Chemopreventive Mechanisms of Natural Products in Oral, Mammary and Skin Carcinogenesis: An Overview

S. Manoharan[1,*], R.B. Singh[2] and S. Balakrishnan[1]

[1]*Department of Biochemistry and Biotechnology, Faculty of Science, Annamalai University, Annamalainagar-608 002, Tamil Nadu, India*

[2]*Halberg Hospital and Research Institute, Civil Lines, Moradabad-10, Uttar Pradesh, India*

Abstract: Cancer is a major cause of morbidity and mortality worldwide and represents a tremendous burden to the individual, family and society. External factors such as tobacco, chemicals, radiation, viruses and internal factors such as inherited mutations and immune status may act together or in sequence to initiate or promote carcinogenesis. Cancer chemoprevention is recognized as the most promising and novel approach to prevent, inhibit or reverse the carcinogenic processes by intervention with natural products or synthetic chemical substances. A large number of traditional medicinal plants and their active principles were reported to have chemopreventive properties. Chemopreventive agents may act on one or several steps [initiation, promotion, progression] of carcinogenesis. Agents that possess antimutagenic, anticarcinogenic, inhibitory effects on cell proliferation, antioxidant function and modulating effect on carcinogen detoxification are considered as good chemopreventive agents. The aim of the present review paper is to provide the list of chemopreventive agents and their mechanism of actions, reported for the past 10 to 15 years, against chemical carcinogen induced oral, mammary and skin carcinogenesis.

Key Words: Chemoprevention, oral cancer, mammary cancer, skin cancer, 7, 12-dimethylbenz[*a*]anthracene.

CANCER

Cancer, a major public health problem worldwide, is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. It affects all people, the young and old, the rich and poor, men, women and children. Cancer is one of the leading causes of death in the world and its incidence is still increasing, particularly in developing countries. It is the second leading cause of death in developed countries, and is among the three leading causes of death for adults in developing countries [1]. In a worldwide population of 6 billion, in the year 2000, approximately 10 million cancers were diagnosed, 5.3 million in men and 4.7 million in women. Today, 24.6 million people are living with cancer and 6.7 million are dying of cancer every year. A steadily increasing proportion of elderly people in the world will result in approximately a 50% increase in new cancer cases over the next 20 years [2]. More men than women get cancer of the lung, stomach, throat and bladder. In richer countries, prostate, breast and colon cancers are more common than in poorer countries [3]. Cancer thus represents a tremendous burden on patients, families and societies.

External factors such as tobacco, chemicals, radiation, infectious organisms and internal factors such as inherited mutations, hormones and immune status can be able to cause cancer. These risk factors may act together or in sequence to initiate or promote carcinogenesis. The American cancer society reported that more than 175, 000 cancer deaths were caused by tobacco use by the year 2005 [4]. Many different types of chemical exposures can increase the incidence of tumors in humans [5]. The only types of radiation proven to cause human cancer are high-frequency ionizing radiation and ultraviolet radiation. Exposure to sunlight causes almost all cases of basal and squamous cell skin cancer and is a major cause of skin melanoma [6]. Cancers triggered by infections are more prevalent in the developing world. Both DNA and RNA viruses were documented as a causative factor of experimental carcinogenesis [7]. More than 100 oncogenes have been identified to date, and many among them have been implicated in carcinogenesis, including ras, c-myc, erb-B2 and epidermal growth factor receptor [8, 9]. Cancer can be treated by surgery, radiation therapy, chemotherapy and immunotherapy. Cancers that are most often cured are breast, cervix, prostate, oral, colon and skin, if they are diagnosed early. Improving the quality of life of patients living with cancer and dying from cancer is therefore an urgent humanitarian need.

MULTI-STEP CARCINOGENESIS

The transformation of normal cell to cancer cell occurs through three distinct phases, initiation, promotion, and progression. Initiation of cancer occurs in the normal cells due to exposure of carcinogenic and mutagenic agents. The initiated cells are irreversibly altered and are at greater risk of neoplastic transformation. However initiation alone is not sufficient for tumor formation [10]. In promotion phase, tumor promoters convert the initiated cells in to neoplastic cells [11, 12]. Progression involves a stepwise evolution of neoplastic cells in to higher degree of malignancy. The ma-

*Address correspondence to this author at the Department of Biochemistry & Biotechnology, Annamalai University, Faculty of Science, Annamalainagar-608002, Tamil Nadu, India; Tel: + 91- 4144-238343; Fax: + 91- 4144-238080; E-mail: sakshiman@rediffmail.com

1876-3960/09

lignant tumor thus formed acquires aggressive characteristics such as clonality, anaplasia, invasion and metastasis [13].

CHEMICAL INDUCED CARCINOGENESIS

Environmental factors, of either biologic or chemical origin, may act as initiators, promoters, or both of carcinogenesis. Chemical carcinogens such as 7, 12-dimethylbenz[*a*] anthracene [DMBA], benz[a]pyrene [BP], 4-nitroquinoline-1-oxide, and N-nitroso-N-methylurea are commonly employed to initiate and promote neoplastic transformation in experimental animals. However, the most commonly employed chemical carcinogen for inducing experimental carcinogenesis is DMBA. DMBA induced experimental carcinogenesis is preceded by a sequence of hyperplasia, dysplasia, and carcinoma [14, 15]. DMBA mediates carcinogenesis through formation of DNA adducts, DNA damage, generating excess reactive oxygen species and by producing chronic inflammation. Several studies suggested that DMBA mediated molecular, biochemical, genetic and histopathological changes were analogous to those observed in human cancers [16, 17]. DMBA-induced experimental carcinogenesis might therefore be used as an ideal model to study the chemopreventive potential of medicinal plants and their active constituents. The evaluated results reported in DMBA induced carcinogenesis may assist the clinician in the diagnosis, prognosis and treatment monitoring of the cancer patients.

NUTRITION AND CARCINOGENESIS

Nutritional factors have been implicated in the pathogenesis as well as prevention of carcinogenic process, together with metabolic and genetic factors. It has been estimated that 3 to 4 million cancer cases worldwide are caused by nutritional deficiencies. Nutritional substances function as antimutagens, chemical inactivators, enzymatic inducers, antioxidants and tumor growth suppressors [18, 19]. Many of these substances might influence carcinogenesis through more than one mechanism (Fig. **1**). High consumption of fruits and vegetables is associated with reduced risk of several cancers including lung, oral, pancreas, larynx, oesophagus, bladder, stomach and cervical cancers [20]. The influence of vitamins (vitamin A, E and C) and the trace elements (zinc, copper etc.) in the pathogenesis of oral cancer has been well documented in experimental oral carcinogenesis. High intake of dark yellow cruciferous and green leafy vegetables reduced the risk of second primary cancers by 40% to 60% among patients with oral and pharyngeal cancers [21]. Certain nutritional deficiencies such as iron and vitamin A, C and E have been associated with oral cavity cancers [22]. An association between high-fat diet and breast cancer has been suggested from several different sources of data. Persons eating diet high in various micronutrients have been shown to have a lower incidence of certain cancers, especially those of breast, colon and uterus. Risk was found to be higher for low intake of beta-carotene, thiamine, riboflavin, folic acid, iron, magnesium and copper [23, 24]. Higher intake of total fat and lower intakes of β-carotene, retinal, vitamin E, vitamin C, vitamin D and long-chain n-3 fatty acids have been associated with increased skin squamous cell carcinogenesis in animal studies [25-27].

CHEMOPREVENTION

Chemoprevention has evolved as a promising and valuable strategy to inhibit, suppress or control the incidence of carcinogenesis by using specific natural and synthetic agents. Chemopreventive agents may act by multiple pathways to block tumorigenesis. Among the diverse pathways, modulation of carcinogen-induced genotoxicity, inhibition of car-

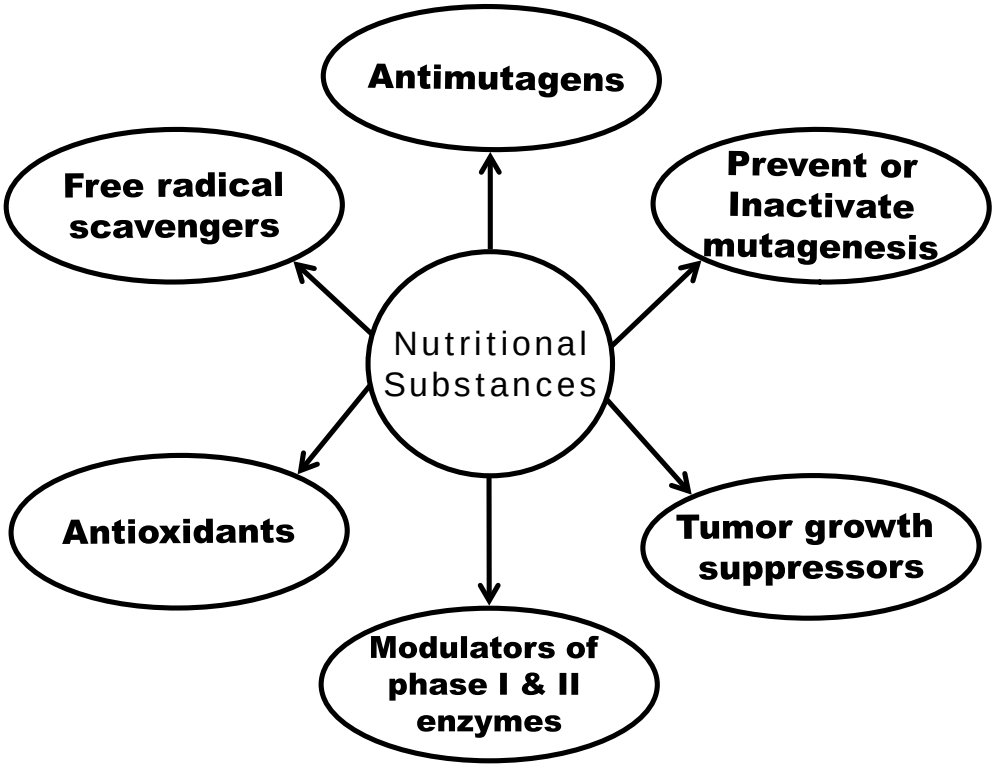

Fig. (1). Possible roles of nutritional substances against carcinogenesis.

