Are sage, rosemary and lemon balm effective interventions in dementia? A narrative review of the clinical evidence

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Title

Are sage, rosemary and lemon balm effective interventions in dementia? A narrative review of the clinical evidence

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Key words: dementia, *Salvia spp*, *Rosmarinus officinalis*, *Melissa officinalis*, rosmarinic acid, narrative review

Introduction

Dementia is a common, progressive disorder impairing brain function and affecting sufferers and caregivers' wellbeing. Numbers of dementia patients will increase as the population ages. Rosmarinic acid is a natural compound with choline esterase inhibitory potency found in members of the botanical family lamiaceae, including sage, rosemary, and lemon balm, suggesting potential efficacy in dementia intervention. This study aimed to evaluate effectiveness of these herbs based on a review of randomised controlled trials.

Methods

Database searches were conducted separately for each herb using PubMed, the Cochrane Library, and ScienceDirect for clinical evidence for sage (*Salvia officinalis* L. or *S. lavandulaefolia* Vahl), rosemary (*Rosmarinus officinalis* L.), and lemon balm (*Melissa officinalis* L.), administered individually.

Results

Database searching identified 235, 112, and 177 articles for sage, rosemary, and lemon balm, respectively. From these, eight for sage, five for rosemary and eight for lemon balm met inclusion criteria. Trials were analysed based on the study designs and summarized as narrative synthesis as data were heterogeneous in terms of the target populations, herbal preparations and administration methods.

Studies suggested sage *spp*. could improve cognitive performance and alertness. Rosemary could improve cognitive performance and alertness. Among eight articles identified on lemon balm, seven studies found it effective in improving mood or cognition. One study found no effect.

Conclusions

Some clinical evidence supports the benefit of these herbs in dementia intervention. However, methodological heterogeneity and variable trial quality made information synthesis difficult. Further research is required to determine dosage and intervention periods.

1. Introduction

1.1. Dementia

Dementia is defined as a long lasting loss of mental ability. Its prevalence was estimated to be 47.5 million worldwide in 2015 (WHO, 2015), and it is likely to rise to 66 million by 2030 and 115 million by 2050 (Wortmann, 2012). Alzheimer's disease (AD) and vascular dementia (VD) are the most common forms of dementia, accounting for 60-70% and 20% of total, respectively (WHO, 2015). Dementia not only affects the quality of life (QoL) of patients but also has a significant influence on the wellbeing of families and caregivers. Global societal and economic impact, including direct medical costs, direct social costs, and the costs of informal care, and is estimated to be 1.0% of the worldwide GDP (WHO, 2015).

Early signs of dementia include having difficulty remembering and solving simple mathematical problems, repeating the same questions, getting lost, and losing things. Later signs include trouble performing simple daily activities, confusion and disorientation, personality changes, hallucinations, and problems with language and speech (Alzheimer's society, 2014a, b; National Institute of Aging US, 2011). Stress and anxiety caused by cognitive impairment, as well as agitation, are also the common features that are highly distressing to patients and their caregivers (Dickson et al., 2012). Although amyloid-β (Aβ) deposition is the well-known hallmark of neuropathology of AD, the aetiological link is not yet resolved as only a small percentage of patients carry genetic mutations in the related genes (De Strooper and Karran, 2016; Lee et al., 2010). Meanwhile, oxidative stress has been found to be an important culprit in the development of AD (De Strooper and Karran, 2016; Lee et al., 2010), suggesting the potentials of anti-oxidants in the prevention of the disease (Kim et al., 2015b; Lee et al., 2010). On the other hand, VD is caused by neuronal loss as a consequence of the lack of oxygen and nutrients due to vascular dysfunctions. Importantly, cardiovascular problems (including high blood pressure, high cholesterol, diabetes), and a history of depression are the common risk factors for both types of dementia (Alzheimer's society, 2014a and 2014b), which indicates the significance of addressing those health issues to prevent the development of AD and VD. Of note, the hippocampus plays significant roles in memory formation and its dysfunctions are implicated in the aetiology of dementia (Lazarov and Hollands, 2016; Raskin et al., 2015).

Currently, there is no cure for dementia, and the mainstream drug intervention approach is to temporarily alleviate the symptoms by targeting the metabolism of acetylcholine (ACh), an essential neurotransmitter involved in cognitive processes. Reduced ACh levels in AD brain is implicated in cognitive decline (Vladimir-Knežević et al., 2014), and ACh-mediated signalling, particularly via nicotinic acetylcholine receptors, is thought to be a promising target in the symptomatic treatment of dementia (Lombardo and Maskos, 2015; Rusted et al., 2000). Donepezil, rivastigmine and galantamine are such drugs approved by Food and Drug Administration (FDA) and the European Medicines Agency (EMA), which are categorised as cholinesterase inhibitors (ChEIs). These drugs enhance the local availability of acetylcholine by inhibiting its degradation enzyme acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). While AChE is known as the major acetylcholine degradation enzyme in the brain, BuChE progressively accumulates in AD brain, indicating the involvement of both enzymes in dementia pathology (Lane et al., 2006). ChEIs have a modest but significant effect on the cognition, mood, and behaviour of AD patients (Grutzendler and Morris, 2001). However, the side effects of those ChEIs include dizziness, diarrhoea, headache, agitation, insomnia, and muscle cramps, which reduce the QoL of both patients and caregivers considerably, thus safer and more effective interventions are desired.

