Tsao et al., 2009).

Black tea was confirmed to have a beneficial effect on OLP (Halder et al., 2005). The BTP (30 to 40 mg/kg bw) exerted its preventive effects by inhibiting cell proliferation, modulating the oxidant-antioxidant status as well as markers of cell proliferation, cell survival, tumor infiltration, angiogenesis, apoptosis and xenobiotic-metabolizing enzymes (Letchoumy et al., 2006; Letchoumy et al 2007; Vidjaya Letchoumy et al., 2008). The dietary administration of solitary or combined bovine lactoferrin (*UniProt*: *Q6LBN7*; 0.2%) and/or BTP (0.05% Polyphenon-B) has been reported to reduce tumor incidence in the hamster buccal pouch (HBP) (Chandra Mohan et al., 2006). Yerba mate tea (236 to 490 mg equiv of chlorogenic/g of dry leaves) is rich in phenolic constituents and can inhibit OSCC proliferation, topoisomerase 1 (*UniProt*: *P11387***)**, topoisomerase 2 (*UniProt*: *P11388***) (**Gonzalez de Mejia et al., 2005).

3. Medicinal Plants (Traditional Chinese Medicine)

Levamisole (*CAS no*: *14769-73-4*; *ATC/DDD*: *P02CE01*; antihelminthic drug) and/or Chinese medicinal herbs (root of *Astragalus*; *NCBI Taxonomy ID*: *20400*; 12 g/day; fruit of *Ligustrum*, *NCBI Taxonomy ID*: *104487*; 9 g/day; and fruit of *Ziziphi jujuba*; *NCBI Taxonomy ID*: *157914*; 9 g/day) can modulate the level of the serum SCC associated antigen. For OLP patients, the combination therapy was superior to the single therapy of levamisole or of Chinese medicinal herbs (Sun & Chiang, 2001). Chinese herbal extracts from *Drynaria bonii* (*NCBI Taxonomy ID*: *272673*), *Angelica sinensis* (*NCBI Taxonomy ID*: *165353*) and *Cornus officinalis Sieb* (*NCBI Taxonomy ID*: *16906*) were investigated for their antitumor potential on human OSCC cell lines (HSC-2 and NA) and the data demonstrated several unique antitumor properties of *Drynaria bonii* (Chu et al., 2009).

Ching waysan (0, 10, 25, 50, 75 and 100 µl/ml, ddm; *tab 1*) induced apoptosis via a Bax (*UniProt*: *Q07812*)-dependent pathway in human OSCC cell lines (OC2 and TSCCa) (Liao et al., 2005). Shenyang *(*1,026 mg or 256.5 mg/100 g bw) had immune modulatory effects in rattus norvegicus, Sprague-Dawley type, with 4-NQO-induced OSCC (Jiang et al., 2007). Zeng sheng ping (6 g/kg bw/day by gavage) has been reported to prevent OSCC in humans with OLP as well as in animal models (Sun et al., 2010).

Herba erigerontis (*NCBI Taxonomy ID*: *124940*) appeared to hamper the possible progression of OLP to becoming a tumor (Zhou et al., 2000). Additionally, Xian huayin (1.7 ml or 11.4 ml/kg bw/day) from China may exhibit a reversal effect on DMBA-induced premalignant lesions in the HBP (Xu et al., 2010). The extract of the rhizome of *Coptidium* (*NCBI Taxonomy ID*: *568508*, 13.5% w/w) induced cytochrome-c (*UniProt*: *P99999*) dependent apoptosis in immortalized and malignant human oropharyngeal keratinocytes via the mitochondrial signaling pathway (Lee et al., 2006).

Verticinone (*CAS no*: *18059-10-4*; different concentrations for different cell lines), an alkaloid from *Fritillaria ussuriensis* (*NCBI Taxonomy ID*: *152096*) induced apoptosis through a caspase pathway mediated by mitochondrial damage in immortalized keratinocytes and OSCC cell lines (Yun et al., 2008). Rhein (*CAS no*: *478-43-3*) is a anthraquinone (*CAS no*: *84-65-1*) compound from *Rheum palmatum* (*NCBI Taxonomy ID*: *137221*; 0, 25, 50, 100 µM) having inhibitory effects on OSCC as do emodin (*CAS no*: *518-82-1*; 0, 20, 30, 40 µM) and aloe-emodin (*CAS no*: *481-72-1*; 2.5, 5, 10, 20, 40 µM or 0, 25, 50, 100 µM) (Xiao et al., 2007; Chen et al., 2010). Shikonin (*CAS no*: *517-89-5*; 0, 10, 20, 30, 40 µM, ddm), a naphthoquinone (*CAS no*: *130-15-4*) pigment, seemed to alter growth and induce apoptosis in the human OSCC cell line Tca-8113 (Min et al., 2008).

