LEADING ARTICLE

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Aromatherapy in the Management of Psychiatric Disorders

Clinical and Neuropharmacological Perspectives

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Abstract

Aromatherapy is currently used worldwide in the management of chronic pain, depression, anxiety, some cognitive disorders, insomnia and stress-related disorders. Although essential oils have been used, reputedly effectively, for centuries as a traditional medicine, there is very little verified science behind this use. The pharmacology of the essential oils and/or their single chemical constituents, therefore, remains largely undiscovered. However, accumulating evidence that inhaled or dermally applied essential oils enter the blood stream and, in relevant molecular, cellular or animal models, exert measurable psychological effects, indicates that the effects are primarily pharmacological.

This review includes evidence from the limited number of clinical trials that have been published of 'psychoaromatherapy' in relation to psychiatric disorders, together with evidence from mechanistic, neuropharmacological studies of the effects of essential oils in relevant *in vitro* and *in vivo* models. It is concluded that aromatherapy provides a potentially effective treatment for a range of psychiatric disorders. In addition, taking into account the available information on safety, aromatherapy appears to be without the adverse effects of many conventional psychotropic drugs. Investment in further clinical and scientific research is clearly warranted.

1. Background

Aromatherapy is the therapeutic use of plant essential oils, whether absorbed via the skin or olfactory system. The term 'aromatherapy', intended to describe the compounds present in the essential oil that are aromatic (i.e. have an aroma), is not entirely precise, as effects are not necessarily related to the aromatic properties of the agent; further terms such as 'essential oil therapy' and 'phyto-essential-pharmacology' might be more applicable.

Essential oils are concentrated steam distillates obtained from a range of aromatic plants, and also include expressions from the peel of citrus fruits. Chemically, plant essential oils are heterogeneous mixtures (often hundreds in total) of, amongst others, the lipophilic volatile hydrocarbon monoter-

penoids (grouped by their different functional groups into, for example, alcohols, oxides, phenols, aldehydes and ketones) and the less volatile sesquiterpenoids (and their alcohols, oxides and aldehydes) [see table I and examples in figure 1]. The myriad of chemical constituents that exist as essential oils, combined with the chemical diversity between essential oils, results in a potentially wide-ranging list of therapeutic activities. The pharmacology behind the actions of many essential oils remains undefined and it is certain to be a long and complex path to full medicinal and pharmacological understanding, paralleling that of medical herbalism and unlike any conventional medicinal substance.

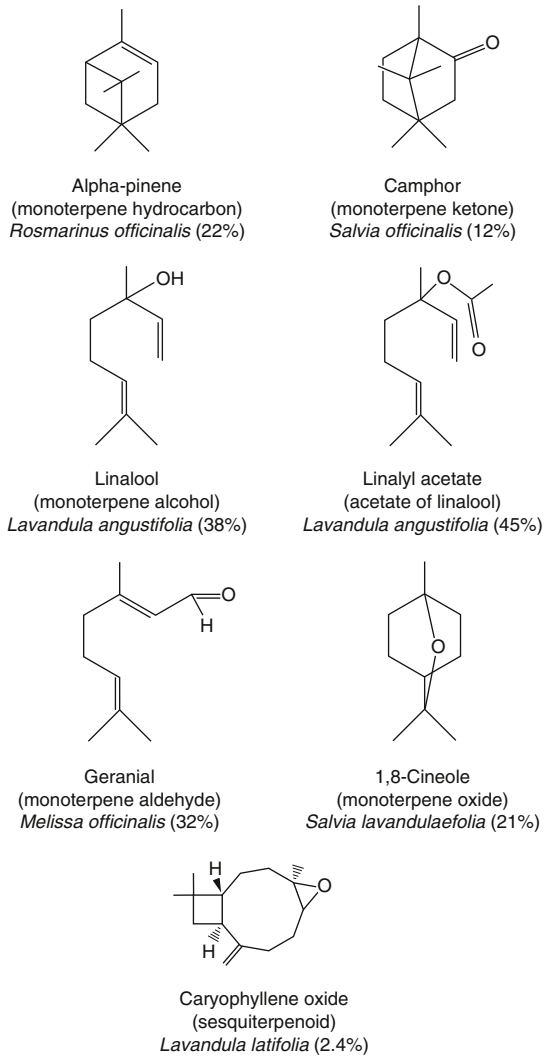

Fig. 1. Examples of frequently occurring essential oil terpenoids from the different chemical classes. **%** indicates the amount of terpenoids present in each oil, e.g. *Lavandula angustifolia* is 38% linalool.

Essential oils can be absorbed into the body in three ways: (i) through the olfactory and respiratory systems (vapour inhalation); (ii) transdermally via lotions or compresses, often involving massage and during bathing; or (iii) orally, via ingestion of essential oils in capsules or as additives to food or medical preparations, for example. The latter option belongs more to the realm of herbal medicine than aromatherapy.

The aromatic oils have been used for over 5000 years; ancient Egyptians used them as perfumes,[3] and there are nearly 200 references in the Bible to their use for mental, spiritual and physical healing.[7] Modern aromatherapy originated in Germany in the 16th century.[8] Gattefosse, a French chemist, investigated the antibacterial and healing properties of essential oils during World War I to treat wounded soldiers[9] and Valnet, a French army surgeon, further revived the application of aromatherapy during World War II.[7]

The effects of an aroma can be instantaneous and include both direct and indirect psychological effects – even thinking about a smell may have a similar effect to the smell itself. However, accumulating evidence that inhaled or dermally applied essential oils enter the blood stream and, in relevant molecular, cellular or animal models, exert measurable psychological effects, indicates that the effects are primarily pharmacological. This conclusion is supported by increasingly reported benefits of aromatherapy using specific essential oils in the management of chronic pain, depression, anxiety and some cognitive disorders, as well as insomnia and stress-related disorders.[10] The subjective effects of aromatic plant oils relevant to CNS/cerebral

Table I. Subjective effects and chemical constituents of aromatic essential oils relevant to cerebral function[a]

Essential oil	Latin name	Reported subjective effects	Main chemical constituents[b]
Bergamot	*Citrus bergamia*	Antidepressant, calming, relaxing, sedative	Limonene 38%, linalyl acetate 28%, linalool 8%, gamma-terpinene 8%, beta-pinene 7%
Chamomile-Roman	*Chamomelium nobilis*	Analgesic, hypnotic, relaxing, sedative	Isobutyl angelate 36%, 2-methylbutyl angelate 15%, methyl angelate 9%
			Linalyl acetate 49%, linalool 24%, germacrene D 3%, alpha-terpineol 3%, geranyl acetate 3%
Geranium	*Pelargonium graveolens*	Analgesic, antidepressant, uplifting	Citronellol 21%, geraniol 17%, linalool 13%, citronellyl formate 8%, geranyl formate 8%
Jasmine	*Jasminum grandiflorum*	Antidepressant, aphrodisiac, euphoric, relaxing, stimulating	Benzyl acetate 22%, benzyl benzoate 15%, phytyl acetate 10%, linalool 6%, methyl cis-jasmonate 3%
Juniper	*Juniperus communis*	Analgesic, aphrodisiac, mentally clearing	Alpha-pinene 33%, myrcene 11%, beta-farnesene 11%, gamma-elemene 3%, beta-caryophyllene 3%
Lavender	*Lavandula angustifolia*	Analgesic, antidepressant, anticonvulsant, anxiolytic, calming, hypnotic, relaxing, sedative	Linalyl acetate 40%, linalool 32%, (Z)-beta-ocimene 7%, beta-caryophyllene 5%, lavandulyl acetate 4%
Lemon	*Citrus limonum*	Mentally stimulating, reviving	Limonene 70%, beta-pinene 11%, gamma-terpinene 8%, citral 2%, trans-alpha-bergamotene 0.4%
Mandarin	*Citrus deliciosa*	Sedative, uplifting	Limonene 71%, gamma-terpinene 19%, alpha-pinene 2%, alpha-sinensal 0.2%, octanal 0.2%
Marjoram	*Origanum majorana*	Analgesic, anxiolytic, aphrodisiac, comforting, sedating	Terpinen-l-ol 15%, Sabinene 8%, mycene 5%, gamma-terpine 17%, linalool 5%
Melissa	*Melissa officinalis*	Anxiolytic, calming, hypnotic, sedative, stimulating, uplifting	Geraniol 40%, neral 35%, 6-methyl-5-heptan-2-ol 3%, beta-caryophyllene 2%, citronellal 2%
Neroli	*Neroli bigarade*	Sedative, uplifting	Linalool 37%, limonene 26%, beta-pinene 12%, geraniol 4%, linalyl-acetate 3%
Patchouli	*Pogostemon cabin*	Calming, sedative, uplifting	Patchouli alcohol 33%, alpha-patchoulene 22%, beta-caryophyllene 20%, beta-patchoulene 13%, beta-elemene 6%
Rose (Egypt)	*Rosa damascena*	Antidepressant, aphrodisiac, relaxing, sedative, soothing, uplifting	2-Phenyl ethyl alcohol 38%, geraniol 16%, citronellol 13%, farnesol 6%, nerol 4%
Rosemary (Tunisia, cineole)	*Rosmarinus officinalis*	Analgesic, anxiolytic, mentally stimulating, clarifying	1,8-Cineole 51%, camphor 11%, alpha-pinene 10%, borneol 8%, alpha-terpineol 4%
Sage[c]	*Salvia officinalis*	Nerve tonic	Alpha-thujone 37%, beta-thujone 14%, camphor 12%, 1,8-cineole 12%, alpha-pinene 4%
Spearmint	*Mentha spica*	Analgesic, stimulating	(−)-Carvone 43%, dihydrocarvone 16%, 1,8-cineole 6%, perillyl alcohol 5%, alpha-terpinenyl acetate 5%
Ylang-Ylang	*Cananga odourata*	Analgesic, aphrodisiac, relaxing	Linalool 19%, beta-caryophyllene 11%, germacrene D 10%, p-cresyl methyl ether 9%, benzyl benzoate 7%
Vetiver	*Vetivera zizanoides*	Calming, nerve tonic, sedative, uplifting	Vetiverol 50%, vetivenes 20%, alpha-vetivol 10%, vetivones 10%, khusimol 1%