cinogen activation by altering the activities of phase I and II detoxification enzymes, and scavenging excess reactive oxygen species [ROS] by improving antioxidant defense systems have assumed significance [28]. Chemopreventive agents inhibit both initiation and promotion during carcinogenesis [29]. The inhibition of initiation may occur by preventing the carcinogen from becoming fully active by enhancing DNA repair and/or the activation of tumor suppressor genes. The inhibition of promotion could result by triggering differentiation. Initiation and promotion may also be inhibited by the elimination of transformed malignant clones of cells [28, 29]. Agents, natural or synthetic, that exhibit any or a combination of these pharmacological characteristics qualify as cancer chemopreventive agents. The most useful cancer chemopreventive agents should have significant ability to reduce tumor incidence, delay tumor onset and prevent tumor progression [30]. Medicinal plants rich in antioxidants and bioactive phytochemicals have received growing attention over the past few years as potential chemopreventive agents [31].

CLASSIFICATION OF CHEMOPREVENTIVE AGENTS

Chemopreventive agents are broadly classified in to three categories, which include blocking agents, suppressing agents and agents that reduce tissue vulnerability to carcinogenesis. Blocking agents exert a barrier function by preventing carcinogenic agents from reaching or reacting with critical target site. Blocking agents can also exert their role by preventing metabolic activation of carcinogens and stimulating detoxification cascade. Chemopreventive agents may act as suppressing agents by preventing the evolution of the neoplastic process in the target cells. Chemopreventive agents make target tissue less vulnerable to neoplastic transformation by producing cellular maturation, decreasing the function of target cells and by decreasing cell proliferation [32, 33]. The absolute classification of chemopreventive agents is however very difficult due to the fact that several chemopreventive agents act through more than one mechanism or by unknown mechanisms of action. The possible mechanisms of chemopreventive agents in experimental carcinogenesis are given in Fig. (**2**).

ORAL CANCER CHEMOPREVENTION

Oral cancer is defined as the cancer of mouth and pharynx, including cancer of the lips, tongue, floor of the mouth, palate, gingiva, alveolar mucosa, buccal mucosa, oropharynx, tonsils, uvula, and salivary glands. Oral squamous cell carcinoma comprises 90% of all intra-oral cancers and is the fifth most frequent cancer worldwide. The incidence of oral cancer is rapidly increasing throughout the world, especially in India where it accounts for 40–50% of all cancers. Epidemiological studies have shown correlation between use of tobacco and high incidence of premalignant and malignant lesions of the oral cavity. The development of oral squamous cell carcinoma in humans is most probably due to carcinogen exposure to oral mucosa lining that occurs during tobacco and alcohol use. Oral cancer most often occurs in people over the age of forty and about half of the patients afflicted will die within five years of diagnosis. The over all 5-year survival rates for oral cancer are still at 50% despite advancement in treatment strategy [34, 35].

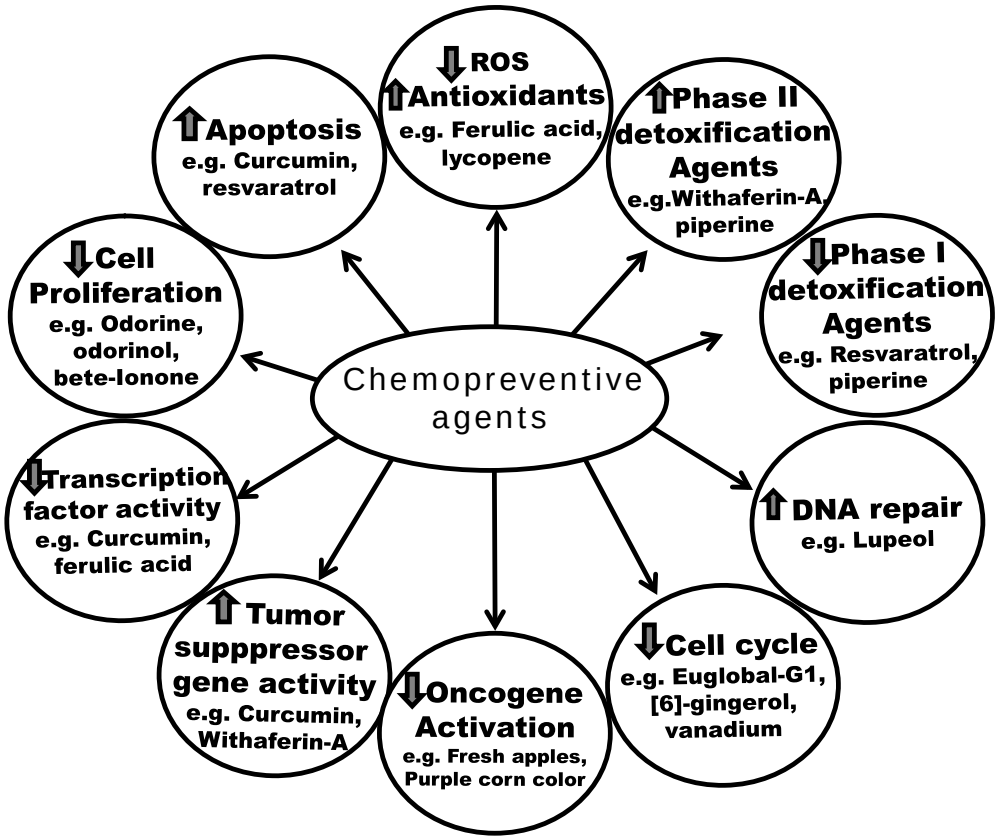

Fig. (2). Possible mechanisms of chemopreventive agents in experimental carcinogenesis.

Reported Chemopreventive Agents in Experimental Oral Carcinogenesis

Manoharan *et al*. [36] demonstrated the chemopreventive potential of curcumin and piperine in DMBA-induced hamster buccal pouch carcinogenesis. They suggested that the antilipidperoxidative and antioxidant efficacy of these phytochemicals are responsible for their chemopreventive potential. Balakrishnan *et al.* [37] demonstrated the chemopreventive potential of ferulic acid in DMBA induced hamster buccal pouch carcinogenesis. They concluded that ferulic acid exerted chemopreventive efficacy through its free radical scavenging and antioxidant properties. Manoharan *et al.* [38] recently demonstrated the chemopreventive efficacy of Withaferin-A in experimental oral carcinogenesis. They suggested that Withaferin–A significantly inhibited the tumor formation, tumor volume and tumor burden in the buccal mucosa of hamsters painted with DMBA alone. The chemopreventive potential is probably due to its antiproliferative, antilipidperoxidative and antioxidant properties.

Letchoumy *et al*. [15] demonstrated the chemopreventive potential of the black tea polyphenols and BTF-35 in DMBA -induced hamster buccal pouch carcinogenesis. They sugested that oral administration of Polyphenon-B and BTF-35 significantly decreased the tumor incidence, oxidative DNA damage, phase-I enzyme activities as well as expression of CYP1A1 and CYP1B1 isoforms, while enhancing phase-II enzyme activities in the buccal pouch and liver. Garg *et al.* [39] reported that the protective effect of dietary turmeric converge on augmenting apoptosis of the initiated cells and decreasing cell proliferation in DMBA-treated animals, which in turn, was reflected in decreased tumor burden multiplicity and enhanced latency period.

Chandramohan *et al*. [40] reported the combined chemopreventive effects of bovine milk lactoferin [bLF] and black tea polyphenols [polyphenon-B] in DMBA-induced hamster buccal pouch carcinogenesis. They concluded that combined administration of bLF and polyphenon-B was more effective in inhibiting DMBA-induced genotoxicity and development of hamster buccal pouch tumors. Srinivasan *et al.* [41] reported the chemopreventive and therapeutic modulation of green tea polyphenols on drug metabolizing enzymes in 4-nitroquinoline-1-oxide-induced oral cancer. They suggested that green tea polyphenols prevents tumor formation by acting as a detoxifying agent. Meier *et al.* [42] reported that 1-alpha, 25-dihydroxy-vitamin D3 inhibited carcinogenesis during hamster buccal pouch carcinogenesis. They suggested that 1-alpha, 25-dihydroxy vitamin D3 delayed tumor formation in the hamster buccal pouch model.

Chandramohan *et al.* [43] demonstrated that green and black tea polyphenols improved the status of antioxidants during DMBA-induced oral carcinogenesis. They suggested that Polyphenon–B is more effective in inhibiting oral carcinogenesis than Polyphenon-E. Subapriya *et al*. [44] demonstrated that ethanolic neem leaf extract inhibited the tumor formation by improving antioxidant defense mechanism against oxidative stress in DMBA induced oral carcinogenesis. Han *et al.* [45] reported the anticarcinogenic potential of black raspberries and concluded that growth inhibitory effects of black raspberries is due to their modifying effect on specific components that target aberrant signaling pathways during cell cycle progression. Tanaka *et al*. [46] demonstrated the chemopreventive efficacy of *Citrus auraptene* in 4-nitroquinoline-1-oxide induced experimental oral carcinogenesis. They suggested that *Citrus auraptene* significantly inhibited the development of oral tumors induced by the carcinogen.

