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REVIEW ARTICLE

Pharmaceutical and Therapeutic Potentials of Essential Oils and Their Individual Volatile Constituents: A Review

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Essential oils and their volatile constituents are used widely to prevent and treat human disease. The possible role and mode of action of these natural products is discussed with regard to the prevention and treatment of cancer, cardiovascular diseases including atherosclerosis and thrombosis, as well as their bioactivity as antibacterial, antiviral, antioxidants and antidiabetic agents. Their application as natural skin penetration enhancers for transdermal drug delivery and the therapeutic properties of essential oils in aroma and massage therapy will also be outlined. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: essential oils; cancer; cardiovascular disease; antimicrobial; antidiabetic; penetration enhancer; aromatherapy; massage therapy.

INTRODUCTION

Aromatic plants had been used since ancient times for their preservative and medicinal properties, and to impart aroma and flavor to food. Hippocrates, sometimes referred to as the 'father of medicine', prescribed perfume fumigations.

The pharmaceutical properties of aromatic plants are partially attributed to essential oils. The term 'essential oil' was used for the first time in the 16th century by Paracelsus von Hohenheim, who named the effective component of a drug, 'Quinta essential' (Guenther, 1950). By the middle of the 20th century, the role of essential oils had been reduced almost entirely to use in perfumes, cosmetics and food flavorings, while their use in pharmaceutical preparations had declined.

Essential oils are natural, complex, multi-component systems composed mainly of terpenes in addition to some other non-terpene components. Several techniques can be used to extract essential oils from different parts of the aromatic plant, including water or steam distillation, solvent extraction, expression under pressure, supercritical fluid and subcritical water extractions.

ESSENTIAL OILS AND CANCER

Most cancer chemotherapy regimens make use of highly cytotoxic drugs that target proliferating cell populations. The non-discriminatory nature of these drugs leads to severe side effects in normal cells with a high proliferative index, such as those of the gastrointestinal tract and bone marrow, thus limiting the effective dose of anticancer drug that can be administered. The diverse therapeutic potential of essential oils has drawn the attention of researchers to test them for anticancer activity, taking advantage of the fact that their mechanism of action is dissimilar to that of the classic cytotoxic chemotherapeutic agents (Rajesh *et al.*, 2003). Early reports had indicated that essential oil components, especially monoterpenes, have multiple pharmacological effects on mevalonate metabolism which could account for the terpene-tumor suppressive activity (Elson, 1995).

Monoterpenes have been shown to exert chemopreventive as well as chemotherapeutic activities in mammary tumor models and thus may represent a new class of therapeutic agents. The mechanism of action of monoterpenes is based on two main approaches, chemoprevention and chemotherapy. Chemoprevention occurs during the initiation phase of carcinogenesis to prevent the interaction of chemical carcinogens with DNA, by induction of phase I and phase II enzymes to detoxify the carcinogen (Wattenberg, 1992). Chemotherapy works during the promotion phase, in which inhibition of tumor cell proliferation, acceleration of the rate of tumor cell death and/or induction of tumor cell differentiation may occur (Morse and Stoner, 1993).

Chemoprevention

It is generally accepted that components that induce Phase I or II drug metabolizing enzymes can protect against chemical carcinogenesis or damage, especially during the initiation phase. Essential oils could be utilized to protect body organs against carcinogenesis; for instance, nutmeg, (*Myristica fragrans*), showed a potent hepatoprotective activity against liver damage

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caused by certain chemicals (Morita *et al.*, 2003). The protective activity was correlated with myristicin, a major constituent. The mechanism of hepatoprotective activity of myristicin includes inhibition of TNF-α release from macrophages and suppression of apoptosis. Myristicin can also induce glutathione-S-transferase, a phase II detoxifying enzyme (Ahmad *et al.*, 1997), in addition to its activity of inhibiting benzo[a]pyrene-induced tumorigenesis in mouse tissues (Zheng *et al.*, 1992). Recently it was found that myristicin induces cytotoxicity in human neuroblastoma SK-N-SH cells by an apoptotic mechanism (Lee *et al.*, 2005).

Citral, which is found in many essential oils and comprises 70%–85% of lemongrass oil, is a novel monoterpene inducer of glutathione-S-transferase class π, ($GSTP_1$). This isozyme is responsible for the increase in the total GST activity of the citral-treated rat hepatocyte cells (Nakamura *et al.*, 2003). Structure–activity relationship studies revealed that *trans*-citral (geranial) was the main contributor for the induction of $GSTP_1$. The aldehyde group conjugated with a *trans*-double bond in *trans*-citral is an essential structural factor for GST induction. On the other hand *cis*-citral (neral) showed no activity. This suggested the exploration of citral as a cancer chemopreventive agent targeted towards inflammation-related carcinogenesis such as skin cancer (Henderson *et al.*, 1998) and colon cancer (Mulder *et al.*, 1995), both of which were found to be due to lack of $GSTP_1$ activity. The high content of citral in lemongrass oil may explain the inhibitory effect of that aromatic plant on the early phase of hepatocarcinogenesis in rats (Puatanachokchai *et al.*, 2002). Citral also increased the hepatic glutathione-S-transferase (GST) and aminopyrine demethylase activities, and reduced glucuronyl transferase activity (Vinitketkumnuen and Lertprasertsuk, 1997).

Although citral is generally recognized as safe for human consumption as a food additive by the FDA (GRAS), it is classified as a potential teratogen and primary irritant (Abramovici and Rachmuth-Roizman, 1983). The National Toxicology Program (2003) concluded that under the conditions of two-year feeding studies there was no evidence of carcinogenic activity of citral in male or female F344/N rats exposed to 1000, 2000 or 4000 ppm. There was no evidence of carcinogenic activity of citral in male B6C3F1 mice exposed to 500, 1000 or 2000 ppm. There was, however, equivocal evidence of carcinogenic activity in female B6C3F1 mice based on the increased incidence of malignant lymphoma, thus the acceptable daily intake (ADI) of citral has been proposed as 0–0.5 mg/kg/day (FAO/WHO 2003).

Other essential oils elicit hepatoprotective activity due to their phenolic and/or monoterpene content: for example, black cumin (*Nigella sativa*), due to thymoquinone (Mansour *et al.*, 2001); orange essential oil, due to *d*-limonene (Bodake *et al.*, 2002); and sweet fennel (*Foeniculum vulgare*) due to both *d*-limonene and β-myrcene (Ozbek *et al.*, 2003). In addition, *d*-limonene exhibits chemopreventive efficacy in preclinical hepatocellular carcinoma models (Parija and Das, 2003; Guyton and Kensler, 2002; Jiri *et al.*, 1999). The mode of action originates, in part, from the induction of the specific cytochrome P450 isozymes including CYP 2B1 and CYP2C (Maltzman *et al.*, 1991). *d*-Limonene is also a candidate for the chemoprevention of skin cancer (Stratton *et al.*, 2000), although it can cause contact dermatitis, especially when oxidized.

