Review

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Anticancer activity of essential oils: a review

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Abstract

Natural essential oil constituents play an important role in cancer prevention and treatment. Essential oil constituents from aromatic herbs and dietary plants include monoterpenes, sesquiterpenes, oxygenated monoterpenes, oxygenated sesquiterpenes and phenolics among others. Various mechanisms such antioxidant, antimutagenic and antiproliferative, enhancement of immune function and surveillance, enzyme induction and enhancing detoxification, modulation of multidrug resistance and synergistic mechanism of volatile constituents are responsible for their chemopreventive properties. This review covers the most recent literature to summarize structural categories and molecular anticancer mechanisms of constituents from aromatic herbs and dietary plants.

Keywords: anticancer mechanisms; essential oils; synergism; terpenes

INTRODUCTION

Cancer is a growing health problem around the world and is the second leading cause of death after heart disease.[1] According to a recent report by the International Agency for Research on Cancer (IARC), in 2008 there were 12.7 million new cancer cases throughout the world. There are now more than 10 million cases of cancer per year worldwide, including a group of more than 100 diseases such as cancer of the liver, lung, stomach, colon, breast, etc.[2,3] The most rational way to affect carcinogenesis is by interfering with the modulation steps (initiation, promotion and progression) as well as the associated signal transduction pathways.[4] There are numerous physiological and biochemical carcinogens, including UV and ionizing radiation, asbestos and tobacco smoke,[5] infections by viruses (e.g. hepatitis B virus causing liver cancer and human papilloma virus causing cervical cancer),[6,7] bacteria (*Helicobacter pylori* causing gastric cancer),[8] parasites (*schistosomiasis* causing bladder cancer)[9] and contamination of food by mycotoxins (e.g. aflatoxins causing liver cancer).[10] Some kinds of cancer are due to oxygen-centred free radicals and other reactive oxygen species, because overproduction of such free radicals can cause oxidative damage to biomolecules (e.g. lipids, proteins and DNA).[11] No extremely effective drug to treat most cancers is available in the market. There is a general call for new drugs that are highly effective, possess low toxicity and have minor environmental impact. Novel natural products offer opportunities for innovation in drug discovery.[12] In fact, natural products play a major role in cancer prevention and treatment. A considerable number of antitumour agents currently used in the clinic are of natural origin. For instance, over half of all anticancer prescription drugs approved internationally between the 1940s and 2006 were natural products or their derivatives.[13] Natural compounds isolated from medicinal plants, as rich sources of novel anticancer drugs, have been of increasing interest since then. Traditional medicinal herbs have been used for pharmaceutical and dietary therapy for several millennia in East Asia, e.g. in China, Japan, India and Thailand, and are currently widely used in cancer therapy.[12] Earlier investigation showed that an average of 35% of overall human cancer-related mortality was attributable to diet.[14] Substantial evidence from population as well as laboratory studies has revealed an inverse relationship between sufficient consumption of fruits and vegetables and the risk of specific cancers; that is, a high dietary intake of fruits and vegetables as well as whole grains is strongly associated with reduced risk of cancer.[15] Many clinical trials on the use of nutritional supplements and modified diets to prevent cancer are on-going.[15] The cancer-protective effects elicited by these dietary compounds are believed to be due to the induction of cellular defence systems, including detoxifying and antioxidant enzyme systems, as well as the inhibition of anti-inflammatory and anti cell growth signalling pathways culminating in cell cycle arrest and/or cell death.[16] It is estimated that more than 5000 individual phytochemicals have been identified in fruits, vegetables, grains and other plants, mainly classified as phenolics, carotenoids, vitamins, alkaloids, nitrogen-containing compounds, organosulfur compounds and essential oils. Among the great structural diversity of phytochemicals, essential oil components have attracted considerable interest and the most attention for their wide variety of bioactivities.[17] In addition, essential oils abundant in flowers, leaves, fruits and barks are reported to play an important role as chemopreventive agents; for example, the volatile components of *Pistacia lentiscus* L. (Chios mastic gum) have been linked with the inhibition of colon, prostate and lung cancers *in vitro*.[18] Many volatile constituents have been reported to possess potent antioxidant activity and to have anticancer or anticarcinogenic/antimutagenic/antiproliferative effects.[18–21] Together, these data strongly support the view that essential oils have potential therapeutic applications in the prevention of cancer. This review discusses the various anticancer mechanisms of essential oils and their components that have been reported recently in scientific journals. List of different plants containing

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essential oil have been discussed in this review with respect to their anticancer activity via different mechanism and represented in Table 1.

