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FOCUS ON: NEUROPHARMACOLOGY

Lemon Balm and Lavender herbal essential oils: Old and new ways to treat emotional disorders?

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Summary Nature is the best chemist. Novel therapeutics derived from natural sources is clearly a worthwhile strategy and has long historic pedigree. Anxiety, depression and psychotic disorders lack ideal medications based on a limited understanding of the underlying causes of these complaints. Many of the current therapeutics display lack of efficacy and/or multiple side effects. There is growing evidence that essential oils derived from plants have useful properties in relieving emotional disorders, particularly those seen in neurodegenerative diseases. This review focuses on two essential oils derived form Melissa and Lavender plants, both of which have useful anti-agitation properties in humans, the former having an additional beneficial property of maintaining attention in patients suffering from dementias.

Introduction

The importance of natural products has a long history and a potential for an equally long future in drug discovery. Novel biologically active natural products will continue to serve as lead compounds for drug development and as biochemical probes for the discovery of pharmacological and biochemical processes.[1] Clearly, the natural products discovered to date have played a vital role in improving the human condition, and this role will continue as long as there are unexplored sources of novel natural products (e.g. microbial, marine and plant). Aromatherapy using extracts of selected plant species offers one possible alternative to pharmacotherapy.[2] Knowledge of the distillation of essential oils and their application to improve health and well-being was introduced into science in the 10th century (reviewed in Ref.[3]). Aromatherapy is currently used worldwide in the management of chronic pain, depression, anxiety, as well as cognitive, sleep- and stress-related disorders.[3]

Essential oils

Although essential oils have been used for centuries as a traditional medicine, there is very limited verified basic science behind this use. The pharmacology of

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the essential oils and/or their single chemical constituents, therefore, remains largely poorly explored. However, the peer-reviewed traditional pharmacological literature has been expanding in the last decade, which confirms how inhaled or dermally applied essential oils do enter the blood stream and in animal models, do exert measurable psychological effects. These studies strongly support a pharmacological mode of action (reviewed in Ref.[3]) Growing scientific evidence in psychiatric disorders and the effects of essential oils on *in vivo* animal models have been published.[2,4,5] In addition, taking into account the available information on safety, aromatherapy appears to lack the adverse effects seen with conventional psychotropic drugs, supporting the need for further investment in clinical and scientific research on essential oils.[3]

Dementias: psychiatric issues

Dementia is increasingly an important management problem as the elderly population increases. Although attention is usually focused on cognitive deficits, greater than half the people with dementia experience behavioural or psychiatric symptoms, known as ''Behavioural and Psychological Symptoms in Dementia'' (BPSD). These symptoms include aggression, agitation, screaming, wandering, hallucination and delusion, and are distressing for both the patients and for their carers, often the reason for placement in residential or nursing home care.[6,7] The most frequent and persistent BPSD syndrome in patients with severe dementia is agitation, usually characterized by a combination of aggression (verbal and/or physical) restlessness, and abnormal vocalization in the context of subjective anxiety. Therefore, particularly for those with severe dementia, there is an urgent need to identify safer and better tolerated treatment regimes for behavioural disturbance, especially for the management of agitation.[7,8]

Although non-pharmacological interventions, including verbal environmental intervention, should be first-line therapy for milder BPSD[9] many psychotropic agents (e.g. antipsychotics, benzodiazepines, antidepressants, anticonvulsants and beta-blockers) have been used to manage more severe behavioural deficits. However, their efficacy is limited[10] and their use has been curtailed due to significant adverse effects such as orthostatic hypotension, arrhythmia, extra-pyramidal symptoms, urinary retention, constipation, sedation and delirium.[6,7]

