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Medicinal and Edible Plants as Cancer Preventive Agents

Ken Yasukawa
School of Pharmacy, Nihon University
Japan

1. Introduction

Cancer chemoprevention is currently one of the most urgent projects in public health. According to epidemiological surveys, the majority of human cancers are related to two factors; diet and smoking (Banning, 2005; Hirayama, 1984). However, in the general population, dairy consumption of certain foods has also been shown to have anticancer effects. This highlights the importance of environmental factors such as diet in cancer chemoprevention (Banning, 2005). It is also evident that an understanding of the mechanisms of carcinogenesis is essential for cancer chemoprevention. Most cancer prevention research is based on the concept of multistage carcinogenesis (Fig. 1.): initiation→promotion→progression (Piot & Dragan, 1991; Morse & Stoner, 1993). In contrast to both the initiation and progression stages, animal studies indicate that the promotion stage occurs over a long time period and may be reversible, at least early on. Therefore, the inhibition of tumor promotion is expected to be an efficient approach to cancer control (Sporn, 1976; Murakami, et al., 1996). Cancer chemoprevention is defined as the use of specific natural and synthetic chemical agents to reverse or suppress carcinogenesis and prevent the development of invasive cancers. There has been a growing awareness in recent years that dietary non-nutrient compounds can have important effects as chemopreventive agents, and considerable work on the cancer chemopreventive effects of such compounds in animal models has been undertaken. In the course of our research on potential antitumor-promoters (cancer chemopreventive agents) from edible plants and fungi, and from crude drugs, we have found that various triterpene alcohols and sterols and their oxygenated derivatives showed inhibitory effects on mouse ear inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA). We have recently reviewed the chemopreventive activities of naturally occurring terpenoids (Akihisa & Yasukawa, 2001; Akihisa, et al., 2003; Yasukawa, 2010). Primary prevention of cancer aims to avoid the development of cancer. Thus, it is important to inhibit the initiation and/or promotion of carcinogenesis. However, the adult population bears tumor cells that cannot revert to normal cells, and thus effective strategies to prevent cancer include avoiding continuous contact between these cells and promoters and/or aggressively inhibiting the tumor promoter effects. Therefore, to prevent cancer, it is essential to find effective compounds (anti-tumor promoters) that delay, inhibit or block tumor promotion, which is a reversible and long-term process. Active research is now being conducted using animal carcinogenesis models on cancer preventing substances

contained in plants and vegetables. In this chapter I review the chemopreventive activity of natural sources, foods, supplements, crude drugs and Kampo medicines (traditional Japanese herbal prescriptions).

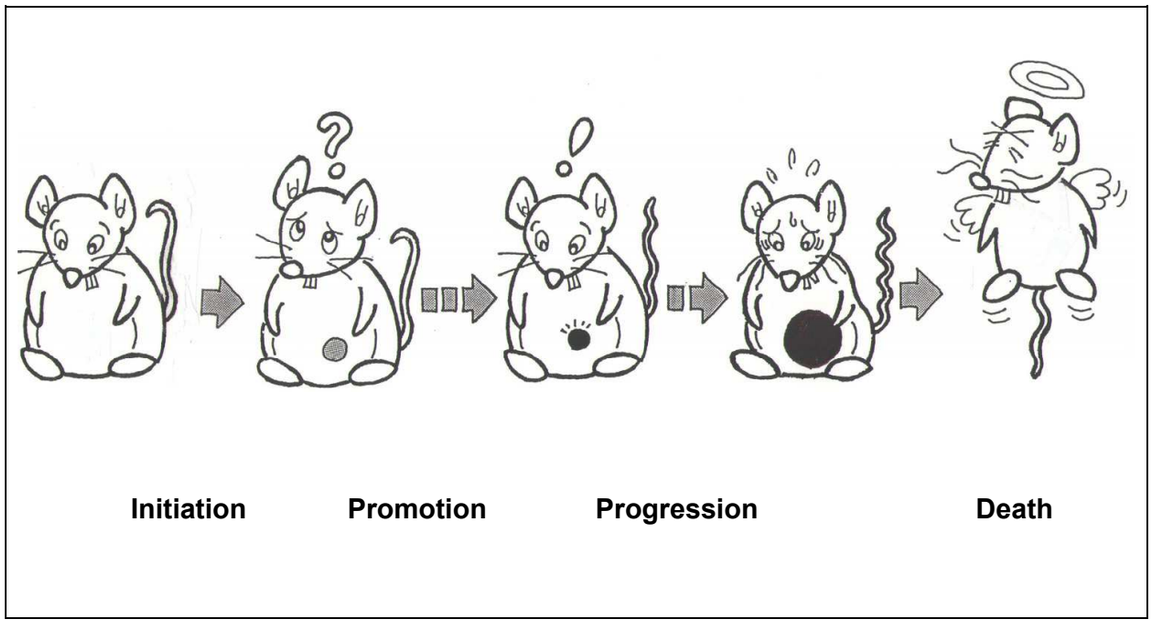

Fig. 1. The theory of two-stage carcinogenesis.

2. Primary screening of antitumor promoters

In general, carcinogenesis has three stages: initiation, promotion and progression (Fig.1). Various bioassay systems are available in the literature for the screening of potentially chemopreventive compounds. Several convenient primary screening tests have been developed to evaluate compounds for their ability to inhibit tumor promotion. These tests are based on the activity of the tumor promoter TPA which has a wide range of activities. For example, at the biochemical level, TPA induces ornithine decarboxylase (ODC) in skin, activates protein kinase C (PKC), stimulates arachidonic acid release and prostaglandin synthesis, and generates superoxide anion radicals. At the cellular and tissue levels, TPA induces inflammation, blocks intercellular signal transduction, stimulates HL-60 cell aggregation and differentiation, and activates Epstein-Barr virus (EBV) (Ohigashi, et al., 1986). Screening tests for tumor promotion inhibition are based on these multiple activities, and based on inhibition of TPA-induced activity, a compound is presumed to be an anti-tumor promoter.

In addition, other tests using cells and enzymes are based on biochemical reactions. These include apoptosis induction, cell proliferation inhibition, cyclooxygenase-2 (COX-2) inhibition, cell differentiation enhancement, farnesyl protein transferase inhibition, phase II detoxification enzyme induction, lipoxygenase inhibition, ODC induction inhibition and superoxide production inhibition. The commonly used primary screening tests are described below.

2.1 Inhibition of TPA-induced inflammation

When TPA is applied to the auricle of mice, erythema and inflammation peak in 6 to 8 h, however erythema can still be observed after 24 h. Based on this phenomenon, testing is performed by applying the test substance before and after TPA application, then measuring auricular edema 6 h after TPA application to evaluate inhibitory activity (Yasukawa, et al., 1989).

2.2 Epstein-Barr virus activation inhibition test

In this test, using EBV non-producing Raji cells (human B lymphocytes) derived from Burkitt's lymphoma containing the EBV genome, TPA and the test substance are added in the presence of *n*-butanoic acid. After culturing for 48 h, indirect immunofluorescence is used to detect early antigen (EA) on the cell surface as an index of EBV activation inhibition by the test substance (Ohigashi, et al., 1986).

3. Anti-carcinogenic tests in animals

Compounds that show effectiveness in primary screening studies, particularly those with potent activity that are available in sufficient quantities, are then evaluated for inhibitory effects in animal model studies. In mice, application of the initiator 7,12-dimethylbenz[*a*]anthracene (DMBA) at trace amounts does not cause skin cancer, however subsequent application of the tumor promoter TPA eventually results in skin cancer (Skin-1; Table 1). Further studies with animal models have been performed for carcinogenesis of skin (Skin-2~Skin-7), bladder (Bladder), colon (Colon-1~Colon-3), liver (Liver-1~Liver-3), lung (Lung-1 and Lung-2), mammary (Mammary-1~Mammary-3), pancreas (Pancreas), tongue (Tongue), uterus (Uterus) and multi-organs (Multi), using natural sources (Table 1).

4. Supplemental and edible plants

While numerous anticarcinogens exist in the diet, an important question is how to use such substances in an effective, directed manner to reduce the cancer risk in humans. The concept of designer foods is one approach for accomplishing this goal, whereby foods would be engineered to contain effective levels of anticarcinogens. This approach is limited by the level of scientific knowledge on which to base such food design. Below, I describe a number of supplemental and edible plants that inhibited cancerogenesis in animal experiment.

4.1 Edible plants

Humans have used leaves as food since time immemorial. Different types of leaves, depending on location and season, have been part of the human diet since prehistoric times. There is historical documentation of certain edible leaves in ancient Greece and Rome and in the Middle ages. Plants of the families *Compositae*, *Cruciferae*, *Cucurbitaceae*, *Leguminosae*, *Liliaceae*, *Rutaceae* and *Zingiberaceae* have many kinds to use as vegetables. The following is an outline of the sources of these plants as well as edible fungi and mushrooms.