Tanaka *et al.* [47] have shown the chemopreventive potential of curcumin and hesperidin in 4-nitroquinoline-1-oxide-induced oral carcinogenesis. They suggested that curcumin and hesperidin caused significant reduction in the frequency of tongue carcinoma. Azuine and Bhide [48] reported that betel leaf and turmeric significantly prevented the tumor incidence, and tumor burden in experimental animals. The chemopreventive potential of neem leaves and turmeric powder has been demonstrated in 4-nitroquinoline-1-oxide-induced oral carcinogenesis [49]. The authors suggested that the chemopreventive efficacy of these plant products is due to their antilipidperoxidative and antioxidant potential.

Manikandan *et al.* [50] have shown the chemopreventive potential of *Azadirachta indica* leaf in DMBA induced oral carcinogenesis. They concluded that the antioxidant property of the neem leaf extract is responsible for its chemopreventive potential. Subapriya *et al.* [51] suggested that the chemopreventive potential of neem leaf extract in DMBA-induced oral carcinogenesis is due to their modulating effect on xenobiotics metabolizing enzymes during carcinogenesis. Bhuvaneswari *et al.* [52] have shown the chemopreventive potential of tomato and garlic in DMBA-induced oral carcinogenesis. They suggested that the chemopreventive potential of tomato and garlic rely on their ability to induce apoptosis in tumor cells. Balasenthil *et al.* [53] have shown the protective effect of S-allyl cysteine in DMBA-induced hamster buccal pouch carcinogenesis. They suggested that the elevation of hepatic glutathione and glutathione dependent enzymes by S-allyl cysteine might play a key role in preventing cancer development in the hamster cheek pouch. Karthikeyan *et al.* [54] have shown the chemopreventive effect of *Ocimum sanctum* in DMBA-induced oral carcinogenesis. They suggested that *Ocimum sanctum* has the ability to prevent the early events of oral carcinogenesis.

Other reported chemopreventive agents of oral carcinogenesis include garlic, chalcone, 2-hydroxy chalcone, quercetin, beta-carotene, vitamin E, xanthophylls, astaxanthin, canthaxanthin, *Spirulina fusiformis*, limonoid, and *Spirulina dunaliella* [55-63]. The reported chemopreventive agents and their mechanism of action in experimental oral carcinogenesis are given chronologically in Table **1**.

MAMMARY CANCER CHEMOPREVENTION

Breast cancer accounts for the highest morbidity and mortality and each year 1.5 million new cases of breast cancer are diagnosed and 400, 000 women die by this cancer worldwide. The annual incidence of breast cancer is increasing both in industrialized and developing countries. Breast cancer is the second most commonly diagnosed cancer among American women, and annually 200, 000 women are diagnosed with and 40, 000 women die by this cancer. In India, breast cancer is the second most common cancer after cervix, where 70, 000 new cases of breast cancer are reported every year [64, 65].

Table 1. Reported Chemopreventive Agents in Experimental Oral Carcinogenesis

Medicinal Plants/ Bioactive Constituents	Mechanism of Action	Reference
Spirulina dunaliella	Suppressed cell proliferation.	Schwartz *et al.* [63]
Limonoid from oranges	Suppressed cell proliferation.	Miller *et al.* [61]
Betel leaf and turmeric	Antitumor promoting effect.	Azuine and Bhide [48]
Curcumin, β-carotene and hesperidin	Anti-tumor initiating and anti-tumor promoting properties.	Tanaka *et al.* [47]
Spirulina fusiformis	Suppressed cell proliferation.	Mathew *et al.* [60]
Xanthophylls, astaxanthin and canthaxanthin	Suppressed cell proliferation.	Tanaka *et al.* [59]
Beta-carotene and vitamin E	Suppressed cell proliferation	Garewal *et al.* [58]
Dietary flavonoids chalcone, 2-hydroxy chalcone, and quercetin	Suppressed cell proliferation	Makita *et al.* [57]
Neem leaf	Antioxidant property.	Manoharan *et al.* [62]
Neem and turmeric	Antilipidperoxidative and antioxidant potential	Nagini *et al.* [49]
Citrus auraptene	Inhibited the development of oral neoplasms.	Tanaka *et al.* [46]
Green tea	Antiproliferative efficacy.	Khafif *et al.* [56]
Ocimum sanctum	Anti-tumor initiative property.	Karthikeyan *et al.* [54]
Garlic	Antiproliferative efficacy.	Meng *et al.* [55]
S-allyl cysteine	Elevation of hepatic glutathione and glutathione dependent enzymes	Balasenthil *et al.* [53]
Tomato and garlic	Induction of apoptosis in tumor cells.	Bhuvaneswari *et al.* [52]
Neem leaf extract	Modulating effect on xenobiotics metabolizing enzymes during carcinogenesis.	Subapriya *et al.* [51]
Black raspberries	Modifying effect on specific components that target aberrant signaling pathways.	Han *et al.* [45]
Azadirachta *indica*	Improved antioxidant defense mechanism.	Subapriya *et al.* [44]
Green and black tea polyphenols	Enhanced the antioxidant status.	Chandra Mohan *et al.* [43]
Black tea Polyphenon-B and BTF-35	Decreased DNA damage and stimulated detoxification cascade.	Letchoumy *et al.* [15]
1-alpha, 25-dihydroxy vitamin D3	Delayed tumor formation.	Meier *et al.* [42]
Azadirachta indica leaves	Antilipidperoxidative potential.	Manikandan *et al.* [50]
Green tea polyphenols	Stimulated detoxification cascade.	Srinivasan *et al.* [41]
Bovine Lactoferin [bLF] and polyphenon-B	Inhibited DMBA-induced genotoxicity and development of hamster buccal pouch tumors.	Chandra Mohan *et al.* [40]
Ferulic acid	Free radical scavenging and antioxidant properties	Balakrishnan *et al.* [37]
Withaferin-A	Antiproliferative, antilipidperoxidative and antioxidant properties	Manoharan *et al.* [38]
Curcumin and piperine	Antilipidperoxidative and antioxidant efficacy	Manoharan *et al.* [36]
Dietary turmeric	Augmenting apoptosis of the initiated cells and inhibited cell proliferation.	Garg *et al.* [39]

Reported Chemopreventive Agents in Experimental Mammary Carcinogenesis

Liu *et al.* [66] have demonstrated the chemopreventive potential of fresh apples in DMBA induced mammary carcinogenesis. They suggested that apple extract suppressed the cell proliferation by down regulating the expression of proliferating cell nuclear antigen, cyclin D_1 and bcl-2 and upregulating the expression of Bax and by apoptosis induction. Moselhy and Al Mslmani [67] reported the chemopreventive effect of lycopene alone or with melatonin against the genesis of oxidative stress and mammary tumors induced by DMBA in Sprague dawely female rats. They suggested that supplementation of diet with lycopene and melatonin provided antioxidant defense with strong chemopreventive activity against DMBA-induced mammary tumors. Girolami *et al.* [68] have shown time-dependent effects of dietary acetyl salicylic acid on liver CYP1A and antioxidant enzymes in DMBA induced mammary carcinogenesis. They proposed that the positive modulation of the hepatic antioxidant systems by acetyl salicylic acid may play a role in the chemoprevention of mammary tumorigenesis induced by DMBA in the female rat.

Fukamachi *et al.* [69] have shown purple corn color suppresses Ras protein level and inhibits DMBA-induced mammary carcinogenesis in the rat. They suggested that purple corn color exhibited chemopreventive activity by inducing apoptosis in mammary tumor cells. Manna *et al.* [70] have shown the chemopreventive potential of dietary

fish oil [eicosapentaenoic acid and decosahexaenoic acid] in DMBA-induced mammary carcinogenesis. They suggested that dietary fish oil exerted chemopreventive effect by inducing apoptosis and modulating expression of Bax and Bcl-2 during DMBA-induced mammary carcinogenesis. Liu *et al.* [71] reported that dietary beta-Ionone suppressed mammary carcinogenesis by inhibiting cell proliferation and inducing apoptosis in the mammary gland of the Sprague-Dawley rat. Anbuselvam *et al.* [72] have demonstrated the protective effect of *Operculina turpethum* against DMBA-induced oxidative stress with reference to breast cancer in experimental rats. They suggested that the antioxidant activity of *Operculina turpethum* played a protective role against DMBA-induced breast cancer.

Kumaraguruparan *et al.* [73] have reported that the chemopreventive potential of black tea polyphenols in DMBA-induced mammary carcinogenesis is due to their modulating effect on xenobiotics metabolizing enzymes, oxidative stress, cell proliferation, apoptosis and angiogenesis. Ray *et al.* [74] suggested that the chemopreventive potential of vanadium, a dietary micronutrient, is due to suppression of cell proliferation, induction of apoptosis and cell cycle arrest during DMBA-induced mammary carcinogenesis. Padmavathi *et al.* [75] have demonstrated the chemopreventive potential of Propolis, a natural beehive product, in DMBA-induced mammary carcinogenesis. They suggested that Propolis exerted its chemopreventive potential by stimulating phase I and phase II detoxification enzymes during mammary carcinogenesis. Whitsett *et al.* [76] suggested that resveratol in the diet suppressed DMBA-induced mammary cancer in rats by modulating mammary gland architecture, cell proliferation and apoptosis. Kolanjiappan and Manoharan [77] have reported that *Jasminium grandiflorum* flowers have potent chemopreventive potential in DMBA-induced mammary carcinogenesis, which is probably due to their antilipidperoxidative and antioxidants properties.

