Review Article

Oxidative Stress and Cancer: Role of Anti-Carcinogenic Herbs and Spices

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ABSTRACT

Numerous scientific reviews and studies described the relationship between the increase in cellular reactive oxygen radicals and the pathogenesis of several chronic diseases, including cancer. Reactive oxygen and nitrogen species are generated from endogenous (normal physiological processes) as well as exogenous sources (xenobiotic interaction). When the antioxidant control mechanisms are overrun, the cellular redox potential shifts towards oxidative stress. As a consequence, the potential for damaging cellular nucleic acids, lipids, and proteins increases. Importantly, oxidative nuclear DNA damage has an important role in neoplasia. Cancer cells exhibit increased reactive oxygen species (ROS) generation that may promote cell proliferation. Many phytochemicals have been implicated in combating oxidative stress-induced diseases such as cancer and other chronic disorders. Many of these phytochemicals have the power to inhibit cell proliferation and also to suppress the promotion and progression of cancer. Phytochemicals like flavonoids inhibit the oxidative enzymes such as 5-lipoxygenase and 12-lipoxygenase. Terpenoids, another class of phytochemicals, suppress tumor growth by inhibiting HMG-CoA reductase activity. Also, they act at various stages of tumor development, inhibit initiation and promotion of carcinogenesis, induce tumor cell differentiation and apoptosis, and suppress tumor angiogenesis. These phytochemicals also inhibit tumor invasion via the NF-κB signaling pathway and thereby modify disease-related cellular targets in cancer. Thus, many of the phytochemicals present in various herbs act in different ways and thereby, inhibit cancer initiation, promotion and also progression.

Keywords: Reactive oxygen species, Oxidative stress, Antioxidants, Cancer, Phytochemicals, DNA damage, Carcinogenesis, Herbs, Spices.

INTRODUCTION

Oxidative stress is defined as a discrepancy between production of free radicals and reactive metabolites, so-called oxidants or reactive oxygen species (ROS),

and their eradication by defending mechanisms, referred to as antioxidants. This disparity leads to damage of important biomolecules and cells, with potential impact on the whole organism. ROS are products of a normal cellular metabolism and play vital roles in the stimulation of signaling pathways in plant and animal cells in response to changes in intra- and extracellular environmental conditions[1]. Most ROS are generated in cells by the mitochondrial respiratory chain. During endogenous metabolic reactions, aerobic cells produce ROS such as superoxide anion (O^{2-}), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\bullet}$), and organic peroxides as normal products of the biological reduction of molecular oxygen. Under hypoxic conditions, the mitochondrial respiratory chain also produces nitric oxide (NO), which can generate reactive nitrogen species (RNS) which can further generate other reactive species, e.g. reactive aldehydes—malondialdehyde and 4-hydroxynonenal—by inducing excessive lipid peroxidation. Proteins and lipids are also significant targets for oxidative attack, and modification of these molecules can increase the risk of mutagenesis[2].

Under a sustained environmental stress, ROS are produced over a long time, and thus significant damage may occur to cell structure and functions and may induce somatic mutations and neoplastic transformation. Indeed, cancer initiation and progression have been linked to oxidative stress by increasing DNA mutations or inducing DNA damage, genome instability, and cell proliferation [3]. Acting to protect the organism against these harmful pro-oxidants is a complex system of enzymatic antioxidants (superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase, catalase etc.) and nonenzymatic antioxidants (glutathione (GSH), vitamins C, D, E etc.). However, the amount of these defensive antioxidant principles present under the normal physiological situation, are sufficient only to cope with the physiological rate of free-radical generation. It is evident, therefore, that any further load of free radicals can tip the free-radical (pro-oxidant) and anti-free-radical (antioxidant) balance leading to oxidative stress, which may result in tissue injury and subsequent diseases[4].

Reactive oxygen species (ROS)

Radicals resulting from oxygen characterize the most imperative class of radical species generated in living systems. Molecular oxygen (dioxygen) has a distinctive electronic configuration and is itself a radical. The addition of one electron to dioxygen forms the superoxide anion radical ($O_2^{\bullet-}$). Superoxide anion, arising either through metabolic processes or following oxygen "activation" by physical irradiation, is considered the "primary" ROS, and can in addition interact with other molecules to create "secondary" ROS, either unswervingly or prevalently through enzyme-metal-catalysed processes[5].

The generation of superoxide occurs generally within the mitochondria of a cell. The mitochondrial electron transport chain is the leading source of ATP in the mammalian cell and thus is elementary for life. During energy transduction, a small amount of electrons "leak" to oxygen impulsively, forming the oxygen free radical superoxide, which has been implicated in the pathophysiology of variety of diseases. Superoxide is produced from both complexes I and III of the electron transport chain, and it gets tremendously charged, once in its anionic form, to voluntarily cross the inner mitochondrial membrane[6].

Hydroxyl radical, the neutral form of the hydroxide ion has high reactivity, making it a very hazardous radical with a very short *in vivo* half-life approximately 10^{-9}s [7]. Thus,

when produced *in vivo*, ·OH reacts close to its site of formation. It has been recommended that iron regulation ensures that there is no free intracellular iron; nevertheless, under stress conditions, an excess of superoxide liberates "free iron" from iron-containing molecules. The liberation of iron by superoxide has been demonstrated for [4Fe-4S] cluster-containing enzymes of the dehydratase-lyase family. The released Fe^{2+} can participate in the Fenton reaction, generating highly reactive hydroxyl radical:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + OH^-$$

Thus under stress conditions, $O_2^{\cdot -}$ acts as an oxidant of [4Fe-4S] cluster-containing enzymes and facilitates ·OH production from H_2O_2 by making Fe^{2+} available for the Fenton reaction [5]. Superoxide radical participates in the Haber–Weiss reaction which combines a Fenton reaction and the reduction of Fe^{3+} by superoxide, yielding Fe^{2+} and oxygen[8]:

$$O_2\bullet- + H_2O_2 \rightarrow O_2 + \bullet OH + OH^-$$

$$Fe^{3+} + O_2\bullet- \rightarrow Fe^{2+} + O_2$$

Supplementary reactive radicals derived from oxygen that can be produced in living systems are peroxyl radicals (ROO•**).** The simplest peroxyl radical (HOO•) is the protonated form of superoxide ($O_2\bullet-$) and is usually termed either hydroperoxyl radical or peroxyl radical. It has been demonstrated that hydroperoxyl radical initiates fatty acid peroxidation by two parallel pathways: fatty acid hydroperoxide-independent (LOOH-independent) and LOOH-dependant[9]. The LOOH-dependant pathway of $HO_2\bullet-$ initiated fatty acid peroxidation may be significant to mechanisms of initiation of lipid peroxidation *in vivo*. Xanthine oxidase (XO, EC 1.1.3.22) and xanthine dehydrogenase (XD, EC 1.1.1.204) are interconvertable forms of same enzyme, known as xanthine oxidoreductase (XOR). In purine catabolism, XOR catalyzes the oxidative hydroxylation of hypoxanthine to xanthine and subsequently of xanthine to uric acid. Uric acid acts as an effective antioxidant and free radical scavenger. XOR has, therefore, vital functions as a cellular defense enzyme against oxidative stress. With both XO and XD forms, but predominantly with the XO form, copious ROS and RNS are synthesized. Thus, the amalgamation of both an antioxidant (uric acid) and numerous free radicals (ROS and RNS) makes XOR an important protective supervisor of the cellular redox potential[10].