Code	Bioassay system	Reference
Bladder	Inhibition of *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BHBN)/sodium saccharin (SS) induced urinary tumors	Sugiyama, et al., 1994
Colon-1	Inhibition of azoxymethane (AOM) induced colon tumors	Vanamala, et al., 2006
Colon-2	Inhibition of 1,2-dimethylhydrazin (DMH) induced colon tumors	Fukushima, et a., 2001
Colon-3	Inhibition of *N*-methyl-*N*-nitrosourea (MNU) induced colon tumor	Narisawa, et al., 1991
Liver-1	Inhibition of diethylnitrosamine (DEN) induced hepatic tumors	Ognanesian, et al., 1997
Liver-2	Inhibition of Aflatoxin B_1 induced liver tumors	Manson,et al., 1998
Liver-3	Inhibition of DEN/phenobarbital induced liver tumors	Kapadia, et al., 2003
Lung-1	Inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (PhIP) induced lung tumors	Kohno, et al., 2001
Lung-2	Inhibition of 4-NQO/glycerol induced lung tumors	Konoshima, et al., 1994
Mammary-1	Inhibition of 2-amino-1-methyl-6-phenylimidazol[4,5-*b*]-pyridine induced mammary tumors	Ohta, et al., 2000
Mammary-2	Inhibition of 7,12-dimethylbenz[*a*]anthracene (DMBA) induced mammary tumors	Tanaka, et al., 1997a
Mammary-3	Inhibition of *N*-methyl-*N*-nitrosourea (MNU) induced mammary tumors	Bresnick, et al., 1990
Multi	Induction DEN, dihydroxy-di-*N*-propylnitrosamine (DHPN), MNU induced multi organ tumors	Kim, et al., 1997
Pancreas	Inhibition of *N*-nitrosobis-(2-oxopropyl)amine (BOP) induced pancreatic tumors	Birt, et al., 1987
Skin-1	Inhibition of DMBA/ 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced skin tumors	Slaga, et al., 1980
Skin-2	Inhibition of benzo[*a*]pyrene/croton oil induced skin tumors	Sadhana, et al., 1988
Skin-3	Inhibition of DMBA/ teleocidin induced skin tumors	Yoshizawa, et al., 1984
Skin-4	Inhibition of DMBA/ TPA+mezerein induced skin tumors	Perchellet, et al., 1990
Skin-5	Inhibition of DMBA/ ultra violet B (UVB) induced skin tumors	Kapadia, et al., 2003
Skin-6	Inhibition of DMBA/fumonisin B1 induced skin tumors	Takasaki, et al.,1999a
Skin-7	Inhibition of (+)-(*E*)-4-methyl 2[(*E*)-hydroxyimino]-5-nitro-6-methoxy-3-hexenamido (NOR-1)/TPA induced skin tumors	Konoshima, et al., 1999
Tongue	Inhibition of 4-NQO induced tongue tumors	Tanaka, et al., 1992
Uterus	Inhibition of MNU/estradiol-17β induced endometrial tumor	Niwa, et al., 2001

Table 1. Bioassay systems related to cancer chemopreventive activities described in this chapter.

4.1.1 *Compositae* plants and their components

Seventy-five methanol extracts obtained from 53 species in 11 tribes of *Compositae* plants were assayed, and *Carthmus tinctorius* (safflower), *Chrysanthemum morifolium* var. *sinensis* forma *esculentum* (edible chrysanthemum) and *Taraxacum officinale* (dandelion) markedly inhibited TPA-induced inflammation in mice (Yasukawa, et al., 1998a).

The artichoke (*Cynara cardunculus* L.) is a perennial thistle originating in Southern Europe around the Mediterranean. The total antioxidant capacity of artichoke flower heads is one of the highest reported for vegetables. Artichokes can also be made into a herbal tea. Topical application of the methanol extract of artichoke flowers suppressed tumor promotion by DMBA/TPA in mouse skin (Yasukawa, et al., 2010). Four triterpenes, α- and β-amyrin, taraxasterol and ψ-taraxasterol, and their acetates were isolated from the active fraction of this extract.

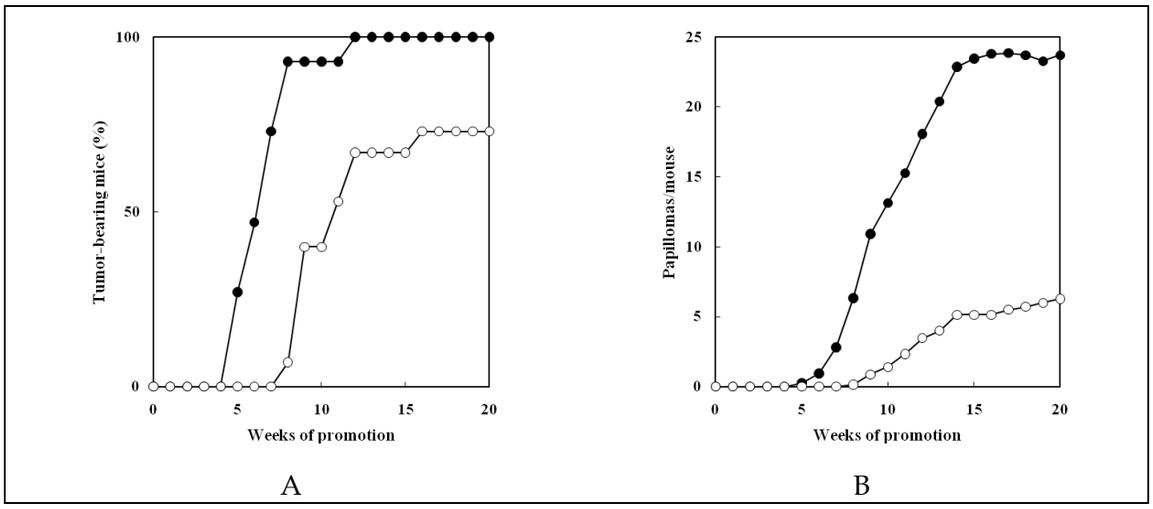

Fig. 2. Inhibitory effects of an artichoke methanol extract on skin papilloma promotion by DMBA/TPA in mice. One week after initiation with a single topical application of DMBA (50 g), 1 g of TPA was applied twice weekly. Topical application of the methanol extract (1 mg) and vehicle was performed 30 min before each TPA treatment. Data are expressed as the percentage of mice bearing papillomas (A), and as the average number of papillomas per mouse (B). ●, +TPA with vehicle alone; ○, +TPA with an artichoke methanol extract. (Yasukawa, et al., 2010).

Fig. 2A illustrates the time course of skin tumor formation in the groups treated with DMBA/TPA, with and without the methanol extract of artichoke flowers. The first tumor appeared at week 6 in the group treated with DMBA/TPA and all 15 mice had tumors at week 12. In the group treated with DMBA/TPA and a methanol extract of artichoke flowers, the first tumor appeared at week 8. The percentage of tumor-bearing mice treated with DMBA/TPA and a methanol extract of artichoke flowers was 73% at week 20. The group treated with DMBA/TPA produced 23.7 tumors per mouse at week 20, while the group treated with DMBA/TPA and a methanol extract of artichoke flowers had 6.3 tumors per mouse (Fig. 2B). Treatment with the methanol extract resulted in a 73% reduction in the average number of tumors per mouse at week 20 (Yasukawa, et al., 2010).

Edible chrysanthemum is a bitter aromatic herb that has been experimentally shown to lower fever, soothe inflammation, dilate the coronary arteries (increasing blood flow to the heart), and inhibit the growth of pathogens. It is used in folk medicine for hypertension, coronary artery disease, angina, feverish colds, and liver-related disorders. Triterpenoids were isolated from edible chrysanthemum flowers, and heliantriol C was found to be the major compound (Yasukawa, et al., 1996d). The activity of heliantriol C was ten times greater than other pentacyclic triterpenes against TPA-induced tumor promotion in mouse skin (Yasukawa, et al., 1998b).

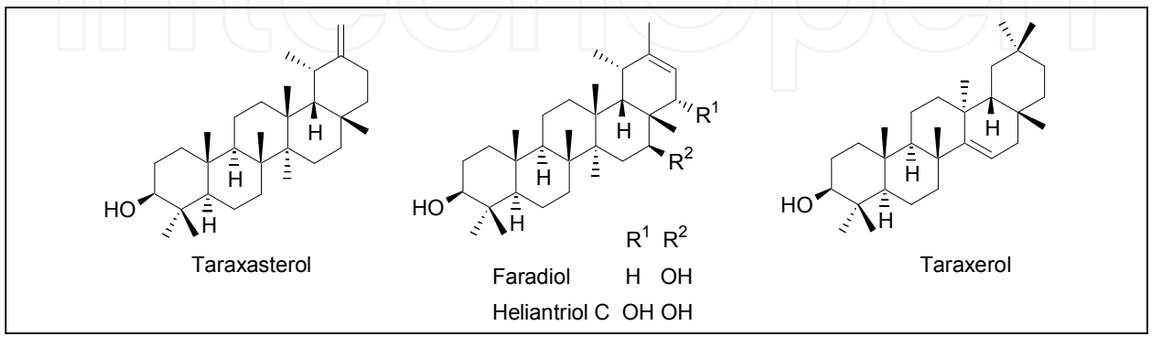

Fig. 3. The chemical structures of triterpenoids from *Compositae* plants.