1.2. Traditional knowledge on sage, rosemary, and lemon balm

Sage (*Salvia officinalis* L.), rosemary (*Rosmarinus officinalis* L.), and lemon balm (*Melissa officinalis* L.) have traditionally been known for their actions on mood and cognition. According to Culpeper (1616-1654), sage ‘is of excellent use to help the memory, warming and quickening the senses’ (Culpeper, 1653). John Gerard (1545–1612) wrote ‘sage is singularly good for the head and brain, it quickeneth the senses and memory’ (Dweck, 2000). Rosemary was mentioned in Hamlet by William Shakespeare (1564-1616): ‘There’s rosemary, that’s for remembrance’ (Hamlet, act IV scene V) (Shakespeare, 2015). The historical use of rosemary as a memory enhancer dates back to ancient Greece. It was mentioned by Pedanius Dioscorides (1st century AD) (Begum et al., 2013; Pengelly et al., 2012), and according to Nicholas Culpeper, rosemary ‘helps a weak memory, and quickens the senses’ (Culpeper, 1653). Culpeper also mentioned the use of lemon balm as a mood enhancer: lemon

balm ‘causes the mind and heart to become merry, and reviveth the heart’ (Culpeper, 1653). According to Avicenna (Ibn-Sīnā, 980-1037), lemon balm was recognised an exhilarant (Alijaniha et al., 2015), while Paracelsus (1493-1541) recommended it for ‘all complaints supposed to proceed from a disordered state of the nervous system’ (Scholey et al., 2014). Of note, all these herbs belong to the same botanical family lamiaceae.

1.3. Rosmarinic acid

Rosmarinic acid (α-o-caffeoyl-3,4-dihydroxyphenyllactic acid) is a natural phenolic compound first isolated from *R. officinalis* by Scarpati and Oriente in 1958 (Petersen and Simmonds, 2003). It is found abundantly in the members of botanical family lamiaceae, particularly in the subfamily nepetoideae (Barros et al., 2013). Table 1 shows the levels of rosmarinic acid in lamiaceae plants (Benedec et al., 2015; Kivilompolo and Hyötyläinen, 2007; Shekarchi et al., 2012; Wang et al., 2004; Zgórka and Głowniak, 2001). Among those, sage (*S. officinalis*), rosemary (*R. officinalis*), and lemon balm (*M. officinalis*) consistently contain high levels of rosmarinic acid (Table 1). Besides a number of important biological activities, such as anti-inflammatory, and anti-oxidative properties (Kim et al., 2015a), rosmarinic acid is a potent inhibitor of AChE and BuChE (Orhan et al., 2008; Vladimir-Knežević et al., 2014). In addition, rosmarinic acid protects hippocampal neurons against injuries (Kantar Gok et al., 2016; Zhang et al., 2016), and can possibly enhance hippocampal functions (Hwang et al., 2016). Considering the involvement of the hippocampus in dementia development (Lazarov and Hollands, 2016; Raskin et al., 2015), rosmarinic acid may prevent or delay the progress of dementia through improving hippocampal functions. Furthermore, rosmarinic acid inhibits γ-Aminobutyric acid (GABA) transaminase (Awad et al., 2009), suggesting additional therapeutic benefits for accompanying symptoms such as anxiety, insomnia, and aggressive behaviour, by increasing GABA levels (Jembrek and Vlainic, 2015).

Importantly, the dose of supposed active constituents in most phytomedicines are very low and it is believed that synergetic interactions between various components of herbs are vital part of their therapeutic efficacy (Williamson, 2001). In fact, lamiaceae plants are rich in volatile constituents with potential therapeutic benefits (Table 2) (Ali et al., 2015; Bozin et al., 2007; de Sousa et al., 2004;

Gachkar et al., 2007; Mimica-Dukic et al., 2004; Porres-Martínez et al., 2015). For example, sage and rosemary are rich in volatile compounds with AChE and BuChE inhibitory properties, such as α-pinene and 1,8-cineole, (Dohi et al., 2009; Orhan et al., 2008; Perry et al., 2003; Savelev et al., 2004). Lemon balm contains high levels of geranial and neral, monoterpene aldehydes related to geraniol and nerol, and these aldehydes are known to be anti-inflammatory (Gbenou et al., 2013; Shen et al., 2015). These volatile constituents can directly enter the blood stream through nasal and lung mucosa and affect autonomic nervous system and behaviour via pharmacological actions, as well as subjective experience of the odours (Herz, 2009; Heuberger et al., 2001). Of note, sedative properties are known for the essential oils of lamiaceae herbs, including *Lavandula angustifolia* Mill. and *M. officinalis*, whereas *R. officinalis* and *S. officinalis* essential oils are classified as stimulatory, in aromatherapy (Perry and Perry, 2006). Due to impaired olfactory abilities in dementia patients, aroma alone may not be sufficiently effective (Snow et al., 2004), however those volatile components, in combination with non-volatile constituents such as rosmarinic acid, could exert an synergetic benefits (Williamson, 2001) in enhancing cognition and mood.

To evaluate potential benefits in dementia intervention of lamiaceae herbs, namely *Salvia spp.* (*S. officinalis* and *S. lavandulaefolia* Vahl), *R. officinalis*, and *M. officinalis*, we addressed the effects of these herbs on cognition, mood and QoL, in both dementia and non-dementia populations.

2. Methods

2.1. Search strategy

Database searches were conducted separately for each of the three herbs. Publications from 1960 to July 2017 were sought using databases PubMed/Medline, Cochrane Library, and ScienceDirect. PubMed searches were conducted in article type ‘Clinical Trial’ using search terms ‘((Salvia officinalis) OR Salvia lavandulaefolia) OR sage’ for sage, ‘(Rosmarinus officinalis) OR rosemary’ for Rosemary, and ‘(Melissa officinalis) OR lemon balm’ for lemon balm. Trials in Cochrane Library were sought using search terms ‘Salvia officinalis’ and ‘Salvia lavandulaefolia’ for sage, ‘Rosmarinus

officinalis' for rosemary, and 'Melissa officinalis' for lemon balm. In ScienceDirect, searches were conducted in the fields of 'Medicine and Dentistry', 'Nursing and Health Professions', and 'Pharmacology, Toxicology and Pharmaceutical Science', using search terms 'dementia AND "Salvia officinalis" OR "Salvia lavandulaefolia" for sage, 'dementia AND "Rosmarinus officinalis"' for rosemary, and 'dementia AND "Melissa officinalis"' for lemon balm. All searches were conducted in July 2017.