More recently, the newer atypical antipsychotics, with a dual serotonin (5-HT_2) and dopamine (D_2) antagonist pharmacology, have been used for the treatment of aggression/agitation in dementia patients. Early double-blind, placebo-controlled trials have demonstrated that some atypical neuroleptics, such as risperidone and olanzapine have beneficial effects and are well tolerated.[11–14] Prescribed cautiously, psychotropic drugs may enhance the physical and psychological well-being of elderly patients. However, this age group appears to be particularly sensitive to undesirable drug effects, which can lead to a decline in medical and functional status. Furthermore, the common use of polypharmacy in these subjects leads to increased risk of drug interactions.[15] Recently, an increased risk of cerebrovascular disease related to the use of risperidone and olanzapine was reported.[11,16] These reports have led to controversy among clinicians.[17] Notably, an increased risk of cerebrovascular disease after administration of atypical antipsychotics was not confirmed in a recent controlled trial[17] and in a population-based retrospective study comparing the incidence of stroke in older adults ($\geqslant$65 years) with dementia receiving atypical (olanzapine, risperidone and quetiapine) or typical antipsychotics.[18] Although atypical antipsychotic drugs are being used with increasing frequency, only a few randomized trials have evaluated their use in BPSD.

In summary and conclusions, treatment of BPSD has not been standardized and currently entails a range of pharmacological and non-pharmacological approaches.[2,3] Pharmacological targets for the reduction of aggression/agitation include the neurotransmitter systems serotonin (5HT), dopamine, acetylcholine (via nicotinic and muscarinic receptors) and GABA. The serotonergic system is particularly implicated in agitation on the basis of genetic linkage data. Agitation-reducing effects of SSRI antidepressant drugs and potent antipsychotic effects of antipsychotic drugs with high affinity for the 5-HT_2 receptors, implicates particularly the $5HT_{2A}$ subtypes. The dopamine D_2 receptor is also implicated as the most consistent target of narcoleptic medication although clinico-pathological evidence implicating dopaminergic dysfunction in neuropsychiatric or behaviour symptoms in dementia is far less convincing than that for the cholinergic system. The nicotinic receptor is also associated with anxiolysis and the $GABA_A$ receptor is the site action of the clinically used anxiolytic agents.[9]

Pharmacological treatment with neuroleptic agents is often the first line treatment for agitation.

There are no trials specifically in people with severe dementia, although placebo-controlled trials have demonstrated moderate efficacy for the treatment of BPSD with neuroleptic agents in people with mild/moderate dementia.[19,20] Neuroleptics are often poorly tolerated by people with dementia, particularly those with severe dementia, and there is a high risk of adverse acute events, including Parkinsonism, drowsiness, falls, accelerated cognitive decline and increased mortality. There is also a detrimental impact on key indicators of quality of life, including general activity, well-being and social interaction.[7] However, even though neuroleptics have been the best-studied class of drugs to date, their modest efficacy and significant potential side effects often limit their use.[10,21]

''Complementary'' or ''alternative'' therapies have grown in popularity and have been applied to a wide range of health problems, including people with dementia.[2] Therapies have included massage (e.g. Ref.[22]), aromatherapy (e.g. Ref.[23] and herbal medicine (e.g. Ref.[24]). Of these aromatherapy is reported to be the most commonly used in the world, and is suggested to be the most widely used complementary therapy for people with dementia.[3]

Aromatherapy is a part of the discipline of phytotherapy (the use of the whole plants or parts of plants for medicinal purposes) and uses pure essential oils from fragrant plants (such as Peppermint, Sweet Marjoram, Lavender and Rose) to help relieve health problems and improve general quality of life.[5,25,26]

Essential oils have been defined as non-oily, highly fragrant essences extracted from plants by distillation[27] and have been used for many years by health-care professionals all over the world for their antibiotic and antiviral properties.[28,29] They are most commonly used in oil burners, in bath water, or massaged into the skin, thus the aroma of the essential oil evaporates and stimulates the olfactory sense. The healing properties of aromatherapy are claimed to include promotion of relaxation and sedation, pain relief and reduction of depression,[28,30] the rationale being that the essential oils have a calming and de-stressing effect. As such, aromatherapy might be of use as an intervention for people who have little or no preserved language function, are confused or for whom verbal interaction is difficult and conventional medicine is seen as of only marginal benefit. Aromatherapy has therefore been used for people with dementia to reduce disturbed behaviour, to promote sleep and to heighten motivational behaviour.[29,30]