4.1.2 *Labiatae* plants and their components

Perilla is a very popular herb in Japan; it is mainly used as a garnish in the same way that parsley is used in Europe. The nettle-like leaves are bright green, reddish or purple. *Perilla frutescens* Britton var. *crispa* Decaisne is a bushy annual, native to southeast Asia, and has long been grown in China for the oil extracted from the its seeds. Perilla oil has been shown to inhibit colon carcinogenesis by MNU in rat (Narisawa, et al., 1991; 1994).

Rosmarinus officinalis L., commonly called rosemary, is a woody perennial herb with fragrant evergreen needle-like leaves that are often used in cooking. It has been found to act both as a stimulant and as a mild analgesic, and has been in folk use to treat headaches and epilepsy. Rosemary methanol extract suppressed tumor promotion by DMBA/TPA in mouse skin (Huang, et al., 1994). The active components, ursolic acid and carnosol, were isolated from the methanol extract, and were shown to inhibit DMBA/TPA-promoted two-stage carcinogenesis in mouse skin (Huang, et al., 1994).

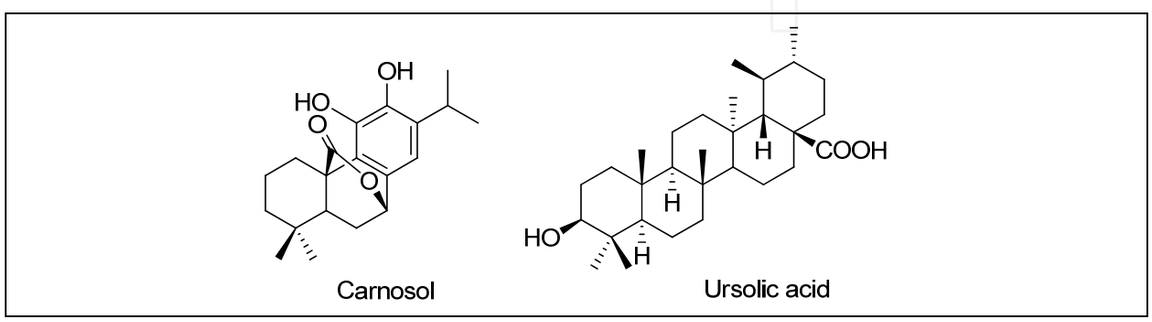

Fig. 4. The chemical structures of terpenoids from rosemary.

4.1.3 Grape and its components

Comparing diets among Western countries, researchers have discovered that although the French tend to eat higher levels of animal fat, their incidence of heart disease remains surprisingly low. This phenomenon has been termed the French Paradox, and is thought to occur from the protective benefits of regularly consuming red wine. Apart from the potential benefits of alcohol itself, including reduced platelet aggregation and vasodilation, polyphenols (e.g., resveratrol), found mainly in the grape skin, provide other suspected health benefits. The ethanol extract of grapes (*Vitis vinifera* L., *Vitaceae*) inhibited tumor promotion by DMBA/TPA in mouse skin (Alam, et al., 2002). In a model of liver carcinogenesis, tumor initiation was performed by a single intraperitoneal injection of DENA, followed by promotion with phenobarbital in the drinking water. Resveratrol dose-dependently reduced the incidence, total number and multiplicity of visible hepatocyte nodules (Bishayee & Dhir, 2009).

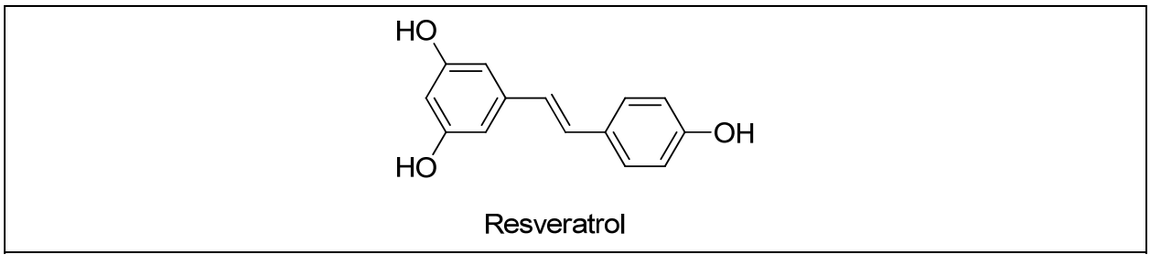

Fig. 5. The chemical structure of resveratrol from grape.

On the other hand, grape seeds are a rich source of monomeric, dimeric and oligomeric proanthocyanidins. Commercial preparations of grape seed extracts are currently marketed as supplements due to their perceived potential health benefits, particularly as antioxidants. The polyphenolic fraction of grape seeds suppressed tumor promotion by DMBA/TPA in mouse skin (Bomser, et al., 1999; Zhao, et al., 1999). The mechanism of its activity is due, in part, to the inhibition of TPA-induced epidermal ODC and myeloperoxidase activities (Bomser, et al., 1999).

4.1.4 *Citrus* plants and their components

Citrus unshiu Marc. (*Rutaceae*) is a seedless, easy-peeling citrus mutant of Japanese origin. In Japan, it is known as mikan or formally unshu mikan. Its fruit is sweet, about the size of the mandarin orange *Citrus reticulate* Blanco. The peel has been used as a crude drug for gastric secretion promotion, anti-allergic action, inhibition of airway contraction, and sedative effect. Oral administration of unshu mikan juice inhibited colon carcinogenesis by azoxymethane (AOM) (Tanaka, et al., 2000), and lung carcinogenesis by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in mice (Kohno, et al., 2001). Unshu mikan contains high amounts of β–cryptoxanthin and hesperidin. β–Cryptoxanthin was shown to inhibit colon carcinogenesis induced by MNU (Narisawa, et al., 1999), while hesperidin inhibited AOM-induced colon carcinogenesis in rat (Tanaka, et al., 1997b).

The grapefruit (*Citrus* × *paradisi* Macfad.), is a subtropical citrus tree known for its bitter fruit, an 18th-century hybrid first bred in Barbados. It is a good source of vitamin C,

contains the fiber pectin, and the pink and red hues contain the antioxidant lycopene. Grapefruit pulp suppressed AOM-induced colon carcinogenesis in rat (Vanamala, et al., 2006). The active components limonin and naringin protected against AOM-induced aberrant crypt foci by suppressing proliferation and elevating apoptosis through anti-inflammatory activities.

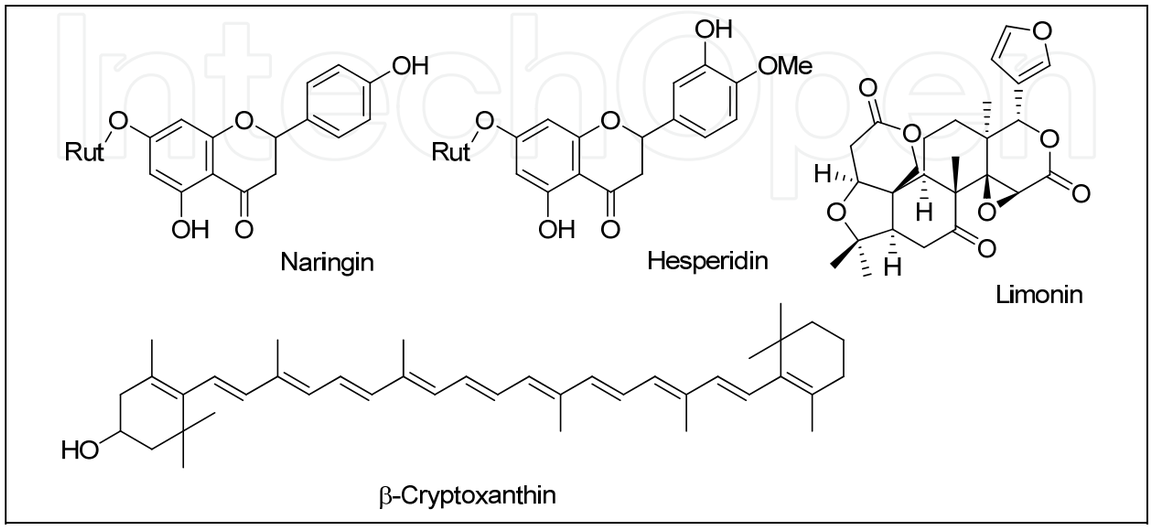

Fig. 6. The chemical structures of flavanons and terpenoids from *Citrus* spp.