ANTICANCER MECHANISMS OF ESSENTIAL OIL

Antioxidant

Antioxidant activity is one of the most intensively studied subjects in essential oil research, because oxidation damages various biological substances and subsequently causes many diseases, including cancer,[22,23] liver disease,[24] Alzheimer's disease,[25] aging,[26] arthritis,[27] inflammation,[28] diabetes,[29] Parkinson's disease,[30,31] atherosclerosis[32] and AIDS.[33] As a result, many diseases have been treated with antioxidants to prevent oxidative damage.[34] Recently, many researchers have been investigating the antioxidant activity of different essential oils in order to search for safe natural antioxidants. Consequently, various studies have shown that essential oils are ideal natural sources of antioxidants.[35] In eukaryotes, hydroxyl radicals that are highly damaging to mitochondrial DNA are produced by superoxide anions and hydrogen peroxide (Fig. 1). Damaged mitochondrial DNA inhibits the expression of electron transport protein, leading to the accumulation of reactive oxygen species (ROS).[36] The free radicals generated by damaged mitochondrial membranes, when combined with essential oil, produce reactive phenoxy radicals that combine with ROS and prevent further damage.[35,37,38] Thyme essential oil exhibited the greatest antioxidant effect among 25 essential oils tested in one study, followed by clove leaf, cinnamon leaf, basil, eucalyptus and chamomile oils.[39] Antioxidant activities of the essential oils of coriander, eucalyptus, juniper, cumin and basil have been reported.[40,41] *Thymus spathulifolius* essential oil also possessed antioxidant activity because of its high content of thymol (**1**) (36.5%) and carvacrol (**2**) (29.8%).[42] The essential oil of Egyptian corn silk showed potent antioxidant activity, which was attributed to its high content of thymol (**1**) (20.5%) and carvacrol (**2**) (58.1%).[43] Tepe *et al.*[44] reported that the essential oils of *Salvia cryptantha* and *Salvia multicaulis* had higher antioxidant activity than ascorbic acid or butylated hydroxytoluene (BHT). In addition, *Curcuma zedoaria* essential oil was found to be an excellent radical scavenger.[45] Many aroma components of essential oils, such as terpenes and terpenoids, have been proposed to contribute to the antioxidant activity of essential oils,[39] including: α-terpinene (**3**), β-terpinene (**4**) and β-terpinolene (**5**) in tea tree (*Melaleuca alternifolia*); 1,8-cineole (**6**) in *Mentha aquatica* L., *Mentha longifolia* L. and *Mentha piperita* L.; menthone (**7**) and isomenthone (**8**) in *Mentha longifolia* and *Mentha piperita*; thymol (**1**), eugenol (**9**) and linalool (**10**) in black cumin, cinnamon bark and ginger; and thymol (**1**) and eugenol (**9**) in thyme and clove leaf[39] (Fig. 2). The essential oils of *Thymus caespititius*, *Thymus camphorates* and *Thymus mastichina*, which showed antioxidant activity comparable to that of α-tocopherol, contained high levels of linalool (**10**) and 1,8-cineole (**6**). The essential oil of lemon balm (*Melissa officinalis* L.), containing neral/citral (**11**), citronellal (**12**), isomenthone (**8**) and menthone (**7**), showed strong antioxidant activity.[46] There have also been reports on the *in vivo* antioxidant activity of essential oils. Dietary supplementation of oregano oil to rabbits delayed lipid oxidation.[47] When the same oil was fed to turkeys, a lipid oxidation reduction effect comparable to that of α-tocopheryl acetate (**13**) was observed.[48] The essential oil of *Achillea millefolium* subsp. *millefolium* (Asteraceae) exhibited a hydroxyl radical-scavenging effect by inhibiting the non-enzymatic lipid peroxidation of rat liver homogenate.[49] These reports suggest that essential oils are rich sources of natural antioxidants and can be used to prevent various degenerative diseases.

Antimutagenic

The antimutagenic property of essential oils is attributed to several mechanisms, including inhibition of penetration of the mutagens into the cells,[50] inactivation of mutagens by direct scavenging (Fig. 3), antioxidant capture of radicals produced by mutagens, activation of cell antioxidant enzymes,[51] inhibition of metabolic conversion by P450 of promutagens into mutagens[52,53] and activation of enzymatic detoxification of mutagens by essential oil constituents.[50] Antimutagenic compounds are effective by promoting error-free DNA repair or by inhibiting error-prone DNA repair.[50] There has been no investigation on the type of antimutagenicity involving DNA repair by terpenic and phenolic compounds from essential oils since the work by Kada and Shimoi (1987)[50] on *Escherichia coli*. Chemical compounds extracted from aromatic plants, such as α-terpinene (**3**), α-terpineol (**14**), 1,8-cineole (**6**), D-limonene (**15**), camphor (**16**), citronellal (**12**) and citral (**11**), modulated hepatic monooxygenase activity by interacting with promutagen or procarcinogen xenobiotic biotransformation.[54] It has been demonstrated that mitochondrial damage and apoptosis/necrosis in the yeast *Saccharomyces cerevisiae* were reduced by essential oils.[55] Recent studies showed that certain essential oils exhibited antimutagenicity towards mutation caused by UV light.[56,57]

