

# Biological effects of essential oils – A review

F. Bakkali <sup>a,b</sup>, S. Aeverbeck <sup>a</sup>, D. Aeverbeck <sup>a,\*</sup>, M. Idaomar <sup>b</sup>

<sup>a</sup> Institut Curie-Section de Recherche, UMR2027 CNRS/IC, LCR V28 CEA, Bât. 110, Centre Universitaire, 91405 Orsay cedex, France

<sup>b</sup> Université Abdelmalek Essâadi, Faculté des Sciences, Laboratoire de Biologie et Santé, BP 2121, Tétouan, Morocco

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## Abstract

Since the middle ages, essential oils have been widely used for bactericidal, virucidal, fungicidal, antiparasitical, insecticidal, medicinal and cosmetic applications, especially nowadays in pharmaceutical, sanitary, cosmetic, agricultural and food industries. Because of the mode of extraction, mostly by distillation from aromatic plants, they contain a variety of volatile molecules such as terpenes and terpenoids, phenol-derived aromatic components and aliphatic components. *In vitro* physicochemical assays characterise most of them as antioxidants. However, recent work shows that in eukaryotic cells, essential oils can act as prooxidants affecting inner cell membranes and organelles such as mitochondria. Depending on type and concentration, they exhibit cytotoxic effects on living cells but are usually non-genotoxic. In some cases, changes in intracellular redox potential and mitochondrial dysfunction induced by essential oils can be associated with their capacity to exert antigenotoxic effects. These findings suggest that, at least in part, the encountered beneficial effects of essential oils are due to prooxidant effects on the cellular level.

*Keywords:* Essential oil; Cytotoxicity; Genotoxicity; Antigenotoxicity; Prooxidant activity

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\* Corresponding author. Tel.: +33 169867188; fax: +33 169869429.

E-mail address: dietrich.aeverbeck@curie.u-psud.fr (D. Aeverbeck).

## 1. Introduction

Essential oils are volatile, natural, complex compounds characterized by a strong odour and are formed by aromatic plants as secondary metabolites. They are usually obtained by steam or hydro-distillation first developed in the Middle Ages by Arabs. Known for their antiseptic, i.e. bactericidal, virucidal and fungicidal, and medicinal properties and their fragrance, they are used in embalment, preservation of foods and as antimicrobial, analgesic, sedative, anti-inflammatory, spasmolytic and locally anesthetic remedies. Up to the present day, these characteristics have not changed much except that more is now known about some of their mechanisms of action, particularly at the antimicrobial level.

In nature, essential oils play an important role in the protection of the plants as antibacterials, antivirals, antifungals, insecticides and also against herbivores by reducing their appetite for such plants. They also may attract some insects to favour the dispersion of pollens and seeds, or repel undesirable others.

Essential oils are extracted from various aromatic plants generally localized in temperate to warm countries like Mediterranean and tropical countries where they represent an important part of the traditional pharmacopoeia. They are liquid, volatile, limpid and rarely coloured, lipid soluble and soluble in organic solvents with a generally lower density than that of water. They can be synthesized by all plant organs, i.e. buds, flowers, leaves, stems, twigs, seeds, fruits, roots, wood or bark, and are stored in secretory cells, cavities, canals, epidermic cells or glandular trichomes.

There are several methods for extracting essential oils. These may include use of liquid carbon dioxide or microwaves, and mainly low or high pressure distillation employing boiling water or hot steam. Due to their bactericidal and fungicidal properties, pharmaceutical and food uses are more and more widespread as alternatives to synthetic chemical products to protect the ecological equilibrium. In those cases, extraction by steam distillation or by expression, for example for Citrus, is preferred. For perfume uses, extraction with lipophilic solvents and sometimes with supercritical carbon dioxide is favoured. Thus, the chemical profile of the essential oil products differs not only in the number of molecules but also in the stereochemical types of molecules extracted, according to the type of extraction, and the type of extraction is chosen according to the purpose of the use. The extraction product can vary in quality, quantity and in composition according to climate, soil composition, plant organ, age and vegetative cycle stage (Masotti et al., 2003; Angioni et al., 2006). So, in order to obtain essential oils of constant composition, they have to be extracted under the same conditions from the same organ of the plant which has been growing on the same soil, under the same climate and has been picked in the same season. Most of the commercialized essential oils are chemotyped by gas chromatography and mass spectrometry analysis. Analytical monographs have been

published (European pharmacopoeia, ISO, WHO, Council of Europe; Smith et al., 2005) to ensure good quality of essential oils.

Essential oils have been largely employed for their properties already observed in nature, i.e. for their antibacterial, antifungal and insecticidal activities. At present, approximately 3000 essential oils are known, 300 of which are commercially important especially for the pharmaceutical, agronomic, food, sanitary, cosmetic and perfume industries. Essential oils or some of their components are used in perfumes and make-up products, in sanitary products, in dentistry, in agriculture, as food preservers and additives, and as natural remedies. For example, d-limonene, geranyl acetate or d-carvone are employed in perfumes, creams, soaps, as flavour additives for food, as fragrances for household cleaning products and as industrial solvents. Moreover, essential oils are used in massages as mixtures with vegetal oil or in baths but most frequently in aromatherapy. Some essential oils appear to exhibit particular medicinal properties that have been claimed to cure one or another organ dysfunction or systemic disorder (Silva et al., 2003; Hajhashemi et al., 2003; Perry et al., 2003).

Owing to the new attraction for natural products like essential oils, despite their wide use and being familiar to us as fragrances, it is important to develop a better understanding of their mode of biological action for new applications in human health, agriculture and the environment. Some of them constitute effective alternatives or complements to synthetic compounds of the chemical industry, without showing the same secondary effects (Carson and Riley, 2003).

## 2. Chemical composition

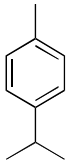
Essential oils are very complex natural mixtures which can contain about 20–60 components at quite different concentrations. They are characterized by two or three major components at fairly high concentrations (20–70%) compared to others components present in trace amounts. For example, carvacrol (30%) and thymol (27%) are the major components of the *Origanum compactum* essential oil, linalol (68%) of the *Coriandrum sativum* essential oil,  $\alpha$ - and  $\beta$ -thuyone (57%) and camphor (24%) of the *Artemisia herba-alba* essential oil, 1,8-cineole (50%) of the *Cinnamomum camphora* essential oil,  $\alpha$ -phellandrene (36%) and limonene (31%) of leaf and carvone (58%) and limonene (37%) of seed *Anethum graveolens* essential oil, menthol (59%) and menthone (19%) of *Mentha piperita* (= *Mentha*  $\times$  *piperita*) essential oil. Generally, these major components determine the biological properties of the essential oils. The components include two groups of distinct biosynthetic origin (Croteau et al., 2000; Betts, 2001; Bowles, 2003; Pichersky et al., 2006). The main group is composed of terpenes and terpenoids and the other of aromatic and aliphatic constituents, all characterized by low molecular weight (see Fig. 1).

## 1. Terpenes

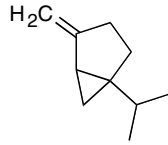
-Monoterpenes

### Carbure monocyclic

Cymene ("y") or p.cymene

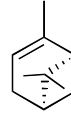


Sabinene

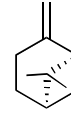


### Carbure bicyclic

Alpha-pinene

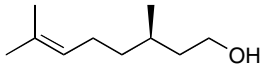


Betapinene

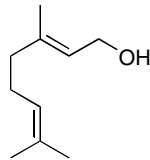


### Alcohol acyclic

Citronellol

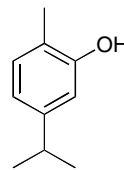


Geraniol

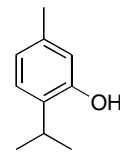


### Phenol

Carvacrol



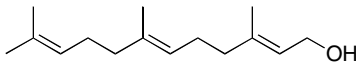
Thymol



-Sesquiterpenes

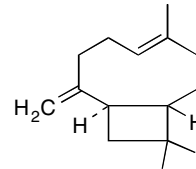
### Carbure

Farnesol



### Alcohol

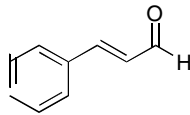
Caryophyllene



## 2. Aromatic compounds

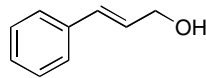
### Aldehyde

Cinnamaldehyde



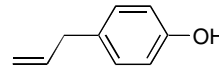
### Alcohol

Cinnamyl alcohol



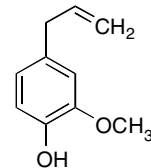
### Phenol

Chavicol



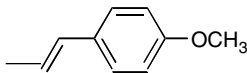
### Phenol

Eugenol



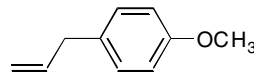
### Methoxy derivative

Anethole



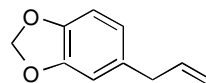
### Methoxy derivative

Estragole



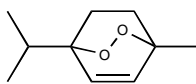
### Methylene dioxy compound

Safrole



## 3. Terpenoides (Isoprenoides)

Ascaridole



Menthol

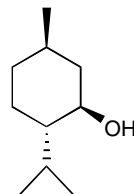


Fig. 1. Chemical structures of selected components of essential oils.

## 2.1. Terpenes

Terpenes form structurally and functionally different classes. They are made from combinations of several 5-carbon-base ( $C_5$ ) units called isoprene. The biosynthesis of the terpenes consists of synthesis of the isopentenyl diphosphate (IPP) precursor, repetitive addition of IPPs to form the prenyldiphosphate precursor of the various classes of terpenes, modification of the allylic prenyldiphosphate by terpene specific synthetases to form the terpene skeleton and finally, secondary enzymatic modification (redox reaction) of the skeleton to attribute functional properties to the different terpenes. The main terpenes are the monoterpenes ( $C_{10}$ ) and sesquiterpenes ( $C_{15}$ ), but hemiterpenes ( $C_5$ ), diterpenes ( $C_{20}$ ), triterpenes ( $C_{30}$ ) and tetraterpenes ( $C_{40}$ ) also exist. A terpene containing oxygen is called a terpenoid.

The monoterpenes are formed from the coupling of two isoprene units ( $C_{10}$ ). They are the most representative molecules constituting 90% of the essential oils and allow a great variety of structures. They consist of several functions:

### Carbures:

- acyclic: myrcene, ocimene, etc.
- monocyclic: terpinenes, *p*-cimene, phellandrenes, etc.
- bicyclic: pinenes, -3-carene, camphene, sabinene, etc.

### Alcohols:

- acyclic: geraniol, linalol, citronellol, lavandulol, nerol, etc.
- monocyclic: menthol,  $\alpha$ -terpineol, carveol
- bicyclic: borneol, fenchol, chrysanthenol, thuyan-3-ol, etc.

### Aldehydes:

- acyclic: geraniol, neral, citronellal, etc.

### Ketone:

- acyclic: tegetone, etc.
- monocyclic: menthones, carvone, pulegone, piperitone, etc.
- bicyclic: camphor, fenchone, thuyone, ombellulone, pinocamphone, pinocarvone, etc.

### Esters:

- acyclic: linalyl acetate or propionate, citronellyl acetate, etc.
- monocyclic: menthyl or  $\alpha$ -terpinyl acetate, etc.
- bicyclic: isobornyl acetate, etc.

### Ethers:

- 1,8-cineole, menthofurane, etc.

### Peroxydes: ascaridole, etc.

### Phenols: thymol, carvacrol, etc.

When the molecule is optically active, the two enantiomers are very often present in different plants: (+)- $\alpha$ -pinene from *Pinus palustris*, (-)- $\beta$ -pinene from *Pinus caribaea* and from *Pinus pinaster*, (-)linalol from coriander, (+)linalol from some camphor trees, etc. In some cases, it is the racemic form which is the most frequently encoun-

tered: ( $\pm$ )-citronellol is widespread, the form (+) is characteristic of *Eucalyptus citriodora*, the form (-) is common to the rose and geranium essential oils.

The sesquiterpenes are formed from the assembly of three isoprene units ( $C_{15}$ ). The extension of the chain increases the number of cyclisations which allows a great variety of structures. The structure and function of the sesquiterpenes are similar to those of the monoterpenes:

Carbures: azulene,  $\beta$ -bisabolene, cadinenes,  $\beta$ -caryophyllene, logifolene, curcumenes, elemenes, farnesenes, zingiberene, etc.

Alcohols: bisabol, cedrol,  $\beta$ -nerolidol, farnesol, carotol,  $\beta$ -santalol, patchoulol, viridiflorol, etc.

Ketones: germacrone, nootkatone, *cis*-longipinan-2,7-dione,  $\beta$ -vetinone, turmerones, etc.

Epoxide: caryophyllene oxide, humulene epoxides, etc.

Examples of plants containing these compounds are angelica, bergamot, caraway, celery, citronella, coriander, eucalyptus, geranium, juniper, lavandin, lavender, lemon, lemongrass, mandarin, mint, orange, peppermint, petit-grain, pine, rosemary, sage, thyme.