Tepsuwan *et al.* [78] have demonstrated the chemopreventive potential of neem flowers in DMBA-induced mammary carcinogenesis. They suggested that the chemopreventive potential of neem flowers is due to their modulating effect on detoxification cascade during carcinogenesis. Kavanagh *et al.* [79] have reported that green tea extracts decreased DMBA-induced mammary tumor burden in rats by inhibiting cell proliferation during DMBA-induced mammary cancer. Lin *et al.* [80] have reported that dietary dibenzoyl methane inhibited mammary gland proliferation by inhibiting the formation of DMBA-DNA adducts in mammary glands and by lowering the proliferation rate of the mammary gland. Tepsuwan *et al.* [81] demonstrated the chemopreventive potential of *Siamese cassia* leaves in DMBA-induced mammary carcinogenesis. They suggested that the chemopreventive potential may be partly due to phase II detoxification cascade inducing capacity as well as phase I detoxification cascade inhibitory activity. The reported chemopreventive agents and their mechanism of action in experimental mammary carcinogenesis are given chronologically in Table **2**.

SKIN CANCER CHEMOPREVENTION

Skin, a major environmental interface for the body, is accidentally or occupationally exposed to a number of chemical mutagens and carcinogens. Skin cancer accounts

Table 2. Reported Chemopreventive Agents in Experimental Mammary Carcinogenesis

Medicinal Plants/ Bioactive Constituents	Mechanism of Action	Reference
Siamese cassia	Phase II detoxification cascade inducing capacity as well as phase I detoxification cascade inhibitory activity.	Tepsuwan *et al.* [81]
Dietary dibenzoyl methane	Inhibited the formation of DMBA-DNA adducts	Lin *et al.* [80]
Green tea	Suppressed cell proliferation.	Kavanagh *et al.* [79]
Neem flowers	Modulating effect on detoxification cascade	Tepsuwan *et al.* [78]
Jasminium grandiflorum	Antilipidperoxidative and antioxidants properties.	Kolanjiappan and Manoharan [77]
Resveratol	Modulating mammary gland architecture, cell proliferation and apoptosis.	Whitsett *et al.* [76]
Propolis	Stimulating phase I and phase II detoxification enzymes.	Padmavathi *et al.* [75]
Vanadium	Suppression of cell proliferation, induction of apoptosis and cell cycle arrest.	Ray *et al.* [74]
Black tea polyphenols	Modulating effect on xenobiotics metabolizing enzymes, oxidative stress, cell proliferation, apoptosis and angiogenesis.	Kumaraguruparan *et al.* [73]
Operculina turpethum	Antioxidant activity.	Anbuselvam *et al.* [72]
Dietary beta-Ionone	Antiproliferative and apoptotic potential.	Liu *et al.* [71]
Dietary fish oil	Induction of apoptosis and modulating expression of Bax and Bcl-2	Manna *et al.* [70]
Purple corn color	Induction of apoptosis.	Fukamachi *et al.* [69]
Dietary acetyl salicylic acid	Positive modulation of the hepatic antioxidant systems.	Girolami *et al.* [68]
Lycopene	Antioxidant potential.	Moselhy and Al Mslmani [67]
Fresh apples	Down regulating the expression of proliferating cell nuclear antigen, cyclin D_1 and bcl-2 and up regulating the expression of Bax and by apoptosis induction.	Liu *et al.* [66]

for 30% of all diagnosed cancers in the world. Epidemiological studies have reported that the incidence of skin cancer is significantly rising worldwide due to increased cumulative ultraviolet exposure. Epithelial tumors, basal cell carcinoma and squamous cell carcinoma are the important skin tumors. Skin cancer is the most common of all cancers and accounts for nearly half of all cancers in the United States. In India, skin cancer accounts for approximately 1-2% of all diagnosed cancers and the annual incidence of skin cancer will increase significantly in future due to its immense population [82-84].

Reported Chemopreventive Agents in Experimental Skin Carcinogenesis

Das and Saha [85] reported that the protective effect of garlic on DMBA-induced skin cancer in mice. They suggested that the chemopreventive potential is due to the induction of cellular defense systems during carcinogenesis. Singh and Kala [86] reported that the chemomodulatory action of *Foeniculum vulgare* in DMBA-induced skin carcinogenesis is due to the induction of phase I and phase II detoxification cascade. Alias *et al.* [87] demonstrated the chemopreventive potential of ferulic acid in DMBA induced skin carcinogenesis. They suggested that the chemopreventive efficacy of ferulic acid is due to its antilipidperoxidative and antioxidant potential. Sarfaraz *et al.* [88] have reported that guggulsterone inhibited skin tumor formation by modulating NF-kappa B pathway during skin carcinogenesis. Patel *et al.* [89] have demonstrated that polymeric black tea polyphenols inhibited cell proliferation during DMBA induced mouse skin carcinogenesis. Kim *et al.* [90] have shown the chemopreventive potential of *Artemisia capillaries* in DMBA-induced mouse skin carcinogenesis. They suggested that the chemopreventive potential is attributed to the presence of chemical compounds of camphor, 1-borncol, coumarin and achillin.

Chaudhary *et al.* [91] reported the chemopreventive potential of *Aloe vera* against DMBA induced skin papillomagenesis in mice. They concluded that the chemopreventive potential is due to their antilipidperoxidative and antioxidant functions during papillomagenesis. Bhukari *et al.* [92] suggested that retinoids inhibited skin carcinogenesis by regressing the formation of premalignant lesions of skin. Rastogi *et al.* [93] have demonstrated the protective effect of *Ocimum sanctum* in DMBA-induced skin carcinogenesis. They suggested that the chemopreventive potential is attributed to its antioxidant and antiproliferative effects and induction of detoxication cascade during skin carcinogenesis. Renju *et al.* [94] have shown the chemopreventive potential of *Clerodendron inerme* leaves in DMBA-induced skin carcinogenesis. They concluded that the chemopreventive effect is attributed to its antilipidperoxidative potential. Chung *et al.* [95] suggested that xanthorrhizol inhibited skin tumor formation by blocking the expression of ornithine decarboxylase, cyclooxygenase-2 and NF-kappaB during skin carcinogenesis. Sancheti and Goyal [96] have shown the modulatory influence of *Rosmarinus officinalis* on DMBA-induced mouse skin carcinogenesis. They suggested that the chemopreventive potential is due to their antilipidperoxidative potential during skin carcinogenesis. Koul *et al.* [97] suggested that the chemopreventive potential of *Azadirachta indica* in skin carcinogenesis is due to their modulating effect on the status of lipidperoxidation, antioxidants and detoxification cascade.

Sancheti *et al.* [98] have shown the chemopreventive potential of *Emblica officinalis* on mouse skin carcinogenesis. They suggested that *Emblica officinalis* significantly inhibited skin tumor formation in mice. Kyriazi *et al.* [99] have shown the cancer chemopreventive effects of *Pinus maritima* bark extract in DMBA-induced skin carcinogenesis. They suggested that *Pinus maritime* has anticarcinogenic effect against DMBA-induced mouse skin carcinogenesis. Gills *et al.* [100] have shown the chemopreventive potential of sulforaphane, a natural product from broccoli, in DMBA-induced skin carcinogenesis. They suggested that sulforaphane has significant chemopreventive potential in DMBA-induced skin carcinogenesis. Prasad *et al.* [101] have shown the modulatory effect of *Morus indica* in DMBA-induced skin carcinogenesis. They suggested that the chemopreventive potential of *Morus indica* is due to their inhibitory effect on the activity of aryl hydrocarbon hydroxylase during skin carcinogenesis. Bharali *et al.* [102] have shown the potent chemopreventive action of *Boerhaavia diffusa* on DMBA-induced skin carcinogenesis in mice.

Saha *et al.* [103] suggested that the anticarcinogenic activity of *Swertia chirata* in DMBA-induced skin carcinogenesis relies on its anti-cell proliferative and apoptotic potential. Sultana and Saleem [104] reported that the chemopreventive potential of *Salix capreal* in skin carcinogenesis is due to their antioxidant function. De *et al.* [105] suggested that the antilipidperoxidative and antioxidant potential of Bitter gourd and tomato are responsible for their chemopreventive effects in DMBA-induced skin carcinogenesis. Alam *et al.* [106] suggested that the chemopreventive effect of *Vitis vinifera* extract on DMBA-induced skin carcinogenesis is due to its antilipidperoxidative potential. Koyama *et al.* [107] have shown the chemopreventive potential of emodin and cassiamin B in mouse skin carcinogenesis. They suggested that emodin and cassiamin significantly inhibited cell proliferation during skin carcinogenesis. Inad *et al.* [108] have shown the chemopreventive activity of odorine and odorinol in mouse skin carcinogenesis. They suggested that odorine and odorinol significantly inhibited cell proliferation during skin carcinogenesis. Davis and Kuttan [109] have shown the chemopreventive effect of *Withania somnifera* in DMBA-induced skin carcinogenesis. They suggested that the chemopreventive property is due to its antioxidant effect. Saleem *et al.* [110] have shown the chemopreventive effect of *Tephrosia purpurea* in DMBA-induced skin carcinogenesis. They suggested that the chemopreventive property is due to its antioxidant effect. Ganguly *et al.* [111] have suggested that the chemopreventive potential of *Momordica charantia* in skin carcinogenesis is due to their modulating effect on enzymes of the biotransformation and detoxification system of the host.