4. Monomeric Compounds from Plants

4.1. Curcumin

Curcumin (diferuloylmethane), a polyphenol from the plant *Curcuma longa* (*NCBI Taxonomy ID*: *136217*), traditionally called turmeric, is used for cancer chemoprevention and treatment (Aggarwal et al., 200). The chemical structures of curcumin and other compounds are well known. Curcumin (0.1, 1.0, 10.0 µM, ddm) was considerably more potent than genistein (*CAS no*: *446-72-0*) isoflavone and quercetin (*CAS no*: *117-39-5*) flavonoid, but *cisplatin* (*ATC/DDD*: *L01XA01*; a platinum-based chemotherapy drug; *CAS no*: *15663-27-1*) was five times more potent than curcumin in inhibition of growth and DNA synthesis in a cell line (SCC-25) *in vitro* (Elattar & Virji, 2000). In metabolism studies, curcumin (1, 5, 10, 25, and 50 µM, ddm) inhibited P-450 1A1 (*UniProt*: *P04798***)**-mediated benzo(a)pyrene diol (*CAS no: 51689-89-5*) bioactivation in both OSCC lines and intact oropharyngeal mucosa (Rinaldi et al., 2002). Curcumin (0.1 µM to 1mM) may also induce reactive oxygen species generation and early apoptotic changes in human gingival fibroblasts and human submandibular gland carcinoma cells (Atsumi et al., 2006). It was reported that peroral administration of curcumin (80 mg/kg bw) and piperine (*CAS no*: *94-62-2*; 50 mg/kg bw) to DMBA-painted hamsters helped to prevent the formation of OSCC (Manoharan et al., 2009).

Dietary turmeric (1%) augmented apoptosis and decreased cell proliferation in DMBA-treated animals, which was reflected by decreased tumor burden, multiplicity and enhanced latency period (Garg et al., 2008). In highly invasive human YD-10B OSCC cell lines, curcumin inhibited cell proliferation and motility through decreased expression of MMP2 and 9, UPA and UPA receptor (*UniProt*: *Q03405***) (**Shin et al., 2010).

4.2. Ferulic Acid

Ferulic acid (hydroxycinnamic acid, *CAS no*: *1135-24-6*), is found in the brans of grasses such as wheat (*Triticum aestivum*; *NCBI*

Taxonomy ID: 4565), rice (*Oryza sativa*; *NCBI Taxonomy ID*: *4530*), and oats (*Avena*; *NCBI Taxonomy ID*: *4496*) (Mathew & Abraham, 2004). It (40 mg/kg bw) has been said to reduce tumor incidence and size in DMBA-painted animals by exhibiting antilipidperoxidative effects as well as by its ability to modulate the status of carcinogen detoxifying agents (Balakrishnan et al., 2008).

4.3. Carnosic Acid

Carnosic acid (*CAS no*: *3650-09-7*; 10 mg/kg bw/day) from rosemary (*Rosmarinus officinalis*; *NCBI Taxonomy ID*: *39367*) has been suggested to chemoprevent against DMBA-induced OSCC possibly due to likely carcinogen detoxification and antilipidperoxidative properties (Manoharan et al., 2010).

4.4. Berberine

Berberine (*CAS no*: *2086-83-1*), an isoquinoline (*CAS no: 119-65-3*) alkaloid present in roots, rhizome, stem and bark of a number of traditional medicinal plants such as *Berberis aquifolium* (*NCBI Taxonomy ID*: *203270*), *Berberis vulgaris* (*NCBI Taxonomy ID*: *258209*), *Berberis aristata* (*NCBI Taxonomy ID*: *659592*) and *Tinospora cordifolia* (*NCBI Taxonomy ID*: *285590*) (Craig, 1999)**.** The tumor size in xenograft mice treated with berberine (10 mg/kg bw) was smaller than that in the non-treated control group (Ho et al., 2009)**.** Prolonged exposure of human HSC-3 OSCC cell lines to berberine (0, 5, 10, 25, 50, 75 µM) increased apoptosis through reduced levels of MMP (*UniProt*: *P03956*), release of cytochrome c and activation of caspase 3 (*UniProt*: *P42574*) (Lin et al., 2007). Moreover, berberine (0, 62.5, 100 µM) was found to down-regulate u-PA, MMP2 and MMP9 expression in SCC-4 cells through the focal adhesion kinase 1 (*UniProt*: *Q05397*), inhibitor of nuclear factor (NF) kappa B and NF kappa B mediated pathways and berberine inhibited the invasive capacity of malignant cells (Ho et al., 2009).

4.5. Flavonoids

Many flavonoids show anti-tumorigenic properties on various types of tumors. One particular natural flavonoid compound, luteolin (*CAS no*: 491-*70-3*) could be an effective chemotherapeutic agent for the treatment of oral squamous cell carcinoma. Luteolin (5 or 10 µM for 5 and 7days.) reduced the viability of SCC-4 cells and induced apoptosis by decreasing the expression of cyclin-dependent kinase (CDKs), cyclins, and phosphor-retinoblastoma (p-Rb) anti-apoptotic protein (Yang et al., 2008). Moreover, prenylated flavonoids significantly enhanced the cytotoxic activity against two human oral tumor cell lines (HSC-2, HSG) (Fukai et al., 2000; Shirataki et al., 2001).

6. A Few Notes on Dosages

Additional searches were conducted to compare the dosages previously discussed with those suggested for humans. The following databases have been interrogated: *ABOUTHERBS*, a web site provided by the Memorial Sloan Kettering Cancer Center (MSKCC Integrative Medicine Service) (Cassileth et al., 2009), *HERBS AT A GLANCE*, and the *COMPLEMENTARY AND ALTERNATIVE MEDICINE* (CAM) subset of *PUBMED* both of which have been established by the National Center for Complementary and Alternative Medicine (NCCAM) (Marcus & Grollman, 2006).