Peroxisomes are known to produce H_2O_2, but not $O_2\bullet-$ under physiologic circumstances. Peroxisomes are chief sites of oxygen expenditure in the cell and participate in several metabolic roles that use oxygen. Oxygen consumption in the peroxisome leads to H_2O_2 production, which is then used to oxidize a wide array of molecules. The organelle also contains catalase, which decomposes hydrogen peroxide and apparently prevents accumulation of this toxic compound. Thus, the peroxisome maintains a fragile balance with respect to the relative concentrations or activities of these enzymes to guarantee no net production of ROS. When peroxisomes are damaged and their H_2O_2 consuming enzymes are down regulated, H_2O_2 releases into the cytosol which drastically contributes to oxidative stress[11].

Reactive Nitrogen Species (RNS)

Nitric oxide radical ($NO^{\bullet}$), a small molecule that contains one unpaired electron on the antibonding $2\pi^*_y$ orbital and is thus, a radical, generated in biological tissues by specific nitric oxide synthases (NOSs), which metabolize arginine to citrulline with the formation of $NO^{\bullet}$ via a five electron oxidative reaction[12]. Nitric oxide ($NO^{\bullet}$) is an abundant reactive radical that acts as an crucial oxidative biological signaling molecule in a huge range of miscellaneous physiological processes, including neurotransmission, blood pressure regulation, defense mechanisms, smooth muscle relaxation and immune regulation. $NO^{\bullet}$ has effects on neuronal transmission as well as on synaptic plasticity

in the central nervous system. In the extracellular milieu, $NO^{\bullet}$ reacts with oxygen and water to form nitrate and nitrite anions. Overproduction of reactive nitrogen species, 'nitrosative stress' may lead to nitrosylation reactions that can modify the structure of proteins and so hinder their normal function[13].

Cells of the immune system generate both superoxide anion and nitric oxide during the oxidative burst triggered during inflammatory processes. Under these conditions, nitric oxide and the superoxide anion may react together to produce considerable amounts of much more oxidatively active molecule, peroxynitrite anion ($ONOO^-$), which is a powerful oxidizing agent that can cause DNA fragmentation and lipid oxidation[14].

Oxidative damage to DNA, lipids, proteins and carbohydrates

At high concentrations, ROS can be chief mediators of damage to cell structures, nucleic acids, lipids, proteins and carbohydrates. The hydroxyl radical is known to react with all components of the DNA molecule, destroying both the purine and pyrimidine bases, especially guanine (**Fig.1)** and also the deoxyribose backbone. The most comprehensively studied DNA lesion is the formation of 8-oxodeoxyguanosine (8-OH-dG). Permanent alteration of genetic material resulting from these "oxidative damage" incidents represents the first step involved in mutagenesis, carcinogenesis, and ageing[15].

It is well known that metal-induced generation of ROS results in an attack not only on DNA, but also on the cellular components which involves polyunsaturated fatty acid residues (PUFA) of phospholipids that are extremely sensitive to oxidation. Once formed, peroxyl radicals ($ROO^{\cdot}$) can be rearranged via a cyclisation reaction to endoperoxides (precursors of malondialdehyde) with the final product of the peroxidation process being malondialdehyde (MDA). The major aldehyde product of lipid peroxidation other than malondialdehyde is 4-hydroxy-2-nonenal (HNE). MDA is mutagenic in bacterial and mammalian cells and carcinogenic in rats. Hydroxynonenal is weakly mutagenic but appears to be the major toxic product of lipid peroxidation[16] (**Fig. 2**).

Mechanisms involved in the oxidation of proteins by ROS were elucidated by studies in which amino acids, simple peptides and proteins were exposed to ionizing radiations under conditions where hydroxyl radicals or a mixture of hydroxyl/superoxide radicals are formed. The side chains of all amino acid residues of proteins, in particular cysteine and methionine residues of proteins are susceptible to oxidation by the action of ROS/RNS. Oxidation of cysteine residues may lead to the reversible formation of mixed disulphides between protein thiol in particular GSH (S-glutathiolation). The concentration of carbonyl groups, generated by many different mechanisms is a good measure of ROS-mediated protein oxidation. A number of highly sensitive methods have been developed for the assay of protein carbonyl groups[17].

Advanced glycation end products (AGEs), a class of complex products result from a process in which reducing free carbonyl groups of carbohydrates react with amino groups of biomolecules called as glycation (Maillard reaction or a non-enzymatic glycosylation). Reducing carbohydrates have been found to produce reactive oxygen species (ROS) through the glycation. Glycation and ROS are suggested to mediate the aging process and age-related human disorders [18]. Most of AGEs are very unstable, reactive compounds and the end products are difficult to be completely analyzed. The brown color of the AGEs is probably related to the name of melanoidins initially proposed by Maillard, and well known from food chemistry. The best

chemically characterized AGE compounds found in human are pentosidine and carboxymethyl lysine (CML)[19].

Heavy metals, oxidative stress and cancer

In addition to ROS, various redox metals, due to their ability to generate free radicals, or non-redox metals, due to their ability to bind to critical thiols, have been implicated in the mechanisms of carcinogenesis and ageing. Iron-induced oxidative stress is considered to be a principal determinant of human colorectal cancer. Occupation exposure to asbestos containing about 30% (weight) of iron is related to increased risk of asbestosis- the second most important cause of lung cancer[20].

Occupational exposure to cadmium has been associated with occurrence of increased oxidative stress and cancer. Cadmium itself is unable to generate free radicals directly, however, via indirect mechanisms; it can cause free radical-induced damage to the gene expression. It has been reported that cadmium can cause activation of cellular protein kinases (protein kinase C), which result in enhanced phosphorylation of transcription factors and consequently lead to the transcriptional activation of target gene expression. It has been suggested that cadmium might also be implicated in the pathogenesis of human pancreatic cancer and renal carcinoma[21].