2.2. Selection of studies

After database searching, abstracts were reviewed by the first author to identify studies that addressed the effect of a single species on cognition mood, or QoL. The exclusion criteria at abstract review were:

1. Herbal formulae or combination of more than one species
2. No clinical diagnostic tests
3. No primary data

Due to the scarcity of data, randomised controlled trials, open-labels, as well as quasi-experimental trials were included, and healthy or cognitively impaired populations. Flow diagrams were generated following PRISMA format (Moher et al., 2009) (Figure 1 – 3). After screening, both authors reviewed the full articles and synthesised the retrieved information.

3. Results

3.1. *S. officinalis* and *S. lavandulaefolia.*

S. officinalis has traditionally been used in European herbal medicine, however due to its high thujone levels, *S. lavandulaefolia* has been suggested to be an safer alternative (Mantle et al., 2000). This review includes both of these species in this review, as it is important to carefully consider the interchangeability and potential differences in efficacies. Total 263 records were retrieved though database searching (192 from PubMed, 36 from Cochrane Library, 35 from ScienceDirect), among which 235 were without overlap. Records were screened and 227 were excluded based on title and abstract, and 8 studies were selected for reviewing (Figure 1). The target population of the selected

studies were heterogeneous: six studies on healthy volunteers (175 subjects in total) and two studies on mild to moderate dementia patients (53 subjects). Table 3 summarises the selected studies that investigated the efficacy of *S. officinalis* and *S. lavandulaefolia* in enhancing cognition and mood. In healthy young volunteers, the single oral administration of *S. officinalis* essential oil (50μL) enhanced cognition, alertness, and calmness (Kennedy et al., 2011; Tildesley et al., 2003; Tildesley et al., 2005), and *S. officinalis* dried leaves reduced anxiety at 300mg, while 600mg led to an increase in calmness and alertness and improved task performance (Kennedy and Scholey, 2006). The aroma of *S. officinalis* oil improved quality of memory, and the aroma of *S. lavandulaefolia* or *S. officinalis* oil enhanced alertness (Moss et al., 2010). *S. officinalis* alcoholic extract was effective in enhancing memory performance and accuracy of attention in healthy older adults at 333mg, while lower (167mg) or higher (666 and 1332mg) doses were ineffective (Scholey et al., 2008). An open trial with AD patients found that, oral administration of *S. lavandulaefolia* essential oil for 6 weeks, increasing dose from 50μL per day to 150μL per day over the course, led to a reduction in neuropsychiatric disturbances and trends towards improved memory and attention, although the latter was not statistically significant (Perry et al., 2003). In a 4-month intervention with AD patients, *S. officinalis* alcoholic extract 60 drops (3-6 mL) per day resulted in a significant cognitive improvement (Akhondzadeh et al., 2003b).

3.2. *R. officinalis*

Total 118 records were retrieved though database searching (62 from PubMed, 19 from Cochrane Library, 37 from ScienceDirect), among which 112 were without overlap. After screening based on title and abstract, 107 were excluded, and five studies were assessed and selected for reviewing (Figure 2). All five studies were conducted on non-dementia subjects (total 234). The effects on cognition and mood have been studied with healthy volunteers, students with test-taking stress, and volunteers with low energy levels (Table 4). Moss *et al.* (2003) found that ambient aroma of *R. officinalis* can enhance mood and improve cognitive functions without speed-accuracy trade-off (Moss et al., 2003), while an active constituent 1,8-cineole was absorbed into the blood circulation

and its serum levels correlated with improved cognitive performance (Moss and Oliver, 2012). McCaffrey *et al*. (2009) studied the effect of the aroma using an inhaler, and found that it can reduce anxiety in test-taking nursing student (McCaffrey et al., 2009). In addition, they compared rosemary and lavender and observed that both aromas were relaxing however *R. officinalis* assisted in concentration and recalling information whereas *Lavandula hybrida* was too relaxing and made it difficult to concentrate (McCaffrey et al., 2009). Lindheimer *et al*. (2013) reported that 1.7g mixture of *R. officinalis* and *R. eriocalyx* Jord. & Fourr. dried leaves (rosmarinic acid 20mg/g) reduced mental fatigue and false alarm errors in young adults with low energy states (Lindheimer et al., 2013), while Pengelly *et al*. (2012) found dose specific effects of *R. officinalis* dried leaves in improving in alertness and speed of memory at 0.75g, whereas 6.0g led to significant cognitive impairment and reduced alertness (Pengelly et al., 2012).

3.3. *M. officinalis*

Among 200 records retrieved though database searching (125 from PubMed, 31 from Cochrane Library, 44 from ScienceDirect), 177 were without overlap. After screening based on title and abstract, 167 records were excluded and 10 studies were assessed for eligibility. Two records were excluded due to the fact that those were conference abstracts with the same contents from the same authors as one of the other records (Figure 3). Target populations of these trials were heterogeneous: 5 studies on non-dementia individuals (total 139 subjects) and 3 studies on dementia patients (total 146 subjects). The study designs and outcomes of the selected records are summarised in Table 5. In healthy volunteers, the oral administration of *M. officinalis* methanolic extract enhanced calmness at 300 and 600mg and increased the speed of mathematical processing at 300mg, however reduced alertness and working and secondary memory at 600mg (Kennedy et al., 2004; Kennedy et al., 2002). Dried leaves was effective in Improving working memory, accuracy, and calmness at 1.6g, however not effective at lower dosages (0.6 and 1.0g) (Kennedy et al., 2003). Scholey *et al*. (2014) found no significant cognitive or mood enhancing effect by aqueous extract of *M. officinalis* (0.3 and 0.6g) (Scholey et al., 2014), however, due to complex matrices used in the study (yoghurt and tea-like drink), it is difficult to interpret the outcome of this trial. On the other hand, a 14-day trial in patients

with heart palpitation using aqueous extract of *M. officinalis* (500mg) showed that it effectively reduced anxiety and insomnia (Alijaniha et al., 2015). In AD patients, a 4-month intervention with *M. officinalis* alcoholic extract 60 drops (3-6 mL) per day resulted in a significant improvement in cognition (Akhondzadeh et al., 2003a). Aroma therapy (massage, using the essential oil) for 12 weeks was effective in improving QoL in AD patients, although it was no more effective than control (massage without the essential oil) in reducing agitation, while massage led to a baseline improvement in agitation (Burns et al., 2011). This finding suggests that, while massage alone can be effective via sensory stimulation and human interaction (Cohen-Mansfield, 2013), there may not be any additional effect of *M. officinalis* essential oil in 3 months. On the other hand, a 4-month intervention with *M. officinalis* aromatherapy significantly reduced agitation and improved QoL in severe dementia patients (Ballard et al., 2002), suggesting that aromatherapy could improve both psychiatric symptoms and QoL when applied for 4 months, but only QoL when applied for 3 months.