Garlic essential oil is a rich source of volatile organosulfur components (OSCs). These compounds are recognized as a group of potential cancer chemopreventive agents due to their activity for modulating phase I and II drug detoxifying enzymes (Milner, 2001). The three major OSCs of garlic essential oil, diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DATS), were found differentially to mediate the transcriptional levels of phase II detoxifying enzymes, NQO1 and HO1, in human hepatoma (HepG2) cells (Chen *et al.*, 2004). DATS, with three sulfur atoms, was found to be the most potent inducer of phase II enzyme gene expression, ARE activation and Nrf2 protein accumulation. The effects of oral administration of garlic essential oil and its three major OSCs on different phase I and phase II hepatic detoxification enzymes in rat showed that the essential oil and DAS significantly increased the activity of the phase I enzyme (PROD) (Wu *et al.*, 2002). DADS and DATS significantly decreased the activity of phase I enzyme (NDMAD). Garlic essential oil, DADS, and DATS significantly increased the activity of glutathione S-transferase, a phase II detoxifying enzyme. The placental form of GST ($GST\pi$) level was also increased by garlic oil and its three major components. $GST\pi$ is one of the GST isozymes which are of special interest due to their relationship with the development of human ovarian cancer (Hamada *et al.*, 1994) and colorectal cancer (Mulder *et al.*, 1995). The highest concentrations of DAS, DADS and DATS, which are decomposition products of allicin, are found in garlic essential oil extracted from crushed cloves using steam or water distillation (Ibrel *et al.*, 1990).

Cancer suppression

Essential oils and their individual aroma components showed cancer suppressive activity when tested on a number of human cancer cell lines including glioma, colon cancer, gastric cancer, human liver tumor, pulmonary tumors, breast cancer, leukemia and others. Glioma is one of the most malignant human tumors (De Angelis, 2001).

α–Bisabolol, a major sesquiterpene alcohol in Chamomile, (*Matricaria chamomilla*) essential oil, could be considered as a promising inducer of apoptosis in highly malignant glioma cells. It is neither toxic in animals nor does it reduce the viability of normal astroglial cells (Cavalieri *et al.*, 2004). A significant effect on the treatment of glioma was reported using the sesquiterpene hydrocarbon elemene which is found in small amounts in many essential oils: it prolonged quality survival time of patients with glioma (Tan *et al.*, 2000).

Geraniol, a monoterpene alcohol, elicited a dramatic reduction in the amounts of thymidylate synthase (TS) and thymidine kinase (TK) expression in colon cancer cells (Carnesecchia *et al.*, 2004). These two enzymes are involved in 5-fluorouracil (5-FU) toxicity, in that a decrease in these enzymes is related to enhanced 5-FU cytotoxicity (Mans *et al.*, 1999). Geraniol lowered the resistance of cancer cells to 5-FU thus potentiating the inhibition of tumor growth by the drug, and increasing the survival time of nude mice grafted with the human colorectal tumor cells TC118. Geraniol acts on at least

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two different targets involved in the resistance of cancer cells to 5-FU: it increases cell membrane permeability leading to enhanced uptake of 5-FU by colon cancer cells and causes a significant change in the resting potential and cell membrane polarization, which may trigger modifications of membrane bound protein activity and alterations in intracellular signaling pathways (Carnesecchi *et al.*, 2002a, 2002b). A major natural source of geraniol is Palmarosa oil (*Cymbopogon martini* var *martini*), also known as East Indian geranium, containing 59%–84% which is much greater than most species of *Geranium* or *Pelargonium* (Sirinivas, 1986).

d-Limonene showed antiangiogenic and proapoptotic effects on human gastric cancer implanted in nude mice, thus inhibiting tumor growth and metastasis (Guang *et al.*, 2004). *d*-Limonene can also induce the formation of apoptotic bodies on BGC-823 gastric cancer cells in a dose- and time-dependent manner (Guang *et al.*, 2003) and its efficacy was increased by combining it with cytotoxic agents such as 5-fluorouracil. Administration of chow pellets containing 1% or 2% *d*-limonene to male Sprague-Dawley rats resulted in significant reductions in chemically induced, hepatocellular carcinomas (Kaji *et al.*, 2001). This effect could be related to its effect in inhibiting cell proliferation and in enhancing apoptosis. *d*-Limonene also increased the survival of lymphoma-bearing mice and modulated the immune response, showing significant potential for clinical application (Del Toro-Arreola *et al.*, 2005). A mechanism that may contribute to *d*-limonene efficacy in the chemoprevention and/or therapy of chemically induced human solid tumor cells has been proposed (Chen *et al.*, 1999; Jiri *et al.*, 1999; Parija and Das, 2003). Briefly, *d*-limonene can, in part, inhibit FPTase activity, inhibit the plasma-membrane associated P21ras expression, and the post-translational isoprenylation of P21ras. *d*-Limonene is found naturally in many essential oils, especially citrus fruit peel where it constitutes 90%–95% of the total oil. It is also found in considerable amounts (26%–34%) in some spearmint essential oils (Edris *et al.*, 2003). The annual production of *d*-limonene was estimated to be 50 000 tonnes (Braddock and Cadwallader, 1995) which makes its price as low as $1–2/kg (Mazzaro, 2000).

Diallyl trisulfide (DATS), a major constituent of garlic essential oil, showed a high activity for arresting the division of human liver tumor cells (J5) at the G2/M phase of the cell cycle (Wu *et al.*, 2004). The mechanism of action probably involves regulating the protein expressions of cyclin B1 and Cdk7. The chemotherapeutic and chemopreventive activity of garlic essential oil and its various organo-sulfur constituents against different types of carcinogenesis have been reviewed elsewhere (Thomson and Ali, 2003; Benjamin *et al.*, 1990).