Despite its frequent use, the rationale for aromatherapy is based on an excess of anecdotal rather than scientific evidence. Moreover, aromatherapy does impose a cost to consumers and it is also frequently used in combination with other therapeutic approaches, such as massage, which adds further to the cost, is more intrusive and increases the vulnerability of the recipients. Additionally, there remain a few concerns regarding the safety of aromatherapy, as some essential oils have been found to have a significantly toxic effect in rodents.[28] Aromatherapy is currently not under any licensing restrictions, and is easily accessible from pharmacies and health product stores, which necessitates a need for the effects of aromatherapy to be adequately documented.[2,30]

There is mounting evidence that links BPSD to specific alterations in neurochemistry, which may underpin the basis of pharmacological manipulation. Dementia is associated with dysfunction in multiple neurotransmitter systems. Although the most well-studied neuronal system dysfunction lies in the cholinergic system, there is also evidence supporting dysfunctions within the serotonergic, noradrenergic, dopaminergic and GABA systems. Since these neurotransmitters are known to regulate behaviours and are amenable to pharmacological intervention, research attention has recently focused on the possible relationship between dysfunctions in non-cholinergic systems and behavioural disorders seen in chronic and acute neuropathologies.[7,31]

The neurotransmitter GABA is often reported to be involved in behaviours such as anxiety and aggression. Animal studies have shown that increasing GABA can decrease aggression.[32] Deficits in the central GABA system have been shown in the brains of patient with dementia.[33,34] Indirect supporting evidence for a role of GABA is provided by some of the drugs that are effective in the treatment of agitation, such as benzodiazepines.[8] Furthermore, valproic acid, which is also effective in aggressive behaviours associated with dementia, is believed to increase GABA.[35] Clearly, direct evidence is required before any link can be validated between disruptions in the GABA system and specific behaviours.[7,8,31]

Specific essential oils

The most commonly used essential oils for aggression/agitation therapy in controlled trials have been Lavender (*Lavendula augustifolia*) and lemon balm (*Melissa officinalis*), singly or in combination.

The trials have involved people with advanced dementia in residential care and have generally assessed behavioural symptoms, particularly agitation as outcome measures. The trials divide equally between inhalation and dermal application, with duration of treatment up to 4 weeks. Given the diversity of trial design and the type of aromatherapy, it is promising to note that all the treatments have resulted in significant benefits, with reduction of agitation, insomnia, wandering, difficult behaviour and social withdrawal (reviewed in Ref.[3]).

M. officinalis

Melissa oil is the essential oil extracted from the leaves of *M. officinalis* L. (Lamiaceae). This plant has been used as a medicinal plant for more than 2000 years. In traditional medicine, *M. officinalis* was used as a calming and strengthening remedy, to treat migraines, neuroses and hysteria. The Commission E Monograph in Germany approves the use of *M. officinalis* for nervous insomnia. In modern alternative medicine, *M. officinalis*, essential oil is used in aromatherapy to alleviate depression, anxiety, stress and insomnia.[36] In addition, the safety of treatment with balm essential oil has been well established in clinical populations (e.g. Ref.[29] A series of case reports in dementia pilot placebo-controlled trials has indicated some potential benefits of aromatherapy; limitations of these studies were the small number of patients and a relatively short period of follow-up assessment. Ballard and colleagues reported a double blind placebo-controlled trial with Melissa oil for treatment of agitation in 71 patients suffering from severe dementia. Aromatherapy with Melissa essential oil was shown to be safe, well tolerated and efficacious with additional benefits on key quality of life parameters. These initial findings have been followed up with the initiation of a larger and longer term multi-center trial with *M. officinalis* to be reported this year.