Hexavalent chromium is considered a potential lung carcinogen; Cr (VI)-induced cytotoxicity is associated with mitochondrial/ lysosomal toxicity substantiated by the enhanced formation of free radicals. Arsenic compounds are well established human carcinogens, capable of binding to –SH groups and thus inhibiting various enzymes, including glutathione reductase. Studies support the hypothesis that arsenic may act as a co-carcinogen not by causing cancer directly, but by allowing other factors, such as cigarette smoke or UV radiation, to cause DNA mutations more effectively[22].

From the above discussion, it is quite clear that free radicals act as signaling species in various normal physiological processes and also that excessive production of free radicals causes damage to biological material which is an essential event in the etiopathogenesis of various disorders. However, a question arises whether uncontrolled formation of ROS species is a primary cause or a downstream consequence of the pathological process. While the role of free radicals as primary species causing damage to DNA in the mechanism of carcinogenesis is clear, the primary role of ROS in various disease states is controversial[23].

Antioxidants in diet and human health

The potential advantageous effects of antioxidants in protecting against disease have been used as an argument for recommending increasing intakes of several nutrients above those derived by conventional methods. A dietary antioxidant can sacrificially scavenge ROS/RNS to stop radical chain reactions, considered as primary chain-breaking antioxidants or free radical scavengers (FRS), or it can inhibit the reactive oxidants from being formed in the first place, considered as secondary or preventive antioxidants. Primary antioxidants, when present in trace amounts, may either delay or inhibit the initiation step by inactivating or scavenging free radicals, thus inhibiting initiation and propagation reactions by reacting with peroxyl or alkoxyl radicals[24].

Antioxidant efficiency is dependent on the ability of the FRS to donate hydrogen to the free radical. As the hydrogen-bond energy of the FRS decreases, the transfer of the hydrogen to the free radical is more energetically promising and rapid. The ability of FRS to donate hydrogen free radical can be predicted from standard one-electron reduction potentials. Efficient FRS also

produces radicals that do not react rapidly with oxygen to form peroxides. In foods, the efficiency of phenolic FRS also depends on additional factors such as volatility, pH sensitivity and polarity[25].

Carotenoids are one of the most widespread phytonutrients found mostly in the flowers, fruits, algae and photosynthetic bacteria. Carotenoids have extensive applications as antioxidants and are therefore, important for human health. The essential role of beta-carotene and others as the main dietary source of vitamin A includes its protective effects against serious disorders such as cancer, heart disease and other disorders. Carotenoids, including xanthophylls (oxygen-containing carotenoids) are naturally occurring colored compounds that are abundant as pigments in plants. To date, about 500 and 600 specific carotenoids have been identified mostly from plants and algae. Carotenoids have the capacity to trap not only lipid peroxyl radicals, but also singlet oxygen species. The antioxidant capacity of carotenoids may also be related to the structure. Larger conjugated system such as astaxanthin is known to have a higher antioxidant activity[26]. Antioxidants such as vitamins C and E are also essential for the protection against ROS. However, majority of the antioxidant activity of herbs may be from compounds such as phenolic acids and flavonoids, rather than from vitamin C, E or β-carotene. Intake of controlled diets rich in herbs, fruits or vegetables increased significantly the antioxidant capacity of plasma. This increase could not be explained by the increase in the plasma α-tocopherol or carotenoid concentration[27].

Dietary phytochemicals as antioxidants

The "phyto" of the word phytochemicals is derived from the Greek word phyto, which means plant. Therefore, phytochemicals are plant chemicals and are bioactive non-nutrient plant compounds in fruits, vegetables, grains and other plant foods. In recent years, many studies have shown that diets containing high content of phytochemicals can provide protection against various diseases. Approximately 90% of all cancer cases correlate with environmental factors, including one's dietary habits and one-third of all cancer deaths are preventable by changing dietary habits [28]. These discoveries have rapidly augmented the consumer awareness of the probable benefits of naturally occurring compounds from plants in health promotion and maintenance, and researches in nutraceuticals, functional foods and natural health products have been given top priority in recent years. The phytochemicals found in herbs and other plant foods prevent and reverse many of the processes which underlie chronic diseases. These phytochemicals can be broadly classified as carotenoids, phenolics, alkaloids, nitrogen-containing compounds, and organosulfur compounds[29]. The most important property of phytochemicals includes their role as antioxidants as a result of which the compounds in plant foods provide protection against the often highly damaging oxidative processes in our bodies that are caused and perpetuated by free radicals. The unpaired electron common to all free radicals makes these molecules highly reactive and, in order to stabilize themselves, they steal electrons from other compounds and oxidize the targeted substances (e.g. proteins, fats and DNA) that are all vulnerable to oxidation[30].

The antioxidant phytochemicals include both enzymatic and non-enzymatic components that prevent radical formation, remove radicals before damage can occur, repair oxidative damage, eliminate damaged molecules, and prevent mutations. A variety of sulfur-containing compounds and precursors in garlic also have antioxidant activity. Thus, due to above mentioned reasons, the protective effects of these

phytochemicals found in fruits, vegetables, spices and herbs were found not only for diabetes and cardiovascular diseases (CVDs), but also for other inflammatory diseases and cancer[31].

Antioxidant phytochemicals and cancer prevention

Cancer results from a multistage carcinogenesis process that involves 3 distinguishable but closely connected stages: initiation (normal cell→transformed or initiated cell), promotion (initiated cell→ preneoplastic cell), and progression (preneoplastic cell→ neoplastic cell) (**Fig. 3**). Initiation is an outcome of rather rapid and irreversible assault to the cell. The attack may be due to the initial uptake of a carcinogen and the subsequent stable genotoxic damage caused by its metabolic activation. Other causes of cancer initiation include oxidative stress, chronic inflammation and hormonal imbalance[32].

Generally, the leaf of a plant used in cooking may be referred to as a culinary herb, and any other part of the plant, often dried, as a spice. Spices can be the buds (cloves), bark (cinnamon), roots (ginger), berries (peppercorns), aromatic seeds (cumin), and even the stigma of a flower (saffron). Herbs and spices have a long history of both culinary use and of providing health benefits, as well as acting as preservatives. Herbs may act through several mechanisms to provide protection against cancer. Phytochemicals present in various herbs have also been proved to have great potential in combating cancer processes (ie, initiation, promotion, growth and metastases) and other chronic diseases that result from oxidative stress induced by free radicals[30]. Researchers have identified a host of cancer chemoprotective phytochemicals in many herbs. In addition, many herbs contain a variety of phytosterols, triterpenes, flavonoids, saponins, and carotenoids, which have been shown to be cancer chemopreventive[29]. These beneficial substances act as antioxidants and electrophile scavengers, stimulate the immune system, inhibit nitrosation and the formation of DNA adducts with carcinogens, inhibit hormonal actions and metabolic pathways associated with the development of cancer and induce phase I or phase II detoxification enzymes [33]. Chemoprevention is the use of chemical substance either natural or synthetic origin to prevent, hamper, arrest, or reverse a disease. Several commonly used herbs such as coriander, cumin, garlic, ginger, mint, oregano, turmeric etc. have been identified by the National Cancer Institute as possessing cancer-preventive properties. Garlic is known to have antitumor properties, owing to its content of a wide variety of organic sulfides and polysulfides. Garlic is reported to enhance immune function by stimulating lymphocytes and macrophages to destroy cancer cells and is also reported to disrupt the metabolism of tumor cells. The inhibition of tumors by garlic seems to be most effective when tumor is small. Garlic can also inhibit the formation of nitrosamines, which are potent carcinogens, and also inhibit the formation of DNA adducts[34].