This part of the study revealed that the current body of literature contains only a few peer reviewed articles on effective clinical dosages in humans specified by good scientific practice and experimental design. At least in part this may be attributable to the fact that botanicals come in a variety of dosage forms such as teas, creams, gels, capsules or tablets, and/or that they can be formulated for various types of drug delivery, supporting extended, sustained or other modes of drug release. Different dosages can therefore be readily extracted as discussed in the body of literature (*tab 2*). Comparative studies are needed to learn more about dose-response relationships in this context and develop

sufficient ontologies and mathematical models.

Conclusion

In the last decade (2000-2010), there were numerous reports from China, Japan, India, Europe, the Middle East and the United States of America concerning specific botanicals and their extracts' chemopreventive activity on OSCC. Botanicals showed gratifying effects on OSCC. More systematic studies are however warranted for sufficient ontology population and mathematical modeling.

References

1. **Aggarwal BB, Kumar A, Bharti AC. (2003). Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res, 23, 363-398.**
2. **Atsumi T, Tonosaki K, Fujisawa S. (2006). Induction of early apoptosis and ROS-generation activity in human gingival fibroblasts (HGF) and human submandibular gland carcinoma (HSG) cells treated with curcumin. *Arch Oral Biol*, 51, 913-921.**
3. **Aviello G, Abenavoli L, Borrelli F, Capasso R, Izzo AA, Lembo F, Romano B, Capasso F. (2009). Garlic: empiricism or science? *Nat Prod Commun*, 4, 1785-1796.**
4. **Babich H, Krupka ME, Nissim HA, Zuckerbraun HL. (2005). Differential *in vitro* cytotoxicity of (-)-epicatechin gallate (ECG) to cancer and normal cells from the human oral cavity. *Toxicol In vitro*, 19, 231-242.**
5. **Balakrishnan S, Menon VP, Manoharan S. (2008). Ferulic acid inhibits 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *J Med Food*, 11, 693-700.**
6. **Balasenthil S, Arivazhagan S, Nagini S. (2000). Garlic enhances circulatory antioxidants during 7, 12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *J Ethnopharmacol*, 72, 429-433.**
7. **Balasenthil S, Nagini S. (2000). Inhibition of 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis by S-allylcysteine. *Oral Oncol*, 36, 382-386.**
8. **Balasenthil S, Ramachandran CR, Nagini S. (2001). Prevention of 4-nitroquinoline 1-oxideinduced rat tongue carcinogenesis by garlic. *Fitoterapia*, 72, 524-531.**
9. **Balasenthil S, Ramachandran CR, Nagini S. (2001). S-allylcysteine, a garlic constituent, inhibits 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *Nutr Cancer*, 40, 165-172.**
10. **Balasenthil S, Rao KS, Nagini S. (2002). Altered cytokeratin expression during chemoprevention of experimental hamster buccal pouch carcinogenesis by garlic. *J Oral Pathol Med*, 31, 42-146.**
11. **Balasenthil S, Rao KS, Nagini S. (2002). Garlic induces apoptosis during 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *Oral Oncol*, 38, 431-436.**
12. **Balasenthil S, Rao KS, Nagini S. (2003). Retinoic acid receptor-beta mRNA expression during chemoprevention of hamster**

cheek pouch carcinogenesis by garlic. *Asia Pac J Clin Nutr*, 12, 215-218.

13. **Bargagna-Mohan P, Hamza A, Kim YE, Khuan Abby Ho Y, Mor-Vaknin N, Wendschlag N, Liu J, Evans RM, Markovitz DM, Zhan CG, Kim KB, Mohan R. (2007). The tumor inhibitor and antiangiogenic agent withaferin A targets the intermediate filament protein vimentin. *Chem Biol*, 14, 623-634.**
14. **Baskar AA, Ignacimuthu S, Paulraj GM, Al Numair KS. (2010). Chemopreventive potential of beta-Sitosterol in experimental colon cancer model - an *in vitro* and *In vivo* study. *BMC Complement Altern Med*, 10, 24-34.**
15. **Bhuvaneswari V, Velmurugan B, Balasenthil S, Ramachandran CR, Nagini S. (2001). Chemopreventive efficacy of lycopene on 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *Fitoterapia*, 72, 865-874.**
16. **Bhuvaneswari V, Rao KS, Nagini S. (2004). Altered expression of anti and proapoptotic proteins during chemoprevention of hamster buccal pouch carcinogenesis by tomato and garlic combination. *Clin Chim Acta*, 350, 65-72.**
17. **Bhuvaneswari V, Velmurugan B, Nagini S. (2004). Dose-response effect of tomato paste on 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *J Exp Clin Cancer Res*, 23, 241-249.**
18. **Bhuvaneswari V, Abraham SK, Nagini S. (2005). Combinatorial antigenotoxic and anticarcinogenic effects of tomato and garlic through modulation of xenobioticmetabolizing enzymes during hamster buccal pouch carcinogenesis. *Nutrition*, 21, 726-731.**
19. **Boehm K, Borrelli F, Ernst E, Habacher G, Hung SK, Milazzo S, Horneber M. (2009). Green tea (Camellia sinensis) for the prevention of cancer. Cochrane Database *Syst Rev*, 8, CD005004.**
20. **Cassileth BR, Heitzer M, Wesa K. (2009). The public health impact of herbs and nutritional supplements. *Pharm Biol*, 47, 761-767.**
21. **Casto BC, Kresty LA, Kraly CL, Pearl DK, Knobloch TJ, Schut HA, Stoner GD, Mallery SR, Weghorst CM. (2002). Chemoprevention of oral cancer by black raspberries. *Anticancer Res*, 22, 4005-4015.**
22. **Chandra Mohan KV, Hara Y, Abraham SK, Nagini S. (2005). Comparative evaluation of the chemopreventive efficacy of green and black tea polyphenols in the hamster buccal pouch carcinogenesis model. *Clin Biochem*, 38, 879-886.**
23. **Chandra Mohan KV, Devaraj H, Prathiba D, Hara Y, Nagini S. (2006). Antiproliferative and apoptosis inducing effect of lactoferrin and black tea polyphenol combination on hamster buccal pouch carcinogenesis. *Biochim Biophys Acta*, 1760, 1536- 1544.**
24. **Chatelain K, Phippen S, McCabe J, Teeters CA, O'Malley S, Kingsley K. (2010). Cranberry and grape seed extracts inhibit the**

proliferative phenotype of oral squamous cell carcinomas. *Evid Based Complement Alternat Med*, 2011, 467691.