Takasaki *et al.* [112] have shown the chemopreventive activity of euglobal-G1from leaves of *Eucalyptus grandis* in DMBA-induced skin carcinogenesis. They suggested that euglobal-G1 significantly inhibited cell proliferation during skin carcinogenesis. Isbir *et al.* [113] have reported the chemopreventive potential of *Brassica oleraceae* in DMBA induced skin carcinogenesis. They suggested that the anticarcinogenicity of *Brassica oleraceae* might be linked to its

Table 3. Reported Chemopreventive Agents in Experimental Skin Carcinogenesis

Medicinal Plants/ Bioactive Constituents	Mechanism of Action	Reference
Dietary curcumin	Antiproliferative efficacy.	Limtrakul *et al.* [132]
Red ginseng	Improved the cell immune system	Xiaoguang *et al.* [131]
[6]-gingerol	Antiproliferative efficacy.	Park *et al.* [117]
Genistein	Blockage of DNA-adduct formation and inhibition of oxidative and inflammatory events.	Wei *et al.* [116]
Black tea polyphenol	Modulated genetic and epigenetic pathways.	Javed *et al.* [115]
Psoralea corylifolia	Antiproliferative efficacy.	Latha *et al.* [114]
Artemisia lactiflora	Antiproliferative efficacy.	Nakamura *et al.* [125]
Brassica oleraceae	Enhanced the activity of GSH-dependent antioxidant defense system.	Isbir *et al.* [113]
Euglobal-G1	Antiproliferative efficacy.	Takasaki *et al.* [112]
Momordica charantia	Modulating effect on enzymes of the biotransformation and detoxification cascade.	Gunguly *et al.* [111]
Bitter gourd and tomato	Antilipidperoxidative and antioxidant function.	De *et al.* [105]
Tephrosia purpurea	Antioxidant effect.	Saleem *et al.* [110]
Withania somnifera	Antioxidant effect.	Davis and Kuttan [109]
Odorine and odorinol	Antiproliferative efficacy.	Inad *et al.* [108]
Emodin and cassiamin B	Antiproliferative efficacy.	Koyama *et al.* [107]
Vitis vinifera	Antilipidperoxidative potential.	Alam *et al.* [106]
Phyllanthus urinaria	Antiproliferative efficacy.	Bharali *et al.* [130]
Beta vulgaris	Antiproliferative efficacy.	Kapadia *et al.* [129]
Boerhaavia diffusa	Antiproliferative efficacy.	Bharali *et al.* [102]
Salix capreal	Antioxidant function.	Sultana and saleem [104]
Swertia chirata	Antiproliferative and apoptotic potential.	Saha *et al.* [103]
Morus indica	Inhibitory effect on aryl hydrocarbon hydroxylase activity.	Prasad *et al.* [101]
Aspalathus linearis	Antiproliferative efficacy.	Marnewick *et al.* [128]
Panax ginseng	Antimutagenic activity.	Panwar *et al.* [127]
Syzygium aromaticum	Antiproliferative efficacy.	Banerjee *et al.* [126]
Emblica officinalis	Antiproliferative efficacy.	Sancheti *et al.* [98]
Tribulus terrestris	Antiproliferative efficacy.	Kumar *et al.* [124]
Mentha piperita	Antiproliferative efficacy.	Sharma *et al.* [123]
Acacia nilotica	Antimutagenic activity.	Meena *et al.* [122]
Sulforaphane	Antiproliferative efficacy.	Gills *et al.* [100]
Pinus maritima	Antiproliferative efficacy.	Kyriazi *et al.* [99]
Azadirachta indica	Modulating effect on the status of lipidperoxidation, antioxidants and detoxification cascade.	Koul *et al.* [97]
Rosmarinus officinalis	Antilipidperoxidative potential.	Sancheti and Goyal [96]
Sarcophine-diol	Antiproliferative and apoptotic potential.	Zhang *et al.* [121]
Lupeol	Inhibited DMBA induced DNA damage.	Nigam *et al.* [120]
Xanthorrhizol	Blocked the expression of Ornithine decarboxylase, cyclooxygenase-2 and NF-kappaB	Chung *et al.* [95]
Clerodendron inerme	Antilipidperoxidative potential.	Renju *et al.* [94]
Ocimum sanctum	Antiproliferative, antioxidant properties and induction of detoxication cascade.	Rastogi *et al.* [93]

Table 3. Contd.…

Medicinal Plants/ Bioactive Constituents	Mechanism of Action	Reference
Retinoids	Regressing formation of premalignant lesions.	Bhukari *et al.* [92]
Aloe vera	Antilipidperoxidative and antioxidant functions.	Chaudhary *et al.* [91]
Tinospora cordifolia	Antiproliferative efficacy.	Chaudhary *et al.* [118]
Artemisia capillaries	Presence of camphor, 1-borncol, coumarin and achillin.	Kim *et al.* [90]
Polymeric black tea polyphenols	Suppressed cell proliferation.	Patel *et al*. [89]
Guggulsterone	Modulating NF-kappa B pathway.	Sarfaraz *et al.* [88]
Foeniculum vulgare	Induction of phase I and phase II detoxification cascade.	Singh and Kala [86]
Resveratrol	Induction of apoptosis.	Roy *et al.* [119]
Ferulic acid	Antilipidperoxidative and antioxidant potential.	Alias *et al.* [87]
Garlic	Induction of cellular defense systems.	Das and Saha [85]

ability to facilitate or enhance the activity of the natural GSH-dependent antioxidant protective system of the epidermal cells during the later stages of skin tumor promotion. Latha and Panikkar [114] reported the chemopreventive potential of *Psoralea corylifolia* seeds in DMBA-induced skin carcinogenesis. They reported that *Psoralea corylifolia* seeds significantly inhibited the growth and delayed the onset of papilloma formation during skin carcinogenesis. Javed *et al.* [115] reported the chemopreventive potential of black tea polyphenol in mouse skin carcinogenesis. They suggested that black tea polyphenols exerts it's antitumorigenic effect by altering both genetic and epigenetic pathways. Wei *et al.* [116] reported that genistein inhibits the initiation and promotion of DMBA-induced skin carcinogenesis. They suggested that the anticarcinogenic effect is probably through blockage of DNA-adduct formation and inhibition of oxidative and inflammatory events *in vivo*. Park *et al.* [117] have shown the inhibitory effect of [6]-gingerol, a major pungent principle of ginger, on phorbol ester-induced inflammation, epidermal ornithine decarboxylase activity and skin tumor promotion in ICR mice. They suggested that the compound significantly inhibited skin tumor formation and inflammation by suppressing the activity of epidermal ornithine decarboxylase. Other chemopreventive agents reported against skin carcinogenesis include, *Tinospora cordifolia*, resveratrol, lupeol, sarchophine-diol, *Acacia nilotica*, *Mentha piperita*, *Tribulus terrestris*, *Artemesia lactiflora*, *Syzygium aromaticum*, *Panax gingeng*, *Aspalathus linearis*, *Beta vulgaris*, *Phyllanthus urinaria*, *Red ginseng* and curcumin [118-132]. The reported chemopreventive agents and their mechanism of action in skin carcinogenesis are given chronologically in Table **3**.

CONCLUSION

The present review paper thus summarized the list of chemopreventive agents and their mechanism of actions, reported for the past 10 to 15 years, against chemical carcinogen induced skin, oral and mammary carcinogenesis. Appropriate experimental animal models help to test the chemopreventive efficacy of these medicinal plants and their constituents. The present review identified various mechanisms of actions reported for the chemopreventive agents that include antiproliferative efficacy, induction of apoptosis and cell cycle arrest, antilipidperoxidative and antioxidant effects, improvement in host immune system and induction of detoxification cascade. Experimental studies on cancer chemoprevention are continued due to the fact that the current status of chemotherapy is for from satisfactory. Furthermore, the efficacy of chemotherapy is limited since severe drug-related side effects are common. The chemopreventive doses arrived from experimental carcinogenesis would be extrapolated to human studies. Some of the reported chemopreventive agents such as curcumin and piperine are now under human clinical trails, which were proved as anticarcinogenic agents in appropriate animal models. The present review therefore helps the oncologist for their cancer chemoprevention studies on oral, mammary and skin carcinogenesis.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Mr.P.Pugalendi, Mr.K.Panjamurthy Ms.Linsa Mary Alias and N.Baskaran Research scholars, Department of Biochemistry and Biotechnology, Annamalai University, Annamalainagar for their valuable assistance in preparing this review article.

REFERENCES

[1] Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocon 2000. Int J Cancer 2001; 94: 153-6.
[2] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108.
[3] Kanavos P. The rising burden of cancer in the developing world. Ann Oncol 2006; 17: 15-23.
[4] American cancer society. Cancer facts and figures 2005. Atlanta: American Cancer Society 2005.
[5] Wogan GN, Hecht SS, Felton JS, Conney AH, Loeb LA. Environmental and chemical carcinogenesis. Semin Cancer Biol 2004; 14: 473-86.
[6] Moan J, Porojnicu AC, Dahlback A. Ultraviolet radiation and malignant melanoma. Adv Exp Med Biol 2008; 624: 104-16.
[7] Shillitoe EJ. Relationship of viral infections to malignancies. Curr Opin Dent 1991; 1: 398-403.
[8] Carbone M, Pass HI. Multistep and multifactorial carcinogenesis: when does a contributing factor become a carcinogen? Semin Cancer Biol 2004; 14: 399-405.
[9] Duesberg P, Liu R. Multistep carcinogenesis: a chain reaction of a neuploidization. Cell Cycle 2003; 2: 202-10.
[10] Farber E. Chemical carcinogens. N Engl J Med 1981; 305: 1379.
[11] Vogelstein B, Kinzler KW. The multistep nature of cancer. Trends Genet 1993; 9: 138-41.