a Among hundreds of essential oils used in aromatherapy, only those referred to in the present review are included in this table. For reviews on subjective effects see Price and Price,[1] Tisserand and Balacs,[2] Lawless,[3] Buckle,[4] and Thomas;[5] for chemical compositions see Bowles.[6]

b The principal chemical constituents are listed in order of concentration, with the highest first (note that proportions may vary according to the source and that many oils contain hundreds of terpenoids).

c Not widely used in aromatherapy because of its high thujone content; *Salvia lavandulaefolia* is thujone-free.

function are summarised in table I; the list is not exhaustive, focusing on the essential oils included in this review. With respect to safety, the evolution and widespread current use of aromatherapeutic practises, together with contemporary clinical trial evidence, indicates that with due attention to the type, dose and mode of application of essential oils (comprehensively outlined by Tisserand and Balacs[2]) aromatherapy can provide treatment for psychiatric disorders that is free of the adverse effects associated with conventional drugs.

In a seminal report, Frey[11] described the rapid intranasal delivery of therapeutic agents, such as nerve growth factor to mouse brain, which allowed the by-passing of the blood brain barrier. The olfactory neural pathway provides both intraneuronal (via axonal transport, and taking hours) and extraneuronal (via bulk flow transport through perineural channels, taking only minutes) access to the brain. Born et al.[12] also described intranasal delivery in humans of neuropeptides to the CSF. Traditional aromatherapeutic practices, dating back thousands of years, are thus verified by 21st century neuroscience. Equally fascinating is the evidence that an odour-enriched environment increases neurogenesis in adult mouse brain.[13] Since agents promoting neurogenesis in adult human brain, including the hippocampus, are being investigated in a variety of psychiatric disorders (e.g. depression, dementia and schizophrenia),[14,15] the possibility that aromatherapy may have long-term protective potential in terms of regeneration is intriguing.

In the US, aromatherapy is the fastest growing of all complementary therapies amongst nurses,[16] and has recently been recognised as a legitimate part of holistic nursing.[17] However, judging by the literature from controlled clinical trials, aromatherapy is only rarely considered by the medical profession. This article reviews the evidence of the clinical efficacy and safety of 'psychoaromatherapy' in relation to psychiatric disorders, together with data from mechanistic, neuropharmacological studies of the effects of essential oils in relevant *in vitro* and *in vivo* models.

There is a vast literature on aromatherapy in non-medical (including nursing and complementary) and non-Western (reflecting the practices of Ayurvedic and traditional Chinese medicines, for example) journals. This review is based primarily on publications in English language medical journals, with the objective of assessing evidence that is both accessible and acceptable to primary- and secondary-care medical practitioners within westernised national health services.

The following databases and search terms were used to assess the literature: 'aromatherapy' and the names of the specific essential oils and plant species, the relevant chemical constituents and the various psychiatric disorders, in articles indexed in MEDLINE (1966–October 2003), EMBASE (1980–October 2003), EMB (Evidence Based Medicine) Reviews (1991–2003) and CINAHL (Cumulative Index to Nursing And Allied Health) [1982–October 2003].[1]

2. Clinical Evidence of Efficacy

Amongst psychiatric disorders, significant numbers of controlled clinical trials of the use of aromatherapy have been conducted only in relation to dementia. This may reflect the lack of prescription medication specifically for dementia until recently, and/or the outstanding need for ameliorative, non-toxic therapeutic strategies for the advanced stages of dementia. With respect to psychiatric disorders other than dementia, little or no evidence from controlled trials of aromatherapy is available. Instead, there exist reports of open-label studies, which may serve, as in dementia, to prompt controlled trials.

1 This review was submitted in May 2004 and accepted in March 2005.

2.1 Behavioural Disorders Associated with Dementia

Controlled clinical trials of aromatherapy in dementia were originally prompted by open-label trials demonstrating beneficial effects, e.g. increased sleep with lavender vapourisation in patients with dementia who were in residential care,[18] reduced agitation in patients with severe dementia following lavender oil vapourisation,[19] and a range of these and other improved outcomes using a mixture of lavender and other oils.[20] The results of the controlled trials are outlined in table II.

The most commonly used essential oils for dementia therapy in controlled trials have been lavender (*Lavandula angustifolia*) and lemon balm (*Melissa officinalis)*, singly or in combination (table II). The trials have involved people with advanced dementia in residential care and have generally assessed behavioural symptoms, particularly agitation, as outcome measures, although one trial did assess cognitive parameters.[25] The trials divide equally between inhalation or dermal application, with a duration of up to 4 weeks. What is remarkable, given the diversity of trial design and type of aromatherapy, is that all treatments have resulted in significant benefit. The benefits include reductions in agitation, insomnia, wandering, difficult behaviour and social withdrawal.

In a more recently published open-label trial, ten patients with dementia were treated for 6 months with a range of essential oils (vaporised mixtures of orange, ylang ylang, patchouli, basil, rosemary, peppermint, rosewood, geranium, bergamot, chamomile and jasmine). A marked decrease in disturbed behaviour was observed in the majority of patients, leading to reductions in psychotropic medications, with overall cost savings.[26] However, Gray and Clair[27] noted no reduction in combative, resistive behaviours in 13 elderly people in residential care treated in an open-label manner with lavender, sweet orange or tea tree oil vapour (delivered, rather atypically, for 1–2 minutes via a cotton wool bud attached to clothing). These studies highlight some of the issues to be resolved in the future.

Sage (*Salvia*) essential oils may be worth investigating as an aromatherapy for the treatment of dementia since certain species possesses a number of relevant bioactivities (cholinesterase inhibition, anti-inflammatory and oestrogenic properties[28]) and in an open-label 4-week trial of ingested capsules of *Salvia lavandulaefolia* (Spanish sage) an improvement in attention and a reduction in behavioural symptoms was noted in 11 patients with Alzheimer's disease.[29] The same oral preparation enhanced memory in normal young volunteers.[30] Although *Salvia officinalis* is not recommended for aromatherapy due to its high thujone content, *S. lavandulaefolia* may be more applicable, although this contains a substantial amount of camphor.