25. **Chen YY, Chiang SY, Lin JG, Ma YS, Liao CL, Weng SW, Lai TY, Chung JG. (2010) Emodin, aloe-emodin and rhein inhibit migration and invasion in human tongue cancer SCC-4 cells through the inhibition of gene expression of matrix metalloproteinase-9. *Int J Oncol*, 36, 1113-1120.**
26. **Chu Q, Satoh K, Kanamoto T, Terakubo S, Nakashima H, Wang Q, Sakagami H. (2009). Antitumor potential of three herbal extracts against human oral squamous cell lines. *Anticancer Res*, 29, 3211-3219.**
27. **Craig WJ. (1999). Health-promoting properties of common herbs. *Am J Clin Nutr*, 70, 491S-499S.**
28. **Cronin H, Draelos ZD. (2010). Top 10 botanical ingredients in 2010 anti-aging creams. *J Cosmet Dermatol*, 9, 218-225.**
29. **Day TA, Davis BK, Gillespie MB, Joe JK, Kibbey M, Martin-Harris B, Neville B, Richardson MS, Rosenzweig S, Sharma AK, Smith MM, Stewart S, Stuart RK. (2003). Oral cancer treatment. *Curr Treat Options Oncol*, 4, 27-41.**
30. **Dhanarasu S, Al-hazimi AM, Sethuraman P, Selvam M. (2010). Chemopreventive and antilipidperoxidative potential of thespesia populnea (L.) on experimental buccal pouch carcinogenesis. *Ibnosina J Med BS*, 2, 269-277.**
31. **Dhillon N, Aggarwal BB, Newman RA, Wolff RA, Kunnumakkara AB, Abbruzzese JL, Ng CS, Badmaev V, Kurzrock R. (2008). Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin Cancer Res*, 15, 4491-4499.**
32. **Donate LE, Blasco MA. (2011). Telomeres in cancer and ageing. *Philos Trans R Soc Lond B Biol Sci*, 366, 76-84.**
33. **Dugoua JJ, Seely D, Perri D, Mills E, Koren G. (2008). Safety and efficacy of cranberry (vaccinium macrocarpon) during pregnancy and lactation. *Can J Clin Pharmacol*, 15, e80-86.**
34. **Elattar TM, Virji AS. (2000). The inhibitory effect of curcumin, genistein, quercetin and cisplatin on the growth of oral cancer cells *in vitro*. *Anticancer Res*, 20, 1733-1738.**
35. **Fleischauer AT, Poole C, Arab L. (2000). Garlic consumption and cancer prevention: metaanalyses of colorectal and stomach cancers. *Am J Clin Nutr*, 72, 1047-1052**
36. **Fukai T, Sakagami H, Toguchi M, Takayama F, Iwakura I, Atsumi T, Ueha T, Nakashima H, Nomura T. (2000). Cytotoxic activity of low molecular weight polyphenols against human oral tumor cell lines. *Anticancer Res*, 20, 2525-36.**
37. **Garg R, Ingle A, Maru G. (2008). Dietary turmeric modulates DMBA-induced p21ras, MAP kinases and AP-1/NF kappa B pathway to alter cellular responses during hamster buccal pouch carcinogenesis. *Toxicol Appl Pharmacol*, 232, 428-439.**
38. **Giglia E. (2008). To Google or not to Google, this is the question. *Eur J Phys Rehabil Med*, 44, 221-230.**