Antiproliferative

Lampronti *et al.*[58] studied the *in vitro* antiproliferative activities of *Satureja hortensis*, *Satureja montana*, *Salvia officinalis*, *Lavandula officinalis*, *Thymus vulgaris*, *Calamintha origanifolia*, *Foeniculum vulgare* and *Mentha arvensis* on human erythroleukemic K562 cells. They reported that the essential oils derived from *Satureja montana* (IC_{50} 56 µm mL^{-1}) and *Mentha arvensis* (IC_{50} 85 µm mL^{-1}) showed the most interesting biological activity in inhibiting growth of the K562 cell line. Common active principles of *Satureja hortensis* and *Satureja Montana*, i.e. α-pinene (**17**), β-terpenene (**18**), 4-terpineol (**19**), α-terpineol (**14**) and caryophyllene (**20**), showed antiproliferative activity with IC_{50} values of 329–98 µm mL^{-1}.[58] In another study the active constituent eugenol (**9**) from *Syzygium aromaticum* (cloves), nutmeg, basil, cinnamon and bay leaves showed antiproliferative activity against various cancer cell lines and animal models.[59] Patil *et al.*[19] reported the apoptosis-mediated proliferation inhibition of human colon cancer cells by volatile constituents of *Citrus aurantifolia*. At 100 µg mL^{-1} concentration, this oil showed 78% inhibition of human colon cancer cells (SW-480) after 48 h. Lime volatile oil showed DNA fragmentation and induction of caspase-3 up to 1.8- and 2-fold after 24 and 48 h respectively, which may be due to the involvement of apoptosis. Analysis of apoptosis-related protein expression further confirmed apoptosis induction by lime volatile oil and suggested that lime volatile oil has potential benefits in colon cancer prevention.[19] Carvacrol (**2**) is one of the phenolic monoterpenes and is present in the volatile oils of *Thymus vulgaris*, *Carum copticum*, origanum. The antiproliferative effects of carvacrol (**2**) in metastatic breast cancer cells (MDA-MB231) were based on activation of the classical apoptosis response, including decrease in mitochondrial membrane potential and increase in cytochrome c released from mitochondria, decrease in Bcl-2/Bax ratio, increase in caspase activity and cleavage of poly(ADP-ribose) polymerase (PARP) and fragmentation of DNA, which belong to

Table 1. List of essential oil-bearing plants with anticancer properties

Plant name	Major constituent(s)	Plant part(s) used	Mechanism(s)	Author(s), year
Achillea ligustica	Santolina alcohol, borneol, sabinol	Flower	Antioxidant	Tuberoso *et al.*, 2005[102]
Agastache rugosa	Methyl chavicol	Herb	Antiproliferative, antimutagenic	Kim *et al.*, 2001[103]
Anisomeles malabarica	α-Thujone, terpenyl acetate	Leaf	Antiproliferative, inducing apoptosis	Preethy *et al.*, 2012[104]
Astrodaucus orientalis	Sabinene, α-pinene, α-thujene	Leaf	Cytotoxic	Razavi *et al.*, 2011[105]
Boswellia sacra	α-Thujene, α-pinene, myrcene	Gum resin	Tumour cell-specific apoptosis	Suhail *et al.*, 2011[106]
Calamintha origanifolia	Hexadecanoic acid, (*Z*,*Z*)-9,12-octadecadienoic acid, tetradecanoic acid	Wood	Antiproliferative	Formisano *et al.*, 2007[107]
Callicarpa americana	α-Humulene, 7-epi-α-eudesmol	Fruit, leaf, twig	Cytotoxic	Jones *et al.*, 2007[108]
Capparis spinosa	Thymol, isopropyl isothiocyanate	Herb	Antioxidant	Kulisic-Bilusic *et al.*, 2012[109]
Carum copticum	Thymol, γ-terpinene	Dried material	Antiproliferative	Yin *et al.*, 2012[110]
Centipeda minima	*trans*-Chrysanthenyl acetate	Aerial parts	Apoptosis induction	Su *et al.*, 2010[111]
Cinnamomum zeylanicum	(*E*)-Cinnamaldehyde	Bark	Cytotoxic	Unlu *et al.*, 2010[112]
Citrus aurantifolia	Eugenol, β-caryophyllene	Mature lime	Antiproliferative	Patil *et al.*, 2009[19]
Commiphora gileadensis	2-Decenoic acid	Balm	Selective apoptosis induction	Amiel *et al.*, 2012[113]
Coriandrum sativum	2-Methyl-5-hexenenitrile, 3-butenyl isothiocyanate	Leaf, seed	Antioxidant	Alenzi *et al.*, 2010[114]
Crambe orientalis	*p*-Cymene, ascaridole	Flowering top, leaf	Antiproliferative	Razavi and Nejad-Ebrahimi, 2009[115]
Croton regelianus	Epicurzerenone, curdione	Leaf	Cytotoxic	Bezerra *et al.*, 2009[116]
Curcuma zedoaria	α-Cadinol, caryophyllene oxide, α-muurolol	Dried rhizome	Antitumour	Chen *et al.*, 2011[117]
Cyperus kyllingia	*syn*-7-Hydroxy-7-anisylnorbornene, pregeijerene	Aerial parts	Cytotoxic	Khamsan *et al.*, 2011[118]
Dictamnus dasycarpus	*cis*-α-Terpineol, 6,11-oxidoacor-4-ene, citronellol	Root bark	Cytotoxic	Lei *et al.*, 2008[119]
Egyptian corn silk	α-Pinene, globulol, aromadendrene	Dried parts	Antioxidant	El-Ghorab *et al.*, 2007[43]
Eucalyptus benthamii	Limonene	Young/adult leaf	Cytotoxic, antiproliferative	Döll-Boscardin *et al.*, 2012[120]
Foeniculum vulgare	1,8-Cineole	Seed	Antioxidant	Mohamad *et al.*, 2011[121]
Genista sessilifolia and *Genista tinctoria*	(*E*)-β-Ionone, hexahydrofarnesylacetone	Aerial parts	Antiproliferative, cytotoxic	Rigano *et al.*, 2009[122]
Helichrysum gymnocephalum	β-Caryophyllene, sabinene	Leaf	Cytotoxic, antioxidant	Afoulous *et al.*, 2011[123]
Lantana camara	1,8-Cineole, 1-*p*-menthen-8-ethyl acetate	Root, leaf	Antineoplastic	Badakhshan *et al.*, 2009[124]
Lavandula officinalis	(*Z*)-Citral, (*E*)-citral	Flower	Cytotoxic	Zamanian-Azodi *et al.*, 2012[125]
Lindera strychnifolia	Eucalyptol	Leaf	Cytotoxic	Yan *et al.*, 2009[126]
Malus domestica	α-Gurjunene, β-selinene	Leaf	Synergistic	Walia *et al.*, 2012[127]
Mangifera indica	1,8-Cineole	Leaf	Cytotoxic	Simionatto *et al.*, 2010[128]
Matricaria recutita	α-BisabololoxideA, (*E*)-β-farnesene	Flower	Antioxidant, antiproliferative	McKay and Blumberg, 2006[129]
Melaleuca alternifolia	α-Thujone	Leaf	Antioxidant	Kim *et al.*, 2004[147]
Melaleuca armillaris	Menthol	Leaf	Cytotoxic	Chabir *et al.*, 2011[130]
Mentha piperita and *Mentha spicata*	α-Phellandrene, *p*-cymene	Leaf	Cytotoxic	Hussain *et al.*, 2010[131]
Moringa oleifera	Myrcene, limonene	Root bark	Antitumour	Bose, 2007[132]
Myrica gale	β-Elemene	Leaf	Cytotoxic	Sylvestre *et al.*, 2005[90]
Nigella sativa and *Nigella damascene*	Methyl cinnamate	Seed	Antioxidant	Edris *et al.*, 2009[133]
Ocimum basilicum	(*E*)-Nerolidol	Leaf	Anticancer	Kathirvel and Ravi, 2012[134]