Turmeric contains active phenolic components that inhibit cancer and also have antimutagenic activity and has been shown to suppress the development of stomach, breast, lung and skin tumors. Its activity is largely due to curcumin, which has been shown to be effective anti-inflammatory agent in humans. Curcumin has been found to increase expression of conjugation enzymes and has been shown to be one of the most potent inhibitors of NF-κB, thereby exerting anti-inflammatory effects. Curcumin has been shown to decrease the proliferation of various cancer cells of the colon, the blood, the submandibular gland, and the liver by downregulating COX-2[35]. One of the novel molecular targets of chemopreventive action of curcumin is β- catenin. The antitumor

effect of curcumin was evidenced by its ability to decrease intestinal tumors in an animal model of familial adenomatous polyposis by reducing the expression of the oncoprotein β- catenin. Some human β-catenin /TCF target genes — including cyclin D, MMP 7, OPN, IL-8, and matrilysin — play a role in tumor promotion and progression. NF-kappa B repression and decreased β- catenin signaling are some of the mechanisms by which curcumin suppresses the promotion and progression of cancer [36, 37] (**Fig.** 4)[37].

Koreans studies suggest that ginseng may lower the risk of cancer in the humans. Ginseng seemed to be most protective against cancer of the ovaries, larynx, pancreas, esophagus, breast, cervical and thyroid cancers which may be attributed to the active ingredients present in ginseng such as ginsenosides[38]. Phytochemicals such as chlorogenic acid have also been found to protect against environmental carcinogen-induced carcinogenesis by the upregulation of phase II conjugating enzymes and suppression of ROS- mediated NF-κB, AP-1, and MAPK activation[39].

Polyphenols such as quercetin, catechins, isoflavones, lignans, flavanones, ellagic acid, red wine polyphenols, resveratrol etc. induce a reduction of the number of tumors or of their growth. These polyphenols act as blocking agents at the initiation stage; influence the metabolism of procarcinogens by modulating the expression of cytochrome P_{450} enzymes involved in their activation to carcinogens and also facilitate their excretion by increasing the expression of phase II conjugating enzymes. This induction of phase II enzymes may have its origin in the toxicity of polyphenols. Polyphenols can form potentially toxic quinones in the body that are, themselves, substrates of these enzymes which then activate these enzymes for their own detoxification and, thus, induce a general boosting of our defenses against toxic xenobiotics. Polyphenols may also limit the formation of initiated cells by stimulating DNA repair[40].

Polyphenols and flavonoids inhibit pro-inflammatory gene expression via inhibition of IκB, thus inhibiting NF-κB transactivation, as well as restoring trans-repressive pathways through the activation of histone deacetylases [41]. In addition, expression of antioxidant genes such as GCL, Mn SOD, HO-1 via modulation of MAPK-ARE-Nrf 2 pathway are upregulated[41].

In vitro anticancer studies have demonstrated that natural products of flavonoids like luteolin and quercetin have the power to inhibit the proliferation of cells in human carcinoma of larynx and sarcoma-180 cell lines [42]. The nitrogenous phytochemicals, phenanthroindolizidine alkaloids i.e. pergularinine and tylophorinidine isolated from *Pergularia pallida* (Roxb.) Wight and Arn (Asclepiadaceae) inhibited the growth of *Lactobacillus leichmanni* cells by binding to thymidylate synthetase[43].

Anthraquinone natural products like rubidianin, isolated from alcoholic extract of *Rubia cordifolia* has demonstrated significant antioxidant activity in a dose-dependent manner. It prevented lipid peroxidation induced by ferrous sulphate and t-butylhydroperoxide. The antioxidant activity of rubidianin was found to be better than mannitol, vitamin E and p-benzoquinone standards[44].

Many phytochemicals from plants also affect lipoxygenase activity which is also a cause for cancer. Lipoxygenase enzymes are found in a wide variety of plant and animal tissues. These enzymes have a non-heme iron serving as a catalytic center for the stereo and regiospecific dioxygenation of select carbon atoms in polyunsaturated fatty acids for their metabolism. Eighteen carbon chain fatty acids (e.g. linoleate) are the primary substrates of the plant lipoxygenases while the mammalian isozymes mainly catalyze the metabolism of

fatty acids of twenty chain carbon length (e.g. arachidonate). The mammalian fatty acid, arachidonic acid is metabolized by one of two enzyme pathways, cyclooxygenase (COX) or lipoxygenase (LOX) generating biologically active metabolites that are involved in carcinogenesis. It has been shown that the LOXs in particular are key regulators of cell survival and apoptosis in cells. It has been shown also that LOX is a regulator of human cancer development and it is over expressed in a variety of tumors including breast, colorectal and prostate cancer, and cancer cell lines. It has been reported that inhibition of oxidative enzymes such as 5-lipoxygenase and 12- lipoxygenase trigger tumor cell apoptosis, reduce tumor cell motility and invasiveness, or decrease tumor angiogenesis and growth[45].

Onions and garlic are well used as food flavours and are used commonly in folk medicines in Asia and Africa. Belman *et al*.,[46] studied the inhibitory effect of soybean lipoxygenase of onion and garlic constituents. The di-(1-propenyl) sulfide was the only irreversible inhibitor while diallyl trisulfide, allyl methyl trisulfide, and diallyl disulfide were competitive inhibitors, while 1-propenylpropyl sulfide and (E, Z)- 4,5,9 trithiadodeca- 1,6,11-triene 9-oxide (ajoene) were mixed inhibitors. Sendl *et al*.,[47] also studied lipoxygenase inhibitory activity of garlic.

Curry leaves, one of the spices used in Indian dishes contain certain phytochemicals like carotenoids and fiber, which may contribute to the antioxidative and anticarcinogenic effects. A study conducted by Khanum *et al*.,[48], on the antioxidant potential of curry leaves in rats treated with a known chemical carcinogen, dimethylhydrazine hydrochloride (DMH) revealed a significant increase in vitamin A content in the liver and no alteration in glutathione (GSH) content, a 50% decline in the micronuclei induced by DMH and a 30% decrease in the activity of *Γ*-glutamyl transpeptidase. These results signify that curry leaves have high potential as reducer of the toxicity of DMH[48].