39. **Gonzalez de Mejia E, Song YS, Ramirez-Mares MV, Kobayashi H. (2005). Effect of yerba mate (ilex paraguariensis) tea on topoisomerase inhibition and oral carcinoma cell proliferation. *J Agric Food Chem*, 53, 1966-1973.**
40. **Grawish ME. (2008). Effects of Spirulina platensis extract on Syrian hamster cheek pouch mucosa painted with 7,12-dimethylbenz[a]anthracene. *Oral Oncol*, 44, 956-962.**
41. **Grawish ME, Zaher AR, Gaafar AI, Nasif WA. (2010). Long-term effect of Spirulina platensis extract on DMBA-induced hamster buccal pouch carcinogenesis (immunohistochemical study). *Med Oncol*, 27, 20-28.**
42. **Grawish ME, Zyada MM, Zaher AR. (2010). Inhibition of 4-NQO-induced F433 rat tongue carcinogenesis by oleuropein-rich extract. *Med Oncol*. 28, 1163-8.**
43. **Gullett NP, Ruhul Amin AR, Bayraktar S, Pezzuto JM, Shin DM, Khuri FR, Aggarwal BB, Surh YJ, Kucuk O. (2010). Cancer prevention with natural compounds. Semin Oncol, 37, 258-281.**
44. **Halder A, Raychowdhury R, Ghosh A, De M. (2005). Black tea (Camellia sinensis) as a chemopreventive agent in oral precancerous lesions. *J Environ Pathol Toxicol Oncol*, 24, 141-144.**
45. **Han C, Ding H, Casto B, Stoner GD, D'Ambrosio SM. (2005). Inhibition of the growth of premalignant and malignant human oral cell lines by extracts and components of black raspberries. *Nutr Cancer*, 51, 207-217.**
46. **Harish Kumar G, Vidya Priyadarsini R, Vinothini G, Vidjaya Letchoumy P, Nagini S. (2010). The neem limonoids azadirachtin and nimbolide inhibit cell proliferation and induce apoptosis in an animal model of oral oncogenesis. *Invest New Drugs*, 28, 392- 401.**
47. **Hayasaka Y, Waters EJ, Cheynier V, Herderich MJ, Vidal S. (2003). Characterization of proanthocyanidins in grape seeds using electrospray mass spectrometry. *Rapid Commun Mass Spectrom*, 17, 9-16.**
48. **Hayashi T, Hayashi K, Maeda M, Kojima I. (1996). Calcium spirulan, an inhibitor of enveloped virus replication, from a blue-green alga spirulina platensis. *J Nat Prod*, 59, 83-87.**
49. **Herranz D, Muñoz-Martin M, Cañamero M, Mulero F, Martinez-Pastor B, Fernandez-Capetillo O, Serrano M. (2010). Sirt1 improves healthy ageing and protects from metabolic syndrome-associated cancer. *Nat Commun*, 1, 3.**
50. **Ho YC, Yang SF, Peng CY, Chou MY, Chang YC. (2007). Epigallocatechin-3-gallate inhibits the invasion of human oral cancer cells and decreases the productions of matrix metalloproteinases and urokinase-plasminogen activator. *J Oral Pathol Med*, 36, 588-593.**
51. **Ho YT, Yang JS, Li TC, Lin JJ, Lin JG, Lai KC, Ma CY, Wood WG, Chung JG. (2009). Berberine suppresses in vitro migration and invasion of human SCC-4 tongue**

squamous cancer cells through the inhibitions of FAK, IKK, NF kappa B, u-PA and MMP-2 and -9. *Cancer Lett*, 279, 155-162.

52. Ho YT, Yang JS, Lu CC, Chiang JH, Li TC, Lin JJ, Lai KC, Liao CL, Lin JG, Chung JG. (2009). Berberine inhibits human tongue squamous carcinoma cancer tumor growth in a murine xenograft model. Phytomedicine, 16, 887-90.

53. Ilavarasan R, Vasudevan M, Anbazhagan S, Venkataraman S. (2003). Antioxidant activity of thespesia populnea bark extracts against carbon tetrachloride-induced liver injury in rats. *J Ethnopharmacol*, 87, 227-230.

54. Jiang C, Ye D, Qiu W, Zhang X, Zhang Z, He D, Zhang P, Chen W. (2007). Response of lymphocyte subsets and cytokines to shenyang prescription in Sprague-Dawley rats with tongue squamous cell carcinomas induced by 4NQO. *BMC Cancer*, 7, 40.

55. Kataria H, Shah N, Kaul SC, Wadhwa R, Kaur G. (2011). Water extract of ashwagandha leaves limits proliferation and migration, and induces differentiation in glioma cells. *Evid Based Complement Alternat Med*, 2011, 267614.

56. Kato K, Long NK, Makita H, Toida M, Yamashita T, Hatakeyama D, Hara A, Mori H, Shibata T. (2008). Effects of green tea polyphenol on methylation status of RECK gene and cancer cell invasion in oral squamous cell carcinoma cells. *Br J Cancer*, 99, 647-654.

57. Khan N, Afaq F, Mukhtar H. (2008). Cancer chemoprevention through dietary antioxidants: progress and promise. *Antioxid Redox Signal*, 10, 475-510.

58. Khater D S. (2010). The influence of ginger as a chemopreventive agent on proliferation and apoptosis in chemically induced oral carcinogenesis. *Nature and Science*, 8, 44-51.

59. Kingsley K, Galbraith GM, Herring M, Stowers E, Stewart T, Kingsley KV. (2011). Why not just Google it? An assessment of information literacy skills in a biomedical science curriculum. *BMC Med Educ*, 11, 17.

60. Kiyono T. (2007). Molecular mechanisms of cellular senescence and immortalization of human cells. *Expert Opin Ther Targets*, 11, 1623-1637.

61. Koul IB, Kapil A. (1993). Evaluation of the liver protective potential of piperine, an activeprinciple of black and long peppers. *Planta Med*, 59, 413-417.

62. Krishnakumar N, Manoharan S, Palaniappan PR, Venkatachalam P, Manohar MG. (2009). Chemopreventive efficacy of piperine in 7,12-dimethyl benz [a] anthracene (DMBA)- induced hamster buccal pouch carcinogenesis: an FT-IR study. *Food Chem Toxicol*, 47, 2813-2820.

63. Lee HJ, Son DH, Lee SK, Lee J, Jun CD, Jeon BH, Lee SK, Kim EC. (2006). Extract of Coptidis rhizoma induces cytochrome-c dependent apoptosis in immortalized and malignant human oral

keratinocytes. *Phytother Res*, 20, 773-779.

64. Letchoumy PV, Chandra Mohan KV, Kumaraguruparan R, Hara Y, Nagini S. (2006). Black tea polyphenols protect against 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *Oncol Res*, 16, 167-178.