Table 1. Continued

Plant name	Major constituent(s)	Plant part(s) used	Mechanism(s)	Author(s), year
Oplopanax horridus	Carvacrol, γ-terpinene, *p*-cymene	Stem, berry	Antiproliferative	Inui *et al.*, 2010[135]
Origanum onites	Citronellol, *trans*-geraniol	Aerial parts	Antimutagenic	Bostancıoğlu *et al.*, 2012[136]
Pelargonium graveolens	10-Epi-eudesmol, pinene	Aerial parts	Antioxidant	Fayed, 2009[137]
Photinia serrulata	Terpinen-4-ol, sabinene, γ-terpinene, β-myrcene	Leaf	Cytotoxic, antioxidant	Hou *et al.*, 2007[138]
Pituranthos tortuosus	1,8-Cineole, α-pinene	Aerial parts	Antioxidant	Abdallah and Ezzat, 2011[139]
Rosmarinus officinalis	Eucalyptol	Aerial parts	Antioxidant	Xue *et al.*, 2012[140]
Salvia libanotica	Santalol	Leaf, flower	Anti-inflammatory, antioxidant	Itani *et al.*, 2008[141]
Santalum album	Carvacrol	Wood	Apoptosis induction	Bommareddy *et al.*, 2012[142]
Satureja hortensis	Bornyl acetate, camphene	Plant	Antiproliferative	Lampronti *et al.*, 2006[58]
Satureja montana	Carvacrol, thymol, thymoquinone	Aerial parts	Antioxidant, antiproliferative	Grosso *et al.*, 2009[143]
Syzygium aromaticum	β-Caryophyllene	Leaf	Antioxidant	Prashar *et al.*, 2006[144]
Tanacetum parthenium	Viridiflorene, β-terpineol	Flower	Antioxidant	Mohsenzadeh *et al.*, 2011[145]
Thuja occidentalis	Thujones, fenchone	Fresh leaf, twig	Apoptosis induction	Biswas *et al.*, 2011[146]

the mitochondrial pathway of the apoptosis.[60] Abdolmohammadi *et al.*[20] reported antiproliferative activity of *Astrodaucus orientalis* on the T47D human breast cancer cell line. *Curcuma wenyujin* oil has been reported to induce apoptosis in HepG2 cells through activation of the mitochondrial and caspase-3 pathways. Moreover, study of the anti-apoptotic effect of *Curcuma wenyujin* oil can lead to identification of new lead compounds and novel drug targets for treatment of liver cancer and diseases.[61]