It is accepted that aberrant angiogenesis is essential for the progression of solid tumors and hematological malignancies. Thus, antiangiogenic therapy is one of the most promising approaches to control cancer. Perillyl alcohol (POH) which is the hydroxylated analogue of *d*-limonene, has the ability to interfere with angiogenesis (Loutrari *et al.*, 2004). POH either alone or with PA (perillic acid, the major metabolite of POH in the body), has a potential use as an anticancer drug that stimulates different types of tumors to apoptosis, inhibits their proliferation, or overcomes their resistance to chemo-/radiotherapy (Yuri *et al.*, 2004; Samaila *et al.*, 2004; Elegbede *et al.*, 2003; Clark *et al.*, 2003; Rajesh *et al.*, 2003; Rajesh and Howard 2003; Ahn *et al.*, 2003; Bardon *et al.*, 2002; Burke *et al.*, 2002; Bardon *et al.*, 1998). The antitumor activity of POH emanates from its activity of modulating cellular processes that control cell growth and differentiation (Azzoli *et al.*, 2003; Clark *et al.*, 2002; Ariazi *et al.*, 1999; Ren and Gould, 1998; Gould, 1997 and Gould, 1995). Thus POH, among other micronutrients, was investigated by the National Cancer Institute (NCI) in NCI-sponsored phase I, II, or III chemoprevention trials for prostate, breast and colon cancers (Greenwald *et al.*, 2002). However, it may not be an effective chemopreventive agent for esophageal cancer in humans (Liston *et al.*, 2003). Unfortunately, despite evidence of anticancer activity of POH *in vitro*, oral administration has not yet shown any clinical antitumor activity (Bailey *et al.*, 2004; Azzoli *et al.*, 2003; Liu *et al.*, 2003; Meadows *et al.*, 2002; Howard *et al.*, 2002). POH is found in small amounts in many aromatic plants including lavender, peppermint, spearmint, perilla and lemongrass (Kelloff *et al.*, 1996). *Conyza newii* oil, (Compositae), contains 4.2% of perillyl alcohol (Omolo *et al.*, 2004) while *Tetradenia riparia* oil, (Labiateae) contains 6.0% POH (Campbell *et al.*, 1997). POH can also be produced from *d*-limonene by microbial biotransformation pathways (Duetz *et al.*, 2003).

Eucalyptol (1,8-cineol) is found in high concentrations (60%–90%) in the essential oil of eucalyptus (*Eucalyptus globulus*) (Juergens *et al.*, 1998) and 59% in cardamom (*Elettaria cardamomum*, Zingbraceae) (Huang *et al.*, 1999). Treatment of human leukemia HL-60 cells with eucalyptol showed morphological changes, (fragmentations of DNA) indicating an induction of apoptosis (Moteki *et al.*, 2002). However, this effect was not shown in human stomach cancer KATO III cells that received the same treatment with eucalyptol.

In addition to the individual terpene components mentioned above, several whole essential oils have also shown anticancer activity *in vitro*. The essential oil of lemon balm (*Melissa officinalis* L) was found to be effective against a series of human cancer cell lines (A549, MCF-7, Caco-2, HL-60, K562) and a mouse cell line (B16F10) (De Sousa *et al.*, 2004) and that of *Artemisia annua* L. induced apoptosis of cultured SMMC-7721 hepatocarcinoma cells (Li *et al.*, 2004). The essential oil of Australian tea tree (*Melaleuca alternifolia*) and its major monoterpene alcohol, terpinen-4-ol, were able to induce caspase-dependent apoptosis in human melanoma M14 WT cells and their drug-resistant counterparts, M14 adriamicin-resistant (Calcabrini *et al.*, 2004). There was evidence to suggest that the effect of the total oil and of terpinen-4-ol was mediated by their interaction with the plasma membrane and subsequent reorganization of membrane lipids.

Hepatic arterial infusion with *Curcuma* oil had a similar positive effect in treating primary liver cancer as that of the chemical drugs (Cheng *et al.*, 2001). The essential oil of *Tetraclinis articulate*, (a conifer tree) showed the hallmarks of apoptosis when tested on a number of human cancer cell lines including melanoma, breast and ovarian cancer in addition to peripheral blood lymphocytes (Buhagiar *et al.*, 1999).

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These results may draw the attention of cancer researchers to further extend their clinical testing of essential oils, and it would be interesting to investigate the antitumor activity of a major individual terpene constituent in comparison with its whole essential oil source.

ESSENTIAL OILS AND CARDIOVASCULAR DISEASES

Atherosclerosis

Atherosclerosis is a process in which deposits of plaque build up in the innermost layer of the artery, the intima (Barter, 2005). Plaque can eventually significantly reduce blood flow, leading to serious health problems. Increased concentrations of oxidatively modified low density lipoproteins (LDLs) in cholesterol play a substantial role in disease initiation (Barter, 2005; Valenzuela *et al.*, 2004; Steinberg, 1997, Daugherty and Roselaar, 1995). Atherosclerosis can therefore be slowed down or inhibited by preventing the oxidation of LDLs using a high daily intake of antioxidants.

Essential oils and their aroma volatile constituents have shown an antioxidative activity against LDL oxidation. Terpinolene, a monoterpene hydrocarbon, can effectively inhibit the oxidation of both the lipid part and the protein part of LDL. This inhibition is due to a retarded oxidation of intrinsic carotenoids of LDL, and not, as is the case with some flavonoids, to the protection of intrinsic α-tocopherol (Grassmann *et al.*, 2003, 2005). Essential oils rich in phenolic constituents such as eugenol and thymol have the highest antioxidative activity against LDL oxidation (Naderi *et al.*, 2004) and these components can also change the affinity of the LDL particles for the LDL receptor. A relationship was found between the quantity and quality of phenolic components in the oil and its protection against LDL oxidation: for instance, copper-catalysed oxidation of human LDL *in vitro* is inhibited by 50%–100% when eugenol is the major component of the essential oil (as in clove oil), while inhibition was only 10%–50% for essential oils containing moderate amounts of the phenolics, thymol, carvacrol or cuminol (Teissedre and Waterhouse, 2000). In addition to the phenolic constituents, the monoterpene hydrocarbon γ-terpinene, was also found to inhibit LDL oxidation, even in the propagation phase. γ-Terpinene generated an antioxidative effect on the Cu^{2+}-induced and AAPH-induced oxidation of human LDL *in vitro* (Takahashi *et al.*, 2003). Tea tree essential oil is considered to be a rich source of γ-terpinene (23.0%) (Brophy *et al.*, 1989) and γ-terpinene is also found in considerable amounts in some citrus peel essential oils such as bergamot (14%), mandarin (17%) and lemon (10%) (Mondello *et al.*, 1995). It has been recommended as an addition to foods and beverages to protect against LDL oxidation and to reduce plaque formation (Takahashi *et al.*, 2003).

Essential oils and some of their individual constituents can also lower total plasma cholesterol and triglyceride levels which contribute to the formation of plaque and consequently, atherosclerosis. Black cumin oil (*Nigella sativa* Linn.) was found to decrease plasma concentrations of cholesterol and triglycerides due to the high content of thymoquinone (Ali and Blunden, 2003). The essential oil of *Satureja khuzestanica*, an endemic plant of Iran, was reported to decrease the normal blood lipid peroxidation level (Abdollahi *et al.*, 2003). Oral administration of dill seed essential oil (*Anethum graveolens*) reduced triacylglyceride levels by almost 42%, although total cholesterol level was not reduced (Yazdanparast and Alavi, 2001). α-Curcumene, the major constituent (approx. 65%) of the essential oil of Javanese turmeric (*Curcuma xanthorrhiza*), exerts triglyceride-lowering activity on serum as well as liver triglycerides (Yasni *et al.*, 1994).