4. Discussion

4.1. *S. officinalis* and *S. lavandulaefolia*

Among over 700 *salvia* species, *S. officinalis* and *S. lavandulaefolia* are the most common species in Europe and thought to have similar therapeutic properties (Perry et al., 1996; Savelev et al., 2004). However Savelev *et al*. (2004) found that essential oil of *S. officinalis* contained high levels of thujone (6.2%), whereas the levels in *S. lavandulaefolia* were below the detection limit (Savelev et al., 2004) (Supplementary table 1). Thujone is a modulator of $GABA_A$ receptor and can act as a convulsant (Höld et al., 2000; Olsen, 2000). EMA states that thujone intake should be limited to maximum 5mg per day and for up to two weeks (EMA, 2009), and *S. lavandulaefolia* has been suggested to be a safer alternative elsewhere (Mantle et al., 2000). However, thujone contents in *S. officinalis* can vary considerably depending on the geographical origin. For example, it may be absent in *S. officinalis* from Bulgaria (Cvetkovikj et al., 2015), as low as 4.5% for Greece origin, or as high as 36.8% for Estonian sample (Raal et al., 2007). In addition, although thujone can be toxic at high doses, it may have benefits within the safety limit, such as anxiolytic and antipsychotic actions of α-thujone (Deiml et al., 2004) and normalising effects on cholesterol and triglyceride levels (Baddar et al., 2011). These

findings suggest that thujone could be beneficial in supressing dementia symptoms, as well as in reducing the risk of dementia development via anti-diabetic actions. *S. officinalis* may be superior in these respects. In fact, while anti-diabetes and anti-hyperlipidaemic effects of *S. officinalis* alcoholic and aqueous extracts have been supported by clinical evidence (Kianbakht et al., 2011; Kianbakht and Dabaghian, 2013), it is unknown whether *S. lavandulaefolia* can be equally effective. Of note, *Salvia spp*. contain camphor, which can be neurotoxic at large doses (Santos and Cabot, 2015), and *S. lavandulaefolia* contains camphor at considerably higher levels than *S. officinalis* (Supplementary table 1).

On the whole, clinical evidence suggests that *Salvia spp.* could have positive effects on cognition and mood. However, as Miroddi *et al*. (2014) pointed out, these clinical studies used a variety of herbal preparations, application methods, dosages, and intervention periods (Miroddi et al., 2014), thus it is difficult to draw a single conclusion from these trials. In addition, while both essential oil and alcoholic extract of *S. officinalis* seem to be effective, only essential oil of *S. lavandulaefolia* was used in the trials, and much less is known as to non-volatile constituents of *S. lavandulaefolia* compared to *S. officinalis*. It is unknown whether the efficacy of *S. officinalis* alcoholic extract in AD patients (Akhondzadeh et al., 2003b) can be replaced by *S. lavandulaefolia*. Considering the safety concern due to thujone toxicity (Mantle et al., 2000), interchangeability of the two species, *S. officinalis and S. lavandulaefolia*, must be further addressed.

The use of *S. officinalis* for cognitive enhancement is not indicated in the EMA's herbal monograph. However, EMA suggests the use of *S. officinalis* for ailments such as dyspepsia and excessive sweating, where alcoholic extract 2-3mL three times daily (6-9mL per day) or aqueous extract (infusion) of herbal substance 1-2g are indicated (EMA, 2009). The finding that 4-month intervention with *S. officinalis* alcoholic extract 3-6mL daily was well tolerated (Akhondzadeh et al., 2003b) suggests that a moderate dosage of *S. officinalis* can be continuously administered for at least 4 months without an major adverse effect for this purpose.

4.2. *R. officinalis*

R. officinalis is rich in phenolic compounds, including rosmarinic acid, and diterpenes, which are strong anti-oxidant and can be neuroprotective (Habtemariam, 2016). In addition, it contains 1,8-cineole and α-pinene in the essential oil, which are also antioxidants (Habtemariam, 2016) and potent AChEIs (Dohi et al., 2009; Perry et al., 2003). The presence of these compounds supports the traditional use of *R. officinalis* as a cognitive enhancer. In fact, the oral administration of *R. officinalis* extract improved spatial memory and enhanced the levels of antioxidants in the hippocampus in middle-aged rats (Rasoolijazi et al., 2015), improved cognitive impairment in scopolamine-induced rat dementia model (Ozarowski et al., 2013), and induced anxiolytic and anti-depressant-like effect in mice (Ferlemi et al., 2015). Clinical evidence suggests that both the oral administration herbal preparations (Lindheimer et al., 2013; Pengelly et al., 2012) and the aroma of essential oil (Moss et al., 2003; Moss and Oliver, 2012) can improve cognition, and the inhalation of essential oil can reduce anxiety (McCaffrey et al., 2009). Posology according to EMA herbal monograph indicates daily dose of 2-6g *R. officinalis* as herbal tea preparation (single dose 1-2g, 2-3 times daily), or liquid extract (1:1 in 45% ethanol) 2-4mL daily, for dyspepsia and mild gastrointestinal spasmodic disorders (EMA, 2010), suggesting that moderate doses below 2g of *R. officinalis* at a time, which is sufficed by the dosages used in the studies (Lindheimer et al., 2013; Pengelly et al., 2012), is safe and sufficient to exert some pharmacological effects.