Ginger (*Z. officinalis* Roscoe, Zingiberaceae) is not only widely used as a dietary condiment but it has also been extensively utilized as a traditional oriental medicine. A study conducted by Abdullah *et al*.,[49] provided evidence that ginger acts as a potent growth inhibitory compound in human colon adenocarcinoma cells and the study supports the possibility of chemopreventive potential of ginger in colon cancer cells. The cytotoxic effect could be as a result of the active component, gingerol that has been reported to inhibit the growth of HCT 116 human colon colorectal and liver HepG2 cancer cells[49]. Azoxymethane-induced intestinal carcinogenesis in rats was significantly suppressed by dietary administration of gingerol. It was also reported that the inhibition mechanism of growth of colon cancer cells by ginger involved obstruction in both cell cycle progression in G0/G1 phase and apoptosis. Thus, it is clear that the antitumor effects on colon cancer cells were exerted by ginger by suppressing their growth, arresting the G0/G1-phase, reducing DNA synthesis and inducing apoptosis[50].

Saffron, used as a spice for flavoring and coloring food preparations, the main constituent of which is picrocrocin, has been reported to be useful in the treatment of numerous human diseases. Extracts of saffron have been shown to inhibit the formation of tumors and/or to retard tumor progression in a variety of experimental animal systems. The topical application of a saffron extract has been shown to inhibit both the initiation and the promotion of cancer by a common carcinogen, 7, 12-dimethylbenz(a) anthracene (DMBA), which is used to induce skin cancer for experimental purposes. Oral administration of saffron extract inhibited the

growth of mouse tumors that were derived from three different kinds of cancer cells (S180, DLA and EAC) and significantly increased (by two- to three-fold) the life span of treated tumor-bearing mice. It has also been found that naturally occurring saffron extract, in combination with two synthetic compounds, sodium selenite or sodium arsenite, may have a synergistic effect with saffron and may, therefore, have an important role in cancer chemoprevention[51].

Cumin (*Cuminum cyminum*) has been a part of the diet, regularly used as a flavoring agent due to its pleasant flavor contributed by a major constituent, cuminaldehyde, in a number of ethnic cuisines. In a study conducted by Gagandeep *et al*.,[52], cancer chemopreventive potentials of different doses of a cumin seed-mixed diet were evaluated against benzo(a)pyrene [B(a)P]-induced forestomach tumorigenesis and 3-methylcholanthrene (MCA)- induced uterine cervix tumorigenesis. Results showed a significant inhibition of stomach tumor burden (tumors per mouse) by cumin. Tumor burden was 7.33 +/- 2.10 in the B(a)P-treated control group, whereas it reduced to 3.10 +/- 0.57 ($P < 0.001$) by a 2.5% dose and 3.11 +/- 0.60 ($P < 0.001$) by a 5% dose of cumin seeds. Cervical carcinoma incidence, compared with the MCA-treated control group (66.67%), reduced to 27.27% ($P < 0.05$) by a diet of 5% cumin seeds and to 12.50% ($P < 0.05$) by a diet of 7.5% cumin seeds. Levels of cytochrome $P\text{-}_{450}$ (cyt $P\text{-}_{450}$) and cytochrome b5 (cyt b(5) were significantly augmented ($P < 0.05$) by the 2.5% dose of cumin seed diet. Lipid peroxidation measured as formation of MDA production showed significant inhibition ($P < 0.05$ to $P < 0.01$) by both doses of cumin. The results strongly suggest the cancer chemopreventive potentials of cumin seed and could be attributed to its ability to modulate carcinogen metabolism[52].

Effect of red chilli (*Capsicum annum* L.), cumin (*Cuminum cyminum* L.), and black pepper (*Piper nigrum* L.) on colon cancer induced in rats by a colon-specific carcinogen, 1,2-dimethylhydrazine (DMH) was investigated by Nalini *et al*.,[53]. The incidence and number of tumors in the colon were observed to be significantly higher in rats administered DMH and /or red chillies when compared to cumin +DMH and black pepper+DMH administered rats after the experimental period of 32 weeks. The levels of fecal bile acids and neutral sterols decreased in DMH and chilli supplemented rats whereas these levels increased significantly in rats supplemented with cumin and black pepper. Also, the levels of cholesterol, cholesterol/phospholipid ratio, 3-hydroxy-3-methylglutaryl-CoA reductase activity were decreased in cumin+DMH and black pepper+DMH-treated rats. Thus, these results confirm that red chilli supplementation promotes colon carcinogenesis, whereas cumin and black pepper suppresses colon carcinogenesis in the presence of the procarcinogen DMH[53].

The chemical constituents of ginger, saffron, cumin and black pepper are given in the **Fig.5**[30].

Terpenoids and cancer prevention

Terpenoids, the largest group of phytochemicals, traditionally used for medicinal purposes in India and China, are currently being explored as anticancer agents in clinical trials. Research has shown that the terpenoids in plants increase tumor latency and decrease tumor multiplicity. Terpenoids in various herbs possess strong antioxidant activities. The isoprenoids are useful cancer chemopreventive agents as they suppress tumor growth by inhibiting HMG-CoA reductase[54].

A large number of terpenoids exhibited cytotoxicity against a variety of tumor cells and also showed cancer preventive as well as anticancer efficacy in preclinical animal models. Epidemiological

and experimental studies propose that monoterpenes may be helpful in the prevention and therapy of several cancers, including mammary, skin, lung, forestomach, colon, pancreatic and prostate carcinomas. A large number of tri- terpenoids have been shown to curb the growth of a variety of cancer cells without exerting any toxicity in normal cells. Numerous preclinical efficacy studies have provided widespread indication that both naturally occurring and synthetic derivatives of triterpenoids possess chemopreventive and therapeutic effects against colon, breast, prostate and skin cancer[55]. These triterpenoids and their derivatives act at various stages of tumor development, inhibit initiation and promotion of carcinogenesis, induce tumor cell differentiation and apoptosis, and suppress tumor angiogenesis, invasion and metastasis through regulation of various transcription and growth factors as well as intracellular signaling mechanisms. Currently, several phase clinical trials have been initiated to evaluate the chemopreventive as well as the anticancer efficacy of a number of triterpenoids[56]. 25-methoxyhispidol A, a novel triterpenoid isolated from the fruit of *Poncirus trifolata*, displayed antiproliferative effects against SK-Hep-1 cells. Apoptosis and G0/G1 phase arrest were suggested as the mechanisms of action. This correlated well with the down regulation of cyclin D1, CDK4, c-myc, and retinoblastoma protein expressions, along with the upregulation of p21[57]. Zerumbone (ZER), a cytotoxic component isolated from the wild ginger, *Zingiber zerumbet* Smith, induced significant antiproliferative activity against HepG2 cells through mechanisms involving an elevation of the apoptotic process with increase in the level of pro-apoptotic protein Bax and decrease of anti-apoptotic protein Bcl-2 without involving p53[58]. Dietary isoprenic derivatives, including β-ionone, a cyclic isoprenoid present in grapes and wine, represent a promising class of chemopreventive agents. β-ionone was found to inhibit hepatic preneoplastic lesions with a decrease in cell proliferation, inhibition of plasma cholesterol and amelioration of DNA damage during the initial phases of hepatocarcinogenesis initiated with diethylnitrosamine (DENA) and promoted by 2-AAF in rats[59] (**Fig. 6**)[55] .