In relation to memory function in normal individuals, Degel and Koster[31] exposed 108 neurologically normal adults to jasmine, lavender or odourless environs and found that jasmine had a positive and lavender a negative effect on memory test performance. Since subjects were not aware of odour, it was concluded that the effects were implicit. Similarly, Ludvigson and Rottman[32] previously noted adverse effects of lavender on arithmetic reasoning. In a controlled trial of the effects of rosemary and lavender essential oils on cognition and mood in 144 healthy volunteers, Moss et al.[33] reported significant enhancement of memory with rosemary, decrements with lavender, but significant increases in contentment with both oils. In contrast, Motomura et al.[34] found that lavender increased arousal rate in 15 stressed healthy adults, indicating that aromatherapeutic effects may be state-dependant.

Encouragingly, in all the published trials of aromatherapy in dementia – a fragile aged population – no adverse effects were reported, despite the fact that they were on the outcome measure list. The only possible exception to this is the trial by Bowles-

Table II. Controlled clinical trials of aromatherapy in patients with severe dementia

Essential oil	Study design	Outcome	Reference
Lemon balm (*Melissa*) and lavender aroma	Placebo controlled; six patients received treatment oils and six control oil; duration 1wk	Treatment oils increased functional abilities and communication, and decreased difficult behaviours (no statistical analysis)	21
Lavender aroma and massage	Randomised, controlled; 21 patients; aromatherapy and massage compared with aroma or massage alone; duration 2wk	Aromatherapy with massage significantly reduced frequency of excessive motor behaviour ($p = 0.05$ vs massage alone)	22
Lavender aroma	Placebo controlled; 15 patients; treatment with oil and placebo (water) on alternative days; duration 10d	Aromatherapy significantly reduced agitated behaviour (as assessed using the Pittsburgh Agitation Scale; $p = 0.016$ [one tailed] vs placebo)	23
Melissa lotion applied to face and arms	Randomised, controlled; 36 patients received *Melissa* and 36 sunflower oil; duration 4wk	Aromatherapy associated with highly significant reductions in measures on the Cohen Mansfield Agitation Inventory and social withdrawal, together with an increase in constructive activities (dementia care mapping) [$p = 0.01$ to $p = 0.0001$ vs sunflower]	24
Lavender, marjoram, patchouli and vetivert applied as a cream to body and limbs	Placebo controlled; 36 patients; treatment vs control cream; duration 4wk	Aromatherapy significantly increased MMSE score (>3 points, $p = 0.015$), but also increased resistance to care (considered due to increase in alertness)	25
Lavender, geranium and mandarin essential oils in almond oil applied to skin[a]	Open label: 39 patients; treatment over unspecified period; patient, staff and carer interviews/rating	Aromatherapy increased alertness, contentment and sleeping at night, and reduced levels of agitation, withdrawal and wandering	20

a This open-label trial is included here because the patient numbers are substantial and the multiple outcomes were measured.

MMSE = Mini-Mental State Examination.

Dilys et al.,[25] in which improved cognitive function was associated with increased resistance to care. In this study, the inclusion of oils such as marjoram, vetivert and patchouli in addition to lavender raises the question of how specific aromatic oils affect individual cerebral functions. Aromatherapy may, thus, be a much safer option than the use of conventional drugs, such as antipsychotics or SSRIs for example.

According to the Cochrane Database Review,[35] aromatherapy demonstrated benefit for people with dementia in the only trial contributing original data to this review (Ballard et al.[24]). Methodological issues were identified highlighting the need for further large scale, randomised, controlled trials to establish the effectiveness of aromatherapy in this group. The following methodological issues, generally applicable to aromatherapy in other psychiatric disorders, need to be addressed in future trials in people with dementia: (i) maintaining 'blindness' in assessors (it is assumed that this issue is not so relevant for patients, anosomnia being prevalent in people with dementia);[36] (ii) selecting the most effective essential oil(s) for symptom management and most effective mode of administration; (iii) standardisation of the essential oil in terms of chemical composition, relevant bioactivities and dosage; (iv) administering aromatherapy as an adjunct to or replacement for other medication such as antipsychotic or cholinergic drugs; and (v) inclusion of physiological, as well as behavioural, outcome measures such as EEG or neuroimaging.

2.2 Psychiatric Disorders Associated with Parkinson's Disease

Ferry et al.[37] conducted a survey of 80 cognitively normal, non-institutionalised patients with Parkinson's disease. Over half of the patients (54%) reported using complimentary therapies, and aromatherapy was one of the most commonly used, although no information is provided in the report on what essential oils were used or which particular symptoms were targeted.

Sleep disorders and apathy are common symptoms in Parkinson's disease and they are not readily treated with orthodox pharmaceuticals without significant adverse effects. An aromatherapeutic approach may be worth considering for such symptoms (see table I for relevant subjective effects of essential oils). The essential oils discussed in section 2.1 are likely to also be useful in the treatment of dementia and its associated behavioural problems that can occur in patients with Parkinson's disease.

2.3 Schizophrenia

Hicks[38] reported on the use of aromatherapy as an adjunct to care in a mental health day hospital in London, UK. Staff and patients perceived aromatherapy to be a beneficial aid to sleep and relaxation, and agreed to the provision of one aromatherapy session a week. The majority of those (n = 20) attending were diagnosed with schizophrenia. Based on user diaries and the aromatherapist's assessment, 70% reported improvements in sleep and 80% in well-being and stress management. The session had the lowest drop-out and nonattendance rate of any group activity in the day hospital, and was reported to be subsequently over-subscribed.

What is missing from this report is any reference to the specific essential oil(s) employed, although it is likely these varied between individuals according to the aromatherapeutic practice of tailoring applications to individual need and/or preference.

2.4 Sleep Disorders

Disrupted sleep patterns, such as insomnia, sleep apnoea and excessive daytime sleepiness, accompany many psychiatric diseases, and also affect general, non-psychiatric populations. In folklore, linen bags were filled with lavender flowers and placed under the pillow to prevent problems in falling asleep. The German Commission E monographs[39]

itemises "states of unrest and difficulty in falling asleep" under indications for the use of lavender, including the volatilised oil.

In ten general hospital patients, improved sleep quality (including reduced restlessness[40] and increased sleep, together with a reduction in the requirement for night sedation[41]) have been reported in open-label trials of aromatherapy. In one study,[41] a blend of basil, juniper, lavender and sweet marjoram was applied by hand massage; satisfactory sleep increased from 73% to 97% of patient nights, while the use of sedatives was reduced from 90% to 36% of patients nights (the study by Hardy et al.[40] used lavender alone). In a multiple crossover study of 23 non-psychiatric female subjects experiencing sleep disorders, lavender demonstrated CNS-depressant activity via EEG recordings.[42] In a controlled, crossover trial of chamomile (Roman) essential oil vapour versus no intervention in 58 elderly hospitalised patients, there was significantly improved sleep (fewer awakenings), more so in non-psychiatric than psychiatric (dementia or depression) cases.[43]

Although no toxicity has been reported for lavender, it does potentiate the sleep-inducing activity of some other agents, such as alcohol, chloral hydrate and hexobarbital.[44]

2.5 Anxiety

In the only reported study (open label) of the use of aromatherapy in patients with a primary diagnosis of anxiety and depression, Edge[45] reported that aromatherapy (individualised with respect to the essential oils) reduced anxiety and improved mood according to visual analogue rating scales in the majority of patients when used over an 8-month period.[45]

Apart from the study by Edge,[45] there have been no clinical trials of aromatherapy in psychiatric patients with anxiety disorders published; however, a number of studies in patients with other types of anxiety have been published.

In a trial involving 122 patients in intensive care, massage aromatherapy using lavender essential oil was compared with rest. The patients receiving aromatherapy reported a statistically significant improvement in mood and reduction in anxiety compared with patients receiving rest.[46] Vaporised orange oil compared to no aroma reduced anxiety in 72 patients undergoing dental procedures.[47] Reductions in anxiety were reported in eight patients with brain tumour who were using lavender or chamomile aromatherapy.[48] The use of lavender aromatherapy (60-minute exposure to vapourised essential oil) was compared with no intervention or humidified water intervention in 17 patients with cancer in a hospice setting.[49] Applied scales for anxiety and depression reflected reductions in the lavender compared to other sessions, although statistical analyses were not applied.