## 2.2. Aromatic compounds

Derived from phenylpropane, the aromatic compounds occur less frequently than the terpenes. The biosynthetic pathways concerning terpenes and phenylpropanic derivatives generally are separated in plants but may coexist in some, with one major pathway taking over (see, cinnamom oil with cinnamaldehyde as major and eugenol as minor constituents, also clove oil, fennel, etc.).

Aromatic compounds comprise:

Aldehyde: cinnamaldehyde

Alcohol: cinnamic alcohol

Phenols: chavicol, eugenol

Methoxy derivatives: anethole, elemicine, estragole, methyleugenols

Methylene dioxy compounds: apiole, myristicine, safrole

The principal plant sources for these compounds are anise, cinnamon, clove, fennel, nutmeg, parsley, sassafras, star anise, tarragon, and some botanical families (Apiaceae, Lamiaceae, Myrtaceae, Rutaceae).

Nitrogenous or sulphured components such as glucosinolates or isothiocyanate derivatives (garlic and mustard oils) are also characteristic as secondary metabolites of diverse plants or of torrefied, grilled or roasted products.

## 3. Biological effects

### 3.1. Cytotoxicity

Because of the great number of constituents, essential oils seem to have no specific cellular targets (Carson et al., 2002). As typical lipophiles, they pass through the cell wall and cytoplasmic membrane, disrupt the structure

of their different layers of polysaccharides, fatty acids and phospholipids and permeabilize them. Cytotoxicity appears to include such membrane damage. In bacteria, the permeabilization of the membranes is associated with loss of ions and reduction of membrane potential, collapse of the proton pump and depletion of the ATP pool (Knobloch et al., 1989; Sikkema et al., 1994; Helander et al., 1998; Ultee et al., 2000, 2002; Di Pasqua et al., 2006; Turina et al., 2006). Essential oils can coagulate the cytoplasm (Gustafson et al., 1998) and damage lipids and proteins (Ultee et al., 2002; Burt, 2004). Damage to the cell wall and membrane can lead to the leakage of macromolecules and to lysis (Juven et al., 1994; Gustafson et al., 1998; Cox et al., 2000; Lambert et al., 2001; Oussalah et al., 2006).

In eukaryotic cells, essential oils can provoke depolarisation of the mitochondrial membranes by decreasing the membrane potential, affect ionic  $Ca^{++}$  cycling (Richter and Schlegel, 1993; Novgorodov and Guduz, 1996; Vercesi et al., 1997) and other ionic channels and reduce the pH gradient, affecting (as in bacteria) the proton pump and the ATP pool. They change the fluidity of membranes, which become abnormally permeable resulting in leakage of radicals, cytochrome C, calcium ions and proteins, as in the case of oxidative stress and bioenergetic failure. Permeabilization of outer and inner mitochondrial membranes leads to cell death by apoptosis and necrosis (Yoon et al., 2000; Armstrong, 2006). It seems that chain reactions from the cell wall or the outer cell membrane invade the whole cell, through the membranes of different organelles like mitochondria and peroxisomes. These effects suggest a phenolic-like prooxidant activity (Sakagami and Satoh, 1997; Cowan, 1999; Sakagami et al., 1999; Fukumoto and Mazza, 2000; Sakihama et al., 2002; Burt, 2004; Barbehenn et al., 2005). Scanning and transmission electron microscopy observations reveal cell ultrastructural alterations in several compartments such as plasma membrane, cytoplasm (swelling, shrivelling, vacuolations, leakage) and nucleus (Soylu et al., 2006; Santoro et al., 2007a,b). Analyses of the lipid profiles by gas chromatography and of the cell envelope structure by scanning electron microscopy of several bacteria treated by some essential oil constituents showed a strong decrease in unsaturated and an increase in saturated fatty acids, as well as alterations of the cell envelopes (Di Pasqua et al., 2007). Disruption of the HSV viral envelope by essential oils could also be observed by electron microscopy preventing the host cells from infection (Schnitzler et al., 2007). The induction of membrane damages has been also confirmed by a microarray analysis showing that *Saccharomyces cerevisiae* genes involved in ergosterol biosynthesis and sterol uptake, lipid metabolism, cell wall structure and function, detoxification and cellular transport are affected by a treatment with  $\alpha$ -terpinene, a monocyclic monoterpene (Parveen et al., 2004).

Cytotoxic effects were observed *in vitro* in most of pathogenic gram positive and gram negative bacteria by agar diffusion method using a filter paper disc or by the dilution method using agar or liquid broth cultures (Williams et al.,

1998; Kalemba and Kunicka, 2003; Arnal-Schnebelen et al., 2004; Burt, 2004; Hong et al., 2004; Rota et al., 2004; Si et al., 2006; Sonboli et al., 2005, 2006a,b), in ADN or ARN virus (Hayashi et al., 1995; De Logu et al., 2000; Jassim and Naji, 2003; Reichling et al., 2005) and in fungi (Manohar et al., 2001; Pitarokili et al., 2002; Hammer et al., 2002; Kosalec et al., 2005) including yeasts (Harris, 2002; Hammer et al., 2004; Wang et al., 2005; Duarte et al., 2005; Pauli, 2006; Carson et al., 2006) (see Table 1). In particular, recent work in the yeast *Saccharomyces cerevisiae*, has shown that the cytotoxicity of some essential oils, based on colony forming ability, differed considerably depending on their chemical composition; essential oil treated cells in stationary phase of growth showed 50% lethality at 0.45  $\mu$ L/mL of *Origanum compactum* essential oil, 1.6  $\mu$ L/mL of *Coriandrum sativum* essential oil, >8  $\mu$ L/mL of *Cinnamomum camphora*, *Artemisia herba-alba* and *Helichrysum italicum* essential oils (Bakkali et al., 2005). Moreover, it depended also on the state of cell growth, dividing cells being much more sensitive probably because essential oils penetrated more efficiently at the budding sites. In general, the cytotoxic activity of essential oils is mostly due to the presence of phenols, aldehydes and alcohols (Bruni et al., 2003; Sacchetti et al., 2005).

This cytotoxic property is of great importance in the applications of essential oils not only against certain human or animal pathogens or parasites but also for the preservation of agricultural or marine products. Essential oils or some of their constituents are indeed effective against a large variety of organisms including bacteria (Holley and Dhaval, 2005; Basile et al., 2006; Schelz et al., 2006; Hüsniü Can Baser et al., 2006), virus (Duschatzky et al., 2005), fungi (Hammer et al., 2002; Velluti et al., 2003, 2004; Serrano et al., 2005; Cavaleiro et al., 2006; Pawar and Thaker, 2006; Soylu et al., 2006), protozoa (Monzote et al., 2006), parasites (Moon et al., 2006; Priestley et al., 2006), acarids (Rim and Jee, 2006), larvae (Hierro et al., 2004; Pavela, 2005; Morais et al., 2006; Amer and Mehlhorn, 2006a,b; Ravi Kiran et al., 2006), worms, insects (Bhatnagar et al., 1993; Lamiri et al., 2001; Liu et al., 2006; Burfield and Reekie, 2005; Yang and Ma, 2005; Sim et al., 2006; Kouninki et al., 2005; Park et al., 2006a,b; Chaiyasit et al., 2006; Cheng et al., 2007) and molluscs (Lahlou and Berrada, 2001) (see Table 2).

Cytotoxic activities of essential oils or their major components, sometimes activated by light, were also demonstrated in mammalian cells *in vitro* by short-term viability assays using specific cell staining or fluorescent dyes including NRU (Neutral Red Uptake) test (Söderberg et al., 1996; Stamatii et al., 1999; Dijoux et al., 2006), MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) test (Fujisawa et al., 2002; Carvalho de Sousa et al., 2004; Sun et al., 2005b; Yoo et al., 2005; Manosroi et al., 2006; Jafarian et al., 2006; Chung et al., 2007), Alamar Blue (resazurin) test (O'Brien et al., 2000), Trypan Blue exclusion test (Budhiraja et al., 1999; Horvathova et al., 2006; Slamenova et al., 2007) or Hoechst 33342

Table 1  
Examples of essential oils tested for their cytotoxic capacities on standard organisms

EOs or components	Organisms	Concentrations	References
<i>Pinus densiflora</i>	<i>Salmonella typhimurium</i>	50 µL of dilutions 1/2, 1/4, 1/8, 1/16	Hong et al. (2004)
<i>Pinus koraiensis</i>	<i>Listeria monocytogenes</i>	on filter paper discs	
<i>Chamaecyparis obtusa</i>	<i>Escherichia coli</i>		
	<i>Staphylococcus aureus</i>		
	<i>Klebsiella pneumoniae</i>		
	<i>Candida albicans</i>		
<i>Tamarix boveana</i>	<i>Staphylococcus aureus</i>	1, 0.8, 0.5, 0.3 mg/mL	Saidana et al. (2007)
	<i>Staphylococcus epidermidis</i>	0.5, 2, 4 mg/filter paper disc	
	<i>Escherichia coli</i>	MICs 0.3, 0.5, 0.8 mg/mL	
	<i>Pseudomonas aeruginosa</i>	80, 200, 500 µg/disc	
	<i>Micrococcus luteus</i>	(no antifungal activity)	
	<i>Salmonella typhimurium</i>		
	<i>Fusarium oxysporum</i>		
	<i>Aspergillus niger</i>		
	<i>Penicillium</i> sp., <i>Alternaria</i> sp.		
<i>Eucalyptus robusta</i>	<i>Staphylococcus aureus</i>		Sartorelli et al. (2007)
<i>Eucalyptus saligna</i>	<i>Escherichia coli</i>		
	<i>Candida albicans</i>		
<i>Melaleuca alternifolia</i>	<i>Candida albicans</i>	0.25–1% (v/v)	Hammer et al. (2004)
	<i>Candida glabrata</i>		
	<i>Saccharomyces cerevisiae</i>		
<i>Melaleuca alternifolia</i>	Filamentous fungi	MFC 0.03–8%	Hammer et al. (2002)
	Dermatophytes	MIC 0.004–0.25%	
<i>Houttuynia cordata</i>	HSV-1	ED50 0.00038–0.0091% w/v	Hayashi et al. (1995)
Methyl <i>n</i> -nonylketone	Influenza virus	ED50 0.0015–0.0062% w/v	
Lauryl aldehyde	HIV-1	2-fold dilution for EO	
Capryl aldehyde		0.0083% for components	
<i>Melissa officinalis</i>	<i>Pseudomonas aeruginosa</i>	20%, 50%	Mimica-Dukic et al. (2004)
	<i>Escherichia coli</i>		
	<i>Salmonella</i>		
	<i>Sarcina lutea</i>		
	<i>Micrococcus flavus</i>		
	<i>Staphylococcus</i>		
	<i>Bacillus subtilis</i>		
	<i>Trichophyton</i>	MIC 15–30 µL/mL	
	<i>Microsporum canis</i>		
	<i>Epidermophyton floccosum</i>		
	<i>Candida albicans</i>		
<i>Ocimum basilicum</i> ,	13 bacteria	20%, 50%	Bozin et al. (2006)
<i>Origanum vulgare</i> ,	6 fungi	MIC 8–15–30 µL/mL	
<i>Thymus vulgaris</i>		MIC 1–2 µL/mL	
		MIC 2–4 µL/mL	
β-triketone	HSV-1, HSV-2	IC50 0.58, 0.96 µg/mL	Reichling et al. (2005)
( <i>Leptospermum scoparium</i> )			
<i>Thymus vulgaris</i> ,	<i>Salmonella enteritidis</i>	MIC < 0.1–5.0 µL/mL	Rota et al. (2004)
<i>Salvia sclarea</i> ,	<i>Salmonella typhimurium</i>		
<i>Salvia officinalis</i> ,	<i>Escherichia coli</i>		
<i>Salvia lavandulifolia</i> ,	<i>Yersinia enterocolitica</i>		
<i>Lavandula latifolia</i> (a),	<i>Shigella flexneri</i>		
<i>Lavandula angustifolia</i> (b),	<i>Listeria monocytogenes</i>		
Three hybrids a × b	<i>Staphylococcus aureus</i>		
<i>Rosmarinus officinalis</i> ,			
<i>Hyssopus officinalis</i> ,			
<i>Satureja montana</i>			
<i>Salvia sclarea</i>	<i>Sclerotinia sclerotiorum</i>	EC50 492.55 µL/L	Pitarokili et al. (2002)
Linalyl acetate	<i>Sclerotium cepivorum</i>	EC50 544.17 µL/L	
Linalool	<i>Fusarium oxysporum</i>	EC50 584.36 µL/L	
		EC50 549.62 µL/L	
		EC50 > 1500 µL/L	
		EC50 > 1500 µL/L	
		EC50 146.15 µL/L	
		EC50 563.94 µL/L	
		EC50 661.76 µL/L	

(continued on next page)

Table 1 (continued)