To summarise, the data indicate that single oral administration of *R. officinalis* leaves at a moderate dose, as well as essential oil aroma, can have positive effects on cognition and mood, while excess dosages have negative impacts, healthy individuals. However, further research must be conducted to address the therapeutic potential in the long-term, including effective dosages, duration, and safety in dementia patients. In addition, as shown by del Baño *et al*. (2003), rosmarinic acid content in *R. officinalis* leaves can vary considerably, ranging from 0.25 to 2.5 % dry weight, depending on harvest time (del Baño et al., 2003) and possibly on the climates and geographic regions, suggesting the necessity of standardisation according to the efficacy.

4.3. *M. officinalis*

Rosmarinic acid is the most abundant phenolic compound in *M. officinalis* (Barros et al., 2013). By AChE inhibitory activity guided fractionation of *M. officinalis* alcoholic extract, rosmarinic acid was suggested to the major active constituent (Dastmalchi et al., 2009). In addition, *M. officinalis* methanol extract has GABA transaminase inhibitory effect, and the active principles are found to be rosmarinic acid, triterpenoids ursolic acid and oleanolic acid (Awad et al., 2009). Preclinical studies found that *M. officinalis* extract reduces serum corticosterone levels, decreases hippocampal GABA transaminase levels, and increases hippocampal neurogenesis (Yoo et al., 2011). Furthermore, it has anxiolytic-like effects under moderate stress conditions and does not alter activity levels (Ibarra et al., 2010), indicating that *M. officinalis* can be effective in cognitive enhancement and protective against stress-related neuropathologies. In fact, clinical data suggest that *M. officinalis* can be beneficial in dementia intervention. While the single administration, in healthy individuals, of *M. officinalis* aqueous extract (0.3 and 0.6g) did not immediately improve cognition and mood (Scholey et al., 2014), the alcoholic extract (0.3 and 0.6g) and dried leaves (1.6g) of *M. officinalis* exerted immediate cognition- and mood-enhancing effects (Kennedy et al., 2004; Kennedy et al., 2002; Kennedy et al., 2003). The aqueous extract of *M. officinalis* (1g daily for 2 weeks) was effective in reducing anxiety and insomnia in heart palpitation patients (Alijaniha et al., 2015), while alcoholic extract (3-6mL daily) improved cognition in 4 months (Akhondzadeh et al., 2003a) and *M. officinalis* essential oil as aroma therapy improved QoL in 3 weeks (Ballard et al., 2002; Burns et al., 2011) and reduced agitation in 4 weeks in AD patients (Ballard et al., 2002). In addition, EMA herbal monograph indicates the use of *M. officinalis* for ‘relief of mild symptoms of mental stress and to aid sleep’, and suggests *M. officinalis* 1.5-4.5g as infusion or ethanolic extract, 1-3 times daily (EMA, 2013).

4.4. Rosmarinic acid or herbal preparations

Although rosmarinic acid is an important common active constituent of *S. officinalis, R. officinalis,* and *M. officinalis,* it is questionable whether the efficacy of herbal preparations can be fully replaced by rosmarinic acid as a single compound. As discussed above, therapeutic actions of an herbal remedy involve multiple compounds, and those complex mechanisms could be beneficial in both enhancing the efficacies and reducing the potential side effects. In addition, unique constituents of each species,

as well as the preparation methods and administration routes, can result in diverse therapeutic properties. For example, the profiles of volatile constituents are considerably different between those species (Table 5), and *R. officinalis*, and *M. officinalis* are used differently in aromatherapy: *M. officinalis* for insomnia and *R. officinalis* for memory loss (Ali et al., 2015).

4.5. Issues and unanswered questions

Most studies were conducted on healthy individuals, addressing acute effects after a single intervention. However, as there are differences in the brain physiology between healthy and demented individuals, and what is needed in dementia care is to recover cognitive ability and reduce aberrant behaviours, as opposed to performance enhancement, it is questionable whether the observations in healthy subjects can be transferable to cognition and mood improvements in dementia patients. In addition, different methodologies employed in those studies (Supplementary table 2) may make a collective interpretation difficult. While most studies on healthy individuals were conducted using direct measures such as Cognitive Drug Research (CDR) computerised assessment battery and Bond–Lader Visual Analogue Scales, cognition and behavioural issues in dementia patients were mainly assessed indirectly via interviews (Cognitive subset of the Alzheimer's disease assessment scale), ratings by proxies or caregivers (Cohen-Mansfield Agitation Inventory, Neuropsychiatric Inventory), or observational ratings (Dementia Care Mapping, Pittsburgh Agitation Scale). In addition, the data discussed here are restricted to pre-defined parameters selected by the researchers, which are established under experimental settings, and we do not have access to parameters not included in the study or factors that are not yet defined in clinical trial settings. Nevertheless, evidence supports the effectiveness of *Salvia spp*. and *M. officinalis* in enhancing cognition and mood in dementia patients (Akhondzadeh et al., 2003a, b; Ballard et al., 2002; Burns et al., 2011; Perry et al., 2003). Although QoL assessment, as a measure of welfare (Bognar, 2005), is theoretically and methodologically complex and controversial (Ready and Ott, 2003), the findings that *M. officinalis* aromatherapy improved dementia patients' QoL (Ballard et al., 2002; Burns et al., 2011) could have an important implication in achieving the ultimate goal of dementia intervention.

Furthermore, as discussed above, the levels of active constituents in herbal materials can be considerably affected by environmental factors, thus standardisation is a critical issue to obtain reliable and reproducible therapeutic effects.

4.6. Limitations of this review

Evidence is limited and there are some obstacles before reaching a final conclusion. Firstly, most studies are performed on healthy volunteers, and there is no data on dementia patients for *R. officinalis*. Secondly, herbal preparations and application methods used in those trials are diverse. More research will be needed on dementia patients using standardised herbal preparations at compound levels, such as rosmarinic acid and the volatile constituents. Finally, as dementia is a complex issue, cognitive performance alone may not be the good index of therapeutic effectiveness. We must consider a variety of beneficial outcomes, such as mood and QoL, to improve the wellbeing of dementia patients. A multifaceted study approach is desired.