Garlic essential oil significantly lowered serum cholesterol and triglycerides while raising the level of high-density lipoproteins in both healthy individuals and patients with coronary heart disease (Bordia, 1981). The hypolipidemic action of garlic oil is primarily due to a decrease in hepatic cholesterogenesis (Mathew *et al.*, 1996). One of the consequences of atherosclerosis is hypertension, and some essential oils exert hypotensive activity when applied *in vivo*. Oral administration of combinations of oregano, cinnamon, cumin, and other essential oils decreased systolic blood pressure in rats (Talpur *et al.*, 2005) and intravenous administration of the essential oil from the aerial parts of *Mentha x villosa* induced a significant and dose-dependent hypotension associated with decreases in heart rate (Guedes *et al.*, 2004). This activity was attributed to the volatile component, piperitenone oxide, which represents 55.4% of the oil. The hypotensive effect induced by the oil is probably due to its direct cardiodepressant action and peripheral vasodilation, which can be attributed to both endothelium-dependent and endothelium-independent mechanisms.

Intravenous administration of the essential oil of basil (*Ocimum gratissimum*) induced an immediate and significant hypotension and bradycardia (Lahlou *et al.*, 2004). The hypotensive activity of the essential oil resulted from its vasodilator effects, acting directly upon vascular smooth muscle. This effect was attributed, at least in part, to the actions of eugenol, which is the major constituent of the oil. Clove bud essential oil is the richest source of eugenol known (about 80%; Deyama and Horiguchi, 1971) but from a safety point of view, care must be taken in dealing with eugenol due to its suspected carcinogenicity and hepatotoxicity (National Toxicology Program, 1983).

Intravenous injection of the monoterpene alcohol terpinen-4-ol decreased mean aortic blood pressure in a dose-related manner, in conscious DOCA-salt hypertensive rats (Lahlou *et al.*, 2003). The mechanism of action was related to the induction of vascular smooth muscle relaxation rather than enhanced sympathetic nervous system activity. Terpinene-4-ol is a major constituent of several essential oils, particularly tea tree (Brophy *et al.*, 1989) and sweet marjoram essential oils (Nykanen, 1986).

Essential oils and thrombosis

Thrombosis is usually associated with platelet activation and the release of eicosanoids which contribute to initiation and aggravation of thrombosis. Prevention of

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thrombogenesis has become one of the most important targets for the prophylaxis and therapy of cardiocirculatory disorders with thromboembolic complications (Fitzgerald, 2001). The antiplatelet agents currently used for this purpose are effective in the prevention of thromboembolic disease, but many have side effects such as gastric erosion (e.g. aspirin), agranulocytosis (e.g. ticlopidine), or show a poor separation between therapeutic efficacy and hemorrhagic complications (Van De Graaff and Steinhubl, 2001). For this reason, plant extracts have been tested for their potential antithrombotic activity. The essential oil of lavender, (*Lavandula hybrida* Reverchon cv.), showed a broad spectrum antiplatelet effect and was able to inhibit platelet aggregation induced by ADP, arachidonic acid, collagen and the stable thromboxane receptor agonist U46619 with no prohemorrhagic properties (Ballabenia *et al.*, 2004). Linalyl acetate (36% of lavender oil) seemed to be the main active antiplatelet agent. Onion (*Allium cepa*) is well known for promoting cardiovascular health, and populations with a high consumption of onions are associated with decreased rates of atherosclerosis or thrombotic disease (Kendler, 1987). This activity is due to inhibition of platelet aggregation and thromboxane formation by the organo-sulfur components in the essential oil (Bordia *et al.*, 1996; Srivastava, 1986). The mechanism of the antiplatelet effect of onion includes TXA2 synthase inhibition and TXA2/PGH2 receptor blockade (Moon *et al.*, 2000). However, garlic was found to be more potent than onion in lowering TXB2 levels (Bordia *et al.*, 1996). Organosulfur components such as allicin, isolated from garlic essential oil, showed a potent inhibition of platelet aggregation (Calvey *et al.*, 1994; Lawson *et al.*, 1992). Allicin is formed from alliin when garlic cloves are crushed or chewed and the enzyme alliinase is released from the cell walls. However, ajoene has the highest specific antithrombotic activity compared with any other organo-sulfur compounds from garlic (Lawson *et al.*, 1992; Apitz-Castro *et al.*, 1983). Ajoene is formed from allicin during steam or water distillation of the essential oil from garlic cloves, or during storage in ethanol (Block *et al.*, 1986, Iberl *et al.*, 1990). The presence of vinyl groups attached by a disulfide bond makes ajoene a highly reactive molecule which can inhibit the release of both dense granules and α-granules (Rendu *et al.*, 1989). Ajoene can reduce platelet aggregation induced by 0.1 U/mL thrombin by 94.7% after a pre-stimulation incubation time for one minute at a dose of 25 μM (Villar *et al.*, 1997). The mechanism of action of ajoene differs to that of other known inhibitors of platelet aggregation. Ajoene penetrates the membrane of intact platelets and reduces the viscosity of the inner part of the lipid bilayer (Rendu *et al.*, 1989), thus interfering with the expression of the fibrinogen receptor α_{IIB} β_3 at the cell surface, thereby inhibiting fibrinogen binding (Apitz-Castro *et al.*, 1986). Ajoene also inhibits platelet aggregation through inhibiting the formation of thromboxane A2 via altering arachidonic acid metabolism. Moreover, it inhibits platelet aggregation induced by adrenaline, collagen, adenosine diphosphate and calcium ionophore A23187 (Srivastava and Tyagi, 1993). Polysulfides, particularly dimethyl trisulfide and diallyl trisulfide, found in both onion and garlic oils also inhibit thromboxane synthesis in platelets (Makheja and Bailey, 1990).

ESSENTIAL OILS AS ANTIBACTERIAL AGENTS

The Ancient Egyptians used aromatic plants in embalming to stop bacterial growth and prevent decay, an effect attributed to a great extent to their essential oils. Strong *in vitro* evidence indicates that essential oils can act as antibacterial agents against a wide spectrum of pathogenic bacterial strains including *Listeria monocytogenes*, *L. innocua*, *Salmonella typhimurium*, *Escherichia coli* O157:H7, *Shigella dysenteria*, *Bacillus cereus*, *Staphylococcus aureus* and *Salmonella typhimurium* (Schmidt *et al.*, 2005; Jirovetz *et al.* 2005; Burt, 2004; Dadalioglu and Evrendilek, 2004; Nguefack *et al.*, 2004; Hulin *et al.*, 1998) and many more (Deans and Ritchie, 1987). Thyme and oregano essential oils can inhibit some pathogenic bacterial strains such as *E. coli*, *Salmonella enteritidis*, *Salmonella choleraesuis* and *Salmonella typhimurium* (Penalver *et al.*, 2005), with the inhibition directly correlated to the phenolic components carvacrol and thymol. The same correlation was also confirmed for oils rich in carvacrol alone (Santoyo *et al.*, 2006). Eugenol and carvacrol showed an inhibitory effect against the growth of four strains of *Escherichia coli* O157:H7 and *Listeria monocytogenes* (Gaysinsky *et al.*, 2005). The presence of a phenolic hydroxyl group, in carvacrol particularly, is credited with its activity against pathogens such as *Bacillus cereus* (Ultee *et al.*, 1999; Ultee *et al.*, 2002). Some essential oils demonstrated antibacterial activity against zoonotic enteropathogens including *Salmonella spp.*, *Escherichia coli O157*, *Campylobacter jejunii* and *Clostridium perfringens.* Thus, these oils could possibly be used as an alternative to antibiotics in animal feed (Wannissorn *et al.*, 2005).