Enhancement of immune function and surveillance

Mechanisms that help improve the immune system are effective when certain factors are taken into consideration, such as stress reduction, supporting good intestinal bacteria and promoting better blood and lymph quality. A predominantly successful strategy is the use of aromatherapy. Aromatherapy is the use of essential oils through various media towards improving immune function (thearomablog.com/essential-oils-for-the-immune-system). It has an important role to play in the enhancement of immune function. It works in several ways, such as by controlling hormones secreted by the adrenal glands, consequently resulting in alleviation of stress, by stimulating the immune response by supporting the lymph to remove toxins, and by stimulating the production of immune boosting cells and destruction of harmful micro-organisms (Fig. 4). One study evaluated *Citrus limonum* and *Lavendula angustifolia* for the effects of aromatherapy on human immune function and found that lemon essential oil inhalation enhanced positive mood and boosted norepinephrine release, but other immunological data gathered did not indicate effectiveness of either essential oil.[62] Inflammation is a response to injury caused by noxious physical or chemical stimuli and is a key component of multiple pathologies such as arthritis, asthma, multiple sclerosis, inflammatory bowel disease and atherosclerosis.[63–65] It is usually an acute phase response, but may become chronic,[66,67] and is marked by the accumulation of a variety of inflammatory cells and by the release of several soluble mediators of inflammation, ROS, lipid mediators, proteases and cytokines.[65,68]

Furthermore, macrophag cells play important roles in the initiation and amplification of a variety of inflammatory conditions, such as those induced by septic shock and chronic inflammatory conditions. Cho *et al.*[69] isolated zedoarondiol (**21**) from *Curcuma heyneana*, which is responsible for the inhibition of iNOS, COX-2 and pro-inflammatory cytokines via down-regulation of the nuclear factor (NF)-κB pathway in lipopolysaccharide (LPS)-stimulated murine macrophages. In another study, Qiu *et al.* (2010) reported that eugenol (**9**), which is the major component of many aromatic plants, suppresses the production of tumour necrosis factor (TNF).[70] Yoon *et al.* reported that *Cryptomeria japonica* essential oil can inhibit NF-κB activation induced by LPS, which is involved in maximum transcription of many cytokines, including TNF-α, IL-1, IL-6 and IL-8, which are responsible for the generation of acute inflammatory responses.[71]

Enzyme induction and enhancing detoxification

The consumption of *Allium* species has been associated in epidemiological studies with a reduced risk of cancer incidence.[72–75] The anticarcinogenic properties of *Allium* can be attributed to organosulfur compounds derived from these plants. Experimental studies on animal models have shown inhibition of chemically induced carcinogenesis in different organs by sulfur-containing compounds.[76–78] Sulfur-containing agents inhibit carcinogenesis and alter the metabolism of procarcinogens. These agents can increase detoxification by increasing the levels of phase II enzymes such as glutathione *S*-transferase (GST), UDP-glucuronyl transferase (UGT) and quinone reductase (QR) or by decreasing the levels of some phase I enzymes such as cytochrome P450.[79,80] Allyl sulfides derived from garlic (*Allium sativum*) have been shown to increase phase II enzymes such as GST, UGT and epoxide hydrolase (EH)[81–84] and to inhibit cytochrome P450 2E1.[83,85–88] In another study, Singletary[89] reported that *Rosmarinus officinalis* (rosemary) can inhibit the carcinogenicity of structurally diverse chemicals in animal models. A mechanism that may be responsible for impairment of the initiation stage of carcinogenesis by

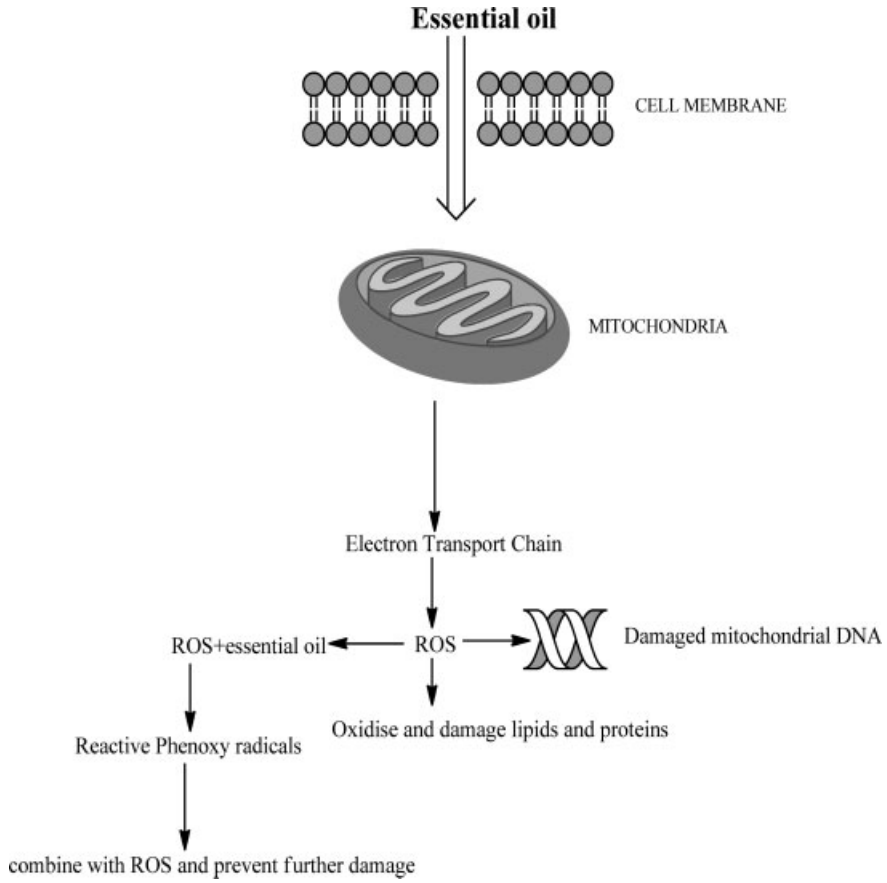

Figure 1. Antioxidant mechanism of essential oils.