65. Letchoumy PV, Mohan KV, Prathiba D, Hara Y, Nagini S. (2007). Comparative evaluation of antiproliferative, antiangiogenic and apoptosis inducing potential of black tea polyphenols in the hamster buccal pouch carcinogenesis model. *J Carcinog*, 6, 19.

66. Li MH, Jang JH, Sun B, Surh YJ. (2004). Protective effects of oligomers of grape seed polyphenols against beta-amyloid-induced oxidative cell death. *Ann N Y Acad Sci*, 1030, 317-329.

67. Li N, Chen X, Liao J, Yang G, Wang S, Josephson Y, Han C, Chen J, Huang MT, Yang CS. (2002). Inhibition of 7,12-dimethylbenz[a]anthracene (DMBA)- induced oral carcinogenesis in hamsters by tea and curcumin. *Carcinogenesis*, 23, 1307-1313.

68. Liao PH, Chen SL, Shih HC, Chou MY. (2005). Induction of apoptosis in human oral cancer cell lines, OC2 and TSCCa, by Ching waysan. *Am J Chin Med*, 33, 21-27.

69. Lin CC, Yang JS, Chen JT, Fan S, Yu FS, Yang JL, Lu CC, Kao MC, Huang AC, Lu HF, Chung JG. (2007). Berberine induces apoptosis in human HSC-3 oral cancer cells via simultaneous activation of the death receptor-mediated and mitochondrial pathway. *Anticancer Res*, 27, 3371-3378.

70. Livny O, Kaplan I, Reifen R, Polak-Charcon S, Madar Z, Schwartz B. (2002). Lycopene inhibits proliferation and enhances gap-junction communication of KB-1 human oral tumor cells. *J Nutr*, 132, 3754-3759.

71. Longo VD, Lieber MR, Vijg J. (2008). Turning anti-ageing genes against cancer. *Nat Rev Mol Cell Biol*, 9, 903-910.

72. Low Dog T. (2009). The use of botanicals during pregnancy and lactation. *Altern Ther Health Med*, 15, 54-58.

73. Luengwilai K, Fiehn OE, Beckles DM. (2010). Comparison of leaf and fruit metabolism in two tomato (solanum lycopersicum L.) genotypes varying in total soluble solids. *J Agric Food Chem*, 58, 11790-11800.

74. Mallery SR, Stoner GD, Larsen PE, Fields HW, Rodrigo KA, Schwartz SJ, Tian Q, Dai J, Mumper RJ. (2007). Formulation and *in vitro* and in-vivo evaluation of a mucoadhesive gel containing freeze dried black raspberries: implications for oral cancer chemoprevention. *Pharm Res*, 24, 728-737.

75. Mallery SR, Zwick JC, Pei P, Tong M, Larsen PE, Shumway BS, Lu B, Fields HW, Mumper RJ, Stoner GD. (2008). Topical application of a bioadhesive black raspberry gel modulates gene expression and reduces cyclooxygenase 2 protein in human premalignant oral lesions. *Cancer Res*, 68, 4945-4957.

76. **Manikandan P, Letchoumy PV, Gopalakrishnan M, Nagini S. (2008). Evaluation of Azadirachta indica leaf fractions for *in vitro* antioxidant potential and *in vivo* modulation of biomarkers of chemoprevention in the hamster buccal pouch carcinogenesis model. *Food Chem Toxicol*, 46, 2332-2343.**
77. **Manoharan S, Kavitha K, Senthil N, Renju GL. (2006). Evaluation of anticarcinogenic effects of clerodendron inerme on 7,12-dimethylbenz(a) anthracene-induced hamster buccal pouch carcinogenesis. *Singapore Med J*, 47, 1038-1043.**
78. **Manoharan S, Panjamurthy K, Pugalendi P, Balakrishnan S, Rajalingam K, Vellaichamy L, Alias LM. (2008). Protective role of withaferin-A on red blood cell integrity during 7,12-dimethylbenz[a]anthracene induced oral carcinogenesis. *Afr J Tradit Complement Altern Med*, 6, 94-102.**
79. **Manoharan S, Balakrishnan S, Menon VP, Alias LM, Reena AR. (2009). Chemopreventive efficacy of curcumin and piperine during 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *Singapore Med J*, 50, 139-146.**
80. **Manoharan S, Vasanthaselvan M, Silvan S, Baskaran N, Kumar Singh A, Vinoth Kumar V. (2010). Carnosic acid: a potent chemopreventive agent against oral carcinogenesis. *Chem Biol Interact*, 188, 616-622.**
81. **Marcus DM, Grollman AP. (2006). Science and government. Review for NCCAM is overdue. *Science*, 313, 301-302.**
82. **Mathew S, Abraham TE. (2004). Ferulic acid: an antioxidant found naturally in plant cell walls and feruloyl esterases involved in its release and their applications. *Crit Rev Biotechnol*, 24, 59-83.**
83. **Min R, Tong J, Wenjun Y, Wenhu D, Xiaojian Z, Jiacai H, Jian Z, Wantao C, Chenping Z. (2008). Growth inhibition and induction of apoptosis in human oral squamous cell carcinoma Tca-8113 cell lines by Shikonin was partly through the inactivation of NF-kappa B pathway. *Phytother Res*, 22, 407-415.**
84. **Monobe M, Ema K, Tokuda Y, Maeda-Yamamoto M. (2010). Enhancement of the phagocytic activity of macrophage-like cells with a crude polysaccharide derived from green tea (Camellia sinensis) extract. *Biosci Biotechnol Biochem*, 74, 1306-1308.**
85. **Nobili S, Lippi D, Witort E, Donnini M, Bausi L, Mini E, Capaccioli S. (2009). Natural compounds for cancer treatment and prevention. *Pharmacol Res*, 59, 365-378.**
86. **Pandey R, Verma RK, Singh SC, Gupta MM. (2003). 4alpha-methyl-24beta-ethyl-5alphacholesta-14,25-dien-3beta-ol and 24beta-ethylcholesta-5, 9(11), 22E-trien-3beta-ol, sterols from clerodendrum inerme. *Phytochemistry*, 63, 415-420.**
87. **Panjamurthy K, Manoharan S, Balakrishnan S, Suresh K, Nirmal MR, Senthil N, Alias LM. (2008). Protective effect of**