4.7. Perspectives

Lamiaceae herbs in general are easy to grow compared to those species that take years before harvesting, and no sustainability concern has been reported, at least for the three species studied in this report. Furthermore, there are other lamiaceae members potentially useful in dementia intervention. For example, *Salvia miltiorrhiza* Bunge (Chinese sage) is clinically used for treating cerebro- and cardio-vascular disorders and can be protective against diabetes-induced cognitive impairment (Cai et al., 2014; Hamidpour et al., 2014; Hügel and Jackson, 2014). It is also notable that *Prunella vulgaris* L. (self-heal) and *Mentha spicata* L. (spearmint) contain significantly high levels of rosmarinic acid (Table 1). Further investigation would be warranted for these species. Finally, while clinical trials can provide robust evidence to support the efficacy of a phytotherapy in a controlled setting, the effectiveness in a realistic environment may not solely be derived from the pharmacological actions of the chemical constituents, but could involve the subjective experiences based on personal and cultural background. This might be particularly the case when addressing mood and QoL, and the nature of traditional herbal medicine as a person-centred therapeutic approach

(Roberti di Sarsina et al., 2012) is likely to play an important role in optimising the effectiveness of dementia intervention.

5. Conclusions

Herbal remedies have traditionally been used to improve cognition and mood, and ginkgo, bacopa, ginseng, sage, and rosemary are among the most frequently recommended. In this study, we have addressed the effectiveness of three lamiaceae members, namely sage, rosemary, and lemon balm. These herbs contain potentially effective constituents at high levels, and clinical evidence supports their effectiveness in improving cognition, mood, and QoL. However, for obvious ethical issues, there are few clinical studies with dementia patients, therefore it is yet to be elucidated what administration methods lead to optimal outcomes and how long it may be administered safely. In addition, the standardisation of herbal products at compound levels, as well as the specification of the safe and effective *Salvia* species, would be necessary before we reach a final conclusion.

Authors: All research done by the authors

Financial support: no

Conflict of interest: none

Word count: 4940

References

Akhondzadeh, S., Noroozian, M., Mohammadi, M., Ohadinia, S., Jamshidi, A.H., Khani, M., 2003a. Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. J Neurol Neurosurg Psychiatry 74, 863-866.

Akhondzadeh, S., Noroozian, M., Mohammadi, M., Ohadinia, S., Jamshidi, A.H., Khani, M., 2003b. Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. J Clin Pharm Ther. 28, 53-59.

Ali, B., Al-Wabel, N.A., Shams, S., Ahamad, A., Khan, S.A., Anwar, F., 2015. Essential oils used in aromatherapy: A systemic review Asian Pacific Journal of Tropical Biomedicine 5, 601-611.

Alijaniha, F., Naseri, M., Afsharypuor, S., Fallahi, F., Noorbala, A., Mosaddegh, M., Faghihzadeh, S., Sadrai, S., 2015. Heart palpitation relief with Melissa officinalis leaf extract: double blind, randomized, placebo controlled trial of efficacy and safety. J Ethnopharmacol. 164, 378-384.

Alzheimer's society, 2014a. What is Alzheimer disease?, Factsheet 401LP, Last reviewed: July 2014 ed, London, United Kingdom.

Alzheimer's society, 2014b. What is dementia?, Factsheet 400LP, Last updated: August 2015 ed.

Awad, R., Muhammad, A., Durst, T., Trudeau, V.L., Arnason, J.T., 2009. Bioassay-guided fractionation of lemon balm (Melissa officinalis L.) using an in vitro measure of GABA transaminase activity. Phytother Res. 23, 1075-1081.

Baddar, N.W., Aburjai, T.A., Taha, M.O., Disi, A.M., 2011. Thujone corrects cholesterol and triglyceride profiles in diabetic rat model. Nat Prod Res. 25, 1180-1184.

Bakan, P., 1959. Extraversion-Introversion and improvement in an auditory vigilance task. British journal of Psychology 50, 325–332.

Ballard, C.G., O'Brien, J.T., Reichelt, K., Perry, E.K., 2002. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. J Clin. Psychiatry 63, 553-558.

Barros, L., Dueñas, M., Dias, M.I., Sousa, M.J., Santos-Buelga, C., Ferreira, I.C., 2013. Phenolic profiles of cultivated, in vitro cultured and commercial samples of Melissa officinalis L. infusions. Food Chem. 2013 Jan 1;136(1):1-8 136, 1-8.

Begum, A., Sandhya, S., Shaffath Ali S., V., K.R., Reddy, S., Banji, D., 2013. An in-depth review on the medicinal flora Rosmarinus officinalis (Lamiaceae). Acta Sci Pol Technol Aliment. 12, 61-73.

Benedec, D., Hanganu, D., Oniga, I., Tiperciuc, B., Olah, N.K., Raita, O., Bischin, C., Silaghi-Dumitrescu, R., Vlase, L., 2015. Assessment of rosmarinic acid content in six Lamiaceae species extracts and their antioxidant and antimicrobial potential. Pak J Pharm Sci. 28, 2297-2303.

Bognar, G., 2005. The Concept of Quality of Life. Social Theory and Practice 31, 561-580.

Bond, A., Lader, M., 1974. The use of analogue scales in rating subjective feelings. British Journal of Medical Psychology 47.

Bozin, B., Mimica-Dukic, N., Samojlik, I., Jovin, E., 2007. Antimicrobial and antioxidant properties of rosemary and sage (Rosmarinus officinalis L. and Salvia officinalis L., Lamiaceae) essential oils. J Agric Food Chem. 55, 7879-7885.

Brooker, D., 2005. Dementia care mapping: a review of the research literature. Gerontologist 45, 11-18.