EOs or components	Organisms	Concentrations	References
<i>Salvia fruticosa</i>	<i>Fusarium oxysporum</i>	50–2000 µL/L	Pitarokili et al. (2003)
1,8-cineole	<i>Fusarium solani</i>	20–500 µL/L	
Camphor	<i>Fusarium proliferatum</i>	MIC > ou = 2000 µL/L	
	<i>Sclerotinia sclerotiorum</i>	MIC > 500 µL/L	
	<i>Rhizoclonia solani</i>		
<i>Salvia desoleana</i>	<i>Staphylococcus aureus</i>	MIC 2 or >2 mg/mL	Peana et al. (1999)
<i>Salvia sclarea</i>	<i>Staphylococcus epidermidis</i>	MIC 1.5–2 mg/mL	
α-Terpineol	<i>Escherichia coli</i>	MIC 0.250–1 or >2 mg/mL	
Linalool	<i>Candida albicans</i>	MIC 1–2 or >2 mg/mL	
	<i>Pseudomonas aeruginosa</i>		
<i>Grammosciadium platycarpum</i>	<i>Bacillus subtilis</i>	MIC 0.5–1.9 mg/mL	Sonboli et al. (2005)
	<i>Enterococcus faecalis</i>	MIC 7.5–15 mg/mL	
Linalool	<i>Staphylococcus aureus</i>	MIC 0.2–2.5 mg/mL	
Limonene	<i>Staphylococcus epidermidis</i>	MIC 0.6–5 mg/mL	
	<i>Escherichia coli</i>		
	<i>Pseudomonas aeruginosa</i>		
	<i>Klebsiella pneumoniae</i>		
<i>Ziziphora clinopodioides</i>	<i>Staphylococcus epidermidis</i>	10 µL/filter paper disc	Sonboli et al. (2006b)
Pulegone	<i>Staphylococcus aureus</i>	MIC 3.75 to >15 mg/mL	
1,8-cineole	<i>Escherichia coli</i>	MIC 1.8–7.2 mg/mL	
	<i>Bacillus subtilis</i>	MIC 0.9–7.2 mg/mL	
	<i>Enterococcus faecalis</i>		
	<i>Klebsiella pneumoniae</i>		
	<i>Pseudomonas aeruginosa</i>		
<i>Pimpinella anisum</i>	<i>Candida albicans</i>	MIC 0.1–1.56% v/v	Kosalec et al. (2005)
	<i>Candida parapsilosis</i>		
	<i>Candida tropicalis</i>		
	<i>Candida pseudotropicalis</i>		
	<i>Candida krusei</i>		
	<i>Candida glabrata</i>		
	<i>Trichophyton rubrum</i>		
	<i>Trichophyton mentagrophytes</i>		
	<i>Microsporium canis</i>		
	<i>Microsporium gypseum</i>		
<i>Origanum</i>	<i>Candida albicans</i>	0.0625, 0.125,	Manohar et al. (2001)
Carvacrol		0.25 mg/mL	
<i>Calamintha officinalis</i> ,	<i>Botrytis cinerea</i>	10–250 ppm	Bouchra et al. (2003)
<i>Lavandula dentata</i> ,			
<i>Mentha pulegium</i> ,			
<i>Origanum compactum</i> ,			
<i>Rosmarinus officinalis</i> ,			
<i>Salvia aegyptiaca</i> ,			
<i>Thymus glandulosus</i> ,			
α-Pinene, Borneol, Thymol,			
Carvacrol, Cineole, <i>p</i> -Cimene			
Linalool, Menthone, R-(+)-Pulegone			
Thyme, Basil,	<i>Shigella sonnei</i>	0.1–10%	Bagamboula et al. (2004)
Thymol, Estragol,	<i>Shigella flexneri</i>	0.05% (lettuce)	
Linalool, Carvacrol,	<i>Escherichia coli</i>		
<i>Coriandrum sativum</i>	<i>Salmonella choleraesuis</i>	6.25 µg/mL	Kubo et al. (2004)
volatiles		12.5 µg/mL	
<i>Anethum graveolens</i> ,	<i>Corynebacterium diphtheriae</i>	4.50, 0.09, 0.04, 0.02 µg per	Singh et al. (2002)
<i>Carum copticum</i> ,	<i>Staphylococcus aureus</i>	filter paper disc agar	
<i>Coriandrum sativum</i> ,	<i>Streptococcus haemolyticus</i>	method	
<i>Cuminum cyminum</i> ,	<i>Bacillus subtilis</i>	IZ: inactive to 36 mm	
<i>Foeniculum vulgare</i> ,	<i>Pseudomonas aeruginosa</i>		
<i>Pimpinella anisum</i> ,	<i>Escherichia coli</i>		
<i>Seseli indicum</i>	<i>Klebsiella species</i>		
	<i>Proteus vulgaris</i>		

Table 1 (continued)

EOs or components	Organisms	Concentrations	References
<i>Carum nigrum</i> essential oil, oleoresin and components	<i>Aspergillus flavus</i>	2000, 3000 ppm	Singh et al. (2006)
	<i>Aspergillus niger</i>		
	<i>Penicillium purpurogenum</i>		
	<i>Penicillium madriti</i>		
	<i>Penicillium viridicatum</i>		
	<i>Bacillus cereus</i>		
	<i>Pseudomonas aeruginosa</i>		
	<i>Acrophialophora fusispora</i>		
	<i>Escherichia coli</i>		
	<i>Salmonella typhimurium</i>		
<i>Anethum graveolens</i> , <i>Coriandrum sativum</i> (seeds) <i>Coriandrum sativum</i> (leaves) <i>Eucalyptus dives</i> and fractions	<i>Escherichia coli</i>	MIC 0.02–0.10–0.47% v/v	Delaquis et al. (2002)
	<i>Salmonella typhimurium</i>		
	<i>Listeria monocytogenes</i>		
	<i>Staphylococcus aureus</i>		
	<i>Pseudomonas fragi</i>		
	<i>Serratia grimesii</i>		
	<i>Enterobacter agglomerans</i>		
	<i>Yersinia enterocolitica</i>		
	<i>Bacillus cereus</i>		
	Group A <i>Streptococcus</i>		
<i>Lactobacillus</i>			
<i>Saccharomyces cerevisiae</i>			
<i>Origanum vulgare</i> , <i>Mentha arvensis</i> , <i>Ocimum basilicum</i> , <i>Salvia officinalis</i> , <i>Coriandrum sativum</i> <i>Sideritis italica</i>	<i>Aspergillus ochraceus</i>	500, 750, 1000 ppm	Basilico and Basilico (1999)
	18 ATCC and clinical bacteria		
	<i>Helicobacter pylori</i>		
	<i>Pseudomonas aeruginosa</i>		
	<i>Proteus mirabilis</i>		
	<i>Proteus vulgaris</i>		
	<i>Salmonella typhimurium</i>		
	<i>Aspergillus niger</i>		
	<i>Penicillium citrinum</i>		
	<i>Mucora rouxii</i>		
75 essential oils Carvone Piperitone ( <i>Artemisia herba-alba</i> ) <i>Anthemis aciphylla</i>	<i>Escherichia coli</i>	MIC 0.06–1.0 mg/mL	Hüsnu Can Baser et al. (2006)
	<i>Staphylococcus aureus</i>		
	<i>Pseudomonas aeruginosa</i>		
	<i>Enterobacter aerogenes</i>		
	<i>Staphylococcus epidermidis</i>		
	<i>Salmonella typhimurium</i>		
	<i>Candida albicans</i>		
	Gram-positive–negative bacteria		
	<i>Drosophila melanogaster</i>		
<i>Hedychium larsenii</i> <i>Mentha pulegium</i> , <i>Mentha spicata</i> , Pulegone, Menthone, Carvone <i>Dracocephalum foetidum</i>	<i>Bacillus subtilis</i>	MIC 26–2592 µg/mL	Lee et al. (2007a)
	<i>Staphylococcus aureus</i>		
	<i>M. luteus</i>		
	<i>E. hirae</i>		
	<i>S. mutans</i>		
	<i>Escherichia coli</i>		
	<i>Candida albicans</i>		
	<i>Saccharomyces cerevisiae</i>		
	<i>Streptococcus</i>		
	<i>Candida albicans</i>		
<i>Lippia sidoides</i> Thymol, Carvacrol 21 essential oils of Cinnamon, Clove, Geranium, Lemon, Camphor, Orange, Rosemary, Aniseed, Eucalyptus, Lime, etc.	<i>Streptococcus</i>	MIC 0.625–10 mg/mL	Botelho et al. (2007)
	<i>Candida albicans</i>		
	<i>Escherichia coli</i>		
	<i>Klebsiella pneumoniae</i>		
	<i>Pseudomonas aeruginosa</i>		
	<i>Proteus vulgaris</i>		
	<i>Bacillus subtilis</i>	1/1, 1/5, 1/10, 1/20 concentrations	Prabuseenivasan et al. (2006)
	<i>Staphylococcus aureus</i>		
	MIC 0.2–25.6 mg/mL		

(continued on next page)



Table 1 (continued)

EOs or components	Organisms	Concentrations	References
<i>Artemisia absinthium</i> , <i>Artemisia dracunculus</i> <i>Artemisia santonicum</i> <i>Artemisia spicigera</i> <i>Lantana achyranthifolia</i>	34 fungi 16 plant bacteria 15 food bacteria 33 clinic bacteria 14 gram-positive and gram-negative bacteria	20 µL/20 mL agar 600, 900, 1200 µg/disc  4.5 mg/agar petridish MIC 0.25–1 mg/mL	Kordali et al. (2005)    Hernandez et al. (2005)
<i>Pulicaria odora</i>	<i>Bacillus cereus</i> <i>Streptococcus</i> <i>Proteus vulgaris</i> <i>Enterococcus faecalis</i> <i>Escherichia coli</i> <i>Pseudomonas aeruginosa</i>	5, 10 µg/filter paper disc	Hanbali et al. (2005)
<i>Thymus eigi</i> <i>Origanum vulgare</i> , <i>Juniperi aetheroleum</i>	14 bacteria  16 bacteria Seven fungi, three yeasts Four dermatophytes	MICs 0.06, 0.14, 0.28, 4.50, 18.00 mg/mL MIC 8–70% v/v MIC < 10% v/v MIC 0.39–2% v/v	Tepe et al. (2004a,b)  Pepeljnjak et al. (2005)
<i>Coriandrum sativum</i> <i>Foeniculum vulgare</i> <i>Thymus algeriensis</i> <i>Chenopodium ambrosioides</i>	27 phytopathogenic bacteria Two mycopathogenic species Four bacteria, two fungi, two yeasts <i>Aspergillus niger</i> <i>Aspergillus fumigatus</i> <i>Botryodiplodia theobromae</i> <i>Fusarium oxysporum</i> <i>Sclerotium rolfsii</i> <i>Macrophomina phaseolina</i> <i>Cladosporium cladosporioides</i> <i>Helminthosporium oryzae</i> <i>Pythium debaryanum</i>	MIQ 217.5–6960 µg MIQ 480–7680 µg MIC 0.5–1.0 µL/mL 100 µg/mL	Lo Cantore et al. (2004)  Dob et al. (2006) Kumar et al. (2007)
<i>Myrtus communis</i> <i>Origanum vulgare</i> <i>Pelargonium graveolens</i> <i>Rosmarinus officinalis</i> <i>Salvia officinalis</i> <i>Thymus serpyllum</i> Citronellol Eucalyptol Geraniol Thymol Carvacrol Triacetin	<i>Bacillus cereus</i> <i>Bacillus subtilis</i> <i>Escherichia coli</i> <i>Staphylococcus aureus</i>	MIC 1.4–11.20 mg/MI MIC 0.35–0.70 mg/mL MIC 0.36–5.60 mg/mL MIC 1.40–11.20 mg/mL MIC 1.40–11.20 mg/mL MIC 0.28–1.40 mg/mL MIC 0.35–1.40 mg/mL MIC 2.80–5.60 mg/mL MIC 0.08–1.40 mg/mL MIC 0.7–1.40 mg/mL MIC 0.35–2.80 mg/mL MIC 22.40 mg/mL	Rosato et al. (2007)
29 essential oils <i>Cymbopogon martini</i> <i>Cymbopogon winterianus</i> <i>Aloysia triphylla</i> <i>Zingiber cassumunar</i>	13 <i>Escherichia coli</i> serotypes	MIC 100–500 µg/mL	Duarte et al. (2007)
<i>Kadsura longepedunculata</i> <i>Schisandra sphenanthera</i>	Gram-positive bacteria Gram-negative bacteria Dermatophytes, Yeasts	6.25–50 vol% MBC 0.62–2.5 vol% MFC 0.31–1.25 vol%	Pithayanukul et al. (2007)
<i>Actinidia macrosperma</i>	Gram-positive bacteria Gram-negative bacteria HepG2 cells <i>Staphylococcus aureus</i> <i>Bacillus subtilis</i> <i>Escherichia coli</i> Three fungi	MIC?  IC50 147, 189 µg/mL MIC 0.78–25.50 µL/mL	Song et al. (2007)  Lu et al. (2007)
<i>Hippomarathrum microcarpum</i> <i>Foeniculum vulgare</i> (FE) (FE1, FE2, FE3) Bifonazol	Eight bacteria, nine fungi, one yeast <i>Alternaria alternata</i> <i>Aspergillus niger</i> <i>Aspergillus ochraceus</i>	MIC 0.78–1.56 µg/mL MIC 62.50–125 µL/mL MIC 1.0–3.0 µL/mL MIC 1.0–2.8 µL/mL MIC 0.8–3.2 µL/mL	Ozer et al. (2007) Mimica-Dukic et al. (2003)

Table 1 (continued)

EOs or components	Organisms	Concentrations	References
Anethole	<i>Aspergillus versicolor</i>	MIC 7.0–15.0 µL/mL	
Fenchone	<i>Aspergillus flavus</i>	MIC 1.3–2.2 µL/mL	
Camphor	<i>Aspergillus terreus</i>	MIC 3.7–5.8 µL/mL	
	<i>Cladosporium cladosporioides</i>	MIC 2.8–6.0 µL/mL	
	<i>Fusarium tricinctum</i>		
	<i>Penicillium ochrochloron</i>		
	<i>Penicillium funiculosum</i>		
	<i>Phonopsis helianthi</i>		
	<i>Trochoderma viride</i>		
	<i>Trichophyton mentagrophytes</i>		
	<i>Microsporum canis</i>		
	<i>Epidermophyton floccusum</i>		

MIC: minimum inhibitory concentration, MBC: minimum bactericidal concentration, ED: effective dose, EC: effective concentration, IC: inhibitory concentration, IZ: inhibition zone, MFC: minimum fungicidal concentration, MIQ: minimal inhibitory quantity.

and propidium iodide test (Fabian et al., 2006). Essential oil cytotoxicity in mammalian cells is caused by induction of apoptosis and necrosis.