[12] Brandau S, Bohle A. Bladder cancer. I. Molecular and genetic basis of carcinogenesis. Eur Urol 2001; 39: 491-97.
[13] Duesberg P, Li R. Multistep carcinogenesis: a chain reaction of aneuploidizations. Cell Cycle 2003; 2: 202-10.
[14] Shklar G, Schwartz JL. Vitamin E inhibits experimental carcinogenesis and tumor angiogenesis. Eur J Cancer B Oral Oncol 1996; 32: 114-9.
[15] Letchoumy PV, Chandra Mohan KV, Kumaraguruparan R, Hara Y, Nagini S. Black tea polyphenols protect against 7, 12-dimethylbenz [a]anthracene-induced hamster buccal pouch carcinogenesis. Oncol Res 2006; 16: 167-78.
[16] Gimenez-Conti IB, Slaga TI. The hamster cheek pouch carcinogenesis model. J Cell Biochem1 1993; 17: 83-90.
[17] Miyata M, Furukawa M, Takahasi K, Gonzalez FJ, Yamazoe Y. Mechanism of 7, 12-dimethylbenz[a]anthracene induced immuotoxicity: role of metabolic activation at the target organ. Jpn J Pharmacol 2001; 86: 302-9.
[18] Shukla Y, Pal SK. Dietary cancer chemoprevention: An overview. Int J Hum Genet 2004; 4: 265-76.
[19] Kohlmeier L, Simonsen N, Mottus K. Dietary modifiers of carcinogenesis. Environ Health Perspect 1995; 103: 177-84.
[20] Krishnaswamy K, Polasa K. Diet, nutrition and cancer – The Indian scenario. Indian J Med Res 1995; 102: 200–9.
[21] Maserejian NN, Giovannucci E, Rosner B, Zavras A, Joshipura K. Prospective study of fruits and vegetables and risk of oral premalignant lesions in men. Am J Epidemiol 2006; 164: 556-66.
[22] Petridou E, Zavras AI, Lefatzis D, *et al*. The role of diet and specific micronutrients in the etiology of oral carcinoma. Cancer 2002; 94: 2981-8.
[23] Wargovich MJ. Nutrition and cancer: The herbal revolution. Curr Opin Clin Nutr Metab Care 1999; 2: 421.
[24] Birt DF. Update on the effect of vitamin A, C and E and selenium on carcinogenesis. Proc Soc Exp Biol Med 1986; 183: 311-20.
[25] Van Dam RM, Huang Z, Giovannucci E, *et al*. Diet and basal cell carcinoma of the skin in a prospective cohort of men. Am J Clin Nutr 2000; 71: 135–41.
[26] De Luca LM, Tarone R, Huynh M, Jones CS, Chen LC. Dietary retinoic acid inhibits mouse skin carcinogenesis irrespective of age at initiation. Nutr Cancer 1996; 25: 249–57.
[27] Orengo IF, Black HS, Kettler AH, Wolf JE. Influence of dietary menhaden oil upon carcinogenesis and various cutaneous responses to ultraviolet radiation. Photochem Photobiol 1989; 49: 71–7.
[28] Steele VE. Current mechanistic approaches to the chemoprevention of cancer. J Biochem Mol Biol 2003; 36: 78-81.
[29] Sharma S, Stutzman JD, Kelloff GJ, Steale VE. Screening of potential chemopreventive agents using biochemical markers of carcinogenesis. Cancer Res 1994; 54: 5848-55.
[30] Tsao AS, Kim ES, Hong WK. Chemoprevention of cancer. CA Cancer J Clin 2004; 54: 150-80.
[31] Aruna K, Sivaramakrishnan VM. Plant products protective against cancer. Indian J Exp Biol 1990; 26: 1008-11.
[32] Levi MS, Borne RF, Williamson JS. A review of cancer chemopreventive agents. Curr Med Chem 2001; 8: 1349-62.
[33] Cai Y, Luo Q, Sun M, Corke H. Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. Life Sci 2004; 74: 2157-84.
[34] Johnson N: Tobacco use and oral cancer: a global perspective. J Dent Educ 2001; 65: 328-39.
[35] Sankaranarayanan R, Dinshaw K, Nene BM, *et al*. Cervical and oral cancer screening in India. J Med Screen 2006; 13: 35-8.
[36] Manoharan S, Balakrishnan S, Menon VP, Linsa Mary A, Reena AR. Chemopreventive efficacy of curcumin and piperine during 7, 12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. Singapore Med J 2009 [In Press].
[37] Balakrishnan S, Menon VP, Manoharan S. Chemopreventive efficacy of ferulic acid in 7, 12-dimethylbenz[a]anthracene induced hamster buccal pouch carcinogenesis. J Med Food 2008; 11: 693-700.
[38] Manoharan S, Panjamurthy K, Menon VP, Balakrishnan S, Alias LM. Chemopreventive and antilipidperxoidative effects of Withaferin-A during 7, 12-dimethylbenz[a]anthracene [DMBA] induced oral carcinogenesis. Indian J Exp Biol 2008; 47: 16-23.
[39] Garg R, Ingle A, Maru G. Dietary turmeric modulates DMBA-induced P21 [ras], MAP Kinases and AP-a/NF-KappaB pathway to alter cellular responses during harmster buccal pouch carcinogenesis. Toxicol Appl Pharmacol 2008; 232(3): 428-39.
[40] Chandramohan KVP, Letchoumy PV, Hara Y, Nagini S. Combination chemoprevention of hamster buccal pouch carcinogenesis by bovine milk lactoferrin and black tea polyphenols. Cancer Invest 2008; 26: 193-201.
[41] Srinivasan P, Suchalatha S, Babu PV, *et al.* Chemopreventive and therapeutic modulation of green tea polyphenols on drug metabolizing enzymes in 4-Nitroguinoline 1-oxide induced oral cancer. Chem Biol Interact 2008; 172: 224-34.
[42] Meier JD, Enepekides DJ, Poirier B, Bradley CA, Albala JS, Farwell DG. Treatment with 1-alpha, 25-dihydroxyvitamin D3 [vitamin D3] to inhibit carcinogenesis in the hamster buccal pouch model. Arch Otolaryngol Head Neck Surg 2007; 133: 1149-52.
[43] Chandramohan KV, Subapriya R, Hara Y, Nagini S. Enhancement of erythrocyte antioxidants by green and black tea polyphenols during 7, 12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. J Med Food 2006; 9: 373-7.
[44] Subapriya R, Bhuvaneswari V, Ramesh V, Nagini S. Ethanolic leaf extract of neem [*Azadirachta indica*] inhibits buccal pouch carcinogenesis in hamsters. Cell Biochem Funct 2005; 23: 229-38.
[45] Han C, Ding H, Casto B, Stoner GD, Ambrosio SM. Inhibition of the growth of premalignant and malignant human oral cell lines by extracts and components of black raspberries. Nutr Cancer 2005; 51: 207-17.
[46] Tanaka T, Kawabata K, Kakumoto M, Matsunaga K, Mori H. Chemoprevention of 4-nitroquinoline 1-oxide-induced oral carcinogenesis by *Citrus auraptene* in rats. Carcinogenesis 1998; 19: 425-31.
[47] Tanaka T, Makita H, Ohinishi M, *et al.* Chemoprevention of 4-nitroquinoline 1-oxide-induced oral carcinogenesis by dietary curcumin and hesperidin: comparison with the protective effect of beta-carotene. Cancer Res 1994; 54: 4653-59.
[48] Azuine MA, Bhide SV. Protective single/combined treatment with betel leaf and turmeric against methyl [acetoxymethyl] nitrosamine-induced hamster oral carcinogenesis. Int J Cancer 1992; 28: 412-5.
[49] Nagini S, Manoharan S. Biomonitoring the Chemopreventive potential of the plant products neem and turmeric in 4NQO induced oral carcinogenesis. J Clin Biochem Nutr 1997; 23: 33-40.
[50] Manikandan P, Letchoumy PV, Gopalakrishnan M, Nagini S. 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 2008; 46: 2332-43.
[51] Subapriya R, Velmurugan B, Nagini S. Modulation of xenobiotic-metabolizing enzymes by ethanolic neem leaf extract during hamster buccal pouch carcinogenesis. J Exp Clin Cancer Res 2005; 24: 223-30.
[52] Bhuvaneswari V, Rao KS, Nagini S. Altered expression of anti and proapoptotic proteins during chemoprevention of hamster buccal pouch carcinogenesis by tomato and garlic combination. Clin Chim Acta 2004; 350: 65-72.
[53] Balasenthil S, Nagini S. Protective effects of S-allylcysteine on hepatic glutathione and glutathione-dependent enzymes during hamster cheek pouch carcinogenesis. J Biochem Mol Biol Biophys 2002; 6: 13-6.
[54] Karthikeyan K, Ravichandran P, Govindasamy S. Chemopreventive effect of *Ocimum sanctum* on DMBA-induced hamster buccal pouch carcinogenesis. Oral Oncol 1999; 35: 112-9.
[55] Meng CL, Shyu KW. Inhibition of experimental carcinogenesis by painting with garlic extracts. Nutr Cancer 1999; 14: 207-17.
[56] Khafif A, Schantz SP, Al-Rawi M, Edelstein D, Sacks PG. Green tea regulates cell cycle progression in oral leukoplakia. Head Neck 1998; 20: 528-34.
[57] Makita H, Tanaka T, Fujitsuka H, *et al.* Chemoprevention of 4-nitroquinoline 1-oxide-induced rat oral carcinogenesis by the dietary flavonoids chalcone, 2-hydroxychalcone and quercetin. Cancer Res 1996; 56; 4904-9.
[58] Garewal HS, Schantz S. Emerging role of beta-carotene and antioxidant nutrients in prevention of oral cancer. Arch Otolaryngol Head Neck Surg 1995; 121: 141-4.
[59] Tanaka T, Makita H, Ohinishi M, Mori H, Satoh K, Hara A. Chemoprevention of rat oral carcinogenesis by naturally occurring xanthophylls, astaxanthin and canthaxanthin. Cancer Res 1995; 55: 4059-64.