rosemary extract is the direction of the metabolism of chemical carcinogens towards the generation of inactive metabolites and/or detoxication of the reactive intermediates through conjugation. Indeed, feeding animals with a diet supplemented with rosemary extract resulted in increases in hepatic GST and NAD(P)H:QR activities.[89,90] Debersac *et al.* (2001) reported that the essential oil of rosemary, which consists mainly of 1,8-cineol (**6**), borneol (**22**), camphor (**16**) and α-terpeniol (**14**), can selectively induce cytochrome P450 (CYP), particularly CYP2B, which can reduce the activity of carcinogens.[91] Nakamura *et al.* (2003) reported that citral (**11**), which is found in many essential oils and constitutes 70–85% of lemon grass oil, is a monoterpene inducer of GST class π (GSTP1).[92] This isozyme is responsible for the increase in total GST activity of citral (**11**)-treated rat hepatocyte cells. Structure–activity relationship studies revealed that *trans*-citral (**11**) is the main contributor to the induction of GSTP1. The aldehyde group conjugated with a *trans* double bond in *trans*-citral (**11**) is an essential structural factor for GST induction. On the other hand, *cis*-citral (**11**) showed no activity. This suggested the exploration of citral (**11**) as a cancer-chemopreventive agent targeted towards inflammation-related carcinogenesis such as skin cancer[93] and colon cancer,[94] both of which were found to be due to lack of GSTP1 activity. The high content of citral (**11**) in lemon grass oil may explain the inhibitory effect of that aromatic plant on the early phase of hepatocarcinogenesis in rats.[95]

Modulation of multidrug resistance

The success of chemotherapeutic agents is often hindered by the development of drug resistance, with multidrug-resistant (MDR) phenotypes reported in a number of tumours, generally involving reduced intracellular drug accumulation and/or impairment of one or more steps of the apoptotic signalling cascades due to increased drug efflux by energy-dependent drug transporters belonging to the ATP-binding cassette (ABC) superfamily.[96] Ravizza *et al.* (2008) reported that linalool (**10**), which is an acyclic monoterpene alcohol found in the essential oils from many aromatic plants, including lavender (*Lavandula officinalis*), coriander seeds (*Coriandrum sativum*), sweet basil (*Ocimum basilicum*)[97] and *Mentha citrata*, reverses doxorubicin (**23**) (Fig. 5) resistance in MCF7 wild-type (WT) and MCF7 adriamycin-resistant (ADR) human breast adenocarcinoma cell lines.[98] In another study, Neidnicht *et al.* (2011) reported that *para*-benzoquinone thymoquinone, which is the active principle of thyme and black seed (*Nigella sativa*) essential oils responsible for their antioxidant, antineoplastic activity, can modulate the multidrug resistance of doxorubicin (**23**).[99] The *in vitro* antitumor activity of tea tree oil (*Melaleuca alternifolia*) was analysed against human melanoma M14 WT cells and their drug-resistant counterparts, M14 ADR cells, selected by prolonged exposure to doxorubicin (**23**). Calcabrini *et al.*[100] (2004) reported that tea tree oil and its main component terpinen-4-ol (**24**) are able to impair the growth of human M14 melanoma cells and appear to be more effective on the drug-selected resistant cell line M14 ADR, which expresses high levels of P-gp in the plasma membrane.[100] γ-Linolenic acid (GLA) is known to have selective tumoricidal action. It is also reported that GLA may increase the cytotoxic activity of cancer-chemotherapeutic agents in some cancer cells. Kong *et al.* reported that GLA pretreatment can modulate the response of multidrug-resistant K562/ADM