Chinese herbs and cancer prevention

Many active compounds have been isolated from Chinese medicinal herbs and have been tested for anti-cancer effects (**Fig. 7)**[60]. Artesunate is a semisynthetic derivative of artemisinin, a natural product from the Chinese herb *Artemisia annua* L. exerted antimalarial activity, and, additionally, artemisinin and its derivatives are active against cancer cells. Artesunate induced apoptosis and necrosis and DNA breakage in a dose dependent manner as shown by single-cell gel electrophoresis. This genotoxic effect was confirmed by measuring the level of gamma-H2AX, which is considered to be an indication of DNA double-strand breaks (DSB). Polymerase beta-deficient cells were more sensitive than the wild-type to artesunate, indicating that the drug induces DNA damage that is repaired by base excision repair irs1 and VC8 cells defective in homologous recombination (HR) due to inactivation of XRCC2 and BRCA2, respectively, were more sensitive to artesunate than the corresponding wild-type. This was also true for XR-V15B cells defective in nonhomologous end-joining (NHEJ) due to inactivation of Ku80. The data indicate that DSBs induced by artesunate are repaired by the HR and NHEJ pathways. They suggest that DNA damage induced by artesunate contributes to its therapeutic effect against cancer cells[61].

Plants of the genus *Taraxacum*, commonly known as dandelions, have a history of use in Chinese, Arabian and Native

American traditional medicine, to treat a variety of diseases including cancer. Three aqueous extracts prepared from the mature leaves, flowers and roots, investigated on tumor progression related processes such as proliferation and invasion showed that the crude extract of dandelion leaf (DLE) decreased the growth of MCF-7/AZ breast cancer cells in an ERK-dependent manner, whereas the aqueous extracts of dandelion flower (DFE) and root (DRE) had no effect on the growth of either cell line. Furthermore, DRE was found to block invasion of MCF-7/AZ breast cancer cells while DLE blocked the invasion of LNCaP prostate cancer cells, into collagen type I. Inhibition of invasion was further evidenced by decreased phosphorylation levels of Focal Adhesion Kinase **(**FAK) and src as well as reduced activities of matrix metalloproteinases, MMP-2 and MMP-9[62].

Wogonin, one of the flavonoids isolated from *Scutellaria baicalensis* Georgi (Huangqin), a Chinese medicinal herb, with its dry herb weight consisting of up to 0.39 mg/100 mg of wogonin[63] has been extensively used in the management of various inflammatory diseases owing to its inhibition of nitric oxide (NO), prostaglandin E2 and pro-inflammatory cytokines production, as well as reduction of cyclooxygenase-2 (COX-2). Wogonin induces apoptosis through the mediation of Ca^{2+} and/or inhibition of NF-κB, shifting O^{2-} to H_2O_2 to some extent; H_2O_2, in turn, serves as a signaling molecule that activates phospholipase Cg. Wogonin may also directly activate the mitochondrial Ca^{2+} channel uniporter and enhance Ca^{2+} uptake, resulting in Ca^{2+} overload and mitochondrial damage. Wogonin is a good anti-cancer candidate due to its broad toxicities to various types of tumor cell lines and the low toxicities to normal tissues, as well as the synergistic effects[64]. Shikonin, a natural anthraquinone derivative isolated from the roots of *Lithospermum erythrorhizon* (Zicao), another Chinese herb, exerts anti-tumor effects mainly by inhibiting cell growth and inducing apoptosis. The fundamental molecular mechanisms differ with cell types and treatment methods. Shikonin modulates an estrogen enzyme by down-regulating the expression of steroid sulfatase, essential for estrogen biosynthesis and also inhibits tumor invasion via the NF-κB signaling pathway in human high-metastatic adenoid cystic carcinoma cells. Consequently, shikonin may directly or indirectly inhibit or alter disease-related cellular targets in cancer[65].

CONCLUSIONS

- Oxidative stress is caused due to imbalance between reactive species and antioxidants and is implicated in a wide range of metabolic and degenerative disorders such as diabetes mellitus, arthritis, Parkinson's disease, Alzheimer's disease and mainly cancer.
- Cancer is a multistage process that involves 3 distinguishable interconnected stages viz. initiation, promotion and progression.
- Naturally occurring antioxidants from plants, phytochemicals, have been proved to have great potential in combating cancer and other chronic diseases that result from oxidative stress induced by free radicals.
- The phytochemicals from various herbs and spices which include polyphenols, flavonoids, flavonols, tannins, terpenoids etc. act at various stages of tumor development, inhibit initiation and promotion of carcinogenesis, induce tumor cell differentiation and apoptosis, and suppress tumor angiogenesis.
- Thus, many of the phytochemicals act in different ways and thereby, inhibit cancer initiation, promotion and also progression.

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human ACC-M cells. Oral Dis 2011; 17: 362-369.