4.1.5 Soy milk

Soy milk, sometimes referred to as soy drink/beverage, is a beverage made from soybean (*Glycine max* L., *Leguminosae*). Soy milk contains about the same proportion of protein as cow's milk. The coagulated protein from soy milk can be made into "tofu", just as milk can be made into cheese. Soy milk inhibited 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced mammary carcinogenesis in rats (Ohta, et al., 2000). Soy beans contain high amounts of isoflavonoids and saponins; isoflavonoids have been shown to have phytoestrogenic activity (Moliteni, et al., 1995).

4.1.6 Cabbage and its components

The leafy green vegetable cabbage is a popular cultivar of the species *Brassica oleracea* L. (*Cruciferae*). It is a herbaceous, biennial, dicotyledonous flowering plant distinguished by a short stem upon which is crowned a mass of leaves, usually green but in some varieties red or purplish, and which forms a characteristic compact, globular cluster while immature. Cabbage is an excellent source of vitamin C and also contains significant amounts of glutamine, an amino acid that has anti-inflammatory properties. Along with broccoli and other brassica vegetables have been shown to include indole-3-carbinol (I3C). In European folk medicine, cabbage leaves are used to treat acute inflammation, and fresh cabbage juice has been shown to promote rapid healing of peptic ulcers. Oral administration of cabbage inhibited *N*-nitrosobis-(2-oxopropyl)amine (BOP)-induced pancreatic carcinogenesis in hamsters; however cabbage was not observed to inhibit tumor promotion by DMBA/TPA in

mouse skin (Birt, et al., 1987). Oral intake of cabbage suppressed mammary carcinogenesis by *N*-methyl-*N*-nitrosourea (MNU) in rat (Bresnick, et al., 1990). In addition, I3C inhibited tumor promotion by DMBA/TPA in mouse skin (Srivastava & Shukla, 1998). DMBA-induced mammary carcinogenesis in rat (Grubbs, et al., 1995), tongue carcinogenesis in rat (Tanaka, et al., 1992), aflatoxin B_1-induced liver carcinogenesis in rat (Manson, et al., 1998), and DEN-induced liver carcinogenesis in mice (Oganesian, et al., 1997). However, I3C enhanced liver and thyroid gland neoplastic development when given during the promotion stage in a rat medium-term multi-organ carcinogenesis model (Kim, et al., 1997).

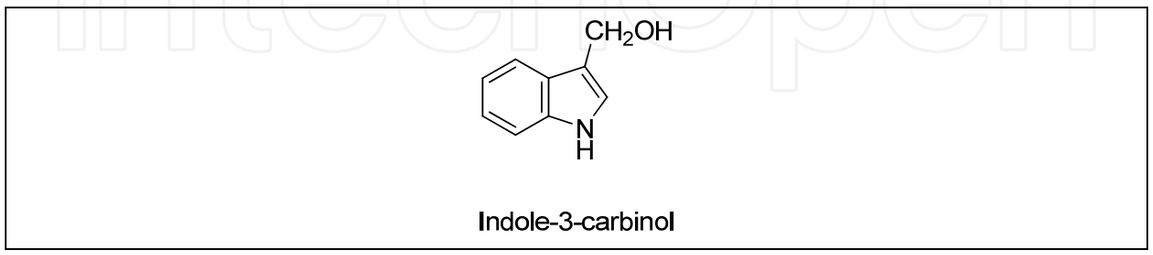

Fig. 7. The chemical structure of indole-3-carbinol from cruciferous vegetables.

4.1.7 Green tea and its components

Green tea (the leaves of *Camellia sinensis* L., *Theaceae*) is derived from a perennial herbaceous plant native to southeastern Asia. Fujiki, et al. first reported that (–)-epigallocatechin gallate (EGCG), a component of green tea, inhibited tumor promotion by DMBA/teleocidin in mouse skin (Yoshizawa, et al., 1987). The polyphenolic fraction of green tea inhibited TPA-induced tumor promotion during two-stage carcinogenesis in SENCAR mouse skin, and also suppressed TPA-induced COX activity (Katijyar, et al., 1992). Green tea catechins inhibited DMBA-induced mammary gland carcinogenesis in female Sprague-Dawley rats (Tanaka, et al., 1997a). Fujiki et al. introduced a new theory in cancer prevention with regard to its mechanism of action: green tea catechins acting as a new class of chemical chaperones (Kuzuhara,et al., 2008). In a pilot study, green tea extract was shown to be an effective supplement for the chemoprevention of metachronous colorectal adenomas (Shimizu, et al., 2008).

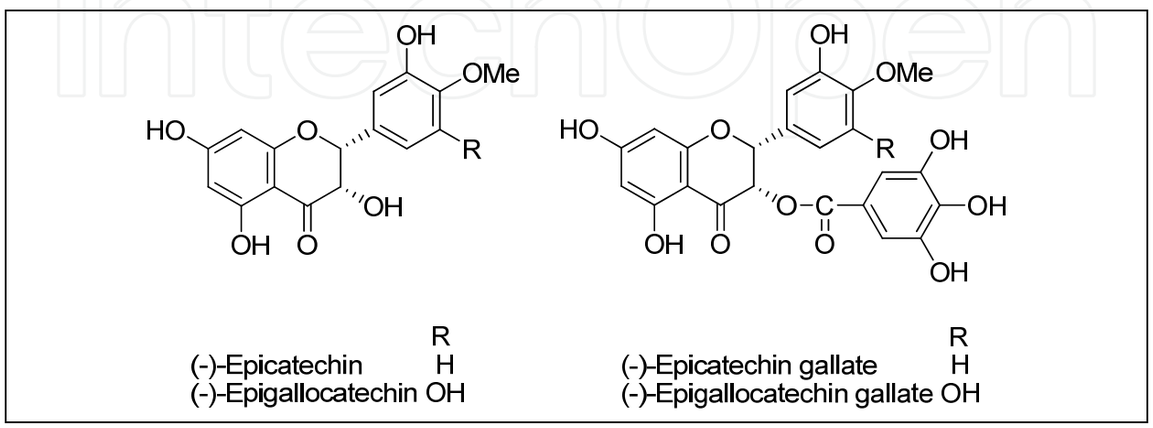

Fig. 8. The chemical structures of polyphenolics from green tea.

4.1.8 Beetroot

The beetroot, also known as table beet, garden beet, red beet or informally simply as beet, is one of the many cultivated varieties of beets (*Beta vulgaris* L., *Chenopodiaceae*) and arguably the most commonly encountered variety in North America, Central America and Britain. The usually deep-red roots are eaten boiled, either as a warm vegetable or as a cold salad with added oil and vinegar, or raw and shredded, either alone or in combination with any salad vegetable. Beetroots are a rich source of potent antioxidants and nutrients, including magnesium, sodium, potassium and vitamin C, as well as betaine, which is important for cardiovascular health. Oral administration of a beetroot extract inhibited tumor promotion by DMBA/TPA in mouse skin, and tumor promotion by 4-nitroquinoline 1-oxide (4NQO)/glycerol in lung carcinogenesis in mice (Kapadia, et al., 1996). In addition, orally administered beetroot extract inhibited mouse skin two-stage carcinogenesis, DMBA/ultraviolet B, and (±)-(*E*)-4-methyl-2-[(*E*)-hydroxyamino]-5-nitro-6-methoxy-3-hexanamide (NOR-1)/TPA, as well as liver carcinogenesis by *N*-nitrosodiethylamine (DEN) plus phenobarbital (Kapadia, et al., 2003).

4.1.9 Ginger and its components

Ginger is the rhizome of *Zingiber officinale* Rosc. (*Zingiberaceae*), and is consumed as a delicacy, medicine, or spice. The characteristic odor and flavor of ginger is caused by a mixture of zingerone, shogaols and gingerols, volatile oils that compose one to three percent of the weight of fresh ginger. Topical application of an ethanol extract of ginger inhibited TPA-induced tumor promotion during two-stage carcinogenesis in mouse skin (Katiyar, et al., 1996). Pre-application of an ethanol extract of ginger onto the skin of SENCAR mice resulted in significant inhibition of TPA-induced epidermal ODC, COX and lipoxygenase activities as well as ODC mRNA expression in a dose-dependent manner. Topical application of [6]-gingerol inhibited tumor promotion by DMBA/TPA in mouse skin, and also suppressed TPA-induced epidermal ODC activity and inflammation (Park, et al., 1998).