Essential oils with high concentrations of thymol and carvacrol e.g. oregano, savory and thyme, usually inhibit Gram-positive more than Gram-negative pathogenic bacteria (Nevas *et al.*, 2004). However the essential oil of *Achillea clavennae* exhibited strong antibacterial activity against the Gram (–)-ve *Haemophilus influenzae* and *Pseudomonas aeruginosa* respiratory pathogens, while Gram (+)-ve *Streptococcus pyogenes* was the most resistant to the oil (Skocibusic *et al.*, 2004).

The major mode of infection transmission in hospital-acquired infections is thought to be through hand carrying of pathogens from staff to patient, and from patient to patient (Boyce and Pittet, 2002; Naikoba and Hayward, 2001), and a relationship between hand hygiene and reduced transmission of infections been reported (Reybrouck, 1986). Most antiseptic agents can damage the skin, leading to a change in microbial flora, and an increased shedding of the original protective bacterial flora of the hand leads to an increased risk of transmission of pathogenic microorganisms (Larson, 2001). Reports suggest that repeated use of formulations containing tea tree essential oil (TTO) does not lead to dermatological problems, nor affect the original protective bacterial flora of the skin (Carson and Riley, 1995), so the antibacterial activity of some skin-wash formulas containing TTO as well as pure TTO was evaluated against *Staphylococcus aureus*, *Acinetobacter baumannii*, *Escherichia coli* and *Pseudomonas aeruginosa* (Messager *et al.*, 2005a, 2005b). All formulations showed antibacterial activity, but the efficacy of

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TTO appeared to be dependent on the formulation and the concentration tested. The antibacterial activity of tea tree essential oil has recently been reviewed (Carson *et al.*, 2006).

In the field of veterinary therapy, a cream formulation containing 10% TTO caused significant and fast relief against canine localized acute and chronic dermatitis compared with commercial skin care cream (Reichling *et al.*, 2004). For the safe use of tea tree essential oil as antibacterial agent for animals or humans, the potential toxicity should be taken into consideration (Carson *et al.*, 2006; Hammer *et al.*, 2005; Carson and Riley, 1995).

The emergence of resistant pathogenic microorganisms in hospitals and in the community represents a problem for both the treatment of patients and control of infection. Topical preparations containing TTO can be considered in regimens for eradication of methicillin-resistant *Staphylococcus aureus* in hospitals (Dryden *et al.*, 2004). The preparations were found to be effective, safe and well tolerated. TTO demonstrated a relatively short killing time (less than 60 min) for multidrug-resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-resistant *Enterococci*, aminoglycoside-resistant *Klebsiellae*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* (May *et al.*, 2000). MRSA showed the highest resistance and longest time for eradication. It was concluded that the antimicrobial activity of TTO is attributed to its high content of terpenen-4-ol.

Other multidrug-resistant pathogens such as *Pseudomonas aeruginosa* and *Escherichia coli* can be effectively inhibited by the essential oil of oregano (Bozin *et al.*, 2006).

Ocimum gratissimum essential oil can also inhibit extracellular protease and the expression of O-lipopolysaccharide rhamnose in virulence and multidrug-resistant strains of 22 *Shigellae* (Iwalokun *et al.*, 2003). Thus, the oil may find a use as a therapeutic measure against shigellosis. Methicillin-resistant *Staphylococcus aureus* can also be inhibited by the application of peppermint and spearmint essential oils (Imai *et al.*, 2001). Essential oils could be used as antibacterial agents against some respiratory tract pathogens. The oil of *Achillea clavennae* showed its maximum activity against *Klebsiella pneumoniae* and penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae*. The oil also exhibited strong activity against *Haemophilus influenzae* and *Pseudomonas aeruginosa* (Skocibusic *et al.*, 2004).

An increased density of *Helicobacter pylori* in the gastric mucosa is associated with severe gastritis and an increased incidence of peptic ulcers (Kelly, 1998). The activities of 60 essential oils against *H. pylori* P1 were evaluated: 30 oils were able to affect the growth *in vitro*, and 15 showed strong activity (Bergonzelli *et al.*, 2003). Among the individual constituents of these oils, carvacrol, isoeugenol, nerol, citral and sabinene exhibited the strongest anti-*H. pylori* effects. Further investigations are underway regarding the ability of essential oils to control *H. pylori* infections (McNulty *et al.*, 2001; Kalpoutzakis *et al.*, 2001; Imai *et al.*, 2001; O'Gara *et al.*, 2000).

Essential oils show bactericidal activity against oral and dental pathogenic microorganisms and can be incorporated into rinses or mouth washes for pre-procedural infection control (Yengopal, 2004a), general improvement of oral health (Yengopal, 2004b), interdental hygiene (Yengopal, 2004c) and to control oral malodor (Yengopal, 2004d). *Croton cajucara* Benth essential oil was found to be toxic for some pathogenic bacteria and fungi associated with oral cavity disease (Alviano *et al.*, 2005) and may be useful for controlling the microbial population in patients with fixed orthodontic appliances. A 6-month controlled clinical study demonstrated that a mouthrinse containing essential oils showed a comparable antiplaque and antigingivitis activity to that containing the synthetic antibacterial agent, chlorhexidine (Charles *et al.*, 2004). Mouth rinses containing essential oils (specially phenolic rich types) with chlorhexidine gluconate are commonly used as preprocedural preparations to prevent possible disease transmission, decrease chances of postoperative infection, decrease oral bacterial load and decrease aerosolization of bacteria (Hennessy and Joyce, 2004). Mouth washes containing essential oils could also be used as a part of plaque-control routine since they can penetrate the plaque biofilm, kill pathogenic-plaque-forming microorganisms by disrupting their cell walls and inhibiting their enzymatic activity (Ouhayoun, 2003). In addition, essential oils in mouth washes prevent bacterial aggregation, slow the multiplication and extract bacterial endotoxins (Seymour, 2003).

The mechanisms by which essential oils can inhibit microorganisms involve different modes of action, and in part may be due to their hydrophobicity. As a result, they get partitioned into the lipid bilayer of the cell membrane, rendering it more permeable, leading to leakage of vital cell contents (Burt, 2004; Juven *et al.*, 1994; Kim *et al.*, 1995). Impairment of bacterial enzyme systems may also be a potential mechanism of action (Wendakoon and Sakaguchi, 1995).