Graham et al.[50] reported that aromatherapy using lavender, bergamot and/or cedar wood oils applied as drops on a paper 'bib' had no benefit in a controlled trial of 313 patients undergoing radiotherapy, as assessed using the Hospice Anxiety and Depression scale. They noted that other oils or methods of administration might reduce anxiety. Wiebe[51] reported that inhalation of the essential oils vetivert, bergamot and geranium had no significant effect compared with placebo in reducing anxiety in 66 women awaiting surgical abortions. Cook and Ernst,[52] in a meta-analysis of six randomised, controlled trials of aromatherapy on anxiety or well-being in patients with cancer who were undergoing cardiac surgery or in intensive care, concluded that aromatherapy massage has a small transient effect on reducing anxiety immediately after administration.

2.6 Depression

Many essential oils are associated with an improvement in mood (table I) indicative of potential application for the treatment of depression. Anecdo-

tal effects are intriguing; for example, Buckle[17] describes the following case:

"Mrs H was an 85 year old woman with depression. Many of her friends were dead and she lived in a nursing home a long way from her family who did not visit her often. She did not sleep well and was prone to hyperventilation and palpitations. She loved the smell of roses, which reminded her of a rose garden she had when her husband was alive. Two drops of rose were inhaled on a facial tissue four times a day. Within 1 week she was smiling, sleeping better, and discussing how she could become involved with looking after the houseplants in the facility."

In 22 healthy adults exposed to chamomile oil or placebo, chamomile significantly improved visual processing and subjective mood ratings.[53] In a pilot, controlled, randomised trial, the effect of citrus fragrance was compared with no fragrance (n = 12 and 8, respectively) in men with depression. The dose of antidepressant drugs was significantly reduced in the active treatment group.[54] Ratings of anxiety were significantly reduced in 14 patients undergoing haemodialysis who were exposed to lavender aroma, compared with no fragrance.[55] In 40 healthy adults, lavender aromatherapy was associated with greater relaxation and less depressed mood.[56]

There is a need for controlled trials of aromatherapy in patients with depression.

2.7 Other Disorders

In 100 patients with intractable epilepsy who opted for treatment with aromatherapy, one-third were no longer taking conventional anticonvulsants and were seizure free at a 2-year follow up.[57] These results, rather surprisingly, indicate efficacy for aromatherapy that is similar or superior to synthetic drugs.

In patients with severe learning disability, no benefit of lavender, lemongrass and orange flower was reported by Lindsay et al.[58]

Buckle[59] reviewed anecdotal evidence indicating that aromatherapy may be of value in the treatment of chronic pain.

Other unexplored clinical psychiatric applications of aromatherapy include: addiction; autism and other developmental disorders; bipolar affective disorder; and, to judge by subjective effects of many essential oils (table I), sexual disorders.

3. Safety, Adverse Effects and Contraindications

In the context of the modern clinical litigious environment, one of the foremost concerns in the application of aromatherapy to clinical practice is the issue of safety, particularly in view of the widespread availability of essential oils in health food stores and other commercial outlets. The products are not licensed, and information on their safety or chemical standardisation is generally not provided. Thus, it is important to consider the use of an essential oil in conjunction with the advice of a professional aromatherapist and with reference to standard texts on essential oil safety.

One of the most comprehensive and widely used texts in aromatherapeutic practice is *'Essential Oil Safety: A Guide for Health Care Professionals'* by Tisserand and Balacs.[60] This provides vital information for each essential oil used in aromatherapeutic practice, including hazards (e.g. dermal or mucous membrane irritation; phototoxicity; neurotoxicity including, for example, convulsant activity), contraindications (e.g. pregnancy, breastfeeding, use in children), and toxicity based on relevant animal data (including LD_{50} values, which are usually in the range of 2–5 g/kg; the clinical dose being between 10 and 100mg per individual). Such safety information from professional aromatherapeutic

practice can be combined with that available from clinical trials of the individual constituents.

The essential oils selected for common use in aromatherapy are those with the least or no toxicities or contraindications within the therapeutic range. Thus, lavender (*L. angustifolia*) is considered to be the safest amongst all oils and there are no contraindications to its use. Other oils without contraindications include basil, chamomile, clary sage, coriander, frankincense, geranium, lemon, melissa, marjoram, napeta, neroli, patchouli, tea tree, thyme and vetiver.[1]

Although there are very few reported contraindications to the aromatherapeutic use of many widely used essential oils, some metabolic products of certain essential oil constituents have been reported to be more harmful than their parent constituents. For example, the ether safrole (and other phenyl methyl ethers) has been found to lower the levels of glutathione (a compound that removes free radicals and other toxic substances) in the liver. Tisserand and Balacs[2] caution against using essential oils containing glutathione-depleting molecules in patients taking paracetamol (acetaminophen) or other drugs that many contain acetaminophen, and in patients with liver disease. Certain essential oils, for example tansy, pennyroyal, rue, savin, juniper, sage and wormwood, are not recommended for use in aromatherapy and have been shown to exhibit abortifacient and/or neurotoxic effects at high doses.[2] Essential oils containing high quantities of ketones, for example thujone and camphor, should not be used on individuals with epilepsy as these constituents have been found to cause epileptiform activity in high doses.[2,60]

As with all substances used medicinally, there are potential adverse effects associated with the overdose of essential oils. Camphor poisoning has been documented for more than 100 years[61] and it produces gastrointestinal and CNS irritation after toxic ingestion. Large quantities (1g taken orally may be fatal in a child) are associated with hepatotoxicity ranging from mild elevation of liver function test values to acute hepatic encephalopathy[62,63] and doses of 50–150 mg/kg have led to status epilepticus in children.[61] Camphor is often combined in cold remedies with eucalyptus oil (*Eucalyptus* globules), which also contains 1,8-cineole (found to correlate with an increase in motor activity following inhalation in mice[64]). This combination has been reported to cause ataxia, slurred speech unconsciousness and convulsions in high doses.[65] Myristicin and elemicin, two ethers found in nutmeg oil, are also neurotoxic at doses suggested to be psychotropic.[2]

Individual sensitivity/allergic reactions may occur with any topically applied substance. In addition, due to their high concentration, skin irritating, sensitising and allergic reactions can occur with repeated exposure to certain essential oils that contain specific constituents, such as certain phenol (e.g. thymol in *Thymus vulgaris*), aldehyde (e.g. neral in *Citrus limonene*), monoterpene (e.g. alpha-pinene in *Eucalyptus* globules), lactone (occurring in small amounts in a few essential oils, e.g. sesquiterpenoid lactones present in chrysanthemums[66]) or ester (e.g. linalyl acetate in *L. angustifolia*) compounds.[2] Although there are substantial reports of the beneficial effects of lavender (*L. angustifolia*) in the treatment of eczema, for example, there are conflicting reports on its sensitising and irritating effects (see review by Cavanagh and Wilkinson[67]).

Essential oils should be treated with the same precautions as any synthetic drug and only used under the advice of a qualified aromatherapist, medicinal herbalist or practicing physician as appropriate. Essential oils should not be used undiluted and storage directions should be followed. With respect to the source of essential oil, the supplier should be selected on the basis of the ability to guarantee the authenticity and purity of their product, together with information on whether the chemical profile of

any particular plant oil conforms to international standards. Information on typical chemical compositions is widely available and includes that outlined in Tisserand and Balacs,[2] Price and Price[1] and Bowles-Dilys et al.,[25] amongst many other professional aromatherapeutic texts. It may be advisable to have samples of oils for clinical use further tested chemically, and services providing relevant analyses such as gas chromatography mass spectrometry are widely available.

Despite potential adverse effects, it should be noted that no adverse effects have been reported from the controlled clinical trials of aromatherapy in psychiatric disorders, such as lavender or melissa used for agitation in dementia (table II). These trials indicate that treatment with these oils compares extremely favourably with the use of antipsychotic drugs commonly prescribed for this condition; these conventional drugs have only modest efficacy[68] and are associated with extrapyramidal symptoms including falls[69] and tardive dyskinesia,[70] sedation[69] and even cognitive decline.[71]

4. Mechanisms of Action

Pharmacological studies, combined with phytochemical analysis, have identified specific neuropharmacological actions for a variety of essential oils and their individual monoterpenoid (and other essential oil) constituents that relate to clinical effects (tables III, IV and V). Individual constituents reach the blood, cross the blood-brain barrier and enter the CNS following inhalation, dermal application, intraperitoneal or subcutaneous injection, and oral administration.[64,72-77]

In vitro and *in vivo* studies in animals confirm that particular essential oils have anxiolytic, sedative and anticonvulsant actions or CNS-stimulant effects that are relevant to the respective treatment of symptoms such as anxiety, agitation, sleeplessness, epilepsy, apathy, lethargy, excessive daytime sleepiness and catatonia, which are present in many psychiatric disorders.