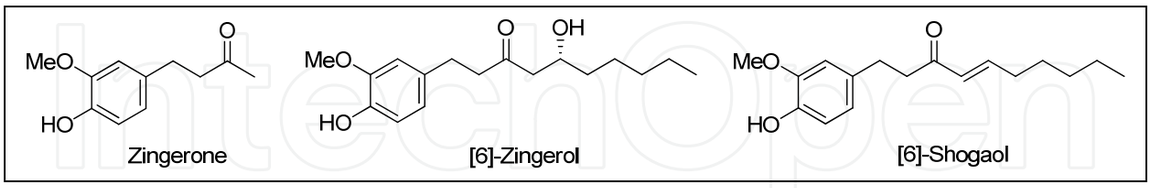

Fig. 9. The chemical structures of phenolics from *Zingiber officinale.*

4.1.10 *Allium* plants

Allium sativum L. (*Liliaceae*) is commonly known as garlic, its close relatives include the onion, shallot, leek, chive, and rakkyo. Garlic is native to central Asia, and has long been a staple in the Mediterranean region, and is a popular seasoning in Asia, Africa, and Europe. It was known to Ancient Egyptians, and has been used throughout its history for both culinary and medicinal purposes. Garlic extract inhibited tumor promotion by DMBA/TPA in mouse skin (Nishino, et al., 1989).

Rakkyo (the bulbs of *Allium chinense* G.Don) is used in folk medicine as tonic to the intestines and a stomach. A 20% ethanol extract of rakkyo bulbs suppressed two-stage carcinogenesis by DMBA/TPA in mouse skin (Okuyama, et al., 1995).

4.1.11 Edible mushrooms and their components

In Japan, mushrooms are a very important food. The beneficial effects of edible and medicinal mushrooms are now being recognized. Studies on mushrooms have been developed within the life sciences discipline worldwide. They have become increasingly popular in Japan as an ordinary food or supplement with the mounting scientific evidence of its useful functions. I believe edible mushrooms contribute to the prevention or treatment of life-style related diseases and can be classified as a functional food. Topical application of methanol extracts from *Mycoleptodonoides aitchisonii* (Berk.) Maas G. (*Steccherinaceae*) and *Hypsizygus marmoreus* (Peck.) Bigelow (*Tricholomataceae*) inhibited tumor promotion by DMBA/TPA in female ICR mouse skin (Yasukawa, et al., 1994a, 1996e). Its active components, ergosterol and its peroxide were isolated from *H. marmorus* (Yasukawa, et al., 1994a) and showed inhibition same carcinogenic test (Yasukawa, et al., 1994a). On the other hand, these sterols were isolated from *Chlorella vulgaris* Beij. (*Chlorophyceae*), a green alga, for anti-inflammatory agents, and ergosterol peroxide inhibited tumor promotion by DMBA/TPA in mouse skin (Yasukawa, et al., 1996a).

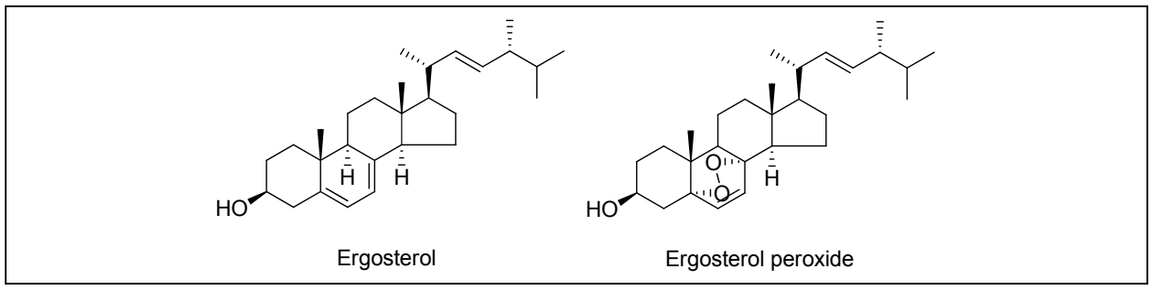

Fig. 10. The chemical structures of sterols from *Hypsizygus marmoreus.*

4.1.12 Red malt molds and their components

Monascus spp. (*M. Purpureus* Went. and *M. Anka* K. Satô, *Monascaceae*) are molds purplish-red in color. Species of *Monascus* have been utilized for hundreds of years for making fermented foods and preserving meat. This fungus is of importance because of its use in the form of red yeast rice in the production of certain fermented foods in Japan. However, the discovery of cholesterol-lowering statins produced by the mold has prompted research into its possible medical uses. The naturally occurring lovastatin and analogs are called monacolin K, L, J, and also occur in their hydroxy acid forms along with dehydroxymonacolin and compactin (mevastatin). The prescription drug lovastatin, identical to monacolin K, is the principal statin produced by *M. purpureus*. Topical application of Monascus Pigment (an ethanol extract of *M. anka*) and monascorubrin, one of the components from *M. anka*, inhibited tumor promotion by DMBA/TPA in mouse skin (Yasukawa, et al., 1994b). Furthermore, oral administration of Monascus pigment inhibited DMBA/TPA two-stage carcinogenesis in mouse skin (Yasukawa, et al., 1996f).

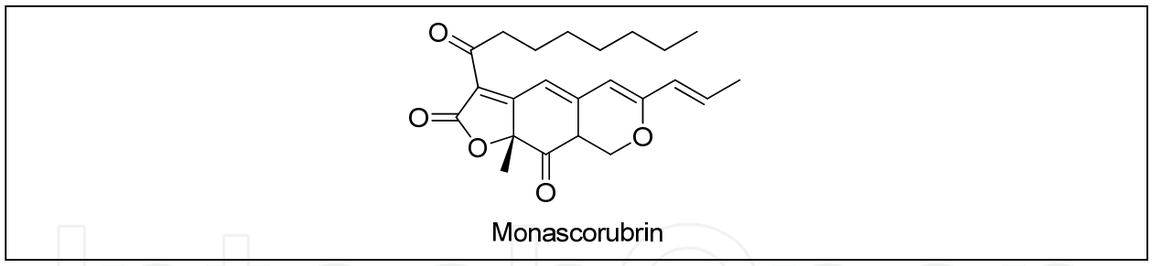

Fig. 11. The chemical structure of monascorubrin from the red malt mold.

4.2 Supplemental plants

With the increase in life expectancy comes a greater focus on health. Supplements are a popular part of health maintenance, and are typically taken separately from the diet. Dietary supplements, also known as food supplements or nutritional supplements, are intended to supplement the diet and provide nutrients, such as vitamins, minerals, fiber, fatty acids, or amino acids, that may be missing or not be consumed in sufficient quantities in the diet. The European Union's Food Supplements Directive of 2002 requires that the safety of supplements be demonstrated, both in dosages and purity. In Japan, many people use supplement because of life-style related diseases and cancer, and I discuss the study of the plant supplements from the viewpoint of cancer prevention.

4.2.1 Ginseng and its components

Oral administration of white and red ginseng (*Panax ginseng* C.A. Mayer, *Araliaceae*) suppressed colon carcinogenesis by 1,2-dimethylhydrazine (DMH) in rat (Fukushima, et al., 2001). In benzo[*a*]pyrene (BP)-induced lung carcinogenesis in mice, 5- or 6- year old ginseng root was more effective than 1.5- to 4-year old ginseng root. The ginsenosides Rg_3, Rg_5 and Rh_2 are active components in ginseng, and act either singularly or synergistically in cancer prevention (Yun, et al., 2001). The methanol extract of san-chi ginseng (the roots of *Panax notoginseng* (Burk.) F.H. Chen) suppressed skin carcinogenesis by DMBA/TPA, liver carcinogenesis by DEN/Phenobarbital, lung carcinogenesis by 4NQO/glycerol in mice (Konoshima, et al., 1996). Moreover, the methanol extract of san-chi inhibited skin carcinogenesis by NOR-1/TPA, as well as DMBA/fumonisin B1 in mice (Konoshima, et al., 1999). The ginsenoside Rg_1 slightly suppressed tumor promotion by DMBA/TPA in mouse skin (Konoshima, et al., 1996).

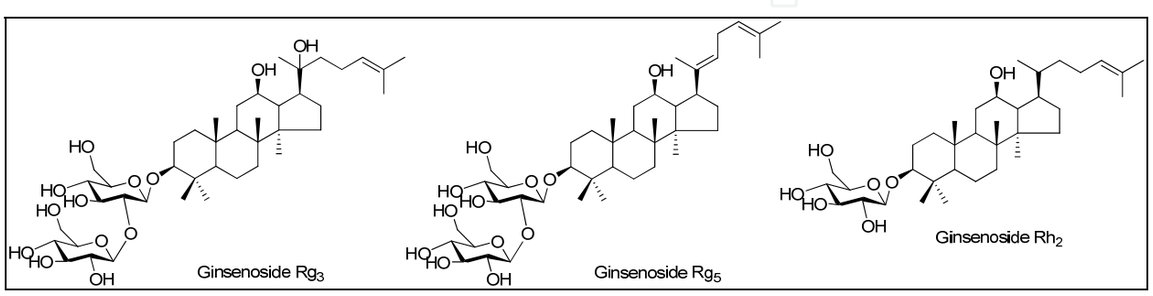

Fig. 12. The chemical structure of ginsenosides from ginseng.