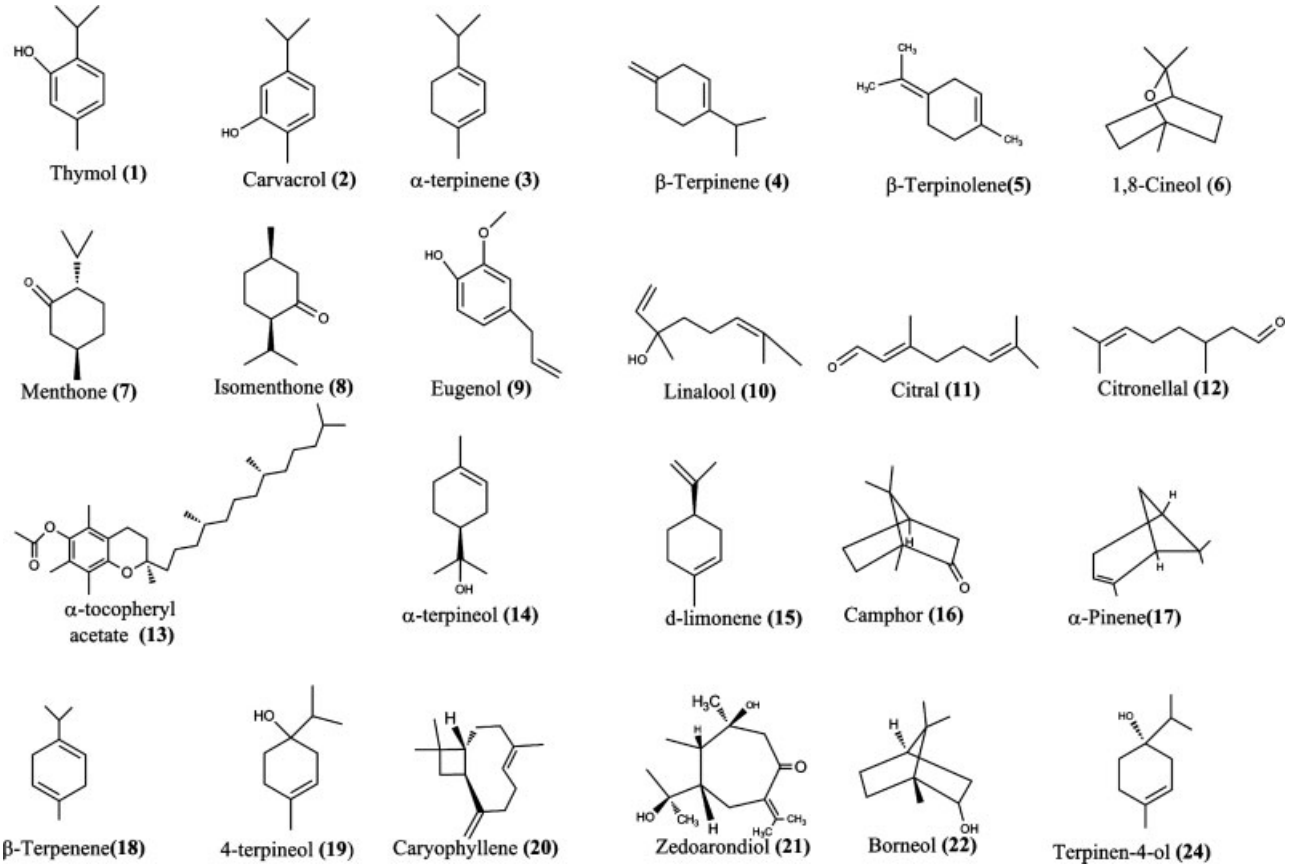

Figure 2. Anticancer components from different essential oils.

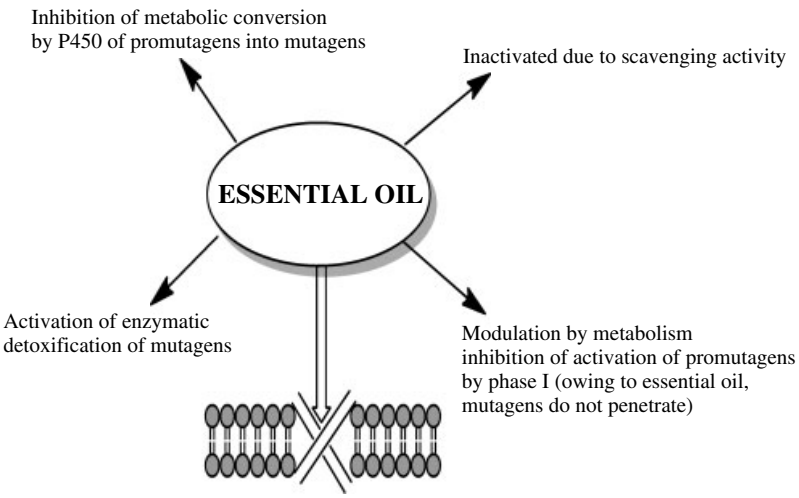

Figure 3. Antimutagenic mechanism of essential oils.

leukemic cells to anticancer drugs.[101] The cell viability assay results showed that GLA at 10 μg mL^{-1} enhanced cell growth inhibition induced by the MDR-type drugs doxorubicin (**23**), etoposide (**25**) and vincristine (**26**) but could not enhance or even attenuate cell growth inhibition induced by the non-MDR-type drugs cisplatin (**27**), mitomycin (**28**) and fluorouracil (**29**) (Fig. 5) in K562/ADM cells. GLA decreased the expression of P-glycoprotein, enhanced the accumulation of doxorubicin (**23**) and rhodamine 123 in K562/ADM cells and inhibited the efflux of rhodamine 123 from K562/ADM cells, which showed that GLA can modulate the response to anticancer agents in P-gp-overexpressing multidrug-resistant cells by decreasing P-gp expression and inhibiting P-gp function.