ESSENTIAL OILS AS ANTIVIRAL AGENTS

Herpes simplex virus (type I, II) causes some of the most common viral infections in humans, and can be fatal. Synthetic antiviral drugs have been used to treat Herpes infections (Fahad and Stepher, 1996; Wagstaff *et al.*, 1994), but not all are efficacious in treating genital herpes infections. HSV-1 and HSV-2 have also developed resistance to one of these (acyclovir) mainly in immuno-compromised hosts (Birch *et al.*, 1990; Wagstaff *et al.*, 1994). Plant extracts, especially essential oils, may afford a potential alternative to synthetic antiviral drugs: they have demonstrated virucidal properties, with the advantage of low toxicity compared with the synthetic antiviral drugs (Baqui *et al.*, 2001; Primo *et al.*, 2001; Schnitzer *et al.*, 2001). Incorporation of *Artemisia arborescens* essential oil in multilamellar liposomes greatly improved its activity against intracellular *Herpes simplex* virus type-1 (HSV-1) (Sinicoa *et al.*, 2005). *Melissa officinalis* L. essential oil can inhibit the replication of HSV-2, due to the presence of citral and citronellal (Allahverdiyev *et al.*, 2004) and the ability to replicate of HSV-1 can be suppressed by incubation with different essential oils *in vitro*. Of these, lemongrass essential oil possessed the most potent anti-HSV-1 activity and completely inhibited viral replication after incubation for 24 h, even at a concentration of 0.1% (Minami *et al.*, 2003). Peppermint

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(*Mentha piperita*) essential oil exhibited high levels of virucidal activity against HSV-1, HSV-2 and acyclovir-resistant strain of HSV-1 in viral suspension tests (Schuhmacher *et al.*, 2003). The antiviral activity of the oil was confirmed when the virus was pretreated with the essential oil prior to adsorption. The essential oil of *Lippia junelliana* and *Lippia turbinate* showed a potent inhibition against Junin virus (Garcia *et al.*, 2003). Australian tea tree essential oil and to a lesser extent, eucalyptus essential oil, demonstrated antiviral activity against HSV-1,2 (Schnitzler *et al.*, 2001). Both oils affected the virus before or during adsorption, but not after penetration into the host cell. The essential oil of *Santolina insularis* showed an antiviral activity *in toto* against HSV-1 and HSV-2 *in vitro* and was capable of preventing cell-to-cell virus spread in infected cells (De Logu *et al.*, 2000). The oil directly inactivated virus particles, thus preventing adsorption of virion to host cells. Isoborneol, a common monoterpene alcohol, showed dual virucidal activity against HSV-1 (Armaka *et al.*, 1999) and specifically inhibited glycosylation of viral polypeptides. Unfortunately, no literature was found concerning the antiviral applications of essential oils against epidemic viruses such as HIV or hepatitis C viruses, but the promising results illustrated here may promote further investigations in this area.

ESSENTIAL OILS AS ANTIOXIDANTS

Free radicals and other reactive oxygen species cause oxidation of biomolecules including proteins, amino acids, unsaturated lipids and DNA, and ultimately produce molecular alterations related to aging, arteriosclerosis and cancer (Gardner, 1997), Alzheimer's disease (Butterfield and Lauderback, 2002), Parkinson's disease, diabetes and asthma (Zarkovic, 2003). The human body is equipped with an inherent defense system which can quench free radicals present in almost all cells (Halliwell and Gutteridge, 1990). An imbalance between free radical production and their removal by the body's antioxidant system leads to a phenomena known as 'oxidative stress' (Abdollahi *et al.*, 2004; McCord, 2000). In this situation, an external supply of antioxidants is necessary to regain a balance between free radicals and antioxidants.

Essential oils, as natural sources of phenolic components, attract investigators to evaluate their activity as antioxidants or free radical scavengers. The essential oils of basil, cinnamon, clove, nutmeg, oregano and thyme have proven radical-scavenging and antioxidant properties in the DPPH radical assay at room temperature (Tomaino *et al.*, 2005). The order of effectiveness was found to be: clove >> cinnamon > nutmeg > basil ≥ oregano >> thyme. The essential oil of *Thymus serpyllus* showed a free radical scavenging activity close to that of the synthetic butylated hydroxytoluene (BHT) in a β-carotene/linoleic acid system (Tepe *et al.*, 2005). The antioxidant activity was attributed to the high content of the phenolics thymol and carvacrol (20.5% and 58.1%, respectively). *Thymus spathulifolius* essential oil also possessed an antioxidant activity due to the high thymol and carvacrol content (36.5%, 29.8%, respectively; Sokmen *et al.*, 2004). The antioxidant activity of oregano (*Origanum vulgare* L., ssp. *hirtum*) essential oil was comparable to that of α-tocopherol and BHT, but less effective than ascorbic acid (Kulisic *et al.*, 2004). The activity is again attributed to the content of thymol and carvacrol (35.0%, 32.0%, respectively). Although dietary supplementation of oregano oil to rabbits delayed lipid oxidation, this effect was less than that of supplementation with the same concentration of α-tocopheryl acetate (Botsoglou *et al.*, 2004). However, when tested on turkeys it showed an equivalent performance to the same concentration of α-tocopheryl acetate in delaying iron-induced, lipid oxidation (Papageorgiou *et al.*, 2003).

The essential oils of *Salvia cryptantha* and *Salvia multicaulis* have the capacity to scavenge free radicals. The activity of these oils was higher than that of curcumin, ascorbic acid or BHT (Tepe *et al.*, 2004). The essential oil of *Achillea millefolium* subsp. *millefolium* (Asteraceae) exhibited a hydroxyl radical scavenging effect in the Fe^{3+}–EDTA–H_2O_2 deoxyribose system and inhibited the non-enzymatic lipid peroxidation of rat liver homogenate (Candan *et al.*, 2003). In addition, *Curcuma zedoaria* essential oil was found to be an excellent scavenger for DPPH radical (Mau *et al.*, 2003).