4.2.2 Seabuckthorn and its components

The fruit of seabuckthorn (*Hippophae rhamnoides* L., *Elaeagnaceae*) is dense in carotenoids, vitamin C, vitamin E, amino acids, dietary minerals and polyphenols. The nutrient and phytochemical constituents of seabuckthorn berries have potential value in the treatment of inflammatory disorders, cancer or other diseases. Seabuckthorn is a herbal remedy reputedly used over centuries to relieve cough, aid in digestion, invigorate blood circulation and alleviate pain.

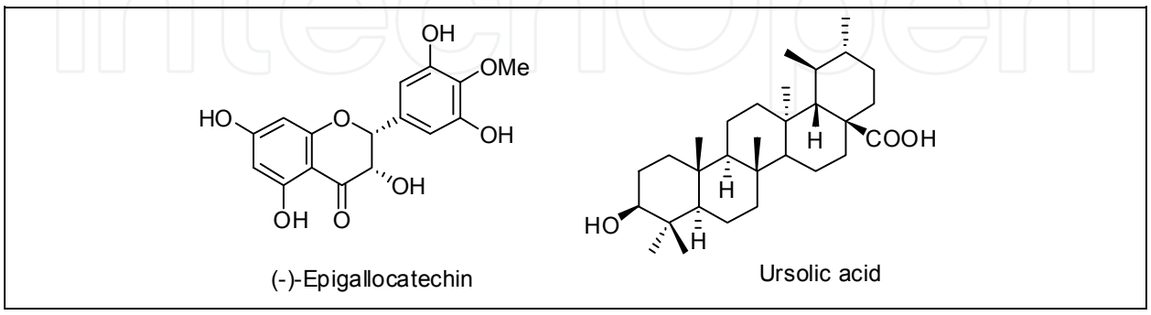

Fig. 13. The chemical structures of (–)-epigallocatechin and ursolic acid from the branches of seabuckthorn.

Its bark and leaves have been used for treating diarrhea and dermatological disorders. The methanol extract of seabuckthorn branches suppressed tumor promotion in two-stage carcinogenesis by DMBA/TPA in mouse skin, and the active components ursolic acid and (–)-epigallocatechin were isolated from the active fractions of the methanol extract (Yasukawa, et al., 2009).

4.2.3 Neem

Azadirachta indica A. Juss. (Neem) is a tree in the mahogany family *Meliaceae*. It is one of two species in the genus *Azadirachta*, and is native to the Indian Subcontinent, growing in tropical and semi-tropical regions. Neem products have been observed to be anthelmintic, antifungal, antidiabetic, antibacterial, antiviral, contraceptive and sedative. It is a major component of Ayurvedic and Unani medicine and is particularly prescribed for skin disease. All parts of the tree are said to have medicinal properties (seeds, leaves, flowers and bark) and are used for preparing many different medical preparations. Neem leaves were found to inhibit tumor promotion by DMBA/TPA in mouse skin (Arora, et al., 2011). Inhibition of carcinogenesis in response to neem treatment was accompanied by an overexpression of signal transducer and activator of transcription 1 (STAT1) and activator protein 1 (AP-1) and decrease in nuclear factor-kappa B (NF-κB) expression (Arora, et al., 2011).

4.2.4 Supplemental mushrooms and their components

Chaga (the sclerotia of *Inonotus obliquus* (Pers. Fr.) Pil., *Hymenochaetaceae*) has been widely used as a folk medicine in the treatment of cancer, cardiovascular disease and diabetes in Russia, Poland, and several Baltic countries. In Japan and Korea, chaga is used as a supplement during cancer treatment. More recently, this herb has been assessed for its

cancer-preventing activity. Oral administration of chaga was found to inhibit tumor promotion by DMBA/TPA in mouse skin (Akita & Yasukawa, 2011). Other researchers have isolated triterpene derivatives from chaga. Of these triterpenes, inotodiol and 3β-hydroxylanosta-8,24-dien-21-al were reported to restrain a cancer-causing promotion process (Nakata, et al., 2007; Taji, et al.,2008).

In Korea, meshima (*Phellinus linteus* (Berk et Curt) Teng, *Hymenochactaceae*) is also the most popular herb used by cancer patients. Oral administration of an aqueous extract of meshima suppressed tumor promotion by DMBA/TPA in mouse skin (Yasukawa, et al., 2007).

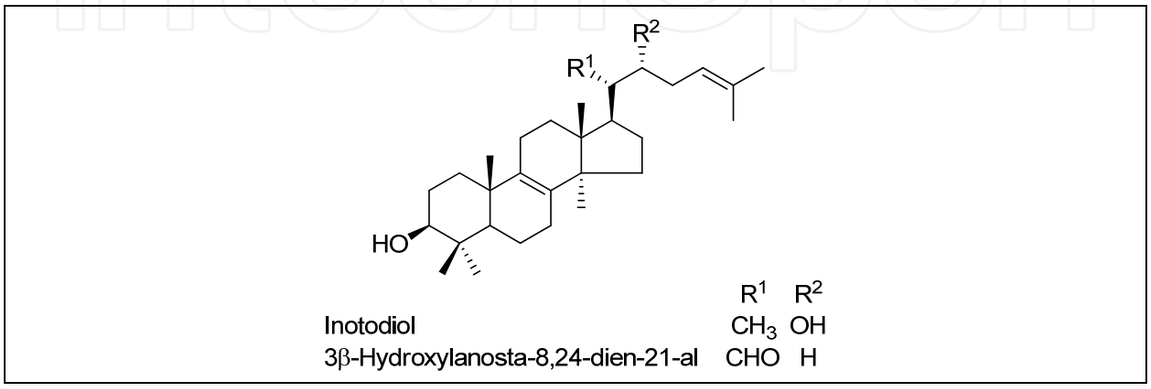

Fig. 14. The chemical structures of triterpenoids from Chaga (*Inonotus obliquus*).

4.3 Crude drugs

A crude drug is any naturally occurring, unrefined substance derived from organic or inorganic sources such as plants, animals, bacteria, organs or whole organisms, and is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. Crude drugs are primary used in disease, but are also used in health maintenance. These medicinal plants are typically taken in the form of spices and as additives. Below, I describe various medicinal plants and mushrooms.

4.3.1 *Compositae* plants and their active components

Several species and subspecies of *Taraxacum* are widely distributed in Japan, and the roots of these plants (*T. Platycarpum* Dahlst., *T. Japonicum* Koidz., etc.) have been used as bitter stomachic, diuretic, anti-mastopathy and anti-inflammatory folk medicines in China and Japan. Interestingly, dandelion (*T. officinale* F.H. Wigg) leaves have been regarded as a vegetable in Europe. The methanol and water extracts of *T. japonicum* inhibited tumor promotion by TPA or fumonisin B1 in DMBA-initiated mice (Takasaki, et al., 1999a). Several triterpenoids have been isolated from the flowers of *T. officinale* and *T. platycarpum* (Akihisa, et al., 1996; Yasukawa, et al., 1996d), taraxasterol and faradiol inhibited tumor promotion by DMBA/TPA in mouse skin (Yasukawa, et al., 1996c). Furthermore, taraxasterol and taraxerol inhibited same experiment (Takasaki, et al., 1999b).

Atractylodis Rhizoma, the rhizome of *Atractylodes japonica* Koidzumi, is traditionally used in Kampo medicine. The methanol extract of Atractylodis Rhizoma inhibited two-stage

carcinogenesis by DMBA/TPA in mouse skin (Yu, et al., 1994). The active component, atractylon, was isolated from the active fraction of the methanol extract of Atractylodis Rhizoma (Yu, et al., 1994).

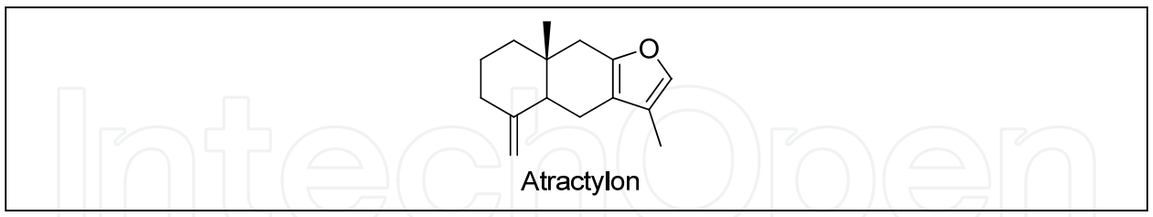

Fig. 15. The chemical structure of atractylon from Atractylodis Rhizoma.