Unscheduled DNA synthesis (UDS) tests were also performed in mammalian cells to detect the presence and removal of adducts in DNA and repair DNA synthesis. For instance, eugenol, isoeugenol, methyleugenol and safrole induce cytotoxicity and genotoxicity in rat and mouse hepatocytes, measured respectively by lactate dehydrogenase release and UDS (Burkey et al., 2000); UDS was also induced by *Ocimum basilicum* essential oil and its main component, estragole, in hamster fibroblastic V79 cells (Muller et al., 1994).

Until now, because of their mode of action affecting several targets at the same time, generally, no particular resistance or adaptation to essential oils has been described. However, a resistance to carvacrol of *Bacillus cereus* has been observed after growth in the presence of a sublethal carvacrol concentration. Pre-treatment with carvacrol diminished the fluidity of the membrane by changing its fatty acid ratio and composition (Ultee et al., 2000; Di Pasqua et al., 2006). Increased tolerance of *Pseudomonas aeruginosa* to *Melaleuca alternifolia* essential oil was also reported involving changes in the barrier and energy functions of the outer membrane (Longbottom et al., 2004). The same effect was produced by hydrogen peroxide (Branco et al., 2004). Even with flavonoids, non-toxic concentrations protected against quercetin cytotoxicity (Oliveira et al., 1997; Dickancaite et al., 1998). Adaptation to sub-lethal concentrations of Tea Tree oil (*Melaleuca alternifolia*) reduced susceptibility to human pathogen antibiotics, probably also due to membrane changes inhibiting antibiotic penetration (McMahon et al., 2007). However, Rafii and Shahverdi (2007) have found a potentiation of the antibiotic nitrofurantoin at a sub-inhibitory concentration by essential oils against enterobacteria. Probably, given the effect of essential oils on cell membranes, the bacterial susceptibility or resistance depend on the mode of application and may suggest that the antibiotic has to be first in contact with the cells (Rafii and Shahverdi, 2007).

### 3.2. Phototoxicity

Some essential oils contain photoactive molecules like furocoumarins. For instance, *Citrus bergamia* (= *Citrus aurantium* ssp. *bergamia*) essential oil contains psoralens which bind to DNA under ultraviolet A light exposure producing mono- and biadducts that are cytotoxic and highly mutagenic (Averbeck et al., 1990). However, in the dark, this oil is not cytotoxic or mutagenic by itself. Dijoux et al. (2006) have shown that *Fusanus spicatus* wood essential oil was not phototoxic but was very cytotoxic. In other words, cytotoxicity seems rather antagonistic to phototoxicity. In the case of cytotoxicity, essential oils damage the cellular and organelle membranes and can act as prooxidants on proteins and DNA with production of reactive oxygen species (ROS), and light exposures do not add much to the overall reaction. In the case of phototoxicity, essential oils penetrate the cell without damaging the membranes or proteins and DNA. Radical reactions by excitation of certain molecules and energy transfer with production of oxygen singlet occur when cells are exposed to activating light. This may cause damage to cellular macromolecules and in some cases the formation of covalent adducts to DNA, proteins and membrane lipids. Obviously, cytotoxicity or phototoxicity depends on the type of molecules present in the essential oils and their compartmentation in the cell, producing different types of radicals with or without light exposure. However, such an antagonism is not quite a strict rule. Dijoux et al. (2006) have shown that *Citrus aurantium dulcis* (= *Citrus gracilis* subf. *dulcis*) and *Cymbopogon citratus* essential oils were phototoxic and cytotoxic. Thus, when studying an essential oil, it may be of interest to determine systematically its cytotoxic as well as its possible phototoxic capacity.

### 3.3. Nuclear mutagenicity

Several studies with various essential oils or their main components have demonstrated that, generally, most of them did not induce nuclear mutations, whatever the organism, i.e. bacteria, yeast or insect, with or without metabolic activation and whatever form of essential oils,

Table 2  
Examples of environmental, agricultural, food and medical applications of essential oils

EOs or components	Organisms	Concentrations	References
Geraniol, Citral, Citronellol, Carvacrol, Eugenol, Cuminaldehyde	<i>Anisakis simplex</i> (larvae)	3.12, 6.25, 12.50 µg/mL	Hierro et al. (2004)
<i>Eucalyptus globulus</i> , <i>M. communis</i> , <i>Pistacia lentiscus</i> , <i>I. graveolens</i> , <i>C. atlantica</i> , <i>Origanum compactum</i> , <i>Ammi visnaga</i> , <i>Citrus sinensis</i> , <i>Tanacetum annuum</i> , <i>Mentha pulegium</i> , <i>Rosmarinus officinalis</i> , <i>T. saturoides</i> , <i>Mentha viridis</i> , <i>Origanum majorana</i> , <i>L. officinalis</i> , <i>Artemisia arborescens</i> , <i>Artemisia herba-alba</i>	Hessian fly <i>Mayetiola destructor</i>	2, 4, 6, 10, 20 µL/L air	Lamiri et al. (2001)
Cinnamon, Clove, Lemongrass, Palmarose, Oregano	<i>Fusarium proliferatum</i> , fumonisin production (maize grain)	500, 1000 µg/g maize	Velluti et al. (2003)
<i>Heterothalamus allenus</i> , <i>Buddleja cordobensis</i>	<i>HSV-1</i> , <i>DENV-2</i> , <i>JUNV</i>	VC50 44.2, 39.0 ppm	Duschatzky et al. (2005)
<i>Nepeta cataria</i> , <i>Thuja occidentalis</i> , <i>Salvia sclarea</i> , <i>Thymus mastichina</i> , <i>Origanum majorana</i> , <i>Pogostemon cablin</i> , <i>Mentha pulegium</i> , <i>Mentha citrata</i> , <i>Origanum vulgare</i> , <i>Origanum compactum</i> , <i>Melissa officinalis</i> , <i>Lavandula angustifolia</i> , etc.	<i>Spodoptera littoralis</i> (larvae)	LC50 10, 20 mL/m <sup>3</sup> LD 0.05 µL/larvae	Pavela, 2005
<i>Origanum syriacum</i> , <i>Thymbra spicata</i> , <i>Lavandula stoechas</i> , <i>Rosmarinus officinalis</i> , <i>Foeniculum vulgare</i> , <i>Laurus nobilis</i> , <i>Sideritis italica</i>	<i>Phytophthora infestans</i> (tomato late blight disease)	0.4–2.0 µg/mL air 6.4, 12.8, 25.6, 51.2 µg/mL (contact phase)	Soylu et al. (2006)
<i>Artemisia princeps</i> , <i>Cinnamomum camphora</i>	<i>Helicobacter pylori</i> <i>Pseudomonas aeruginosa</i> <i>Proteus mirabilis</i> <i>Salmonella typhimurium</i> <i>Proteus vulgaris</i>	3.9–250 µg/mL	Basile et al. (2006)
Oregano, Cinnamon, Lemongrass, Clove, Palmarose	<i>Sitophilus oryzae</i> L., <i>Bruchus rugimanus</i> Bohem (storage pests, germination)	250–1000 µg/g 500 µg/mL	Liu et al. (2006)
Phenolics from Oregano and cranberry	<i>Fusarium graminearum</i> zearalenone, deoxynivalenol production (maize grain)	500, 1000 mg/kg	Velluti et al. (2004)
<i>Thymus vulgaris</i>	<i>Helicobacter pylori</i>	0.1 mg/filter paper disc	Lin et al. (2005)
Thymol	<i>Aspergillus</i> , <i>Penicillium</i> , <i>Alternaria</i> , <i>Ulocladium</i> , <i>Absidia</i> , <i>Mucor</i> , <i>Cladosporium</i> , <i>Trichoderma</i> , <i>Rhizopus</i> , <i>Chaetomium</i> , <i>Stachybotrys chartarum</i> (moulds from damp dwellings)	MIC 20, 50.20 µg/mL 82 µg/L (vapor)	Segvic-Klaric et al. (2007)

Table 2 (continued)

EOs or components	Organisms	Concentrations	References
Eugenol	<i>Microsporium gypseum</i>	MIC 0.01–0.03 %	Lee et al. (2007b)
Nerolidol	(guinea pig infection)	MIC 0.5–2 %	
<i>Achillea millefolium</i> , <i>Syzygium aromaticum</i> , <i>Ocimum basilicum</i>	<i>Trypanosoma cruzi</i> (epimastigotes, trypomastigotes)	LC50 99.5 µg/mL LC50 57.5 µg/mL	Santoro et al. (2007a)
Eugenol, linalool			
<i>Origanum vulgare</i> , <i>Thymus vulgaris</i>	<i>Trypanosoma cruzi</i> (epimastigotes, trypomastigotes)	IC50 175, 115 µg/mL IC50 77, 38 µg/mL IC50 62, 53 µg/mL	Santoro et al. (2007b)
Thymol			
Parsley, Thyme, Anis, Coriander,	<i>Ochlerotatus caspius</i> (mosquito, larvae)	LC50 15–156 ppm	Knio et al. (2007)
Thymol, Sabinene, Carvacrol, Anethole, Linalool			
<i>Santolina rosmarinifolia</i>	<i>Staphylococcus aureus</i> <i>Sarcina lutea</i> <i>Bacillus cereus</i> <i>Escherichia coli</i> <i>Candida albicans</i>	Filter paper discs 1, 5, 10 µL MIC (flowers) 0.3 µL/mL MIC (leaves) 0.6 µL/mL	Ioannou et al. (2007)
<i>Zingiber officinale</i>	<i>HSV-1</i> (acyclovir-sensitive, resistant)	CC50 0.004% EC50 0.0002%	Schnitzler et al. (2007)
<i>Thymus vulgaris</i>		CC50 0.007% EC50 0.001%	
<i>Hyssopus officinalis</i>		CC50 0.0075% EC50 0.0001%	
<i>Santalum album</i>		CC50 0.0015% EC50 0.0002%	
<i>Carum carvi</i>	<i>Anopheles dirus</i>	LC50 24.61–54.62 ppm	Pitasawat et al. (2007)
<i>Apium graveolens</i> , <i>Foeniculum vulgare</i> , <i>Zanthoxylum limonella</i> , <i>Curcuma zedoaria</i>	<i>Aedes aegypti</i> (larvae)		
Cinnamon, Orange, Thyme, Bergamot, Clove, Lemon, Cypress, Eucalyptus, Fennel, Lavander, Mint, Rosemary, Sage	<i>Streptococcus pyogenes</i> <i>Streptococcus agalactiae</i> <i>Streptococcus pneumoniae</i> <i>Klebsiella pneumoniae</i> <i>Haemophilus influenzae</i> <i>Staphylococcus aureus</i> <i>Stenotrophomonas maltophilia</i> VERO cell line	10 µL/filter paper disc MIC 0.00125–0.050 µL/mL  250 µL/well of dilutions 0.001–0.00005 µL/mL MNTC 0.00005–0.0005 µL/mL	Fabio et al. (2007)
<i>Citrus paradisi</i> , <i>Citrus aurantium</i>	MCF-7 cell line Hela cell line	IC50 0.8 µg/mL IC50 14 µg/mL IC50 1.2 µg/mL IC50 0.5 µg/mL	Jafarian et al. (2006)
<i>Eucalyptus citriodora</i> , <i>Cymbopogon citratus</i> , <i>Callistemon lanceolatus</i> , <i>Cinnamomum camphora</i> , <i>Citrus limon</i> , <i>Tagetes patula</i>	<i>Candida</i>	8.50 mm µL <sup>(-1)</sup> 5.63 mm µL <sup>(-1)</sup>	Dutta et al. (2007)
<i>Cinnamomum camphora</i>	<i>Aedes aegypti</i>	0.1 mg/cm <sup>2</sup> (repellency)	Yang et al. (2004a)
54 essential oils	<i>Pediculus humanus capitis</i>	LT50 (min) at 0.0625, 0.125, 0.25 mg/cm <sup>2</sup> (direct contact)	Yang et al. (2004b)
Eucalyptus, Marjoran, Pennyroyal, Rosemary, Cade, Cardamone ceylon, Clove, Myrtle, Rosewood, Sage		LT50 (min) at 0.25 mg/cm <sup>2</sup> (fumigation)	
<i>Artemisia herba-alba</i>	<i>Leishmania tropica</i> <i>Leishmania major</i>	2 µg/mL	Hatimi et al. (2001)
Essential oil constituents	<i>Pediculus humanus</i> (human louse and eggs)	600 µL dilutions 10%, 5%, 2%, 1% (w/v, v/v)	Priestley et al. (2006)
Monoterpenoids	<i>Pediculus humanus capitis</i>		Abou El Ela et al. (2004)