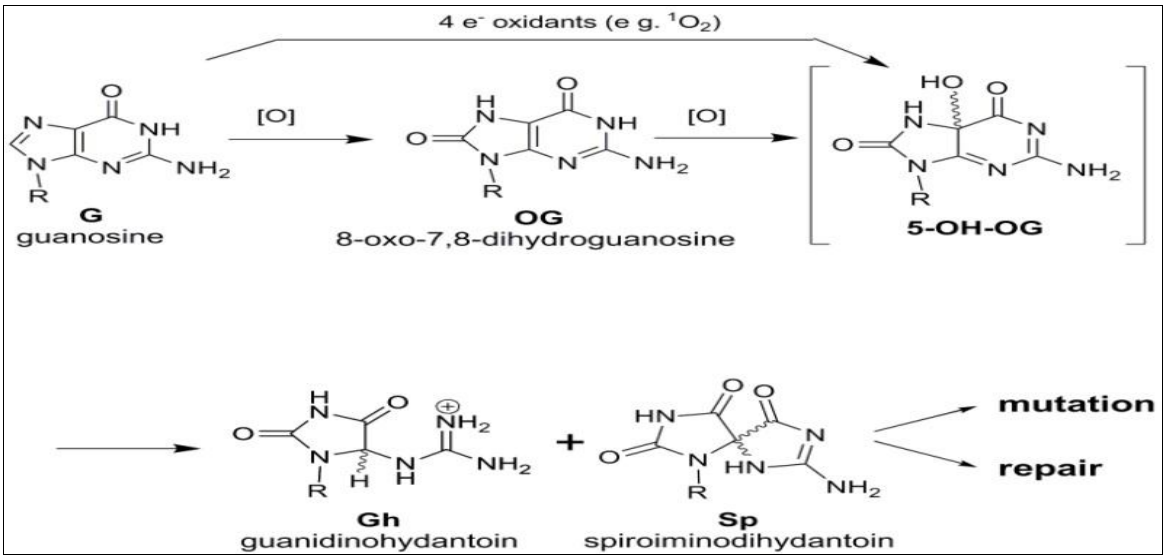

Figure.1. Oxidative damage to guanosine in DNA

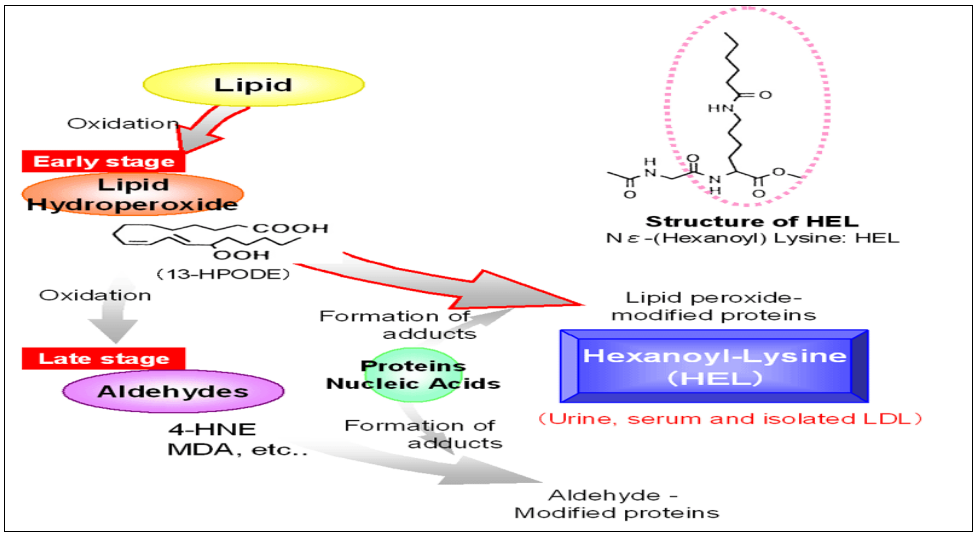

Figure.2. Oxidative damage to lipids causing lipid peroxidation (Mao *et al*., 1999)

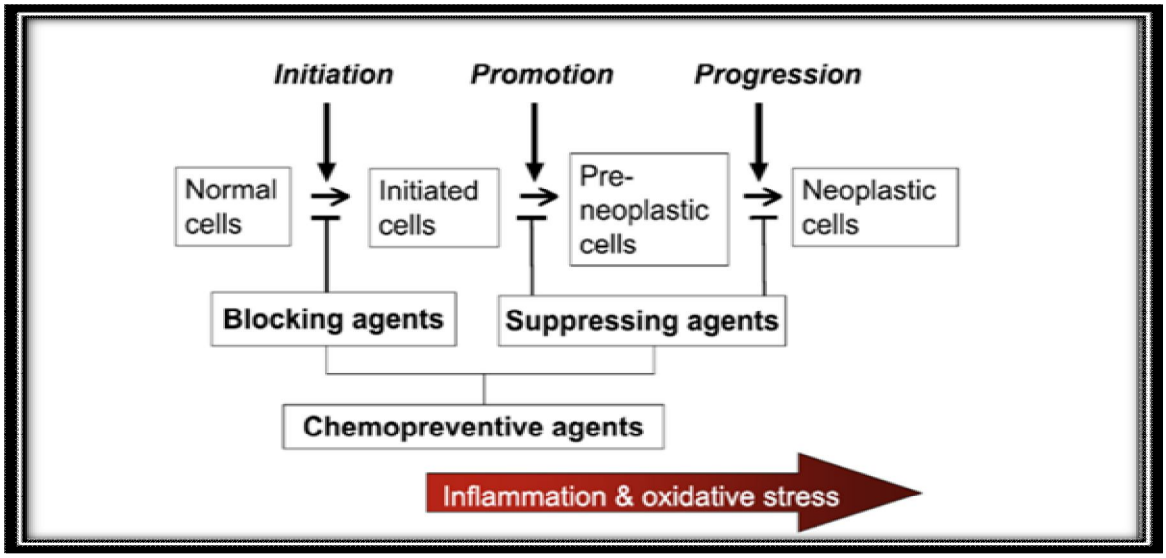

Figure.3. Cancer- a multistep process (Anand *et al*., 2008)

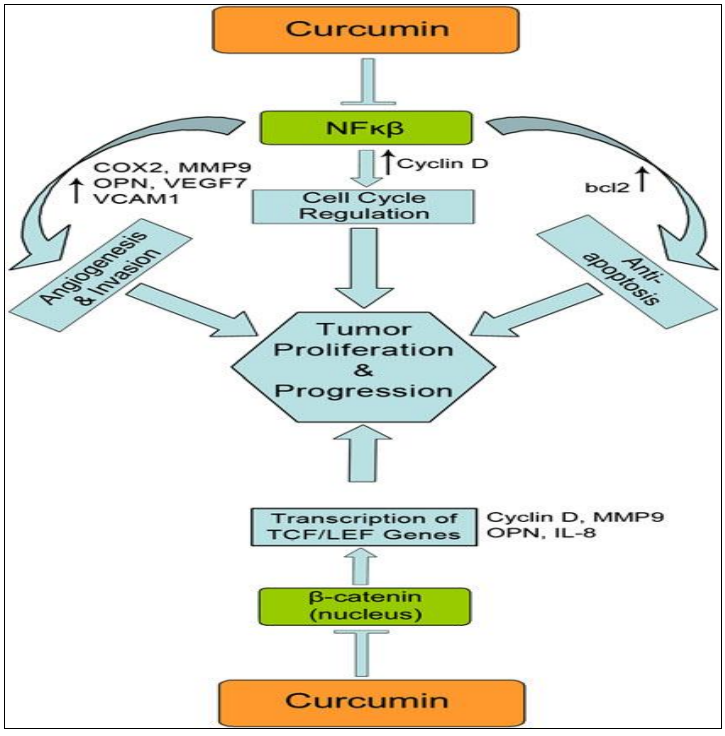

Figure.4. Schematic representation of chemopreventive targets of curcumin in curtailing tumor progression and Proliferation (Thangapazham *et al*., 2006)