Safflower (*Carthamus tinctorius* L.) is a highly branched, herbaceous, thistle-like annual. It is commercially cultivated for the vegetable oil extracted from its seeds. The pigment in safflower is benzoquinone-based carthamin, and is a quinone-type natural dye. Dried safflower flowers are used in traditional Chinese medicine to alleviate pain, increase circulation, and reduce bruising. Topical application of the methanol extract of safflower inhibited tumor promotion by DMBA/TPA in mouse skin. The active agents, stigmasterol and other phytosterols were isolated from the active fraction of safflower, and stigmasterol inhibited tumor promotion by DMBA/TPA in mouse skin (Kasahara, et al., 1994). Subsequently, alkane-6,8-diols were isolated from other active safflower fractions (Akihisa, et al., 1994, 1997). Alkanediol from safflower and synthetic C29-alkane-6,8-diol inhibited tumor promotion by DMBA/TPA in mouse skin (Motohashi, et al., 1995; Yasukawa, et al., 1996b).

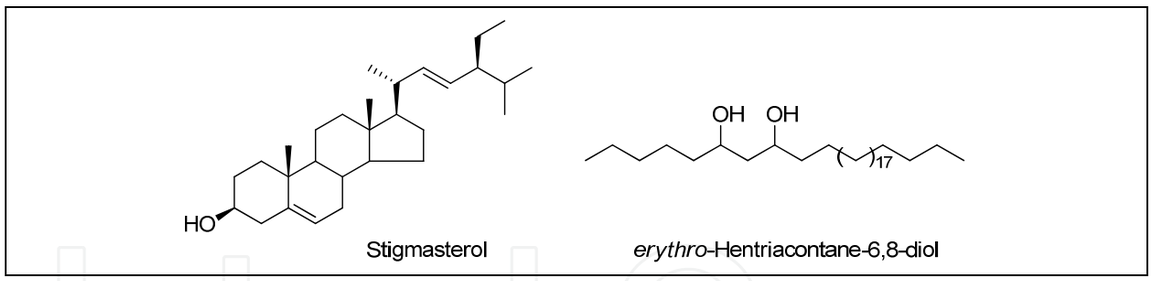

Fig. 16. The chemical structures of stigmasterol and alkane-6,8-diol from safflower.

4.3.2 Pruni Cortex and its active components

Cherry blossoms are the flowers of any of several trees of the genus *Prunus*, including the Japanese cherry (*Prunus serrulata* Franch, *Rosaceae*), which is sometimes called sakura in Japanese. Edible cherries generally come from cultivars of the related species *Prunus avium* L. and *Prunus cerasus* L. Pruni Cortex (the bark of *Prunus jamasakura* Sieb. ex Koidz.) is used for infectious diarrhea, food poisoning and catarrhal gastritis. The methanol extract of Pruni Cortex inhibited two-stage carcinogenesis by DMBA/TPA in mouse skin (Yasukawa, et al., 1998c). The active agent, octacosyl ferulate was isolated from the active fraction of Pruni Cortex, and inhibited tumor promotion by DMBA/TPA in mouse skin (Yasukawa, et al., 1998c). Octacosyl ferulate inhibited the phosphorylation of histone by protein kinase C (PK-C) in a concentration-dependent manner.

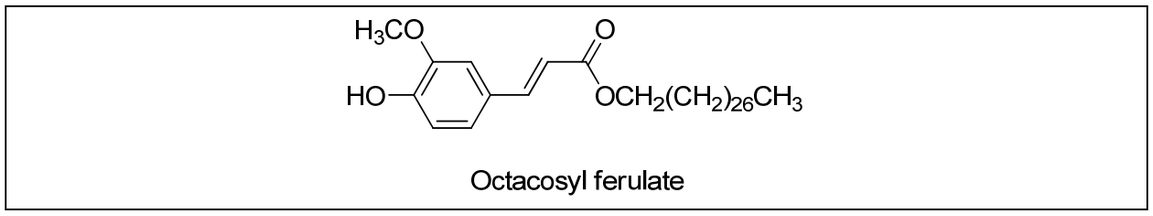

Fig. 17. The chemical structures of octacosyl ferulate from Pruni Cortex.

4.3.3 Achyranthes aspera

Achyranthes aspera L. (*Amaranthaceae*) is an indigenous medicinal plant of Asia, South America and Africa, and its leaves are commonly used by traditional healers in the treatment of fever (especially malarial fever), dysentery, asthma, hypertension and diabetes. The dried herb is used to treat colicky children and also as an astringent in gonorrhea treatment. The topical application of a methanol extract of *A. aspera* leaves suppressed two-stage carcinogenesis by DMBA/TPA in mouse skin (Chakraborty, et al., 2002).

4.3.4 Galangal and its active components

Galangal (the rhizome of *Alpinia officinarum* Hance, *Zingiberaceae*) is a perennial herbaceous plant native to southeastern Asia. Galangal has been used externally for skin infections, skin cancer and gum diseases, and internally for digestive upsets, chronic gastritis, gastric ulceration and epigastric and rheumatic pain. A methanol extract of galangal inhibited TPA-induced tumor promotion DMBA/TPA in mouse skin. Seven diarylheptanoids were isolated from the methanol extract for inhibitory activity against TPA-induced inflammatory ear edema in mice (Yasukawa, et al., 2008).

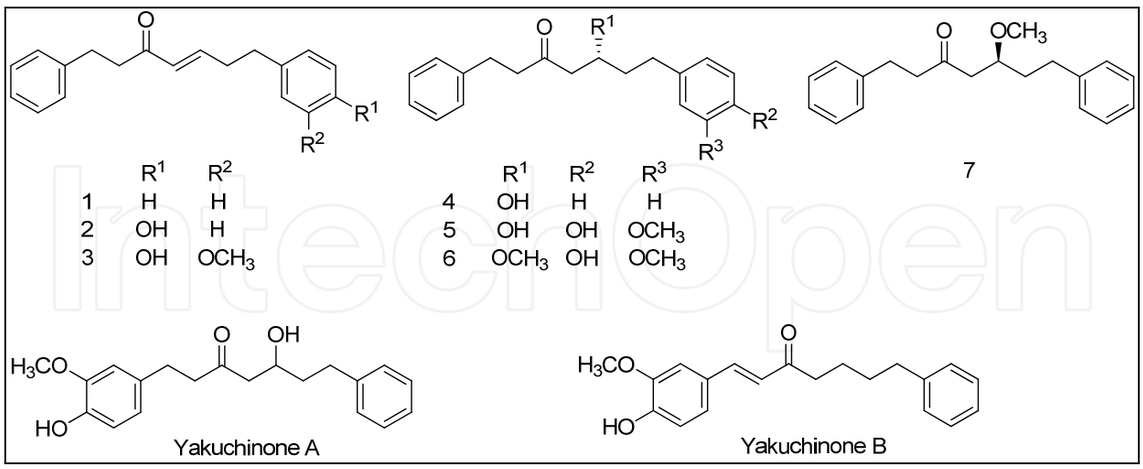

Fig. 18. The chemical structures of diarylheptanoids from *Alpinia* plants.

Lee et al. reported that a methanol extract *Alpinia oxyphylla* Miquel (*Zingiberaceae*) fruits suppressed tumor promotion by DMBA/TPA in mouse skin (Lee, et al., 1998). Yakuchinones A and B were isolated from the active fraction of the methanol extract as active components.

4.3.5 Medicinal mushrooms and their active components

The sclerotium of *Poria cocos* Wolf (*Polyporaceae*) is traditionally used in Kampo medicine as a diuretic and as a sedative. Many lanostane-type and 3,4-secolanostane-type triterpene acids have been isolated from *P. cocos*. The methanol extract of *P. cocos* inhibited tumor promotion by DMBA/TPA in mouse skin (Kaminaga, et al., 1996b). Of these triterpene acids, pachymic acid, 3-*O*-acetyl-16α-hydroxytrametenolic acid, and poricoic acid B inhibited tumor promotion by DMBA/TPA in mouse skin (Kaminaga, et al.,1996a). The activity of these triterpene acids was ten times greater than other lanostane-type triterpenes against TPA-induced tumor promotion in mouse skin.

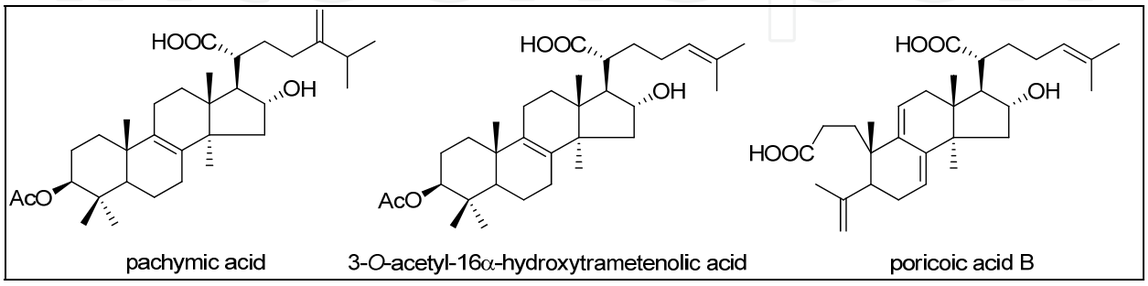

Fig. 19. The chemical structures of triterpenoids from Poria (*Poria cocos*).