4.1 Pharmacology of Essential Oils with Sedative Activity

The pharmacological profile of lavender (*L. angustifolia*), the essential oil that has been the most widely investigated, provides a model for the pharmacological activity of an essential oil and its individual constituents. The actions of lavender may be significant in the quest for novel anxiolytic agents that lack the dependency issues associated with current therapies such as benzodiazepines.[57]

Inhalation of the essential oil of *L. angustifolia* has been found to block pentetrazol-, nicotine- and electroshock-induced convulsions[79] and exhibit dose-dependent anti-conflict effects in mice similar to those of diazepam.[78] Inhalation of *L. angustifolia* (and its main constituents linalool and linalyl acetate) for 1 hour decreased the motility of normal mice, and reversed caffeine-induced over-agitation in mice.[72,73] This sedative and anxiolytic activity was directly correlated with blood concentrations (3–11 ng/mL of linalool and linalyl acetate).[73,75] However, *L. angustifolia* extracts exhibited no antidepressant effects in a forced swimming test in rats.[92] Such extracts protected neurons against glutamate toxicity in rat cerebellar granular cell culture.[81]

The main constituent of lavender, the monoterpenoid linalool, possessed anticonvulsant properties in glutamate-related seizure models and effects on NMDA receptor binding.[86,88,89] It also inhibited potassium-stimulated glutamate release and decreased glutamate uptake in mice cortical synaptosomes,[90] and modified the kinetics of the nicotinic receptor ion channel at the mouse neuromuscular junction.[91]

There is evidence for a distinction between the pharmacology of the enantiomers of linalool. (*R*)-(−)-Linalool (present in lavender oil) produced a

Table III. CNS effects of lavender species[a] essential oil and constituents

Lavender species [% constituents]	Main CNS effect	*In vitro* and *in vivo* pharmacology	References
Lavandula angustifolia Mill. (syn. *Lavandula officinalis*),	Anticonflict	Dose-dependent (400–1600 mg/kg, SC) anti-conflict effects in the Geller conflict test, with effects similar to diazepam	78
French lavender [linalyl acetate 45%, (*R*)-(−)-linalool 38%, (Z)-β-*cis*-ocimene 10%]	Anticonvulsant	Inhalation of oil blocked pentetrazol-, nicotine- and electroshock- but not strychnine-induced convulsions in mice. A dose of 33mg decreased motility of normal mice and reversed caffeine-induced over-agitation in mice; serum concentration of linalool correlated with effects on motility	72,79
	Sedative/anticonvulsant	Increased pentobarbital-induced sleeping time. Sedative effects in certain tests in mice. Suppressed the population spike amplitude in the CA1 region of rat hippocampal slice preparation following application of essential oil (IC_{50} 65 μg/mL); effects comparable to the $GABA_A$ agonist muscimol (Perry N et al., unpublished data)	80
	Neuroprotective	Extract of flowers protected against glutamate-induced neurotoxicity in rats (100 mg/L)	81
	Spasmolytic	Spasmolytic action on guinea-pig ileum smooth muscle (postsynaptic, not atropine like)	82
	Anaesthetic	Concentrations of 0.01–10 μg/mL produced dose-dependent local anaesthetic activity in the rabbit conjunctival reflex test. Restorative effects on stress-induced immunosuppression	83,84
Lavandula stoechas L.	Anticonvulsant/sedative	600 mg/kg (aqueous-methanolic) extract of flowers reduced severity and increased latency of pentylenetetrazole-induced convulsions; prolonged pentobarbital-induced sleeping time in mice, with effects similar to diazepam	85
Lavandula vera D.C.	Anticonvulsant	Prevented metrazol-induced convulsions (200–300 mg/kg, IP) in 60–70% of mice and rats. 108–164 mg/kg (IP) inhibited electroshock-induced convulsions in rats	44
	Sedative	10–300 mg/kg potentiated narcotic effects of hexobatbital sodium, alcohol and chloral hydrate, and inhibited spontaneous motor activity in mice	
Linalool [30–40%]	Anticonvulsant	Competitive antagonism of [^{3}H]-glutamate and non-competitive antagonism of [^{3}H]-dizocilpine (NMDA receptor antagonist) binding in rat cortical membranes. Evidence that optically active linalools may have different CNS effects. Delayed NMDA-induced convulsions and blocked QUIN-induced convulsions; partial inhibition and significant delay of behavioural expression of pentylenetetrazole-induced kindling in mice. Protection against pentylenetetrazol- and picrotoxin-induced convulsions and non-competitive inhibition of [^{3}H]-dizocilpine binding (IC_{50} 2.97 mmol/L) but no effect on [^{3}H]-muscimol binding in mice. Significantly inhibited (at concentrations of 1 and 3 mmol/L) potassium-stimulated [^{3}H]-glutamate release and decreased its uptake in mice cortical synaptosomes	86-90
	Sedative	Inhalation (of 27mg) decreased motility of normal mice and reversed caffeine-induced over-agitation in mice	72,73
	Anaesthetic	Modified the kinetics of the nicotinic receptor ion channel at the mouse neuromuscular junction. Inhibited basal adenylate cyclase activity	86,91
Linalyl acetate [10–20%]	Sedative	Inhalation of 23mg caused a particular decrease in motility in normal mice and reversed caffeine-induced over-agitation in mice. No antidepressant effects in forced swimming test in rats	72,73,92

a The main lavender species used in aromatherapy is *Lavandula angustifolia*, although other species include *L. latifolia*, *L. stoechas* and *L. x intermedia*. These species do not have the same phytochemistry and may have differing biological activities.[67]

IC_{50} = concentration that inhibited the effect by 50%; **IP** = intraperitoneal; **QUIN** = quinolinic acid; **SC** = subcutaneous.

decrease in beta wave activity (~13Hz) following inhalation in healthy 20- to 26-year-old subjects that was similar to that of (*RS*)-(±)-linalool. However, (*S*)-(+)-linalool had no effect on this parameter.[131]

Available data suggest that the anticonvulsant and CNS depressant effects of *L. angustifolia* and its main constituent linalool (and its acetate) are likely to occur via modulation of components of the glutamatergic system (i.e. NMDA receptor subtype), although more direct cellular mechanisms such as inhibition of adenylate cyclase (affecting cyclic adenosine monophosphate second messenger activity) and ion channel activity (affecting neurotransmitter release) may also be relevant to clinical effects.[82,86,90,91] Such physiological mechanisms are consistent with the extensive use of lavender as a sedative/CNS depressant and anti-anxiety agent in aromatherapy and herbal medicine (for reviews see Cavanagh and Wilkinson,[67] Buchbauer et al.[73] and Kirk-Smith[132]).

Several essential oils have anxiolytic and sedative actions; the pharmacological action(s) of species such as melissa (*M. officinalis*) and neroli (*Citrus aurantium*), which are used in aromatherapy massage and inhalation for this purpose, are listed in table IV.