The antioxidant activity of essential oils cannot be attributed only to the presence of phenolic constituents; monoterpene alcohols, ketones, aldehydes, hydrocarbons and ethers also contribute to the free radical scavenging activity of some essential oils. For instance, the essential oil of *Thymus caespititius*, *Thymus camphoratus* and *Thymus mastichina* showed antioxidant activity which in some cases was equal to that of α-tocopherol (Miguel *et al.*, 2004). Surprisingly, the three species are characterized by high contents of linalool and 1,8-cineole, while thymol or carvacrol are almost absent. The essential oil of lemon balm (*Melissa officinalis* L.) shows an antioxidant and free radical scavenging activity (Mimica-Dukic *et al.*, 2004) with the most powerful scavenging constituents comprising neral/geranial, citronellal, isomenthone and menthone. Tea tree (*Melaleuca alternifolia*) oil has been suggested as a natural antioxidant alternative for BHT (Kim *et al.*, 2004) with the inherent antioxidant activity attributed mainly to the α-terpinene, γ-terpinene and α-terpinolene content. Essential oils isolated from *Mentha aquatica* L., *Mentha longifolia* L. and *Mentha piperita* L., were able to reduce DPPH radicals into the neutral DPPH-H form (Mimica-Dukic *et al.*, 2003). The most powerful scavenging constituents was found to be 1,8-cineole for the oil of *M. aquatica* while menthone and isomenthone were the active principles of *M. longifolia* and *M. piperita.*

It is clear that essential oils may be considered as potential natural antioxidants and could perhaps be formulated as a part of daily supplements or additives to prevent oxidative stress that contributes to many degenerative diseases.

ESSENTIAL OILS AS ANTIDIABETIC AGENTS

Diabetes is a disease in which the body does not produce or properly use insulin.

Investigators have conducted few studies exploring the potential benefits of essential oils as hypoglycemic agents and publications on the subject are scarce. Some

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essential oils may aggravate diabetes: for instance, rosemary essential oil showed hyperglycemic and insulin release inhibitory effects in diabetic rabbits (Al-Hader *et al.*, 1994). Broadhurst *et al.* (2000) have emphasized that the lipophilic fraction of aromatic plants (i.e. essential oils) are not generally responsible for any antidiabetic activity showed by these plants, but Talpur *et al.* (2005) indicated that an oral administration of a combination of essential oils including cinnamon, cumin, fennel, oregano, myrtle besides others, was able to enhance insulin sensitivity in type 2 diabetes, in addition to lowering circulating glucose in the tolerance testing in rats. The essential oil of *Satureja khuzestanica* resulted in significant decreases in fasting blood glucose level in diabetic rats (Abdollahi *et al.*, 2003). More research is needed to confirm the veracity of the hypoglycemic activity of other essential oils and to elucidate their mechanism of action.

ESSENTIAL OILS AS SKIN PENETRATION ENHANCERS FOR TRANSDERMAL DRUG DELIVERY

The oral and nasal routes are the most common non-invasive paths for drug administration but are not suitable for some drugs, either due to stomach acidity or hepatic first-pass metabolism (Balfour and McTavish, 1992; Corson, 1993). Nasal delivery is often characterized by poor absorption of lipophilic drugs (Orive *et al.*, 2003). Thus, the skin can present a promising route for administration of drugs in a non-invasive way. This phenomena is called topical or transdermal drug delivery. The principle barrier to topical drug delivery is the stratum corneum (SC) which is the outer most layer of the skin. The permeability of the SC can be increased by using skin penetration enhancers (Barry, 1991). Detailed reviews describing synthetic enhancers are available (Williams and Barry, 2004; Ghafourian *et al.*, 2004).

Essential oils and their terpene constituents may be acceptable natural alternatives to synthetic skin penetration enhancers. They are characterized by their relatively low price and promising penetration enhancing activities. The mechanism of skin penetration enhancing activity of terpenes was postulated (Vaddi *et al.*, 2002; Higaki *et al.*, 2003; Cornwell and Barry, 1994; Barry, 1991; Cornwell and Barry, 1991; Williams and Barry, 1991; Williams and Barry, 1989). Due to the popularity of these essential oils, their toxicities are well documented (Opdyke, 1974–1976), and found to be relatively low compared with most synthetic penetration enhancers. The evaluation of the sensitization, carcinogenicity and toxicity of these oils and their individual terpene constituents are continuously carried out by organizations such as the Research Institute for Fragrance Materials (RIFM), International Flavor and Fragrance Association (IFRA), Flavor Essence Manufacturers Association (FEMA) and the National Toxicology Program (NTP).

Terpenes such as menthol and cineole were employed as natural enhancers to improve the skin penetration of propranolol, a β-blocker, which has a short biological half-life and is subjected to extensive hepatic first-pass metabolism (Amnuaikit *et al.*, 2005). Cineole and menthol are reported to improve the skin permeation of hydrophilic drugs better than other terpenes (Narishetty and Panchagnula, 2004). Menthol and limonene produced maximum permeation of melatonin along with traditional enhancers including fatty alcohols and fatty acids (Kanikkannan *et al.*, 2004). On the other hand, menthol and menthone failed to enhance the penetration of high-molecular-weight, lipophilic drugs such as paclitaxel (Panchagnula *et al.*, 2004). The combination of two penetration enhancers of different classes such as terpenes (e.g. cineole) and fatty acids (e.g. oleic acid), synergistically enhanced transdermal flux of zidovudine in addition to reducing lag time. On the other hand, combinations of menthol with oleic or linolenic acid did not enhance transdermal delivery (Thomas and Panchagnula, 2003). The proper choice of the terpene enhancer is dictated by the lipophilicity or hydrophicity of the drug (El-Kattan *et al.*, 2001).

Some essential oils themselves have been investigated as potential skin penetration enhancers. Basil essential oil showed an enhancing activity for accelerating transdermal delivery of indomethacin (Fang *et al.*, 2004). The mechanism of action is probably due to the increased skin–vehicle partitioning by the oils. Niaouli essential oil showed a high activity for the permeation of estradiol through hairless mouse skin *in vitro* (Monti *et al.*, 2002). In addition, eucalyptus and chenopodium essential oils caused a near 30-fold increase in the 5-fluorouracil permeability coefficient (Williams and Barry, 1989).

ESSENTIAL OILS, AROMATHERAPY AND MASSAGE THERAPY

The word 'aromatherapy' combines two words: aroma (a fragrance or swee smell) and therapy (a treatment). Aroma and massage therapy are the practice of using essential oils for psychological and physical well-being via inhalation or massage.

The term 'aromatherapy' may be confusing to non-specialists because it is used to describe a wide range of practices involving odorous substances. Thus, massage therapy, even when using essential oils, cannot be considered as aromatherapy. Only aroma delivery through inhalation, to induce psychological or physical effects, can be defined as aromatherapy (Buchbauer and Jirovetz, 1993, 1994). Nevertheless, the clinical use of essential oils and their volatile constituents via inhalation or massage has expanded worldwide.