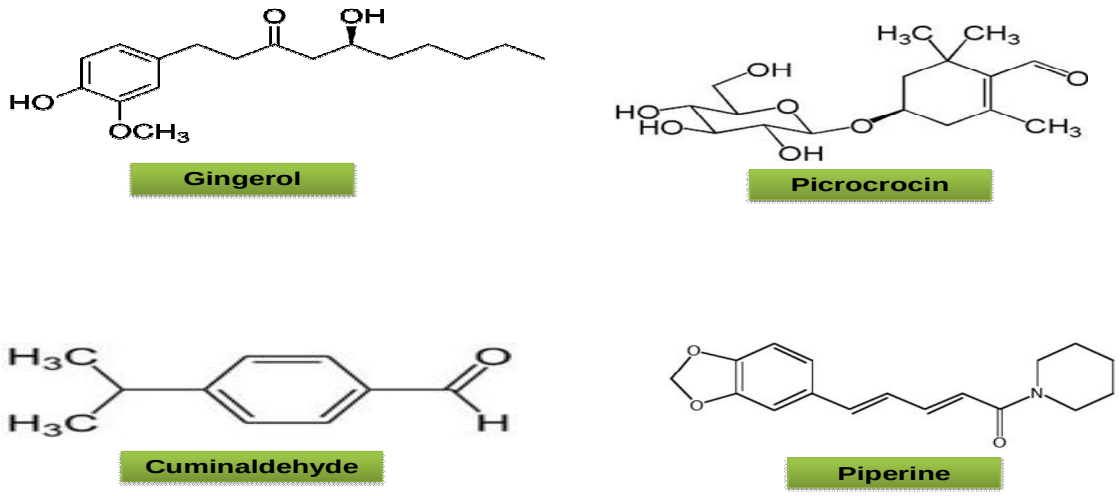

Figure.5. Bioactive constituents of ginger, saffron, cumin and black pepper (Scott, 2006)

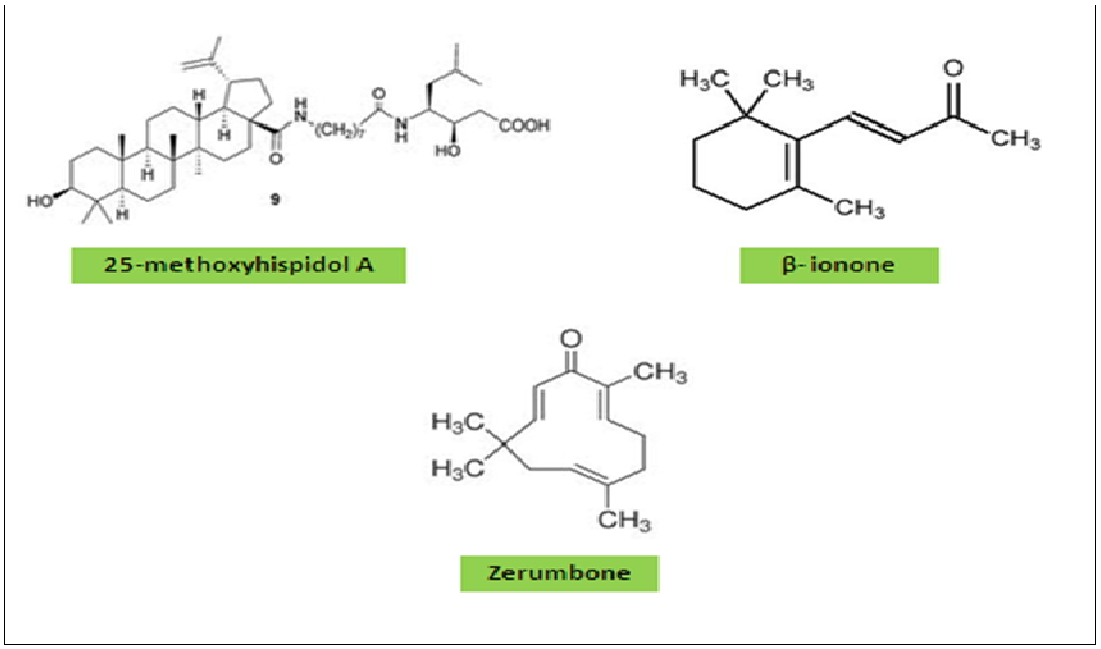

Figure.6. Structure of terpenoids- 25-methoxyhispidol A, β-ionone and zerumbone (Liby *et al*., 2007)

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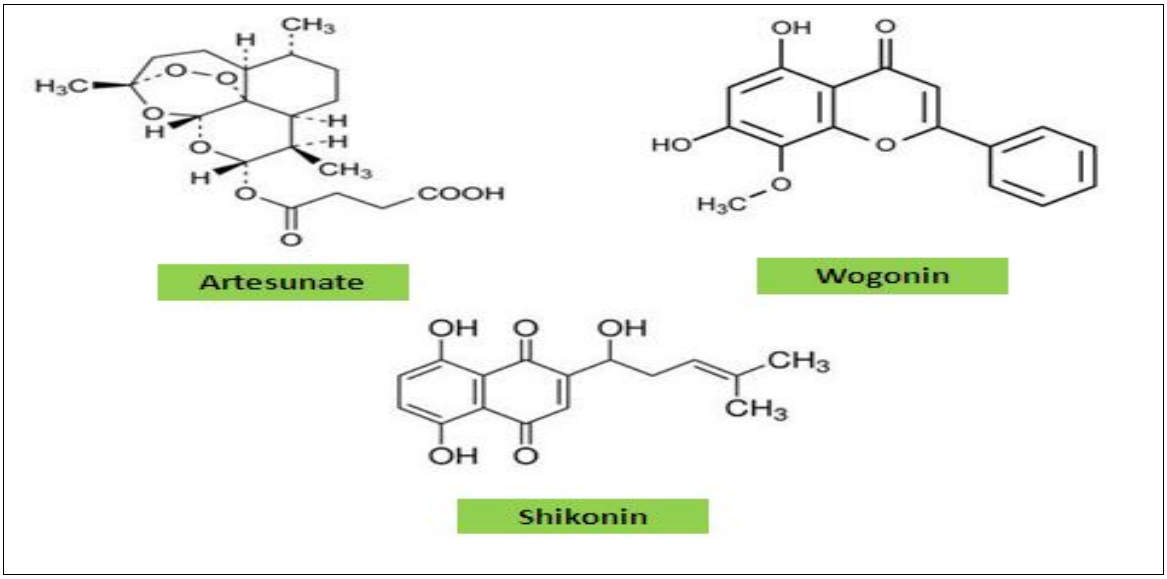

Figure.7. Active compounds in Chinese medicinal herbs (Tan *et al*., 2011)