withaferin-A on micronucleus frequency and detoxication agents during experimental oral carcinogenesis. *Afr J Tradit Complement Altern Med*, 6, 1-8.

88. **Priyadarsini RV, Manikandan P, Kumar GH, Nagini S. (2009). The neem limonoids azadirachtin and nimbolide inhibit hamster cheek pouch carcinogenesis by modulating xenobiotic-metabolizing enzymes, DNA damage, antioxidants, invasion and angiogenesis. *Free Radic Res*, 43, 492-504.**
89. **Rinaldi AL, Morse MA, Fields HW, Rothas DA, Pei P, Rodrigo KA, Renner RJ, Mallery SR.. (2002). Curcumin activates the aryl hydrocarbon receptor yet significantly inhibits (-)-benzo(a)pyrene-7R-trans-7,8-dihydrodiol bioactivation in oral squamous cell carcinoma cells and oral mucosa. *Cancer Res*, 62, 5451-5456.**
90. **Roberts RJ. (2001). PubMed Central: The GenBank of the published literature. *Proc Natl Acad Sci U S A*, 98, 381-382.**
91. **Rodrigo KA, Rawal Y, Renner RJ, Schwartz SJ, Tian Q, Larsen PE, Mallery SR. (2006). Suppression of the tumorigenic phenotype in human oral squamous cell carcinoma cells by an ethanol extract derived from freezedried black raspberries. *Nutr Cancer*, 54, 58-68.**
92. **Rosenbloom RA, Chaudhary J, Castro-Eschenbach D. (2011). Traditional botanical medicine: an introduction. *Am J Ther*, 18, 158-161.**
93. **Roy MK, Kobori M, Takenaka M, Nakahara K, Shinmoto H, Isobe S, Tsushida T. (2007). Antiproliferative effect on human cancer cell lines after treatment with nimbolide extracted from an edible part of the neem tree (azadirachta indica). *Phytother Res*, 21, 245-250.**
94. **Sankaranarayanan R, Dinshaw K, Nene BM, Ramadas K, Esmy PO, Jayant K, Somanathan T, Shastri S. (2006). Cervical and oral cancer screening in India. *J Med Screen*, 1, S35-38.**
95. **Sato H, Genet C, Strehle A, Thomas C, Lobstein A, Wagner A, Mioskowski C, Auwerx J, Saladin R. (2007). Anti-hyperglycemic activity of a TGR5 agonist isolated from Olea europaea. *Biochem Biophys Res Commun*, 362, 793-798.**
96. **Saunders FR, Wallace HM. (2010). On the natural chemoprevention of cancer. *Plant Physiol Biochem*, 48, 621-626.**
97. **Schwarz S, Obermüller-Jevic UC, Hellmis E, Koch W, Jacobi G, Biesalski HK. (2008). Lycopene inhibits disease progression in patients with benign prostate hyperplasia. *J Nutr*, 138, 49-53.**
98. **Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, Marczylo TH, Morgan B, Hemingway D, Plummer SM, Pirmohamed M, Gescher AJ,Steward WP. (2004). Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clin Cancer Res*, 10, 6847- 6854.**
99. **Shin HK, Kim J, Lee EJ, Kim SH. (2010). Inhibitory effect of**

curcumin on motility of human oral squamous carcinoma YD-10B cells via suppression of ERK and NF-kappaB activations. *Phytother Res*, 24, 577-582.

100. Shirataki Y, Kawase M, Saito S, Kurihara T, Tanaka W, Satoh K, Sakagami H, Motohashi N. (2000). Selective cytotoxic activity of grape peel and seed extracts against oral tumor cell lines. *Anticancer Res*, 20, 423-426.

101. Shirataki Y, Motohashi N, Tani S, Sakagami H, Satoh K, Nakashima H, Mahapatra SK, Ganguly K, Dastidar SG, Chakrabarty AN. (2001). In vitro biological activity of prenylflavanones. *Anticancer Res*, 21, 275-80.

102. Silverman S Jr, Kerr AR, Epstein JB. (2010). Oral and pharyngeal cancer control and early detection. *J Cancer Educ*, 25, 279-281.

103. Singh M, Krishanappa R, Bagewadi A, Keluskar V. (2004). Efficacy of oral lycopene in the treatment of oral leukoplakia. *Oral Oncol*, 40, 591-596.

104. Srinivasan P, Suchalatha S, Babu PV, Devi RS, Narayan S, Sabitha KE, Shyamala Devi CS. (2008). Chemopreventive and therapeutic modulation of green tea polyphenols on drug metabolizing enzymes in 4-nitroquinoline 1-oxide induced oral cancer. *Chem Biol Interact*, 172, 224-234.