CONCLUSIONS

Essential oils have been shown to positively affect the immune system on a chemical level despite their direct effect on tumour cells. For removing foreign material and microbes from the body, essential oils enhance the activity of white blood cells, making them

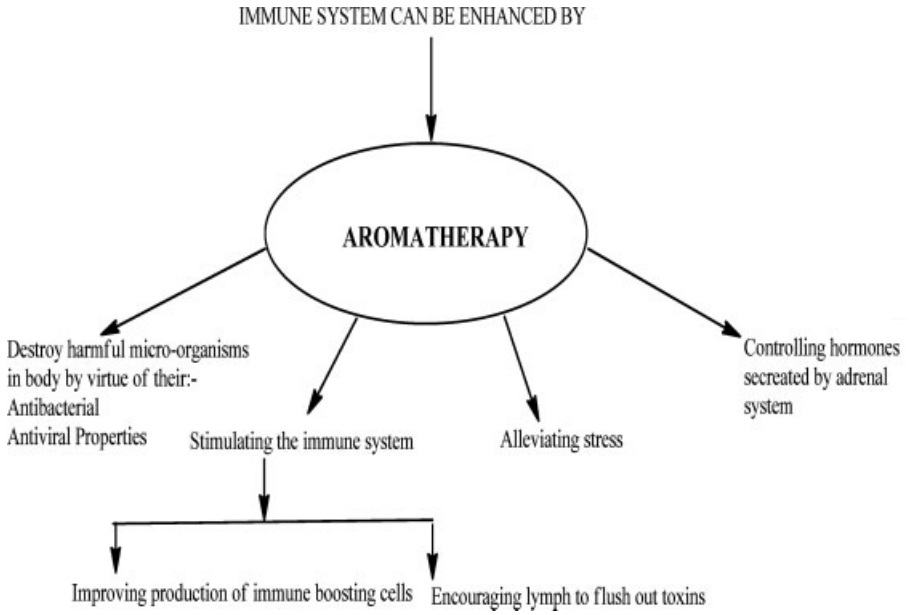

Figure 4. Mechanism by which essential oils enhance function of immune system.

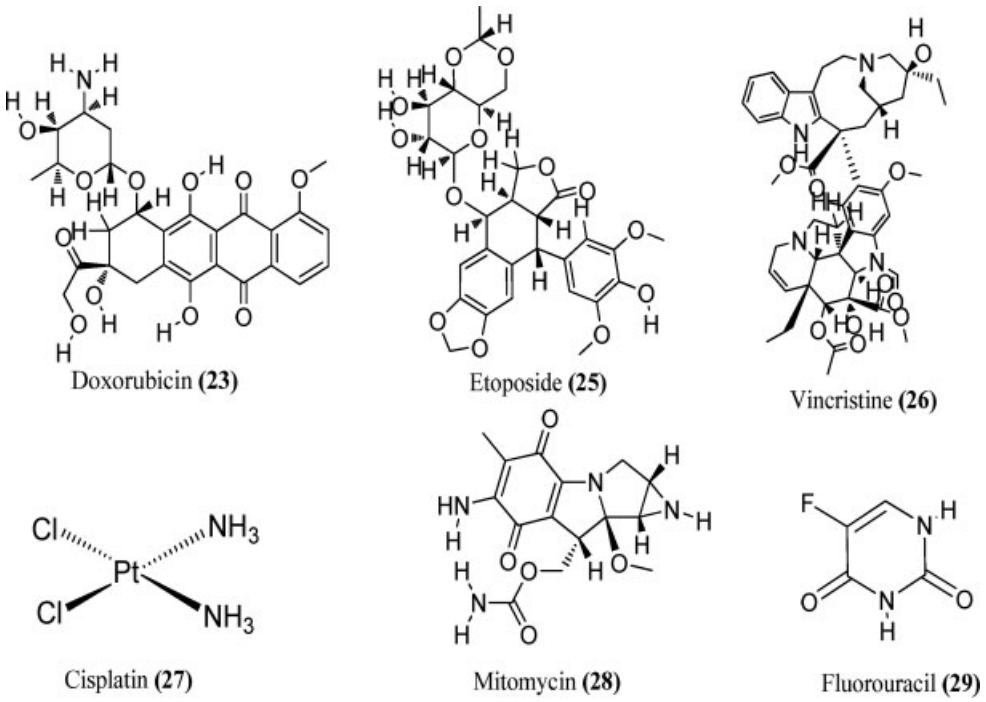

Figure 5. Modulation of anticancer activity of resistant anticancer molecules by essential oils.

more efficient. It is likely that the activity of the main components of essential oils is modulated by other minor molecules. Moreover, it is probable that several components have a significant role in the fragrance, density, texture, colour and, above all, cell penetration, lipophilic or hydrophilic attraction and fixation on cell walls and membranes, and cellular distribution. However, for biological purposes, it is more important to study an entire essential oil rather than some of its components, because the theory of synergism appears to be more significant. Therefore, like many plant medicines, essential oils work on a number of stages for many diseases, cancer being one of them. It is further desired to screen some more novel essential oils and unknown molecules for their anticancer properties. Moreover, individual molecules need to be modified synthetically to enhance their activity. On the whole, the picture is very bright for the use of essential oils in cancer treatment, and further investigation is certainly justified by the scientific and medical communities for the development of effective medical protocols for this profoundly life-altering condition.

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