[60] Mathew B, Sankaranarayan R, Nair PP, Varghese C, Somanathan T. Evaluation of chemoprevention of oral cancer with *Spirulina fusiformis*. Nutr Cancer 1995; 24: 197-202.

[61] Miller EG, Gonzales-Sanders AP, Couvillon AM, Wright JM, Hasegowa S, Lam LKJ. Inhibition of hamster buccal pouch carcinogenesis by limonin 17-β-D-glycopyranoside. Nutr Cancer 1992; 17: 1-7.

[62] Manoharan S, Ramachandran CR, Ramachandran V, Nagini, S. Inhibition of 4NQO induced oral carcinogenesis by plant products. J Clin Biochem Nutr 1996; 21: 141-9.

[63] Schwartz J, Shklar G, Reid S, Trickler D. Prevention of experimental oral cancer by extracts of *Spirulina dunaliella* algae. Nutr Cancer 1988; 11: 127-34.

[64] Ronckers CM, Land CE, Neglia JP, Meadows AT. Breast cancer. Lancet 2005; 366: 1605-6.

[65] Hortobagyi GN, Jde SL, Pritchard K, *et al.* The global breast cancer burden: variations in epidemiology and survival. Clin Breast Cancer. 2005; 6: 391-401.

[66] Liu JR, Dong HW, Chen BQ, Zhao P, Liu RH. Fresh apples suppress mammary carcinogenesis and proliferative activity and induce apoptosis in mammary tumors of the Sprague-Dawley rat. J Agric Food Chem 2009; 57: 297-304.

[67] Moselhy SS, Al Mslmani MA. Chemopreventive effect of lycopene alone or with melatonin against the genesis of oxidative stress and mammary tumors induced by 7, 12 dimethyl[a]benzanthracene in sprague dawely female rats. Mol Cell Biochem 2008; 319: 175-80.

[68] Girolami F, Abbadessa G, Racca S, *et al.* Time-dependent acetylsalicylic acid effects on liver CYP1A and antioxidant enzymes in a rat model of 7, 12-dimethylbenzanthracene [DMBA]-induced mammary carcinogenesis. Toxicol Lett 2008;181:87-92.

[69] Fukamachi K, Imada T, Ohshima Y, Xu J, Tsuda H. Purple corn color suppresses Ras protein level and inhibits 7, 12-dimethylbenz[a]anthracene-induced mammary carcinogenesis in the rat. Cancer Sci 2008; 99: 1841-6.

[70] Manna S, Chakraborty T, Ghosh B, *et al.* Dietary fish oil associated with increased apoptosis and modulated expression of Bax and Bcl-2 during 7, 12-dimethylbenz[alpha]anthracene-induced mammary carcinogenesis in rats. Prostaglandins Leukot Essent Fatty Acids 2008; 79: 5-14.

[71] Liu JR, Sun XR, Dong HW, *et al.* Beta-Ionone suppresses mammary carcinogenesis, proliferative activity and induces apoptosis in the mammary gland of the Sprague-Dawley rat. Int J Cancer 2008; 122: 2689-98.

[72] Anbuselvam C, Vijayavel K, Balasubramanian MP. Protective effect of *Operculina turpethum* against 7, 12-dimethyl benz[a]anthracene induced oxidative stress with reference to breast cancer in experimental rats. BMC Genet 2007; 8: 39.

[73] Kumaraguruparan R, Seshagiri PB, Hara Y, Nagini S. Chemoprevention of rat mammary carcinogenesis by black tea polyphenols: modulation of xenobiotic-metabolizing enzymes, oxidative stress, cell proliferation, apoptosis, and angiogenesis. Mol Carcinog 2007; 46: 797-806.

[74] Ray RS, Ghosh B, Rana A, Chatterjee M. Suppression of cell proliferation, induction of apoptosis and cell cycle arrest: chemopreventive activity of vanadium *in vivo* and *in vitro*. Int J Cancer 2007; 120: 13-23.

[75] Padmavathi R, Senthilnathan P, Sakthisekaran D. Therapeutic effect of propolis and paclitaxel on hepatic phase I and II enzymes and marker enzymes in dimethylbenz[a]anthracene-induced breast cancer in female rats. Comp Biochem Physiol C Toxicol Pharmacol 2006; 143: 349-54.

[76] Whitsett T, Carpenter M, Lamartiniere CA. Resveratrol, but not EGCG, in the diet suppresses DMBA-induced mammary cancer in rats. J Carcinog 2006; 5: 15.

[77] Kolanjiappan K, Manoharan S. Chemopreventive efficacy and antilipid peroxidative potential of *Jasminum grandiflorum* Linn. on 7, 12-dimethylbenz[a]anthracene-induced rat mammary carcinogenesis. Fundam Clin Pharmacol 2005; 19: 687-93.

[78] Tepsuwan A, Kupradinun P, Kusamran WR. Chemopreventive potential of neem flowers on carcinogen-induced rat mammary and liver carcinogenesis. Asian Pac J Cancer Prev 2002; 3: 231-8.

[79] Kavanagh KT, Hafer LJ, Kim DW, *et al.* Green tea extracts decrease carcinogen-induced mammary tumor burden in rats and rate of breast cancer cell proliferation in culture. J Cell Biochem 2001; 82: 387-98.

[80] Lin CC, Lu YP, Lou YR, *et al*. Inhibition by dietary dibenzoylmethane of mammary gland proliferation, formation of DMBA-DNA adducts in mammary glands, and mammary tumorigenesis in Sencar mice. Cancer Lett 2001; 168: 125-32.

[81] Tepsuwan A, Kupradinun P, Kusamran WR. Effect of *Siamese cassia* leaves on the activities of chemical carcinogen metabolizing enzymes and on mammary gland carcinogenesis in the rat. Mutat Res 1999; 428: 363-73.

[82] Ridky TW. Nonmelanoma skin cancer. J Am Acad Dermatol 2007; 57: 484-501.

[83] Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B 2001; 63: 8-18.

[84] Deo SV, Hazarika S, Shukla NK, Kumar S, Kar M, Samaiya A. Surgical management of skin cancers: experience from a regional cancer centre in North India. Indian J Cancer 2005; 42: 145-50.

[85] Das I, Saha T. Effect of garlic on lipid peroxidation and antioxidation enzymes in DMBA-induced skin carcinoma. Nutrition 2008; doi:10.1016/j.nut.2008.10.014. [In Press].

[86] Singh B, Kale RK. Chemomodulatory action of Foeniculum vulgare [Fennel] on skin and forestomach papillomagenesis, enzymes associated with xenobiotic metabolism and antioxidant status in murine model system. Food Chem Toxicol 2008; 46: 3842-50.

[87] Alias LM, Manoharan S, Vellaichamy L, Balakrishnan S, Ramachandran CR. Protective effect of ferulic acid on 7, 12-dimethylbenz[a]anthracene-induced skin carcinogenesis in Swiss albino mice. Exp Toxicol Pathol 2008; doi:10.1016/j.etp.2008.09.001.[In Press].

[88] Sarfaraz S, Siddiqui IA, Syed DN, Afaq F, Mukhtar H. Guggulsterone modulates MAPK and NF-kappaB pathways and inhibits skin tumorigenesis in SENCAR mice. Carcinogenesis 2008; 29: 2011-8.

[89] Patel R, Krishnan R, Ramchandani A, Maru G. Polymeric black tea polyphenols inhibit mouse skin chemical carcinogenesis by decreasing cell proliferation. Cell Prolif 2008; 41: 532-53.

[90] Kim YS, Bahn KN, Hah CK, Gang HI, Ha YL. Inhibition of 7, 12-dimethylbenz[a]anthracene induced mouse skin carcinogenesis by *Artemisia capillaris*. J Food Sci 2008; 73: T16-20.

[91] Chaudhary G, Saini MR, Goyal PK. Chemopreventive potential of *Aloe vera* against 7, 12-dimethylbenz[a]anthracene induced skin papillomagenesis in mice. Integr Cancer Ther 2007; 6: 405-12.

[92] Bukhari MH, Qureshi SS, Niazi S, *et al.* Chemotherapeutic/chemopreventive role of retinoids in chemically induced skin carcinogenesis in albino mice. Int J Dermatol 2007; 46: 1160-5.

[93] Rastogi S, Shukla Y, Paul BN, Chowdhuri DK, Khanna SK, Das M. Protective effect of *Ocimum sanctum* on 3-methylcholanthrene, 7, 12-dimethylbenz[a]anthracene and aflatoxin B1 induced skin tumorigenesis in mice. Toxicol Appl Pharmacol 2007; 224: 228-40.

[94] Renju GL, Manoharan S, Balakrishnan S, Senthil N. Chemopreventive and antilipidperoxidative potential of *Clerodendron inerme* [L] Gaertn in 7, 12-dimethylbenz[a]anthracene induced skin carcinogenesis in Swiss albino mice. Pak J Biol Sci 2007; 10: 1465-70.