4.4 Kampo medicines

The fundamentals of Chinese medicine came to Japan between the 7th and 9th centuries. Currently, herbal medicines in Japan are regulated as pharmaceutical preparations; their ingredients are exactly measured and standardized, unlike other places such as the U.S.A., Europe, and China. Both industry and government conduct extensive monitoring of agricultural and manufacturing processes as well as post-marketing surveillance to guarantee the safety of these preparations. Kampo prescriptions follow the Standard Kampo formula nomenclature ver. 1.0, March 5th, 2005.

4.4.1 Shoseiryuto (Xiao-Qing-Long-Tang)

Shoseiryuto is a mixture of eight herbal components (Pinellia tuber, Glycyrrhiza, Cinnamon bark, Schisandra fruit, Asiasarum root, Paeony root, Ephedra herb and Ginger), and has been used in Japan for the treatment of pulmonary diseases such as asthma, and bronchitis as well as allergic diseases. Oral administration of Shoseiryuto suppressed skin tumors induced by DMBA/TPA, pulmonary tumors induced by 4NQO/glycerol, liver tumors induced by DEN/phenobarbital in mice (Konoshima, et al., 1994).

4.4.2 Juzentaihoto (Shi-Quan-Da-Bu-Tang)

Juzentaihoto has been used as a nourishing agent, a so-called "Hozai" (in Japanese), for improving disturbances and imbalances in the homeostatic condition of the body. This drug is composed of ten components (Glycyrrhiza, Atractylodes rhizome, Ginseng, Astragalus root, Cinnamon bark, Rehmannia root, Paeony root, Cnidium Rhizome, Japanese Angelica root and Poria sclerotium) and has been used effectively for plausible

complaints of consumption of vital energy, lack of appetite, night sweats, circulatory problem and anemia. Oral administration of Juzentaihoto suppressed endometrial carcinogenesis by MNU/estradiol-17β in mice (Lian, et al., 2002; Niwa, et al., 2001). Moreover, Juzentaihoto orally suppressed tumor promotion by DMBA/TPA in mouse skin (Haranaka, et al., 1987).

4.4.3 Rikkunshito (Liu-Jun-Zi-Tang)

Rikkunshito consist of eight components (Glycyrrhiza, Ginger, Atractylodes rhizome, Jujube, Citrus unshiu peel, Ginseng, Pinellia tuber, and Poria sclerotium). In Japan, Rikkunshito has been used to treat functional dyspepsia and dyspepsia associated with organic disease. Topical application of a methanol extract of Rikkunshito inhibited tumor promotion by DMBA/TPA in mouse skin (Yasukawa, et al., 1995). Furthermore, oral administration of Rikkunshito suppressed skin tumors induced by DMBA/TPA in mice (Yasukawa, et al., 1996g). It was also observed that treatment with Rikkunshito reversed immunosuppression during DMBA/TPA-induced carcinogenesis (Yasukawa, et al., 1996g).

4.4.4 Shousaikoto (Xiao-Chai-Hu-Tang)

The Kampo medicine Shousaikoto has been used clinically to treat various inflammatory diseases including chronic hepatitis. Shousaikoto contains seven components (Glycyrrhiza, Ginger, Bupleurum root, Jujube, Scutellaria root, Ginseng and Pinellia tuber). This prescription has been used in the treatment of pneumonia and pulmonary tuberculosis since ancient times and is frequently used in the treatment of inflammatory respiratory diseases. In animal experiments, oral administration of Shousaikoto suppressed DMH-induced colonic carcinogenesis in rats (Sakamoto, et al., 1993).

4.4.5 Choreito (Zhu-Ling-Tang)

Choreito has been used for urinary frequency, feeling of residual urine, hematuria. Choreito consist of five components (Asini corii colla, Talc stone, Alisma rhizome, Polyporus sclerotium, Poria sclerotium), and is used as a diuresis of the kidney, and bladder, as well as in the treatment of uropathy. Oral administration of Choreito suppressed urinary bladder carcinogenesis induced by *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BHBN)/sodium saccharin (SS) in rats (Sugiyama, et al., 1994). Of the components of Choreito, Polyporus sclerotium seems to be a key component in its inhibitory activity in the bladder tumor promotion test.

4.5 Essential oils

An essential oil is a concentrated hydrophobic liquid containing volatile aromatic compounds derived from plants. Essential oils are generally extracted by distillation, and other processes include expression, or solvent extraction. Various essential oils have been used medicinally at different periods in history, while many common essential oils have medicinal properties that have been applied in folk medicine since ancient times and are still widely used today (Burt, 2004; Prabuseenivasan, et al., 2006).

4.5.1 Sage (*Salvia libanotica*) oil

Salvia libanotica Boiss. & Gaill. (*Labiatae*) is a strongly aromatic perennial shrub. Its healing properties are well known and it is widely used by herbalists for the treatment of headache, stomachache and respiratory problems. The oil extract contains ketones such as camphor and α- and β-thujone, terpenes such as limonene and α- and β-pinene, and alcohols such as borneol and linalool. Moreover, oxides such as 1,8-cineol and esters such as linalyl acetate are also found in sage oil. Sage oil was observed to inhibit tumor promotion by DMBA/TPA in mouse skin (Gali-Muhtasib, & Affara, 2000).

4.5.2 Garlic (*Allium sativum*) oil

Garlic oil from *Allium sativum* L. (*Liliaceae*) is rich in sulfur compounds, and a major component is diallyl disulphide, and is a suspected irritant. It was found that garlic oil inhibited tumor promotion by DMBA/TPA in mouse skin (Belman, 1983; Perchellt, et al., 1990).

4.5.3 Onion (*Allium cepa*) oil

Onion oil from the seeds of *Allium cepa* L. (*Liliaceae*) may present a risk of skin irritation and/or sensitization similar to garlic oil. Onion oil inhibited tumor promotion by DMBA/TPA (Belman, 1983; Perchellt, et al., 1990) and by BP/croton oil (Sadhana, et al., 1988) in mouse skin.

4.5.4 Sandalwood (*Santalum album*) oil

Sandalwood (*Santalum album* L., *Santalaceae*) comes from medium-sized fragrant trees and its oil has found wide use in the cosmetics industry. Sandalwood oil inhibited tumor promotion by DMBA/TPA in mouse skin (Dwivedi & Abu-Ghazaleh, 1997; Dwivedi & Zhang, 1999). The mechanism of its activity is due, in part, to the inhibition of TPA-induced epidermal ODC activity (Dwivedi & Zhang, 1999).

5. Conclusion

Humans have used plants as foods and natural medicines since ancient times. Crude drugs, typically safer than synthetic drugs, have been used as both spices and supplements. Natural medicines have been used as anti-cancer agents by inhibiting the promotion process, and it is important that these are consumed in small quantities for extended periods of time. The study of cancer prevention using plants is generating vast amounts of information regarding their benefits. This paper provides, an outline of studies focusing on plant extracts. Several active components have been isolated, and their chemical structures have been and continue to be determined. In addition, structure-activity relationships, elucidation of physiological activities at the molecular level, and development of strategies that allow for the production of sufficient supplies of these agents are issues for further investigation. The continued search for natural medicines is necessary for finding additional sources of active components that are suitable for clinical application. For this purpose, we will harness the strength of researchers from various fields with the goal for cancer prevention.

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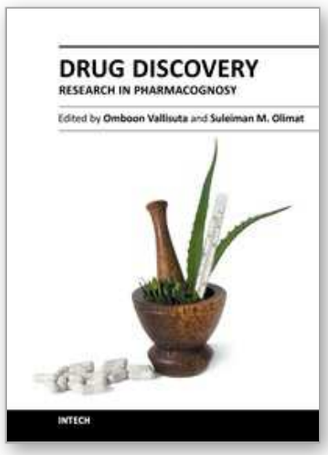

Drug Discovery Research in Pharmacognosy
Edited by Prof. Omboon Vallisuta

ISBN 978-953-51-0213-7
Hard cover, 244 pages
Publisher InTech
Published online 16, March, 2012
Published in print edition March, 2012

This book, Drug Discovery Research in Pharmacognosy provides a full picture of research in the area of pharmacognosy with the goal of drug discovery from natural products based on the traditional knowledge or practices. Several plants that have been used as food show their potential as chemopreventive agents and the claims of many medicinal plants used in traditional medicine are now supported by scientific studies. Drug Discovery Research in Pharmacognosy is a promising road map which will help us find medicine for all!

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Ken Yasukawa (2012). Medicinal and Edible Plants as Cancer Preventive Agents, Drug Discovery Research in Pharmacognosy, Prof. Omboon Vallisuta (Ed.), ISBN: 978-953-51-0213-7, InTech, Available from: http://www.intechopen.com/books/drug-discovery-research-in-pharmacognosy/medicinal-and-edible-plants-as-cancer-preventive-agent

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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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