4.2 Pharmacology of Essential Oils with Stimulant Activity

Some essential oils are traditionally used as stimulants, although there are fewer of these than sedative oils (table V). Essential oils with stimulant properties include rosemary (*Rosmarinus officinalis*), sage (*Salvia sp.*) and jasmine (*Jasminum grandiflora*). Data (mainly from studies on locomotor activity in animals) indicate that these oils have pharmacological activity consistent with their therapeutic application (table I and table V). For example, inhalation and oral administration of rosemary oil stimulated locomotor activity in mice and this was correlated with blood concentrations of 1,8-cineole (the major constituent of this oil).[64] 1, 8-Cineole has been shown to increase global cerebral blood flow after 20 minutes inhalation in human subjects; interestingly, and importantly in relation to physiological versus psychological mechanisms, the same effects were seen in an anosmic subject.[133] Furthermore, Kagawa et al.[98] showed that the sesquiterpenoid cedrol (a component of pine essential oils) had sedative effects in normal and anosmic (zinc sulphate treated) rats (table IV). This substantiates the view that the effects of certain inhaled essential oil constituents are independent of olfactory function.[98] However, some essential oils may not affect those who are olfactory deprived, since a chamomile and lavender oil mix reduced pentobarbital-induced sleep time in normal but not anosmic mice and rats.[98]

The effects of essential oils with stimulant activity may occur through the modulation (antagonism) of $GABA_A$ receptor activity,[134] cholinergic (nicotinic and muscarinic) receptors[110] or transmitter-related enzymes (acetylcholinesterase, adenylate cyclase).[124,127] Such stimulant effects may be relevant to the treatment of memory disorders and apathy – common to a variety of psychiatric disorders (e.g. Parkinson's disease, frontotemporal dementia, progressive supranuclear palsy and catatonic schizophrenia).

4.3 Pharmacokinetics and Pharmacodynamics

From the data available, blood concentrations of essential oil constituents following inhalation or oral administration are generally in the nL/mL blood range (tables III, IV and V). The therapeutic effects of oral versus inhalation/dermal application may differ, since metabolism of the constituents may occur at differing rates before circulation in the body. An unexplored aspect of naturally occurring terpenoids is the significance of their metabolites in relation to neuropharmacological mechanisms and

Table IV. The main essential oils used in aromatherapy and their constituents that show pharmacological sedative activities

Essential oil, common name if known (family) [main constituents[a]]/constituent with activity [essential oil/s found in]	Main CNS effect	*In vitro* effects and *in vivo* pharmacology	References
Acorus gramineus, Solander (Araceae) [α- and β-asarone]	Anticonvulsant, neuroprotective, sedative	Inhibited the binding of an NMDA receptor-ion channel blocker [^{3}H]-dizocilpine, but not a ligand selective for the glycine binding site. Rhizome essential oil 0.3 mg/mL inhibited glutamate- (but not AMPA-) induced excitotoxicity in primary cultured rat cortical neurons. Rhizome essential oil inhalation in mice delayed appearance of pentylenetetrazole-induced convulsions, prolonged pentobarbital-induced sleeping time and inhibited activity of GABA transaminase	94,95
Artemisia annua L. (Asteraceae) [camphor 22.7%, 1,8-cineole 20.4%, *p*-cymeme 12.2%]	Sedative	470 mg/kg (IP) produced CNS depressant activity in rats	96
Benzyl alcohol [in e.g. *Tilia cordata*]	CNS depressant	Decreased motility of mice following inhalation. Inhalation of its acetate produced no effect on pentobarbital-induced sleeping time in mice	72,97
Cedrol [in cypresses and pines, e.g. *Juniperus virginiana* L.]	Sedative	Decreased spontaneous motor activity in normal, caffeine-treated and hypertensive rats and mice, and prolonged pentobarbital-induced sleeping time in normal and anosmic rats (408 μg/mL in air 1.0 L/min)	98
1,8-Cineole [in e.g. *Rosmarinus officinalis*]	Sedative	30 mg/kg (IP) decreased motor activity in mice	99
Citral [in e.g. *Melissa officinalis*]	Sedative, antidepressant	Increased duration of barbiturate-induced sleeping time and had motor relaxant effects (100–200 mg/kg IP) in rats. 0.1 mL/h significantly reduced total immobility time and potentiated the imipramine-induced reduction of total immobility time in a forced swimming test in rats	92,100
Citronellol [in e.g. *Rosa centifolia*]	Anticonflict	400–800 mg/kg (IP) possessed anticonflict effect similar to diazepam in Geller and Vogel tests in mice	101,102
Citrus aurantium L., neroli (Rutaceae) [linalool 37.5%, limonene 16.6%, β-pinene 11.8%]	Anticonvulsant, anxiolytic, sedative	0.5 g/kg peel essential oil increased latency period of tonic seizures in pentylenetetrazole- and electroshock-induced convulsions in mice and 1 g/kg increased the sleeping time induced by pentobarbital. Anxiolytic effect in the elevated plus maze test. Inhalation of Subsp. a*urantium* reduced motility of mice by 65%. Inhalation decreased motility of normal but not caffeine-injected mice	103
Citrus bergamia Risso, bergamot (Rutaceae) [limonene 38%, linalyl acetate 28%, linalool 8%]	CNS depressant	10–40 mg/kg (IP) nonvolatile extract of essential oil reduced spontaneous activity, potentiated sodium pentobarbital-induced sleeping time and protected against pentylenetetrazole-induced convulsions in mice	104
Eugenia caryophyllata, clove (Myrtaceae) [eugenol 77%, β-caryophyllene 10%]	Anticonvulsant	0.050–0.1 mL/kg (IP) suppressed tonic electroshock-induced convulsions and mortality in mice	105
Laurus nobilis Linn. (Lauraceae) [cineol, eugenol, sabinene, 4-terpineol]	Anticonvulsant, sedative	Protected mice against electroshock- and pentylenetetrazole-induced convulsions and at 0.75–1 mL/kg (IP) produced sedation and motor impairment in mice, though LD_{50} value was 1.45 (1.22–1.71) mL/kg	106

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Table IV. Contd

Essential oil, common name if known (family) [main constituents[a]]/constituent with activity [essential oil/s found in]	Main CNS effect	*In vitro* effects and *in vivo* pharmacology	References
Lavandula species	See table III	See table III	See table III
d-Limonene [in e.g. *C. bergamia*]	Sedative	50–200 mg/kg (IP) increased duration of barbiturate-induced sleeping time and had motor relaxant effects	100
Matricaria chamomilla L., Roman chamomile (Asteraceae) [see below]	Anxiolytic	Inhalation decreased restriction stress-induced increases in plasma ACTH level in normal and ovariectomised rats in the same manner as diazepam. Effect was blocked by pretreatment with the benzodiazepine receptor antagonist flumazenil. 200–800 mg/kg (SC) exhibited no anticonflict effects in the Vogel or Geller conflict tests in mice	107
Matricaria recutita L., German chamomile (Asteraceae) [farnesene 27%, chamazulene 17%, (−)-α-bisabolol 14%, (−)-α-bisabololoxides A and B 11%]	Anticonvulsant	Extracts of chamomile reduced the latency in the onset of picrotoxin-induced convulsions and decreased mortality rate. Flavonoids present in herb (e.g. apigenin) demonstrated a low affinity for the benzodiazepine receptor, with no effects at muscarinic or α_1-adrenergic receptors, or the GABA binding site of the $GABA_A$ channel	108,109
Melissa officinalis, lemon balm (Labiatae) [geranial 31.9%, neral 22.3%, β-caryophyllene 9.7]	CNS depressant, anticonflict, analgesic, sedative, cholinergic, antioxidative	Suppression of the population spike amplitude in the CA1 region of rat hippocampal slice preparation following application of essential oil (IC_{50} 128 μg/mL), comparable to the $GABA_A$ agonist muscimol. 3–100 μL/kg did not influence behavioural parameters in the staircase test in mice and inhalation produced no effect on the motility of mice. 12–800 mg/kg extract decreased behavioural parameters measured in a non-familiar environment test (staircase test) and familiar environment test (two compartment test). 400–1600 mg/kg extract produced peripheral analgesia by reducing acetic acid-induced pain; 3–6 mg/kg extract (and not 100 μL/kg essential oil) induced sleep in mice after treatment with an infrahypnotic dose of pentobarbital; 6 and 50 mg/kg potentialised sleep induced by pentobarbital. 25 and 50 mg/kg extract produced sedative and hypnotic effects and potentiated barbiturate-induced sleep time. Extracts (ethanolic) displaced [^{3}H]-(*N*)-nicotine and [^{3}H]-(*N*)-scopolamine in receptor binding studies using human cerebral cortical cell membranes. Leaves contain compounds with 10-fold greater radical scavenging ability than ascorbic acid and α-tocopherol (Perry N et al., unpublished data)	110-115
Mentha rotundifolia, L. mint (Labiatae) [rotundifolone 10.4%, piperitol 57.6%], *Mentha longifolia*, mint (Labiatae) [rotundifolone 33.2%, diosphenol 47.7%]	Sedative	CNS depressant effect (100–400 mg/kg) in spontaneous activity and curiosity test, potentiation of pentobarbital-induced sleep (50 mg/kg) in mice and rats	116
Menthone [in e.g. *Calamintha sylvatica*]	Sedative	30 mg/kg (IP) decreased motor activity in mice	99
Passiflora incarnate L., passiflora (Passifloraceae) [matol, 2-phenylethanol]	Sedative	Decreased motility of caffeine-induced over-agitated mice but not normal mice following inhalation	73