(continued on next page)

Table 2 (continued)

EOs or components	Organisms	Concentrations	References
<i>Juniperus communis</i>	<i>Aspergillus niger</i>	MIC (leaf) 0.08–10 µL/mL	Cavaleiro et al. (2006)
<i>Juniperus oxycedrus</i>	<i>Aspergillus fumigatus</i>	MIC (berry) 0.32–20 µL/mL	
<i>Juniperus turbinata</i>	<i>Aspergillus flavus</i>	MLC (leaf) 0.08–20 µL/mL	
	<i>Candida albicans</i>	MLC (berry) 0.32–20 µL/mL	
	<i>Candida krusei</i>		
	<i>Candida tropicalis</i>		
	<i>Candida glabrata</i>		
	<i>Candida parapsilosis</i>		
	<i>Microsporium canis</i>		
	<i>Microsporium gypseum</i>		
	<i>Trichophyton rubrum</i>		
	<i>Trichophyton mentagrophytes</i>		
	<i>Epidermophyton floccosum</i>		
44 essential oils	<i>Cadra cautella</i> (Lepidoptera Pyralidae)	2.4, 4.7 mg/cm <sup>2</sup> 64.7 mg/L air	Sim et al. (2006)
<i>Croton nepetaefolius</i>	<i>Aedes aegypti</i> (larvae)	LC50 84 ppm	Morais et al. (2006)
<i>Croton argyrophyloides</i>		LC50 102 ppm	
<i>Croton sonderianus</i>		LC50 104 ppm	
<i>Croton zehntneri</i>		LC50 28 ppm	
41 essential oils from Camphor, Thyme, Amyris, Lemon, Cedarwood, Frankincense, Dill, Myrtle, Juniper, Black pepper, Verbena, Helichrysum, Sandalwood, etc.	<i>Aedes aegypti</i> <i>Anopheles stephensi</i> <i>Culex quinquefasciatus</i> (larvae)	LC50 1–101.3 ppm LC50 9.7–101.4 ppm LC50 1–50.2 ppm	Amer and Mehlhorn (2006a)
11 essential oils from <i>Litsea cubeba</i> , <i>Melaleuca leucadendron</i> , <i>Melaleuca quinquenervia</i> , <i>Viola odorata</i> , <i>Nepeta cataria</i> , etc.	<i>Aedes</i> , <i>Anopheles</i> , <i>Culex</i> (mosquito)	Mixtures of five oils (1% each) in solvent 100 µL/30 cm <sup>2</sup> human arm (repellency)	Amer and Mehlhorn (2006b)
<i>Chenopodium ambrosioides</i>	<i>Leishmania amazonensis</i>	30 mg/kg mice	Monzote et al. (2006)
Seven essential oils <i>Xylopi aethiopica</i> , <i>Ocimum gratissimum</i> , <i>Hyptis spicigera</i> , <i>Ammona senegalensis</i> , etc.	<i>Sitophilus zeamais</i> (coleoptera)	1% (contact) 300 µL/800 mL air fumigation	Kouninki et al. (2005)
<i>Curcuma aromatica</i> Asteraceae, Rutaceae, Citronella, Mentha × piperita Carvacryl, Eucalyptus <i>Chloroxylon swietenia</i>	<i>Aedes aegypti</i> (larvae, adult) <i>Aedes albopictus</i> (mosquito)	LC50 36.30 ppm LC50 2.86 µg/mg 7%, 15% (repellency)	Choochote et al. (2005) Yang and Ma (2005)
Pregeijerene Geijerene Germacrene D	<i>Aedes aegypti</i> <i>Anopheles stephensi</i> (larvae)	2–100 µg/mL LC50 16.5, 14.9 µg/mL LC50 28.3, 25.8 µg/mL LC50 43.4, 41.2 µg/mL LC50 63.6, 59.5 µg/mL	Ravi Kiran et al. (2006)
Pennyroyal, Ylang Ylang, Citronella, Lemongrass, Tea tree, Rosemary	<i>Dermatophagoides farinae</i> <i>Dermatophagoides pteronyssinus</i>	0.1, 0.05, 0.025, 0.0125, 0.00625 µL/cm <sup>2</sup>	Rim and Jee (2006)
40 essential oils <i>Armoracia rusticana</i> , <i>Pimpinella anisum</i> , <i>Allium sativum</i> , <i>Chenopodium ambrosioides</i> , <i>Eucalyptus globulus</i> , <i>Eucalyptus smithii</i>	<i>Lycoriella ingenua</i> (diptera)	10, 5 µL/L air 1.25, 0.625 µL/L air	Park et al. (2006a)
Allyl isothiocyanate, Trans-anethole, Diallyl disulfide, p-Anisaldehyde		LC50 0.15, 0.20, 0.87, 1.47 µL/L air	

Table 2 (continued)

EOs or components	Organisms	Concentrations	References
21 essential oils <i>Acorus gramineus</i> <i>Schizonepeta tenuifolia</i> <i>Zanthoxylum piperitum</i> Pulegone, Menthone, Limonene <i>Lavandula angustifolia</i>	<i>Lycoriella ingenua</i> (larvae)	25, 12.5, 3.125 µg/mL air	Park et al. (2006b)
<i>Apium graveolens</i> , <i>Carum carvi</i> , <i>Curcuma zedoaria</i> , <i>Piper longum</i> , <i>Illicium verum</i> <i>Allium sativum</i> <i>Allium cepa</i> <i>Allium fistulosum</i>	<i>Giardia duodenalis</i> <i>Trichomonas vaginalis</i> <i>Hexamita inflata</i> <i>Aedes aegypti</i> (adult)	LC50 1.21, 6.03, 15.42 µg/mL air 0.1%, 1% 5.44–8.83 µg/mg	Moon et al. (2006) Chaiyasit et al. (2006)
11 essential oils from Coniferous trees <i>Curcuma zedoaria</i>	<i>Trichophyton rubrum</i> <i>Trichophyton erinacei</i> <i>Trichophyton soudanense</i> <i>Coptotermes formosanus</i> (termite)	MICs 64 µg/mL 10 mg/g LC50 2.6 mg/g	Pyun and Shin (2006) Cheng et al. (2007)
18 essential oils	<i>Aedes aegypti</i> (larvae)	LC50 33.45 ppm LC99 83.39 ppm	Champakaew et al. (2007)
<i>Salvia macrochlamys</i> <i>Salvia rognita</i>	<i>Aedes albopictus</i> <i>Anopheles dirus</i> <i>Culex quinquefasciatus</i> (mosquitoes) <i>Plasmodium falciparum</i> <i>Candida albicans</i> <i>Cryptococcus neoformans</i> <i>Aspergillus fumigatus</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> <i>Mycobacterium intracellulare</i>	10 % solution (repellency) IC50 17, 12 µg/mL 200 µg/mL	Tawatsin et al. (2006) Tabanca et al. (2006)
Oregano Thyme Clove Cinnamon Carvacrol Thymol Eugenol Coriander Savory Clove Oregano Rosemary Thyme with or without CAB bacteriocin (in vitro activity ) (Oregano and Savory activity in pork meat w or w/o CAB)	<i>Escherichia coli</i> Caco-2 cells	0.05, 0.01% 0.05, 0.01% 0.05, 0.01% 0.05, 0.01% 1.83, 0.37, 0.06 mM 0.80, 0.17, 0.06 mM 2.50, 0.52, 0.06 mM	Fabian et al. (2006)
Oregano, Thyme thymol, Cinnamon bark, Lemongrass, Clove, Palmarose, Peppermint, Lavender, Geranium, Tea tree, Thyme geraniol with heat and salt (in foot bath)	<i>Listeria monocytogenes</i> M <i>Escherichia coli</i> 10536 <i>Salmonella</i> serotype Typhi CWBI-H1	5 µL/well diffusion assay IZ 8–25 mm In pork meat: 3.0–0.0 log <sub>10</sub> CFU/g	Ghalfi et al. (2007)
<i>Mentha spicata</i> , <i>Anethum graveolens</i> , <i>Mentha longifolia</i> , <i>Mentha piperita</i> Carvone, Camphor, Limonene, Menthone, Piperitone	<i>Trichophyton mentagrophytes</i> <i>Trichophyton rubrum</i> <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> <i>Enterobacter cloacae</i> <i>Enterobacter aerogenes</i> <i>Serratia marcescens</i> <i>Citrobacter freundii</i> <i>Proteus vulgaris</i> <i>Proteus mirabilis</i>	MFC to kill 99.99% 2, 4, 8, 16 µL/disc (with sub-inhibitory conc. 30 µg Nitrofurantoin per mL agar plate) IZ 15–53 mm IZ 0–24 mm	Inouye et al. (2007) Rafi and Shahverdi (2007)

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Table 2 (continued)

EOs or components	Organisms	Concentrations	References
<i>Artemisia scoparia</i>	<i>Rhizoctonia solani</i>	EC50 41.4 µL/L	Farzaneh et al. (2006)
<i>Artemisia sieberi</i>	<i>Tiarospora phaseolina</i>	MIC 1000 µL/L EC50 203.4 µL/L	
<i>Artemisia aucheri</i>	<i>Fusarium moniliforme</i>	MIC 750 µL/L EC50 211.0 µL/L	
	<i>Fusarium solani</i>	MIC 750 µL/L EC50 188.1 µL/L	
Tea tree oil	<i>Acne vulgaris</i>	MIC 250 µL/L EC50 121.8 µL/L	
<i>Coridothymus capitatus</i>	<i>Salmonella typhimurium</i>	Topical 5%	Enshaieh et al. (2007)
<i>Cinnamomum cassia</i>	<i>Listeria monocytogenes</i>	1% wt/vol in 2 or 20% wt/vol CaCl <sub>2</sub> solution on Alginate-based Films	Oussalah et al. (2007)
<i>Satureja montana</i>	(in Bologna and ham slices)		
<i>Chenopodium ambrosioides</i>	<i>Planococcus citri</i>	4.0, 11.3, 18.9 mL/946 mL	Cloyd and Chiasson (2007)
(in QRD 400: emulsifiable concentrate at 25% active oil)	<i>Pseudococcus longispinus</i>	0.3, 0.6, 1.0 mL/60 mL	
	<i>Frankliniella occidentalis</i>		
	<i>Bradysia coprophila</i>		
	(greenhouse insect pests)		
<i>Scaligeria tripartita</i>	<i>Colletotrichum acutatum</i>	0.3, 3.0, 30.0 µM	Tabanca et al. (2007)
	<i>Colletotrichum fragariae</i>		
	<i>Colletotrichum gloeosporioides</i>		
	<i>Fusarium oxysporum</i>		
	<i>Botrytis cinerea</i>		
	<i>Phomopsis obscurans</i>		
Tea tree oil	<i>Madurella mycetomatis</i>	MIC 0.008–0.25 % v/v	Van de Sande et al. (2007)
Artemisinin		MIC 0.03 to >16 mg/L	
<i>Calocedrus decurrens</i>	<i>Ixodes scapularis</i>	0.02–5.0 µg/mL	Dolan et al. (2007)
<i>Chamaecyparis lawsoniana</i>	<i>Xenopsylla cheopis</i>	LC50 0.096, 0.31, 0.29 µg/mL	
<i>Juniperus occidentalis</i>	<i>Aedes aegypti</i> (adult)	LC50 0.24, 1.21, 0.31 µg/mL	
		LC50 0.005, 0.051, 0.041 µg/mL	
<i>Cinnamomum zeylanicum</i>	<i>Escherichia coli</i>	MIC 8.7–52.4–131.0 µL/L air	Lopez et al. (2007)
<i>Thymus vulgaris</i>	<i>Yersinia enterocolitica</i>	MIC 26.2–87.3–175.0 µL/L air	
<i>Origanum vulgare</i>	<i>Pseudomonas aeruginosa</i>	MIC 4.4–34.9–175.0 µL/L air	
	<i>Salmonella choleraesuis</i>		
	<i>Listeria monocytogenes</i>		
	<i>Staphylococcus aureus</i>		
	<i>Bacillus cereus</i>		
	<i>Enterococcus faecalis</i>		
	<i>Penicillium islandicum</i>		
	<i>Aspergillus flavus</i>		
	<i>Candida albicans</i>		
<i>Citrus limon</i>	<i>Arcobacter butzleri</i>	MIC > 4% v/v	Fisher et al. (2007)
<i>Citrus sinensis</i>		MIC > 4% v/v	
<i>Citrus bergamia</i>		MIC 0.125, 0.5, 2.0% v/v	
Citral		MIC 0.03, 0.06, 0.125% v/v	
Limonene		MIC > 4% v/v	
Linalool		MIC 0.06, 0.125, 0.25% v/v	
<i>Lavandula angustifolia</i>	<i>Resseliella oculiperda</i>	(Repellency)	Van Tol et al. (2007)
<i>Juniperus virginiana</i>			
<i>Cinnamomum camphora</i>			
a-terpineol, Citronellal,			
R-Carvone, Linalool,			
R-Fenchone			

MIC: minimum inhibitory concentration, LC: lethal concentration, LD: lethal dose, EC: effective concentration, IC: inhibitory concentration, VC: virucidal concentration, CC: cytotoxic concentration, IZ: inhibition zone, MNTC: minimum nontoxic concentration, MFC: minimum fungicidal concentration, MLC: minimal lethal concentration, LT: lethal time.

complete formula or isolated components, were considered (see Table 3).