Burns, A., Perry, E., Holmes, C., Francis, P., Morris, J., Howes, M.J., Chazot, P., Lees, G., Ballard, C., 2011. A double-blind placebo-controlled randomized trial of Melissa officinalis oil and donepezil for the treatment of agitation in Alzheimer's disease. Dement Geriatr Cogn Disord. 31, 158-164.
Cai, H., Lian, L., Wang, Y., Yu, Y., Liu, W., 2014. Protective effects of Salvia miltiorrhiza injection against learning and memory impairments in streptozotocin-induced diabetic rats. Exp Ther Med. 8, 1127-1130.
Cohen-Mansfield, J., 2013. Nonpharmacologic Treatment of Behavioral Disorders in Dementia. Current Treatment Options in Neurology 15, 765-785.
Cohen-Mansfield, J., Marx, M.S., Rosenthal, A.S., 1989. A description of agitation in a nursing home. Journal of Gerontology: Medical Sciences 44, M77-M84.
Culpeper, N., 1653. Culpeper's Complete Herbal.
Cummings, J.L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D.A., Gornbein, J., 1994. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 44, 2308-2314.
Cvetkovikj, I., Stefkov, G., Karapandzova, M., Kulevanova, S., Satović, Z., 2015. Essential oils and chemical diversity of southeast european populations of Salvia officinalis L. Chem Biodivers. 12, 1025-1039.
Dastmalchi, K., Ollilainen, V., Lackman, P., Boije af Gennäs, G., Dorman, H.J., Järvinen, P.P., Yli-Kauhaluoma, J., Hiltunen, R., 2009. Acetylcholinesterase inhibitory guided fractionation of Melissa officinalis L. Bioorg Med Chem. 17, 867-871.
de Sousa, A.C., Alviano, D.S., Blank, A.F., Alves, P.B., Alviano, C.S., Gattass, C.R., 2004. Melissa officinalis L. essential oil: antitumoral and antioxidant activities. J Pharm Pharmacol. 56, v.
De Strooper, B., Karran, E., 2016. The Cellular Phase of Alzheimer's Disease. Cell 164, 603-615.
Deiml, T., Haseneder, R., Zieglgänsberger, W., Rammes, G., Eisensamer, B., Rupprecht, R., Hapfelmeier, G., 2004. Alpha-thujone reduces 5-HT3 receptor activity by an effect on the agonist-reduced desensitization. Neuropharmacology 46, 192-201.
del Baño, M.J., Lorente, J., Castillo, J., Benavente-García, O., del Río, J.A., Ortuño, A., Quirin, K.W., Gerard, D., 2003. Phenolic diterpenes, flavones, and rosmarinic acid distribution during the development of leaves, flowers, stems, and roots of Rosmarinus officinalis. Antioxidant activity. J Agric Food Chem. 51, 4247-4253.
Dickson, K., Lafortune, L., Kavanagh, J., Thomas, J., Mays, N., Erens, B., 2012. Non-drug treatments for symptoms in dementia: an overview of systematic reviews of non-pharmacological interventions in the management of neuropsychiatric symptoms and challenging behaviours in patients with dementia. Policy Innovation Research Unit Publication.
Dohi, S., Terasaki, M., Makino, M., 2009. Acetylcholinesterase inhibitory activity and chemical composition of commercial essential oils. J Agric Food Chem. 57, 4313-4318.
Dweck, A.C., 2000. The folklore and cosmetic use of various salvia species, in: Hardman, R. (Ed.), Medicinal and Aromatic Plants—Industrial Profiles. Harwood Academic Publishers imprint, part of the Gordon and Breach Publishing Group, Amsterdam, The Netherlands, p. 1.
EMA, 2009. Community herbal monograph on Salvia officinalis L., folium. European Medicines Agency, London.
EMA, 2010. Community herbal monograph on Rosmarinus officinalis L., folium, London.
EMA, 2013. Community herbal monograph on Melissa officinlias L., folium, London.
Ferlemi, A.V., Katsikoudi, A., Kontogianni, V.G., Kellici, T.F., Iatrou, G., Lamari, F.N., Tzakos, A.G., Margarity, M., 2015. Rosemary tea consumption results to anxiolytic- and anti-depressant-like behavior of adult male mice and inhibits all cerebral area and liver