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Table IV. Contd

Essential oil, common name if known (family) [main constituents[a]/constituent with activity [essential oil/s found in]	Main CNS effect	*In vitro* effects and *in vivo* pharmacology	References
2-Phenethyl alcohol [in *R. centifolia*]	Anticonflict	400–800 mg/kg (IP) possessed anticonflict effect similar to diazepam in Geller and Vogel tests in mice	101,102
Pulegone [in e.g. *C. sylvatica*]	Sedative	30 mg/kg (IP) decreased motor activity in mice	99
R. centifolia, rose (Rosaceae) [2-phenethyl alcohol, citronellol, geraniol]	Anxiolytic	400–800 mg/kg (IP) possessed anticonflict effect similar to diazepam in Geller and Vogel tests in mice. Inhalation produced no effects on pentobarbital-induced sleep time in mice. Restorative effects on stress-induced immunosuppression in mice	101,102,117,118
Safrol [in e.g. *Licaria puchury-major*]	Sedative	100–500 mg/kg (IP) reduced motor activity, impaired the performance in the rotarod test and protected against electroshock-induced convulsions in mice	119
α-Terpineol [in e.g. *Lavendula* sp.]	Sedative	Inhalation decreased motility of normal and over-agitated mice	73
Terpineol [in e.g. *Eucalyptus globulus*], terpinyl acetate	Anaesthetic, sedative	Dose-dependent (300–600μM) reversible blockade of the compound action potential of rat sciatic nerve, suggested to be 'clinically' relevant (i.e. concentration reached in dermal tissues during massages with essential oils). Inhalation increased pentobarbital-induced sleep time in mice	117,120

a Taken from the individual references detailed or from Bowles.[93] The principal chemical constituents are listed in order of concentration, highest first; note that proportions may vary according to source and that many oils contain hundreds of terpenoids.

ACTH = adrenocorticotropic hormone; **IC_{50}** = concentration that caused 50% inhibition; **IP** = intraperitoneal; **LD_{50}** = dose lethal to 50% of animals; **SC** = subcutaneous.

to psychological and clinical psychiatric effects. In addition, chiral differences influence the pharmacokinetic behaviour, as well as affecting the biological activity, of constituents.[10,64,131,135,136]

The pharmacokinetic profile of monoterpeniods so far studied indicate a two-phase elimination – rapid and slow rate – with accumulation in adipose tissue.[64,73,137] The cytochrome P450 enzymes metabolise certain essential oil constituents by addition of a sulphate or glucuronate group (e.g. linalool shows part conjugation to glucuronic acid) and, thus, some contraindications associated with hepatotoxicity are evident (see section 3).

5. Conclusions and Challenges

The essential oils with reputed sedative actions such as lavender, lemon balm and neroli have pharmacological actions consistent with reducing CNS activity (tables III and IV) and, likewise, those with a stimulant reputation, for example rosemary, sage and jasmine, have comparable CNS stimulant-like *in vitro* and *in vivo* activities (table V). Thus, there are no apparent contradictions between the anecdotal and scientific literature, or clinical effects and pharmacological profiles. There is, however, a need to establish a phytochemical and pharmacological profile (database) of specific putative clinical essential oil agents in order to establish phytochemical standardisation, mechanism of action and any clinical contraindications.

Relevant 'psychoaromatherapeutic' effects of essential oils so far studied occur through a direct action of chemical constituents on: CNS receptors, including cholinergic,[110,138] GABAergic[128,134] and glutamatergic subtypes;[88,89,94] ion channels, including potassium and calcium;[85,90,91,124,139,140] and enzymes, for example adenylate cyclase and acetylcholinesterase.[13,76,84,86,126,127,141-145] However, to date, all of the pharmacological studies of terpenoids have involved established bioassays generally based on receptor targets of established neurotrans-

Table V. The main essential oils used in aromatherapy that show pharmacological stimulant activities

Essential oil, common name (family) [main chemical constituents[a]]/single constituents (% in oil)	Main effect	*In vitro* and *in vivo* pharmacology	References
Citrus limonum, lemon (Rutaceae) [citral, geranyl acetate]	Antidepressant, stimulant, neuroimmunomodulatory	0.1 mL/h vapour reduced total immobility time and potentiated the imipramine-induced reduction of total immobility time in a forced swimming test in rats. Shortened pentobarbital-induced sleep time in normal but not anosmic (via zinc sulphate) mice. Long-term inhalation of lemon 'fragrance' in mice induced suppression of plaque-forming cells in blood (immune response) induced by high-pressure stress. Inhalation modulated the behavioural and neuronal (acetylcholine release) responses related to nociception and pain differently in male and female rats. Restorative effects on stress-induced immunosuppression in mice	92,117,118,121-123
Isoborneol and isoeugenol	Stimulant in normal, anxiolytic in stressed	Inhalation increased locomotor activity of mice under normal conditions, though decreased it in over-agitated mice pretreated with caffeine	73
Jasminum grandiflora L., Jasmine [benzyl acetate 22%, benzyl benzoate 14.5%, phytyl acetate 10.2%)	Stimulant, spasmolytic	Stimulant on inhalation in animals and humans. Shortened pentobarbital-induced sleep time in normal but not anosmic mice. 200–800 mg/kg (IP) exhibited no anticonflict effect using the Geller-type conflict test in mice or antidepressant effects in forced swimming test in rats. Spasmolytic activity on guinea-pig ileum and rat uterus, suggested mediation via (rise in) cAMP	7,8,10,78,97,117,124
Mentha piperita L., peppermint (Labiatae) [menthol 43%, menthone 19%)		400 and 800 mg/kg (IP and IV) increased ambulatory activity of mice. Note other *Mentha* species with distinct photochemistry (e.g. *Mentha longifolia*) may have CNS depressant activity (table IV)	116,125
Rosmarinus officinalis L., rosemary (Labiatae) [α-pinene 22%, camphor 17%, 1,8-cineole 17%]	Stimulatory	Increase in locomotor activity observed after inhalation and oral administration. Following 0.5mL rosemary oil per cage for 1 hour, the concentration of 1,8-cineole in the blood was 11.15 nL/mL (approaching that in the breathing air, 13.65 nL/mL). Inhalation and oral administration produced dose-related increase in blood levels of 1,8-cineole. There was rapid elimination after 10 min ($t_{½}$ 6 min) and slower elimination after 45 min. Extracts delayed the onset of picrotoxin-induced seizures and decreased the mortality rate in mice	64,108,126
Salvia officinalis L., French sage (Labiatae) [α-thujone 37%, β-thujone 14%, camphor 12%, 1,8-cineole 12%]	Cholinergic, stimulatory, GABAergic, antioxidant	0.1 mg/mL and certain constituent monoterpenoids inhibited erythrocyte acetylcholinesterase. Extracts (ethanolic) of certain *Salvia sp.* displaced [^{3}H]-(*N*)-nicotine and [^{3}H]-(*N*)-scopolamine in receptor binding studies using human cerebral cortical cell membranes. 0.07 mg/mL initially increased population spike amplitude and within minutes caused epileptiform activity, followed by suppression in population spike amplitude in the CA1 region of rat hippocampal slice preparation. α-Thujone (neurotoxic in high doses) is believed to modulate $GABA_A$ receptor. Plant diterpenes (e.g. carnosol and carnosic acid) inhibited TBPS binding to the chloride channel of the GABA receptor complex, but not muscimol or diazepam binding in rat brain membranes. Monoterpenoids, extracts and phenolic components exhibited antioxidant activity on lipid peroxidation (Perry N et al., unpublished data)	29,76,110,127