However, some exceptions should be noted. For example, the test with *Artemisia dracunculus* essential oil was positive in rec-*Bacillus subtilis* (Zani et al., 1991). *Mentha spicata* essential oil was genotoxic in the *Drosophila melanogaster* somatic mutations and recombination test (SMART) (Franzios et al., 1997; Karpouhtsis et al.,

1998). *Anethum graveolens* essential oil gave also positive results in the *Drosophila melanogaster* SMART assay, in the sister chromatid exchange (SCE) test and the chromosomal aberration (CA) test on human lymphocytes (Lazutka et al., 2001). Essential oils extracted from *Pinus sylvestris* and *Mentha piperita* (= *Mentha × piperita*) were also genotoxic in the SMART assay and on CA in lymphocytes (Lazutka et al., 2001). Concerning isolated constitu-

Table 3  
Examples of essential oils devoid of mutagenicity

Essential oils or components	Organisms	References
<i>Pimpinella anisum</i> , <i>Cinnamomum cassia</i> , <i>Cinnamomum zeylanicum</i> <i>Eugenia caryophyllata</i> <i>Foeniculum vulgare</i> Anethol, Cinnamaldehyde, Cinamylic alcohol, Eugenol, Methyl eugenol, Isoeugenol, Isosafrol, piperonal	<i>Salmonella typhimurium</i> <i>Escherichia coli</i>	Sekizawa and Shibamoto (1982)
<i>Mentha piperita</i> , Menthol, Pulegone	<i>Salmonella typhimurium</i>	Andersen and Jensen (1984)
<i>Anthemis nobilis</i> , <i>Salvia officinalis</i> , <i>Salvia sclarea</i> , <i>Satureja hortensis</i> , <i>Satureja montana</i> , <i>Thymus capitatus</i> , <i>Thymus × citriodoris</i> , <i>Thymus vulgaris</i> , <i>Citrus bergamia</i>	<i>Bacillus subtilis</i> <i>Salmonella typhimurium</i>	Zani et al. (1991)
Camphor, 1,8-Cineole, Citral, Citronellal, Menthol, $\beta$ -Myrcene, $\alpha$ -Terpinene, $\alpha$ -Pinene, $\alpha$ -Bisabolol	<i>Salmonella typhimurium</i>	Gomes-Carneiro et al. (1998, 2005)
<i>Origanum onites</i> <i>Melaleuca alternifolia</i> <i>Lavandula angustifolia</i> <i>Salvia officinalis</i> , Thujone, 1,8-Cineole, Camphor, Limonene	<i>Salmonella typhimurium</i> <i>Salmonella typhimurium</i> , <i>Escherichia coli</i>	Ipek et al. (2005) Evandri et al. (2005)
<i>Origanum compactum</i> , <i>Artemisia herba-alba</i> , <i>Cinnamomum camphora</i> , <i>Coriandrum sativum</i> <i>Mentha pulegium</i> , Pulegone, Carvone <i>Helichrysum italicum</i> , <i>Ledum groenlandicum</i> , <i>Ravensara aromatica</i> <i>Origanum vulgare</i> , <i>Coridothymus capitatus</i> , <i>Satureja thymbra</i> , <i>Mentha pulegium</i>	<i>Saccharomyces cerevisiae</i> <i>Saccharomyces cerevisiae</i> <i>Salmonella typhimurium</i>	Bakkali et al. (2005) Bakkali et al. (unpublished)
<i>Origanum compactum</i> (sub-fractions and constituents)	<i>Drosophila melanogaster</i>	Franzios et al. (1997)
Estragole	<i>Drosophila melanogaster</i>	Idaomar et al. (2002)
	<i>Drosophila melanogaster</i>	Karpouhtsis et al. (1998)
	<i>Drosophila melanogaster</i>	Mezzoug et al. (2007)
	V79 (chrom. aberrations)	Muller et al. (1994)

ents from essential oils, several monoterpenes and alkenylbenzenes were studied. For example, menthone of the *pepper mentha* essential oil gave positive results in the Ames test (Andersen and Jensen, 1984). Menthone was also found genotoxic in SMART test (Franzios et al., 1997). Anethol from fennel and anise essential oils was active in the Ames test (Nestman and Lee, 1983; Hasheminejad and Caldwell, 1994), however, according to Gorelick (1995), it was not, although it was active in the mouse lymphoma assay (MLA). Asarone from *Acorus calamus* essential oil was found mutagenic in the Ames test (Goggelmann and Schimmer, 1983) and in hepatocytes (Hasheminejad and Caldwell, 1994); it induced SCE in human lymphocytes and in mouse bone marrow (Abel, 1987; Morales-Ramirez et al., 1992). The oxidized metabolic intermediates of these two molecules, *trans*-anethole oxide and *trans*-asarone oxide, were genotoxic in the Ames test and induced liver and skin cancers (Kim et al., 1999). Terpeneol was found

active in the Ames test (Gomes-Carneiro et al., 1998). Cinnamaldehyde, carvacrol, thymol and carvone exerted weak mutagenic effects in the Ames test (Stammati et al., 1999). Eugenol was found genotoxic by inducing CA and endoreduplications in V79 cells (Maralhas et al., 2006).

### 3.4. Cytoplasmic mutagenicity

Most of the mutagenicity (and anti-mutagenicity) studies on essential oils were performed on bacteria (*Salmonella typhimurium* with Ames test, *Escherichia coli* with SOS Chromotest, *Bacillus subtilis* with DNA Repair test) or mammalian cells (MLA, human lymphocytes and hepatocytes) or on insect (*Drosophila melanogaster* SMART assay). In these test systems it is impossible to distinguish the mode of action of essential oils and their targets. Usually, cytotoxicity, mutagenicity or anti-mutagenicity are assessed without being able to take into account possible



defects in energy metabolism and respiration as direct or indirect causes. In this respect, tests in yeast (*Saccharomyces cerevisiae*) have been shown to be potentially very useful. As a facultative anaerobic organism, yeast can survive with damaged mitochondria and even without mitochondria, and detrimental effects on the respiratory system can be tested without directly affecting cell survival. This is in contrast to what can be observed in bacteria and mammalian cells where the induction of defects in the respiratory system is usually directly associated with cell death. Taking advantage of the yeast system, it is possible to show that, among others, mitochondria are very important cellular targets for essential oils. Indeed, a relation between the deterioration of mitochondria and immediate changes of respiratory metabolism was demonstrated after treatment of yeast cells (*Saccharomyces cerevisiae*) with the tea tree essential oil (Schmolz et al., 1999). Cells of *Saccharomyces cerevisiae* showed a delay in ethanol production in the presence of cinnamon, clove, garlic, onion, oregano and thyme essential oils, as estimated by the measure of the CO<sub>2</sub> volume produced (Conner et al., 1984). In plants, the mitochondria could not perform oxidative metabolism in the presence of  $\alpha$ -pinene (Abraham et al., 2003).

Moreover, it has been shown that exposure to essential oils could induce mitochondrial damage involving mitochondrial membranes and DNA leading to the formation of respiratory deficient cytoplasmic petite mutants. The rates of this induction depended, as cytotoxicity, on the composition of essential oils. Cells in logarithmic growth phase (budding cells) were also more sensitive to the induction of cytoplasmic petite mutants. Absence of the formation of sectorized colonies indicated that essential oils damage the whole mitochondria and mitochondrial DNA of the mother cells which are immediately converted into respiratory deficient rho<sup>0</sup> cells characterized by mitochondrial dysfunction and loss of mitochondrial DNA (Bakkali et al., 2005).

### 3.5. Carcinogenicity of the essential oils

Since most essential oils have been found to be cytotoxic without being mutagenic, it is likely that most of them are also devoid of carcinogenicity. However, some essential oils or rather some of their constituents may be considered as secondary carcinogens after metabolic activation (Guba, 2001). For example, essential oils like those from *Salvia sclarea* and *Melaleuca quinquenervia* provoke estrogen secretions which can induce estrogen-dependent cancers. Some others contain photosensitizing molecules like flavins, cyanin, porphyrins, hydrocarbures which can cause skin erythema or cancer. Psoralen, a photosensitizing molecule found in some essential oils, for instance from *Citrus bergamia* (= *Citrus aurantium* ssp. *bergamia*), can induce skin cancer after formation of covalent DNA adducts under ultraviolet A or solar light (Averbeck et al., 1990; Averbeck and Averbeck, 1998). Pulegone, a component of essential oils from many mint species, can induce carcinogenesis through metabolism generating the glutathione depletory

*p*-cresol (Zhou et al., 2004). Safrole, the major constituent of *Sassafras albidum* and *Ocotea pretiosa* (= *Mespilodaphne pretiosa*) essential oils, induces carcinogenic metabolites in rodents (Miller et al., 1983; Burkey et al., 2000; Liu et al., 2000). Methyleugenol from *Laurus nobilis* and *Melaleuca leucadendron* essential oils has also been shown to be carcinogenic in rodents (Burkey et al., 2000). D-Limonene, a monoterpene found in *Citrus* essential oil, was carcinogenic in male rats, by a male-rat specific mechanism (NTP, 1990). Estragole, a constituent of *Ocimum basilicum* and *Artemisia dracuncululus* essential oils, has shown carcinogenic properties in rat and mouse (Miller et al., 1983; Anthony et al., 1987).

### 3.6. Antimutagenic properties of essential oils

Until now, most studies indicated that anti-mutagenic properties may be due to inhibition of penetration of the mutagens into the cells (Kada and Shimoi, 1987; Shankel et al., 1993), inactivation of the mutagens by direct scavenging, antioxidant capture of radicals produced by a mutagen or activation of cell antioxidant enzymes (Hartman and Shankel, 1990; Sharma et al., 2001; Ipek et al., 2005), inhibition of metabolic conversion by P450 of promutagens into mutagens (Ramel et al., 1986; De Flora and Ramel, 1988; Kuo et al., 1992; Waters et al., 1996; Gomes-Carneiro et al., 2005), or activation of enzymatic detoxification of mutagens for instance by plant extracts. Less known is a possible antimutagenic interference with DNA repair systems after induction of genotoxic lesions. Some antimutagenic agents can either inhibit error-prone DNA repair or promote error-free DNA repair (Kada and Shimoi, 1987; Kuroda and Inoue, 1988; De Flora et al., 1985, 1992a,b; Bronzetti et al., 1992; Vukovic-Gacic et al., 2006).

The biochemistry of anti-mutagenic interference with promutagen metabolism to prevent mutagenesis is known and relatively well documented, as well as, during recent years, the role and reactions of ROS scavengers, such as glutathione, superoxide dismutase, catalase, *N*-acetylcysteine, provitamins like retinoids, carotenoids and tocopherols, flavonoids and other polyphenols, etc. (Odin, 1997; De Flora et al., 1999). However, since the work of Kada and Shimoi (1987) and Kuroda and Inoue (1988) on *Escherichia coli*, nobody has examined in more detail this type of antimutagenicity possibly involving interference with DNA repair via intracellular prooxidant reactions of the latter compounds or terpenic and phenolic compounds from aromatic plants.