The main constituents of *M. officinalis* (0.01–0.20%) essential oil number at least 70 components including: monoterpenes ($>60\%$), mainly aldehydes, citronellal (30–40%), citral (20–30%), citronellal, nerol, gerniol and β-ocimene. Sesquiterpene ($>35\%$), β-carophyllene and germacrene D.[28,37,38]

Furthermore, the *M. officinalis* leaf extract was reported to alleviate mild anxiety and nervousness in a double-blind study alone and in combination with *Valeriana officinalis* root. It was also reported to be as effective as the benzodiazepine, triazolam, but, importantly, did not cause drowsiness or impair concentration.[39] A hydroalcohol (30% ethanol) extract of *M. officinalis* leaf was sedative in mice and potentiated barbiturate-induced sleep, but *M. officinalis* essential oil again did not demonstrate these sedative effects.[40]

Kennedy and colleagues reported attenuation of laboratory-induced psychological stress in human after acute administration of Melissa leaf extracts.[41–43] Other activities of *M. officinalis* extracts that may be useful for dementia therapy include antioxidant effects[5] and binding to muscarinic and nicotinic receptors *in vitro*,[25,42–44] which suggests that favourable effects on cholinergic function may occur in patients with dementia.

L. angustifolia

Lavender oil is the essential oil obtained from the aerial part of *L. angustifolia* Mill (Lamiaceae). The plant is used in traditional and folk medicines in different parts of the world for the treatment of several gastrointestinal, nervous and rheumatic disorders. It is also used as an anti-bacterial, anti-fungal, anti-depressant carminative, smooth muscle relaxing agent and sedative.[45–47]

The main constituents of 1–3% essential oils, number at least 150 components; major constituents include linalyl acetate (30–55%) and linalool (20–35%), with small quantities of nerol, borneol, β-ocimen, geraniol cineole, caryophyllene-epoxide and camphene.[48]

The pharmacological profile of Lavender essential oil has been the most widely investigated and provides a prototype for the pharmacological activity of essential oils and its individual constituents.[3,49] The action of Lavender may be significant in the quest for novel anxiolytic agents that lack the dependency issues associated with current therapies, exemplified by the benzodiazepines.[50] Inhalation of the essential oil *L. angustifolia* has been found to block pentetrazol-, nicotine- and electroshock-induced convulsions[51] and exhibit dose-dependant anti-conflict effects in mice similar to those seen with diazepam.[52] The main constituents of Lavender, the monoterpenoid linalool, possess anticonvulsant properties in glutamate-related seizure models and effects on NMDA receptor binding.[51,53] It also inhibited potassium-stimulated glutamate release[53] and modified the kinetics of the nicotinic receptor ion channel at the mouse neuromuscular junction.[54] Available data suggest that the anticonvulsant and CNS depressant effects of *L. angustifolia* and its main constituent linalool 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 adenylyl cyclase and ion channel activity (affecting neurotransmitter release) may be more relevant to its clinical effect.[54–57] Such physiological mechanisms are consistent with the extensive use of Lavender as a sedative/CNS depressant and antianxiety agent in aromatherapy and herbal medicine. The effects on anxiety require formal confirmation in a *bone fide* animal test.[58,59]

Summary and conclusions

There is growing pharmacological and clinical evidence for the rational use of Melissa and Lavender essential oils and extracts in a wide range of therapeutic settings, including agitation/aggression, epilepsy and acute and chronic emotional disorders, while displaying minimal side effects. Selection of the most appropriate aromatic oil/combination of oils for therapeutic use should be based on chemical and pharmacological criteria. It is important to determine the mechanism of action of the aromatic essential oil to be tested, not only to provide rational for treatment selection, but also so that treatment effects can be reproduced and optimized in future preclinical studies and clinical practice, and to identify key chemical constituents that are active in scientific-based investigations.[60] There is limited information regarding the detailed pharmacological effects of herbal plants since most studies use ethno-pharmacological approaches for selecting plant species for their effect on symptoms such as anxiety, restlessness, excitability and depression.

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