[95] Chung WY, Park JH, Kim MJ, *et al*. Xanthorrhizol inhibits 12-O-tetradecanoylphorbol-13-acetate-induced acute inflammation and two-stage mouse skin carcinogenesis by blocking the expression of ornithine decarboxylase, cyclooxygenase-2 and inducible nitric oxide synthase through mitogen-activated protein kinases and/or the nuclear factor-kappa B. Carcinogenesis 2007; 28: 1224-31.

[96] Sancheti G, Goyal P. Modulatory influence of *Rosemarinus officinalis* on DMBA-induced mouse skin tumorigenesis. Asian Pac J Cancer Prev 2006; 7: 331-5.

[97] Koul A, Ghara AR, Gangar SC. Chemomodulatory effects of *Azadirachta indica* on the hepatic status of skin tumor bearing mice. Phytother Res 2006; 20: 169-77.

[98] Sancheti G, Jindal A, Kumari R, Goyal PK. Chemopreventive action of *Emblica officinalis* on skin carcinogenesis in mice. Asian Pac J Cancer Prev 2005; 6: 197-201.

[99] Kyriazi M, Yova D, Rallis M, Lima A. Cancer chemopreventive effects of *Pinus Maritima* bark extract on ultraviolet radiation and ultraviolet radiation-7, 12, dimethylbenz[a]anthracene induced skin carcinogenesis of hairless mice. Cancer Lett 2006; 237: 234-41.

[100] Gills JJ, Jeffery EH, Matusheski NV, Moon RC, Lantvit DD, Pezzuto JM. Sulforaphane prevents mouse skin tumorigenesis during the stage of promotion. Cancer Lett 2006; 236: 72-9.

[101] Prasad L, Khan TH, Sehrawat A, Sultana S. Modulatory effect of *Morus indica* against two-stage skin carcinogenesis in Swiss albino

mice: possible mechanism by inhibiting aryl hydrocarbon hydroxylase. J Pharm Pharmacol 2004; 56: 1291-8.

[102] Bharali R, Azad MR, Tabassum J. Chemopreventive action of *Boerhaavia diffusa* on DMBA-induced skin carcinogenesis in mice. Indian J Physiol Pharmacol 2003; 47: 459-64.

[103] Saha P, Mandal S, Das A, Das PC, Das S. Evaluation of the anticarcinogenic activity of *Swertia chirata* Buch.Ham, an Indian medicinal plant, on DMBA-induced mouse skin carcinogenesis model. Phytother Res 2004; 18: 373-8.

[104] Sultana S, Saleem M. *Salix caprea* inhibits skin carcinogenesis in murine skin: inhibition of oxidative stress, ornithine decarboxylase activity and DNA synthesis. J Ethnopharmacol 2004; 91: 267-76.

[105] De S, Chakraborty J, Das S. Oral consumption of bitter gourd and tomato prevents lipid peroxidation in liver associated with DMBA induced skin carcinogenesis in mice. Asian Pac J Cancer Prev 2000; 1: 203-6.

[106] Alam A, Khan N, Sharma S, Saleem M, Sultana S. Chemopreventive effect of *Vitis vinifera* extract on 12-O-tetradecanoyl-13-phorbol acetate-induced cutaneous oxidative stress and tumor promotion in murine skin. Pharmacol Res 2002; 46: 557-64.

[107] Koyama J, Morita I, Tagahara K, *et al*. Chemopreventive effects of emodin and cassiamin B in mouse skin carcinogenesis. Cancer Lett 2002; 182: 135-9.

[108] Inad A, Nishino H, Kuchide M, *et al*. Cancer chemopreventive activity of odorine and odorinol from Aglaia odorata. Biol Pharm Bull 2001; 24: 1282-5.

[109] Davis L, Kuttan G. Effect of *Withania somnifera* on DMBA induced carcinogenesis. J Ethnopharmacol 2001; 75: 165-8.

[110] Saleem M, Ahmed Su, Alam A, Sultana S. *Tephrosia purpurea* alleviates phorbol ester-induced tumor promotion response in murine skin. Pharmacol Res 2001; 43: 135-44.

[111] Ganguly C, De S, Das S. Prevention of carcinogen-induced mouse skin papilloma by whole fruit aqueous extract of *Momordica charantia*. Eur J Cancer Prev 2000; 9: 283-8.

[112] Takasaki M, Konoshima T, Etoh H, Pal Singh I, Tokuda H, Nishino H. Cancer chemopreventive activity of euglobal-G1 from leaves of Eucalyptus grandis. Cancer Lett 2000; 155: 61-5.

[113] Isbir T, Yaylim I, Aydin M, *et al*. The effects of *Brassica oleraceae* var capitata on epidermal glutathione and lipid peroxides in DMBA-initiated-TPA-promoted mice. Anticancer Res 2000; 20: 219-24.

[114] Latha PG, Panikkar KR. Inhibition of chemical carcinogenesis by *Psoralea corylifolia* seeds. J Ethnopharmacol 1999; 68: 295-8.

[115] Javed S, Mehrotra NK, Shukla Y. Chemopreventive effects of black tea polyphenols in mouse skin model of carcinogenesis. Biomed Environ Sci 1998; 11: 307-13.

[116] Wei H, Bowen R, Zhang X, Lebwohl M. Isoflavone genistein inhibits the initiation and promotion of two-stage skin carcinogenesis in mice. Carcinogenesis 1998; 19: 1509-14.

[117] Park KK, Chun KS, Lee JM, Lee SS, Surh YJ. Inhibitory effects of [6]-gingerol, a major pungent principle of ginger, on phorbol ester-induced inflammation, epidermal ornithine decarboxylase activity and skin tumor promotion in ICR mice. Cancer Lett 1998; 129: 139-44.

[118] Chaudhary R, Jahan S, Goyal PK. Chemopreventive potential of an Indian medicinal plant [*Tinospora cordifolia*] on skin carcinogenesis in mice. J Environ Pathol Toxicol Oncol 2008; 27: 233-43.

[119] Roy P, Kalra N, Prasad S, George J, Shukla Y. Chemopreventive Potential of Resveratrol in Mouse Skin Tumors through Regulation of Mitochondrial and PI3K/AKT Signaling Pathways. Pharm Res 2009; 26: 211-7

[120] Nigam N, Prasad S, Shukla Y.Preventive effects of lupeol on DMBA induced DNA alkylation damage in mouse skin. Food Chem Toxicol 2007; 45: 2331-5.

[121] Zhang X, Kundoor V, Khalifa S, Zeman D, Fahmy H, Dwivedi C. Chemopreventive effects of sarcophine-diol on skin tumor development in CD-1 mice. CancerLett 2007; 253: 53-9.

[122] Meena PD, Kaushik P, Shukla S, Soni AK, Kumar M, Kumar A. Anticancer and antimutagenic properties of *Acacia nilotica* [Linn.] on 7, 12-dimethylbenz[a]anthracene-induced skin papillomagenesis in Swiss albino mice. Asian Pac J Cancer Prev 2006; 7: 627-32.

[123] Sharma A, Kumar A. Effect of *Mentha piperita* on the xenobiotic metabolism enzymes/antioxidant status and lipidperoxidation in mice. Pharmacol Online 2006; 1: 40-60.

[124] Kumar M, Soni AK, Shukla S, Kumar A. Chemopreventive potential of *Tribulus terrestris* against 7, 12- dimethylbenz [a] anthracene induced skin papillomagenesis in mice.Asian Pac J Cancer Prev 2006; 7: 289-94.

[125] Nakamura Y, Kawamoto N, Ohto Y, Torikai K, Murakami A, Ohigashi, H. A diacetylenic spiroketal enol ether epoxide, AL-1 from *Artemista lactiflora* inhibits 12-0-tetradecanoylphorbol-13-acetate-induced tumor promotion possibly by Suppressing of Oxidative Stress. Pharmacol Res 1999; 36: 121-9.

[126] Banerjee S, Das S. Anticarcinogenic effects of an aqueous infusion of cloves on skin carcinogenesis. Asian Pac J Cancer Prev 2005; 6: 304-8.

[127] Panwar MM, Kumar M, Samarth R, Kumar A. Evaluation of chemopreventive action and antimutagenic effect of the standardized Panax ginseng extract, EFLA400, in Swiss albino mice. Phytother Res 2005; 19: 65-71.

[128] Marnewick J, Joubert E, Joseph S, Swanevelder S, Swart P, Gelderblom W. Inhibition of tumor promotion in mouse by extracts of rooibos [*Aspalathus liniaris*], unique South African herbal teas. Cancer Lett 2005; 224: 193-202.

[129] Kapadia GJ, Azuine MA, Sridhar R, Sridhar, Okuda Y. Chemoprevention of DMBA induced UV-B promoted, NOR-1 induced TPA promoted skin carcinogenesis and DEN induced Phenobarbital promoted liver tumors in mice by extract of beet root. Nutr Res 2003; 26: 147-51.

[130] Bharali R, Tabassum J, Azad MR. Chemopreventive action of *Phyllanthus urinaria* Linn on DMBA-induced skin carcinogenesis in mice. Indian J Exp Biol 2003; 41: 1325-8.

[131] Xiaoguang C, Hongyan L, Xiaohong L, *et al.* Cancer chemopreventive and therapeutic activities of red ginseng. J Ethnopharmacol 1998; 60: 71-8.

[132] Limtrakul P, Lipigorngoson S, Namwong O, Apisariyakul A, Dunn FM. Inhibitory effect of dietary curcumin on skin carcinogenesis in mice. Cancer Lett 1997; 116: 197-203.

Received: January 26, 2009 Revised: January 28, 2009 Accepted: February 6, 2009