Inhalation

Inhalation of essential oils or their individual volatile terpenes has a significant role in controlling the central nervous system. For instance, aroma inhalation of *Storax pill* essential oil and preinhalation of *Acorus gramineus* rhizome essential oil are used in Chinese folk medicine in the treatment of epilepsy (Koo *et al.*, 2004; Koo *et al.*, 2003). The oils showed an inhibitory effect on the central nervous system via the gamma-aminobutyric acid (GABA)-ergic neuromodulation system. This effect originates from the enhancement of GABA levels in the brain (Koo *et al.*, 2003). The fragrance compounds,

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cis-jasmone and methyl jasmonate, which characterize the aroma of *Jasminum grandiflorum* have a tranquillizing effect on the brain upon inhalation (Hossain *et al.*, 2004). They significantly increased the sleeping time of mice induced by pentobarbital. This indicates that these fragrant compounds were absorbed by the brain and thereby potentiated the GABA receptor response. Cedrol, which is a major component of cedarwood essential oil, showed a sedative effect and prolonged pentobarbital-induced sleeping time in rats upon inhalation (Kagawa *et al.*, 2003). The vapor of lavender essential oil or one of its main components, linalool, may contribute to relieving tension when inhaled. They may also be applicable to the treatment of menopausal disorders via inhalation (Yamada *et al.*, 2005). Lavender (*Lavandula hybrida* Reverchon 'Grosso') essential oil demonstrated an interesting analgesic activity, mainly relevant after inhalation, at doses devoid of sedative side effects (Barocelli *et al.*, 2004). In the field of complementary and alternative respiratory medicine, inhalation of peppermint essential oil vapors has been suggested as an adjunct in combined multidrug therapy in patients with disseminated and infiltrative pulmonary tuberculosis. The action of the oil is mainly due to the antimicrobial activity of its volatile constituents (Shkurupii *et al.*, 2002). Cinnamon and clove oils also showed an inhibition to different Gram (+)-ve and Gram (–)-ve pathogenic bacteria from the vapor phase (Lopez *et al.*, 2005). Aroma inhalation of lavender, peppermint, rosemary and clary-sage essential oils can significantly decrease symptoms associated with anxiety and stress. Inhalation of essential oils can also modulate sympathetic activity in normal adults: for example, the inhalation of pepper, estragon, fennel or grapefruit essential oils resulted in 1.5- to 2.5-fold increase in relative sympathetic activity. In contrast, fragrance inhalation of rose oil or patchouli oil caused a 40% decrease in relative sympathetic activity. On a hormonal level, inhalation of pepper oil induced a 1.7-fold increase in plasma adrenaline concentration compared with the resting state, while inhalation of rose oil caused a 30% decrease in adrenaline concentration (Haze *et al.*, 2002). The rise in rat plasma adrenocorticotrophic hormone caused by stress was significantly reduced by inhalation of chamomile essential oil (Yamada *et al.*, 1996). The same effect can be achieved by the intraperitoneal injection of diazepam, a synthetic tranquillizer. The mode of action of Chamomile essential oil is at least in part via benzodiazepine-sensitive receptors, probably GABA. Other essential oils also have sedative properties upon inhalation (Buchbauer *et al.*, 1992, 1993).

Inhalation of the volatile fractions of lavender and monarda essential oils (0.1–0.2 mg/m^3 air) reduced the cholesterol content in the aorta and also atherosclerotic plaques (Nikolaevskii *et al.*, 1990), but had no effect on the content of cholesterol in the blood.

Massage

Inflammatory diseases, such as allergy, rheumatism and arthritis are often alleviated using essential oil massage therapy (Maruyama *et al.*, 2005; Lawless, 1997). Allergic symptoms can be suppressed by tea tree oil (Brand *et al.*, 2002a; Koh *et al.*, 2002), lavender oil (Kim and Cho, 1999) and the volatile constituent, terpenene-4-ol (Hart *et al.*, 2000). This action is mainly due to the suppression of histamine release (Brand *et al.*, 2002b) and cytokine production (Brand *et al.*, 2001). Cutaneous delivery of geranium essential oil using massage can suppress the inflammatory symptoms with neutrophil accumulation and edema (Maruyama *et al.*, 2005). A lavender fragranced cleansing gel had a significant transient effect of improving mood and making people feel more relaxed (Field *et al.*, 2005). Aromatic materials, topically applied, showed positive effects on lung mucus clearance in patients with chronic airway obstruction (Hasani *et al.*, 2003). Even foot soaking in warm water containing lavender essential oil followed by reflexology treatment with jojoba oil containing lavender, appeared to be effective for alleviating fatigue in terminally ill cancer patients (Kohara *et al.*, 2004). Massage therapy using essential oil can be useful in the treatment for people suffering from dementia. The term 'dementia' is used to describe the symptoms that occur when the brain is affected by specific diseases and conditions, including Alzheimer's disease, stroke and other rarer conditions. Symptoms of dementia include loss of memory, confusion and problems with speech and understanding. Preliminary reports have indicated positive effects of massage therapy using selected essential oils for managing behavioral and psychological symptoms in dementia. The essential oil of *Melissa officinalis* (lemon balm) applied cutaneously in a lotion to patients with severe dementia was found to be an effective treatment (Ballard *et al.*, 2002). The potential efficiency of massage therapy with essential oils to decrease agitation in patients suffering dementia raise the question of whether inhalation of the essential oil or its cutaneous delivery through massage is responsible for the alleviative effect. Snow *et al.* (2004) indicated that inhalation of lavender essential oil did not decrease agitation in severely demented patients and a similar result had previously been reported by Holmes *et al.* (2002). Cutaneous application of the essential oil through massage may therefore be necessary to achieve the alleviative effect in patients with dementia.

Care should be taken when dealing with essential oils in massage. Some essential oils have the potential to be toxic (Prashar *et al.*, 2004; Hayes and Markovic, 2003), while others initiate allergic reactions when applied to the skin via massage (Veien *et al.*, 2004; Schnuch *et al.*, 2004; Crawford *et al.*, 2004; Maddocks-Jennings, 2004; Scardamaglia *et al.*, 2003; Mozelsio *et al.*, 2003; Bleasel *et al.*, 2002; Vilaplana and Romaguera, 2002; Romaguera and Vilaplana, 2000). These allergic reactions arise from certain constituents, e.g. benzyl alcohol, cinnamyl alcohol, eugenol, isoeugenol, hydroxycitronellal, geraniol and many others (European Parliament, 2002). For this reason, warnings must be printed on the label of essential oils containing these components, and aromatherapy practitioners and massage therapists should be also aware of the potential for these adverse effects – and be equipped to deal with them if they should arise (Maddocks-Jennings and Wilkinson, 2004). At the same time, physicians and other health professionals should be able to differentiate between aesthetic applications of odors and clinical uses of essential oils in order to advise and better inform patients.

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CONCLUSIONS

This review attempts to shed light on the therapeutic potential of essential oils and their aroma volatile constituents in the prevention or therapy of disease. The results reviewed in this article are aimed at attracting the attention of researchers seeking new drugs from natural products as well as those investigating the pharmaceutical diversity of essential oils. The data presented provide a basis for reviving the old art of 'essential oil therapy' based on our modern scientific knowledge of their mode of action, supported by safety issues described here. Thus essential oils and their constituents can hopefully be considered in the future for more clinical evaluations and possible applications, and as adjuvants to current medications.

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