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Table V. Contd

Essential oil, common name (family) [main chemical constituents[a]/single constituents (% in oil)	Main effect	*In vitro* and *in vivo* pharmacology	References
Salvia lavandulaefolia Vahl., Spanish sage (Labiatae) [camphor 22%, 1,8-cineole 21%, borneol 13%, α-thujone 1%]	Neurochemical/putative memory-enhancing, stimulatory, antioxidant, anti-inflammatory	Essential oil (IC_{50} 0.03 mg/mL) and certain constituent monoterpenoids inhibited erythrocyte acetylcholinesterase. 20 and 50µL essential oil inhibited rat striatal and hippocampal acetylcholinesterase following oral administration. 0.07 mg/mL increased population spike amplitude with no epileptiform activity in the CA1 region of rat hippocampal slice preparation. Essential oil and certain monoterpenoid constituents exhibit *in vitro* antioxidant and anti-inflammatory activity (Perry N et al., unpublished data)	28,29,76,127
Tagetes minuta L., 'chinchilla' (Asteraceae) [*c*-ocimene, *t*-ocimene, dihydrotagetone]	Anxiogenic	45 µg/mL inhibited binding of the benzodiazepine [^{3}H]-flunitrazepam to rat and chick brain membranes. 0.3 mg/kg (SC) displayed anxiogenic and antidepressant-like effects in rats in elevated plus maze and forced swimming tests. 0.04–0.45 mg/kg exhibited anxiogenic effects on chick behaviour in T-maze and tonic immobility tests	128-130
Thymol	Stimulant in normal, anxiolytic in stressed	Inhalation increased locomotor activity of mice under normal conditions, though decreased it in over-agitated mice pretreated with caffeine	73

a Taken from the individual references or from Boelens BACIS ESO database;[6] principal chemical constituents listed in order of concentration, highest first; note that proportions may vary according to source and that many oils contain hundreds of terpenoids.

cAMP = cyclic adenosine monophosphate; IC_{50} = concentration that caused 50% inhibition; **IP** = intraperitoneal; **IV** = intravenous; **SC** = subcutaneous; $t_{½}$ = elimination half-life; **TBPS** = t-butylbicyclophosphorothionate.

mitters, which are almost all amines or nitrogen-containing. Terpenoids, in contrast, generally being hydrocarbons, may interact with the CNS in as yet undiscovered ways, raising the exciting prospect of uncovering novel receptors, molecular targets or endogenous chemical signals in the CNS. This parallels the discovery of the endogenous cannabinoids and their receptors, which were identified originally based on the interaction of plant-based terpenoids from *Cannabis sativa* with CNS receptors.

Some of the challenges for further research that can presently be identified are summarised in table VI. As well as considering potential contraindications and/or adverse effects of certain essential oils (including skin sensitivities and toxicities and abortifacient effects), in the event that clinical efficacy is established for particular oils and this efficacy is attributable to specific terpenoids, the question then arises as to whether future treatment should involve the use of single chemical constituents or combinations of these. This would satisfy those that seek simple, standardised formulations as medicines but most probably not the vast majority of aromatherapeutic practitioners who believe in the value of the whole essential oil.

The linking of subjective or objective behavioural evaluations to potential objective assessments, such as neuroimaging or EEG, when assessing essential oils would help establish aromatherapy in clinical practice. Several studies have reported results from such assessments. In healthy individuals, 8–10Hz EEG reductions in parietal and temporal regions were reported after lavender oil inhalation, associated with subjective ratings of feeling comfortable.[146] In 15 healthy adults exposed to lavender or single 'aromatic' chemicals (e.g. ethyl aceto acetate and camphor), autonomic measures including skin potential and respiratory and heart rates altered in conjunction with hedonic effects.[147] Other potential physiological measures that are affected by lavender include auditory reaction time

Table VI. Challenges for further research into the use of aromatherapeutic agents for psychiatric disorders

Clinical trials	Conducting suitably powered, controlled trials, fulfilling the rigid criteria for blinded, randomised, controlled trials, or developing other criteria for establishing clinical efficacy
Selection and standardisation of oils	Selecting appropriate aromatic oil(s), based on relevant bioactivities and chemical composition as well as traditional use, together with standardisation of commercial preparations, application procedure and dose delivery
Chemical constituents	Establishing the active constituent(s) in order to understand the pharmacology, toxicology and interactions that may occur between constituents
Anosmic issues	Identifying and separating the psychological and pharmacological effects and relevance to anosmic patients
Adverse reactions, interactions and contraindications	Developing awareness of which essential oils do or no not have contraindications, potential interactions with other medications, and individual dermal or other adverse reactions
Individuality	Aromatherapeutic practice tailors the application to the individual as opposed to standardised symptomatic treatment; this poses obvious challenges
Acceptance	Bridging the gap between preferences and practices between nursing and medical practitioners; accumulating scientific evidence, clinical trial data and relevant pharmacology to enable, e.g. general practitioners, to consider prescribing the use of specific essential oils as an adjunct to conventional medicine in psychiatric disorders; availability of standardised 'aromaceuticals' with information on clinical and pharmacological effects; including such information in medical student education; acceptance of complex, synergistic effects of a therapeutic agent
Research support	Identifying research support – the absence of economic incentives for the pharmaceutical industry and the insufficient resources of commercial suppliers of essential oils indicate the need for government and charity support

and critical flicker fusion frequency.[146] Preliminary evaluations to select the most appropriate 'aromatic' oil for individual symptoms could, thus, include standardised physiological and perhaps also psychological assessment measures.

One of the major challenges in conducting controlled trials of aromatherapy is the issue of individuality, not only in terms of treatment response but also the selection of the essential oil on the basis of subjective preference and context. Sugawara et al.[87] evaluated the perception of a range of oils (ylang ylang, orange, geranium, cypress, bergamot, spearmint and juniper) in 24 healthy young adults, based on a range of responses including 'soothing', 'pleasant' and 'comfortable', while performing different types of work. They reported various results, including that juniper was found to be more favourable during mental work, whereas geranium and orange were unfavourable under this condition. This and other reports[84,131] raise the issue of whether such subjective sensory tests should be incorporated into preliminary clinical trials of essential oils.

Since aromatherapy, like any pharmacotherapy, potentially affects all systems, the indirect effects of essential oil therapy on cerebral function, such as those on the cardiovascular system and autonomic function, may need to be considered. Heuberger et al.[10] reported that inhalation of (+)-limonene increased systolic blood pressure, together with subjective alertness and restlessness, whereas (−)-limonene had only effects on blood pressure (also incidentally indicating that molecular chirality is relevant in terms of mechanisms). Similar peripheral changes affected by lavender inhalation were noted in healthy volunteers who liked, as opposed to did not like, the fragrance.[148] Nagai et al.[149] observed that odours of choice, including rose, jasmine or lavender, reduced an increase in diastolic blood pressure induced by exercise in healthy adults, and Komori et al.[54] showed that citrus odours restored stress-induced immunosuppression.

Thus, it may not be possible to fully assess the clinical value of aromatherapy in psychiatry without taking into account the additional pharmacology of

essential oils that contributes to general physical well-being. Essential oil constituents that penetrate the nasal passages, skin or lungs have direct actions on the autonomic nervous system that can be grouped as relaxing or stimulating in terms of basic responses such as heart rate, blood pressure and respiration, in addition to localised dermal and bronchial effects.[10,131,138,147,149-151] In addition to the direct neuropharmacological properties of an essential oil, the smell of the oil may exert a pleasant familiar learnt response, via the olfactory system. This, in turn, alters the hypothalamic control of hormones and neurotransmitters. Further antiviral, antibacterial, antifungal, antioxidant, anti-inflammatory and immuno-restorative properties of certain essential oils[54,84,97,141,142,144,145] support a multiplicity of CNS and autonomic nervous system effects.

In conclusion, based on relevant neuropharmacological and limited clinical evidence, aromatherapy is a treatment with major, but relatively unexplored, potential in the field of clinical psychiatry. Together with the outstanding need to provide an evidence base derived from controlled trials, is the requirement for information on safety, drug interactions and sources of standardised preparations. While lavender is the most widely used essential oil, there is immense scope for exploring other oils that have distinct chemical and relevant physiological effects. This may lead to the identification of specific plant-based essential oils for the treatment of psychiatric disorders that are as effective as synthetic pharmaceuticals, and perhaps also safer and with fewer adverse effects.

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