105. Stanković M, Tesević V, Vajs V, Todorović N, Milosavljević S, Godevac D. (2008). Antioxidant properties of grape seed extract on human lymphocyte oxidative defence. *Planta Med*, 74, 730-735.

106. Subapriya R, Bhuvaneswari V, Nagini S. (2005). Ethanolic neem (Azadirachta indica) leaf extract induces apoptosis in the hamster buccal pouch carcinogenesis model by modulation of Bcl-2, Bim, caspase 8 and caspase 3. *Asian Pac J Cancer Prev*, 6, 515-520.

107. Subapriya R, Bhuvaneswari V, Ramesh V, Nagini S. (2005). Ethanolic leaf extract of neem (Azadirachta indica) inhibits buccal pouch carcinogenesis in hamsters. *Cell Biochem Funct*, 23, 229-238.

108. Sun A, Chiang CP. (2001). Levamisole and/or Chinese medicinal herbs can modulate the serum level of squamous cell carcinoma associated antigen in patients with erosive oral lichen planus. *J Oral Pathol Med*, 30, 542-548.

109. Sun Z, Guan X, Li N, Liu X, Chen X. (2010). Chemoprevention of oral cancer in animal models, and effect on leukoplakias in human patients with Zeng sheng ping, a mixture of medicinal herbs. *Oral Oncol*, 46, 105-110.

110. Svendsen L, Rattan SI, Clark BF. (1994). Testing garlic for possible anti-ageing effects on long-term growth characteristics, morphology and macromolecular synthesis of human fibroblasts in culture. *J Ethnopharmacol*, 43, 125-133.

111. Syed DN, Mukhtar H. (2011). Botanicals for the prevention and treatment of cutaneous melanoma. *Pigment*

***Cell Melanoma Res*, 24, 688-702**

112. Tanaka T, Kohno H, Sakata K, Yamada Y, Hirose Y, Sugie S, Mori H. (2002). Modifying effects of dietary capsaicin and rotenone on 4-nitroquinoline 1-oxide-induced rat tongue carcinogenesis. *Carcinogenesis*, 23, 1361-1367.

113. Tang FY, Chiang EP, Chung JG, Lee HZ, Hsu CY. (2009). S-allylcysteine modulates the expression of E-cadherin and inhibits the malignant progression of human oral cancer. *J Nutr Biochem*, 20, 1013-1020.

114. Tsao AS, Liu D, Martin J, Tang XM, Lee JJ, El-Naggar AK, Wistuba I, Culotta KS, Mao L, Gillenwater A, Sagesaka YM, Hong WK, Papadimitrakopoulou V. (2009). Phase II randomized, placebo-controlled trial of green tea extract in patients with high-risk oral premalignant lesions. *Cancer Prev Res (Phila)*, 2, 931-941.

115. Van Patten CL, de Boer JG, Tomlinson Guns ES. (2008). Diet and dietary supplement intervention trials for the prevention of prostate cancer recurrence: a review of the randomized controlled trial evidence. *J Urol*, 180, 2314-2321.

116. Vidjaya Letchoumy P, Chandra Mohan KV, Stegeman JJ, Gelboin HV, Hara Y, Nagini S. (2008). Pretreatment with black tea polyphenols modulates xenobiotic-metabolizing enzymes in an experimental oral carcinogenesis model. *Oncol Res*, 17, 75-85.

117. Walters WH. (2009). Google scholar search performance: comparative recall and precision. *Portal Libr Acad*, 9, 5-24.

118. Warnakulasuriya S. (2010). Living with oral cancer: epidemiology with particular reference to prevalence and life-style changes that influence survival. *Oral Oncol*, 46, 407-410.

119. White B. (2007). Ginger: an overview. *Am Fam Physician*, 75, 1689-1691.

120. Williamson EM. (2002). Major Herbs of ayurveda. 1st ed. Oxford, UK: Churchill Livingstone.

121. Wittekind CH, Meyer HJ, Bootz F. (2010). *TNM-Klassifikation maligner Tumoren*. 7th ed. Berlin, Heidelberg, New York, London, Tokyo, Pa: Springer-Verlag GmbH.

122. Xiao B, Guo J, Liu D, Zhang S. (2007). Aloe-emodin induces *in vitro* G2/M arrest and alkaline phosphatase activation in human oral cancer KB cells. *Oral Oncol*, 43, 905-910.

123. Xu YZ, Qiu YL, An ZG, Yang FY. (2010). Role of the Chinese herbal medicine Xian huayin on the reversal of premalignant mucosal lesions in the golden hamster buccal pouch. *Int J Oral Sci*, 2, 53-58.

124. Yang SF, Yang WE, Chang HR, Chu SC, Hsieh YS. (2008). Luteolin induces apoptosis in oral squamous cancer cells. *J Dent Res*, 87, 401-6.

125. Yun YG, Jeon BH, Lee JH, Lee SK, Lee HJ, Jung KH; Jun-Lee, Jun CD, Lee SK, Kim EC. (2008). Verticinone induces cell cycle arrest and apoptosis in

immortalized and malignant human oral keratinocytes. *Phytother Res*, 22, 416-423.

resistance of Herba Erigerontis. Chin J Dent Res, 3, 56-62.

Zhou Z, Zhang S, Hua L, Zhong W, Jin Z. (2000). Leukoplakia and angiopoiesis