Kuo et al. (1992) found that the natural compounds, tannic acid and apigenine, reduced the frequency of SCEs induced by nitropyrenes in CHO cells. Hernandez-Ceruelos et al. (2002) showed that *Matricaria chamomilla* essential oil inhibits SCEs induced by daunorubicine and methyl methane sulfonate in mouse bone marrow cells. Gomes-Carneiro et al. (2005) showed by Ames test that  $\alpha$ -bisabolol inhibits very well aflatoxin B<sub>1</sub>, 2-aminoanthracene, benzo-a-pyrene and 2-aminofluorene induced-mutagenesis,

but less so for 4-nitroquinoline-*N*-oxide and 2-nitrofluorene induced-mutagenesis and not at all for sodium azide and nitro-*o*-phenylenediamine induced-mutagenesis; this antimutagenic effect is due to  $\alpha$ -bisabolol interaction with promutagen biotransformation enzymes or to inhibition of hepatic mono-oxygenases acting on P450 cytochromes. The same authors showed also in the Wistar rat inhibitor effects on CYP2B1 responsible for the metabolism of cyclophosphamide into teratogenic precursors (Gomes-Carneiro et al., 2003). Evandri et al. (2005) showed by Ames test and *Escherichia coli* uvrA that *Melaleuca alternifolia* and *Lavandula angustifolia* essential oils strongly inhibit 2-nitrofluorene induced-mutagenesis. Vukovic-Gacic et al. (2006) showed that *Salvia officinalis* and major components thuyone, 1,8-cineole, camphor and limonene inhibit UVC-induced mutagenesis in *Salmonella typhimurium*, *Escherichia coli* and *Saccharomyces cerevisiae*. De-Oliveira et al. (1997, 1999) have demonstrated that (–)-menthol, (–)- $\alpha$ -pinene, (+)- $\alpha$ -pinene,  $\alpha$ -terpinene,  $\alpha$ -terpineol, 1,8-cineole, d-limonene, camphor, citronellal and citral modulate hepatic mono-oxygenase activity such as CYP1A1 and CYP2B1 interacting with promutagen or procarcinogen xenobiotic biotransformation. Idaomar et al. (2002) have found by SMART test that *Helichrysum italicum*, *Ledum groenlandicum* (= *Rhododendron groenlandicum*) and *Ravensara aromatica* (= *Cinnamomum camphora*) essential oils and their mixture reduce the urethane-induced mutation frequency in *Drosophila melanogaster*. In a more recent study, they showed in the same system that *Origanum compactum* essential oil and some of its sub-fractions and constituents are antimutagenic against the indirect-acting mutagen urethane and also against the direct-acting mutagen methyl methanesulfonate (Mezzoug et al., 2007).

It is now accepted that prooxidant activities can induce late apoptosis and necrosis (Schwartz, 1996; Sakagami et al., 1999; Hadi et al., 2000). Prooxidant activities may damage cellular membranes, in particular those of mitochondria, and thus promote the release of  $Ca^{++}$ , cytochrome C and ROS. This leads to cell death, at least in mammalian cells, whereas yeast cells are able to survive in spite of mitochondrial damage (Bakkali et al., 2005, 2006; Averbeck et al., 1990).

It has been recently demonstrated in the yeast *Saccharomyces cerevisiae* that induction of mitochondrial damage transforming Rho<sup>+</sup> cells into rho<sup>0</sup> cells and the induction of apoptosis/necrosis by a combined exposure to essential oils and nuclear mutagens caused a striking reduction of the frequency of nuclear genetic events. Typical mutagenic agents were used such as ultraviolet C (UVC) radiation which forms pyrimidine dimers and 6-4 photoproducts, 8-methoxypsoralen (8-MOP) activated by ultraviolet A (UVA) radiation which forms DNA mono- and biadducts, or methyl methanesulfonate (MMS) which methylates DNA bases. The reduction in mutant frequency in the presence of essential oils was accompanied by a strong synergistic induction of cytoplasmic “petite” mutants (Bakkali et al., 2006).

The anti-mutagenic effect was independent of the type of mutations, i.e. reversion, intra- or intergenic recombination. The extent of this anti-mutagenic effect depended on the mutagen and oil concentrations. However, unexpectedly, the mechanism of the decrease of mutagenicity did not depend on the type of essential oil but on the type of mutagen, thus on the type of lesions and consequently on the DNA repair or lesion avoidance system involved.

In fact, after combined treatment by UVC or 8-MOP/UVA plus essential oils, the transformation of Rho<sup>+</sup> cells into rho<sup>0</sup> cells resulted in a decrease of the frequency of mutants accompanied by a slight resistance of the survival (Brun et al., 2003; Bakkali et al., 2006). After UVC or 8-MOP/UVA alone, less mutants were also found in a rho<sup>0</sup> mutant, i.e. a complete BET-induced rho<sup>0</sup> selected by the alkaloid lycorine, than in the wild type Rho<sup>+</sup>. In that case, the reduction in mutation frequency was the same as that after the combined treatments confirming the importance of mitochondrial dysfunction for these effects (Bakkali et al., 2006).

The same decrease of mutant frequencies was also found in a nucleotide excision repair (NER) defective rad3 mutant after UVC/essential oil combined treatment. Thus, the error-free NER repair system does not play any role in this decrease and probably not the error-free homologous recombination in the case of 8-MOP/UVA. It seems that translational synthesis involving an error-free polymerase is favoured by the energy deficit in rho<sup>0</sup> cells rather than true DNA repair that would much more lead to higher cell survival and rely on repair enzymes highly dependent on ATP and energy supply.

Concerning the combined treatment MMS/essential oils, there was a slight decrease of the mutant frequencies but a strong additional decrease of the survival by the essential oils. However, as a function of survival, this additional cytotoxicity caused a notable reduction of the mutant frequencies for a same survival level. The decrease of cell survival was also accompanied by a synergistic increase of cytoplasmic petite mutants. Thus, in this case, the essential oils contributed to the elimination of the cells already affected by MMS, leading potential mutants to death by late apoptosis and necrosis (Bakkali et al., 2006).

The reduction by essential oils of the frequency of mutations induced by the mutagens was always accompanied by a synergistic induction of complete petite mutants. Moreover, essential oils alone or in combined treatments mainly induced necrosis rather than apoptosis. This corroborates with the fact that petite mutants were true rho<sup>0</sup> mutants unable to perform apoptosis but only able to passively undergo necrosis, since functional mitochondria are necessary to induce apoptosis (Van Houten et al., 2006).

#### **4. Underlying mechanisms: mitochondrial damage and prooxidant cytotoxic effects**

Several studies have demonstrated that complex natural nutrients like vegetables, fruits, herbs and spices contain

numerous antioxidant molecules such as carotenoids, retinoids, tocopherols, ascorbic acid, phenolic acids, flavonoids and polyphenols (Chu et al., 2000; Vinson et al., 2001; Luximon-Ramma et al., 2002; Cheung et al., 2003; Wu et al., 2004; Shyamala et al., 2005; Grassmann, 2005; Soobrattee et al., 2005; Saura-Calixto and Goni, 2006). Essential oils also include antioxidants such as terpenoid and phenolic components. The antioxidant property of essential oils and components has been very often verified *in vitro* by physical-chemical methods (Ruberto and Baratta, 2000; Pizzale et al., 2002; Candan et al., 2003; Alma et al., 2003; Kulisic et al., 2004; Tepe et al., 2004a; Mimica-Dukic et al., 2004; Sacchetti et al., 2005; Tuberoso et al., 2005; Singh et al., 2006; Basile et al., 2006; Trevisan et al., 2006; Bozin et al., 2006). In particular, the antioxidant capacity of some phenolic compounds has been invoked to promote their use as natural food additives (Aeschbach et al., 1994).

For example, some essential oils showing different levels of cytotoxicity exhibited different antioxidative capacities depending on the composition of the oil and especially on their phenolic content (Bakkali, data not shown). This raised the obvious question how such antioxidants, although non-mutagenic, could be cytotoxic.

In eukaryotes, mitochondria produce superoxide anions and hydrogen peroxide which react with their iron content to generate reactive intermediates like hydroxyl radical which is highly damaging to mitochondrial DNA. Damaged mitochondrial DNA inhibits the expression of electron transport proteins leading to the accumulation of ROS (Van Houten et al., 2006). In line with this, the following reaction mechanism for essential oils can be envisaged: essential oils by penetrating through the cell wall and cytoplasmic membrane disrupt and permeabilize them and especially damage mitochondrial membranes. The mitochondria, by changes in electron flow through the electron transport chain, produce free radicals which oxidize and damage lipids, proteins and DNA. Moreover, some phenolic components of essential oils are oxidized by contact with ROS producing very reactive phenoxyl radicals which add to the ROS released by mitochondria. These types of radical reactions are dependent on and enhanced by the presence of cell transition metal ions such as  $\text{Fe}^{++}$ ,  $\text{Cu}^{++}$ ,  $\text{Zn}^{++}$ ,  $\text{Mg}^{++}$  or  $\text{Mn}^{++}$  (Stadler et al., 1995; Cao et al., 1997; Sakihama et al., 2002; Jimenez Del Rio and Velez-Pardo, 2004; Azmi et al., 2006).

These reactions were demonstrated in the yeast *Saccharomyces cerevisiae* by employing antioxidants like glutathione and catalase, and the iron chelator deferoxamine (inhibiting the Fenton reaction) which lowered the cytotoxicity of tested essential oils depending on the two types of agents and the oil (Bakkali et al., 2005). Protective effects by antioxidants like *N*-acetyl-cysteine, glutathione or Trolox were also observed on eugenol- or essential oil-induced DNA fragmentation, cytotoxicity or apoptosis (Fujisawa et al., 2002; Yoo et al., 2005; Paik et al., 2005; Wu et al., 2006).

The origin and site of prooxidation phenomena in cells seem controversial. In the work of Galati et al. (2002) on prooxidant activity of phenoxyl radicals of polyphenolics, phenol ring-containing phenolic compound oxidation appears to take place in the cytosol by contact with peroxidase/ $\text{H}_2\text{O}_2$  to form phenoxyl radical which may cooxidize glutathione (GSH) forming thiol radical; the latter react with GSH giving rise to disulfide radical anion which reduces  $\text{O}_2$  to form superoxide anion  $\text{RSO}^\circ$  or  $\text{RSOO}^\circ$  and GSSG. In the work of Sakihama et al. (2002) on plant phenolic prooxidant activity mediated by metals, in the presence of  $\text{O}_2$ , transition  $\text{Cu}^{++}$  and  $\text{Fe}^{++}$  metal ions catalyze the oxidation of phenol ring forming phenoxyl radical leading to the formation of ROS and hydroxyl radical. However, according to Galati and O'Brien (2004), this metal ion-mediated redox cycling concerns the catechol ring which is initially oxidized by  $\text{Cu}^{++}$  and generates a semiquinone radical that reacts with  $\text{O}_2$  to form superoxide anion; the latter oxidizes catechol and forms again a semiquinone radical plus  $\text{H}_2\text{O}_2$  which is converted by  $\text{Cu}^{++}$  into hydroxyl radical in a Fenton-like reaction. Anyhow, for both authors, phenoxyl, thiyl and hydroxyl radicals and ROS then damage mitochondria involving collapse of the membrane potential (Galati and O'Brien, 2004). This scheme seems to be supported also by Fujisawa et al. (2002) and Yoo et al. (2005).

On the contrary, according to Yoon et al. (2000), Morin et al. (2001), Burt (2004) and Van Houten et al. (2006), it can be inferred that lipophilic phenolic compounds themselves permeabilize the mitochondrial membranes where transition metal ions  $\text{Fe}^{++}$  and  $\text{Cu}^{++}$  are sequestered in the intermembrane space (Yang et al., 2005; Mehta et al., 2006), and provoke a leakage of these ions and ROS from mitochondria which also contain GSH (Hansen et al., 2006). This context suggests that phenolic compounds are oxidized during permeabilization and leakage giving rise to phenoxyl (or semiquinone) radicals which continue prooxidant chain reactions as above and with proteins and DNA, and generate new ROS. In other words, mitochondrial membranes are first damaged by permeabilization resulting in a prooxidant status thereafter. This is supported by the results obtained on the induction of petite mutants in yeast after treatment by GSH and catalase antioxidants and the iron chelating agent deferoxamine and essential oils. The frequency of petite mutants did not decrease (data not shown) with increasing survival in the presence of these agents (Bakkali et al., 2005). This is in line with the fact that prooxidant reactions are initiated at the mitochondrial level and antioxidants or the Fenton reaction inhibitor protect the cells against oxygen radical mediated reactions from permeabilized mitochondria thus increasing survival. In case of prooxidant reactions occurring in the cytosol, antioxidants would also have protected the mitochondria leading to decreased frequency of petite mutants associated with increased survival.

Moreover, the fact that in yeast (*Saccharomyces cerevisiae*) induction of repair DNA genes by essential oils (Bakkali et al., 2005) was relatively weak but significant in comparison to the rather strong induction observed by true nuclear mutagens like ultraviolet C or 8-methoxypsoralen plus ultraviolet A (Averbeck and Averbeck, 1994, 1998) or methyl methanesulfonate (Bakkali et al., 2005), which induce intrastrand, interstrand crosslinks and double strand breaks or base methylations, respectively, and that the essential oils were not mutagenic clearly shows that the nuclear DNA lesions induced arose through reactive species such as phenoxyl, thiyl, hydroxyl, peroxy and superoxide radicals which rather induce base modifications and single strand breaks which are repairable without giving rise to significant nuclear mutagenic effects. Furthermore, the tested essential oils induced cytoplasmic petite mutants which indicates dysfunction or absence of mitochondria (Bakkali et al., 2005).

Several studies have shown antioxidant properties *in vitro* of many natural products including essential oils. From this, it was inferred that they could be beneficial for human health in line with recent findings and common belief that many diseases are due to an overload of oxidative stress reactions following excessive consumption of fat, sugar, meat, etc. Antioxidants are believed to be directly antimutagenic (Clark, 2002) and anticarcinogenic due to their radical scavenging properties (Ames et al., 1993; Birt et al., 2001; Surh, 2002; Ferguson et al., 2004; Collins, 2005).

However, some compounds of natural products like vitamins A, C, E, flavonoids, polyphenolics or especially phenolic components which show antioxidant capacities *in silico*, can be, after penetrating cells, oxidized by ROS and thus generate additional radical species like phenoxyl, hydroxyl and superoxide radicals and hydrogen peroxide (Schwartz et al., 1993; Albanes et al., 1995; Schwartz, 1996; Sakagami and Satoh, 1997; Bijur et al., 1997; Young and Lowe, 2001; Lowe et al., 2003). Indeed, antioxidants by interacting with ROS are converted into prooxidants which are able to oxidize lipids, proteins and DNA (Metodiewa et al., 1999; Cowan, 1999; Galati et al., 2002; Galati and O'Brien, 2004; Fujisawa et al., 2002; Sakihama et al., 2002; Nemeikaite-Ceniene et al., 2005; Barbehenn et al., 2005; Atsumi et al., 2005). Apparently, the intracellular defenses based on glutathione peroxidase, glutathione reductase, catalase, superoxide dismutase, are insufficient to inhibit these prooxidant reactions, and the natural antioxidant cellular defenses can be overwhelmed. Volatil terpenic and phenolic components of essential oils can function as prooxidants by affecting the cellular redox status. This may lead to late apoptosis and/or necrosis including damage to proteins and DNA and overall cytotoxic effects (Bakkali et al., 2006).

Nevertheless, prooxidant effects may depend on the concentration of natural extracellular antioxidant compounds, such as gallic acid from tannin or some ascorbic

acid derivatives, which penetrated the cells (Sakagami et al., 1999). In fact, assuming that the major source of oxidation is of mitochondrial origin, if the antioxidant concentration is too weak to permeabilize mitochondrial membranes, conversion into prooxidant may not occur, and the antioxidant would keep its activity and act as such. This could explain the results reported by Aydin et al. (2005), who noticed that non-cytotoxic low concentrations of thymol, carvacrol and  $\gamma$ -terpinene protected against DNA strand breakage induced by semiquinone and oxygen radicals formed by 2-amino-3-methylimidazo(4,5-f)-quinoline (IQ) and mitomycin C (MMC) in lymphocytes, whereas high concentrations increased DNA damage. Fan and Lou (2004) found that some polyphenols were good antioxidants at low concentration but, at higher concentration, they induced cellular DNA damage. Also, at low concentrations, retinol and tocopherol showed antioxidant and antimutagenic activities, whereas, at high concentration, they became themselves genotoxic (Bronzetti et al., 2001). Palozza et al. (2004) observed also inhibition or enhancement of apoptosis depending on carotenoid concentration. Ramassamy (2006) reported greater neuroprotective effects by green tea, curcumin and ginkgo biloba extracts at small doses than at high doses. Vitamin E has prooxidant effects at high concentrations (Foti and Ingold, 2003). In such cases, low concentrations could not damage mitochondria, the antioxidant was not oxidized and could scavenge radicals. In contrast, high concentration could damage and permeabilize mitochondria, the antioxidant was oxidized and could react as prooxidant damaging DNA and proteins. It seems that the switch from anti- to prooxidant reactions occurs at low antioxidant concentrations in a very narrow range (Bolton, 2002). This concentration-dependent effect is in favour of the notion that mitochondrial membranes may be the target and their permeabilization the primary event to convert antioxidants into prooxidants.

In contrast to the established notion that the antioxidant properties of natural compounds such as fruit and vegetable polyphenols or herb and essential oil phenols and terpenes determine their protective effect against mutagens (Diplock et al., 1998; Weisburger, 1999; Chu et al., 2000; Clark, 2002; Wu et al., 2004; Collins, 2005; Skerget et al., 2005; Grassmann, 2005; Romero-Jimenez et al., 2005; Saura-Calixto and Goni, 2006), it has become clear that also the prooxidant properties of these compounds can play a significant "protective" role by removing damaged cells by apoptosis (Sakagami et al., 1999; Hadi et al., 2000; Liu et al., 2001; Sun et al., 2005a; Vukovic-Gacic et al., 2006; Bakkali et al., 2006). An interesting new aspect of antioxidants would be their possible prooxidant activity in cells (Martin, 2006). In the latter case, protection is quite indirect since it involves mitochondrial damage which either reduces by lack of energy the cell capacity to perform an error-prone repair and to mutate (Bakkali et al., 2006), or produces apoptosis and necrosis, thus eliminating potential mutants.

In cells, the redox balance is very sensitive. Probably, compounds showing antioxidant activity can reduce the main load of oxidative stress but when there is an imbalance between oxidizing and reducing equivalents where the former predominates (Sies and Cadenas, 1985), for example when the antioxidant is oxidized and thus converted into a prooxidant, the antioxidant cellular defenses cannot fully keep up with the oxidative stress and important cellular constituents are damaged. From results of the literature on polyphenolic and phenolic compounds, it can be inferred that essential oils can act mainly as prooxidants by intermediate of their volatile constituents like phenolic constituents, terpenes or terpenoids, which turn themselves into prooxidants (Sakagami et al., 1999; Sakihama et al., 2002; Fujisawa et al., 2002; Barbehenn et al., 2005; Bakkali et al., 2006).

Thus, the fact that, *in silico*, some compounds behave like antioxidants does not at all predict their biological effects in living cells. For example, *Origanum compactum* essential oil was characterized by a high antioxidant activity *in silico* and a prooxidant activity *in vitro* due to the presence of phenolic components which confer high cytotoxicity to whole cells and damage to mitochondria associated with antimutagenic activity. On the contrary, *Helichrysum italicum* essential oil, which possessed a good antioxidant activity *in silico*, did not show any cytotoxic effects, induced no cytoplasmic petite mutants and was not antimutagenic, probably because it did not affect mitochondria and thus exhibited no prooxidant activity. *Artemisia herba-alba* and *Cinnamomum camphora* essential oils showed a very weak antioxidant activity *in silico*, however, they were cytotoxic, they induced many cytoplasmic petite mutants and showed a high antimutagenic effect probably due to prooxidant activity (Bakkali, unpublished data; Bakkali et al., 2005, 2006).

## 5. Specificity of essential oils

The question of specificity of the different essential oils also arises. Very few studies have analyzed enough essential oils and biological endpoints to determine whether there is a specificity for different effects according to different oils or not. Clearly, it has been shown by Bakkali et al. (2005, 2006) that the tested essential oils presented a specificity in the amplitude, but not in the mode of action, of the biological effects, i.e. cytotoxicity, cytoplasmic mutant induction, gene induction and antigenotoxic effects. However, they did exhibit a specificity of the mode of action concerning production of ROS, probably due to differences in their actual composition corresponding to differences in compartmentation of the oxidative stress (Hansen et al., 2006). Concerning antigenotoxicity, the tested essential oils showed the same protective activity. However, the mode of protection differed, not according to the type of oil, but according to the mutagens, i.e. to the type of lesions induced and thus, to the type of their

enzymatic recognition and processing leading to translational synthesis or late apoptosis/necrosis (Bakkali et al., 2005, 2006).

## 6. Synergism between the components of essential oils

Regarding their biological properties, it has to be kept in mind that essential oils are complex mixtures of numerous molecules, and one might wonder if their biological effects are the result of a synergism of all molecules or reflect only those of the main molecules present at the highest levels according to gas chromatographical analysis. In the literature in most cases, only the main constituents of certain essential oils like terpineol, eugenol, thymol, carvacrol, carvone, geraniol, linalool, citronellol, nerol, safrole, eucalyptol, limonene, cinnamaldehyde, were analyzed. Generally, the major components are found to reflect quite well the biophysical and biological features of the essential oils from which they were isolated (Ipek et al., 2005), the amplitude of their effects being just dependent on their concentration when they were tested alone or comprised in essential oils. Thus, synergistic functions of the various molecules contained in an essential oil, in comparison to the action of one or two main components of the oil, seems questionable. However, it is possible that the activity of the main components is modulated by other minor molecules (Franzios et al., 1997; Santanarrios et al., 2001; Hoet et al., 2006). Moreover, it is likely that several components of the essential oils play a role in defining the fragrance, the density, the texture, the colour and above all, cell penetration (Cal, 2006), lipophilic or hydrophilic attraction and fixation on cell walls and membranes, and cellular distribution. This last feature is very important because the distribution of the oil in the cell determines the different types of radical reactions produced, depending on their compartmentation in the cell. In that sense, for biological purposes, it is more informative to study an entire oil rather than some of its components because the concept of synergism appears to be more meaningful.

## 7. Medicinal and future medical applications

The cytotoxic capacity of the essential oils based on a prooxidant activity can make them excellent antiseptic and antimicrobial agents for personal use, i.e. for purifying air, personal hygiene, or even internal use via oral consumption, and for insecticidal use for the preservation of crops or food stocks.

A big advantage of essential oils is the fact that they are usually devoid of long-term genotoxic risks. Moreover, some of them show a very clear antimutagenic capacity which could well be linked to an anticarcinogenic activity. Recent studies have demonstrated that the prooxidant activity of essential oils or some of their constituents, as also that of some polyphenols, is very efficient in reducing local tumor volume or tumor cell proliferation by apoptotic

and/or necrotic effects (Schwartz, 1996; Zheng et al., 1997; Ohizumi et al., 1997; Crowell, 1999; Buhagiar et al., 1999; Legault et al., 2003; Hata et al., 2003; Salim and Fukushima, 2003; Mazières et al., 2003, 2004; Carvalho de Sousa et al., 2004; Carnesecchi et al., 2004; Chen et al., 2004; Shen et al., 2004; Kloog and Cox, 2004; Paik et al., 2005; Yoo et al., 2005; Dudai et al., 2005; Tsuneki et al., 2005; Manosroi et al., 2006; Sylvestre et al., 2005, 2006; Wu et al., 2006; Kachadourian and Day, 2006). Sylvestre et al. (2005, 2006) have shown that *Myrica gale* essential oil has an anticancerogenic activity on the lung and colon cancer cell lines. Salim and Fukushima (2003) have shown an antiproliferative activity and inhibition of 1,2-dimethylhydrazine-induced cancer in the rat by *Nigella sativa*. Manosroi et al. (2006) have shown an inhibition of the proliferation of murine leukemia and human mouth epidermal carcinoma cell lines by *Ocimum sanctum*, *Citrus citratus*, *Alpinia officinarum*, *Lavandula angustifolia*, *Vetiveria zizanioides*, *Zingiber montanum*, *Piper nigrum*, *Cymbopogon nardus*, *Curcuma longa*, *Ocimum basilicum*, *Citrus hystrix*, *Piper betle*, *Albizia lebeck*, *Ocimum americanum*, *Mentha spicata* and *Psidium guajava* essential oils. Yoo et al. (2005) demonstrated that eugenol from *Eugenia caryophyllata* (= *Syzygium aromaticum*) inhibits the proliferation of cancerous cells. Geraniol inhibits also colon cancer cell proliferation by inducing membrane depolarisation and interfering with ionic canals and signalling pathways. Carnesecchi et al. (2004) have also demonstrated that geraniol inhibits DNA synthesis and reduces the volume of colon tumours. Mazières et al. (2003, 2004) and Kloog and Cox (2004) showed that farnesyle and geranyl-geranyl inhibit the post-translational modification necessary to the transformant capacity of the gene *ras* and thus prevent the tumour formation. Tsuneki et al. (2005) showed inhibition of angiogenesis by  $\beta$ -eudesmol from *Atractylodes lancea*. Many tumor cells are characterized by severe changes in energy metabolism, mitochondrial overproduction and permanent oxidative stress (Czarnecka et al., 2006). Essential oils, due to their capacity to interfere with mitochondrial functions, may add prooxidant effects and thus become genuine antitumor agents. Many radical producing agents are in fact used in antitumor treatments. In the case of essential oils, radical production could be very well controlled and targeted without presenting by itself any toxic or mutagenic side-effects to healthy tissues. Essential oils or their active constituents could be included in vectorized liposomes (Sinico et al., 2005; Lai et al., 2006; Fang et al., 2006) that would allow to better define the quantities applied. Thus, essential oils could make their way from the traditional into the modern medical domain.

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