cholinesterase activity; phytochemical investigation and in silico studies. Chem Biol Interact. 237, 47-57.
Forester, B.P., Oxman, T.E., 2003. Measures to Assess the Noncognitive Symptoms of Dementia in the Primary Care Setting. Prim Care Companion J Clin Psychiatry 5, 158-163.
Gachkar, L., Yadegari, D., Rezaei, M.B., Taghizadeh, M., Astaneh, S.A., Rasooli, I., 2007. Chemical and biological characteristics of Cuminum cyminum and Rosmarinus officinalis essential oils. Food Chemistry 102, 898-904.
Gbenou, J.D., Ahounou, J.F., Akakpo, H.B., Laleye, A., Yayi, E., Gbaguidi, F., Baba-Moussa, L., Darboux, R., Dansou, P., Moudachirou, M., Kotchoni, S.O., 2013. Phytochemical composition of Cymbopogon citratus and Eucalyptus citriodora essential oils and their anti-inflammatory and analgesic properties on Wistar rats. Mol Biol Rep. 40, 1127-1134.
Grutzendler, J., Morris, J.C., 2001. Cholinesterase Inhibitors for Alzheimer's Disease. Drugs 61, 41-52.
Habtemariam, S., 2016. The Therapeutic Potential of Rosemary (Rosmarinus officinalis) Diterpenes for Alzheimer's Disease. Evid Based Complement Alternat Med. 2016.
Hamidpour, M., Hamidpour, R., Hamidpour, S., Shahlari, M., 2014. Chemistry, Pharmacology, and Medicinal Property of Sage (Salvia) to Prevent and Cure Illnesses such as Obesity, Diabetes, Depression, Dementia, Lupus, Autism, Heart Disease, and Cancer. J Tradit Complement Med. 4, 82-88.
Hasson, D., Arnetz, B.B., 2005. Validation and Findings Comparing VAS vs. Likert Scales for Psychosocial Measurements. International Electronic Journal of Health Education 8.
Herz, R.S., 2009. Aromatherapy facts and fictions: a scientific analysis of olfactory effects on mood, physiology and behavior. Int J Neurosci. 119, 263-290.
Heuberger, E., Hongratanaworakit, T., Böhm, C., Weber, R., Buchbauer, G., 2001. Effects of chiral fragrances on human autonomic nervous system parameters and self-evaluation. Chem Senses 26, 281-292.
Höld, K.M., Sirisoma, N.S., Ikeda, T., Narahashi, T., Casida, J.E., 2000. Alpha-thujone (the active component of absinthe): gamma-aminobutyric acid type A receptor modulation and metabolic detoxification. Proc Natl Acad Sci U S A. 97, 3826-3831.
Hügel, H.M., Jackson, N., 2014. Danshen diversity defeating dementia. Bioorg Med Chem Lett. 24, 708-716.
Hwang, E.S., Kim, H.B., Choi, G.Y., Lee, S., Lee, S.O., Kim, S., Park, J.H., 2016. Acute rosmarinic acid treatment enhances long-term potentiation, BDNF and GluR-2 protein expression, and cell survival rate against scopolamine challenge in rat organotypic hippocampal slice cultures. Biochem Biophys Res Commun. 475, 44-50.
Ibarra, A., Feuillere, N., Roller, M., Lesburgere, E., Beracochea, D., 2010. Effects of chronic administration of Melissa officinalis L. extract on anxiety-like reactivity and on circadian and exploratory activities in mice. Phytomedicine 17, 397-403.
Jembrek, M.J., Vlainic, J., 2015. GABA Receptors: Pharmacological Potential and Pitfalls. Curr Pharm Des. 21, 4943-4959.
Kantar Gok, D., Ozturk, N., Er, H., Aslan, M., Demir, N., Derin, N., Agar, A., Yargicoglu, P., 2016. Effects of rosmarinic acid on cognitive and biochemical alterations in ovariectomized rats treated with D-galactose. Folia Histochem Cytobiol. 53, 283-293.
Kennedy, D.O., Dodd, F.L., Robertson, B.C., Okello, E.J., Reay, J.L., Scholey, A.B., Haskell, C.F., 2011. Monoterpenoid extract of sage (Salvia lavandulaefolia) with cholinesterase inhibiting properties improves cognitive performance and mood in healthy adults. J Psychopharmacol. 25, 1088-1100.

Kennedy, D.O., Little, W., Scholey, A.B., 2004. Attenuation of laboratory-induced stress in humans after acute administration of Melissa officinalis (Lemon Balm). Psychosom Med. 66, 607-613.
Kennedy, D.O., Scholey, A.B., 2006. The psychopharmacology of European herbs with cognition-enhancing properties. Curr Pharm Des. 12, 4613-4623.
Kennedy, D.O., Scholey, A.B., Tildesley, N.T., Perry, E.K., Wesnes, K.A., 2002. Modulation of mood and cognitive performance following acute administration of Melissa officinalis (lemon balm). Pharmacol Biochem Behav. 72, 953-964.
Kennedy, D.O., Wake, G., Savelev, S., Tildesley, N.T., Perry, E.K., Wesnes, K.A., Scholey, A.B., 2003. Modulation of mood and cognitive performance following acute administration of single doses of Melissa officinalis (Lemon balm) with human CNS nicotinic and muscarinic receptor-binding properties. Neuropsychopharmacology 28, 1871-1881.
Kianbakht, S., Abasi, B., Perham, M., Hashem Dabaghian, F., 2011. Antihyperlipidemic effects of Salvia officinalis L. leaf extract in patients with hyperlipidemia: a randomized double-blind placebo-controlled clinical trial. Phytother Res. 25, 1849-1853.
Kianbakht, S., Dabaghian, F.H., 2013. Improved glycemic control and lipid profile in hyperlipidemic type 2 diabetic patients consuming Salvia officinalis L. leaf extract: a randomized placebo. Controlled clinical trial. Complement Ther Med. 21, 441-446.
Kim, G.D., Park, Y.S., Jin, Y.H., Park, C.S., 2015a. Production and applications of rosmarinic acid and structurally related compounds. Appl Microbiol Biotechnol. 99, 2083-2092.
Kim, G.H., Kim, J.E., Rhie, S.J., Yoon, S., 2015b. The Role of Oxidative Stress in Neurodegenerative Diseases. Exp Neurobiol. 24, 325-340.
Kivilompolo, M., Hyötyläinen, T., 2007. Comprehensive two-dimensional liquid chromatography in analysis of Lamiaceae herbs: Characterisation and quantification of antioxidant phenolic acids. J Chromatogr A 1145, 155-164.
Lane, R.M., Potkin, S.G., Enz, A., 2006. Targeting acetylcholinesterase and butyrylcholinesterase in dementia. Int J Neuropsychopharmacol. 9, 101-124.
Lazarov, O., Hollands, C., 2016. Hippocampal neurogenesis: Learning to remember. Prog Neurobiol. 138-140, 1-18.
Lee, H.P., Zhu, X., Casadesus, G., Castellani, R.J., Nunomura, A., Smith, M.A., Lee, H.G., Perry, G., 2010. Antioxidant approaches for the treatment of Alzheimer's disease. Expert Rev Neurother. 10, 1201-1208.
Lindheimer, J.B., Loy, B.D., O'Connor, P.J., 2013. Short-term effects of black pepper (Piper nigrum) and rosemary (Rosmarinus officinalis and Rosmarinus eriocalyx) on sustained attention and on energy and fatigue mood states in young adults with low energy. J Med Food 16, 765-771.
Lombardo, S., Maskos, U., 2015. Role of the nicotinic acetylcholine receptor in Alzheimer's disease pathology and treatment. Neuropharmacology 96, 255-262.
Mantle, D., Pickering, A.T., Perry, E.K., 2000. Medicinal Plant Extracts for the Treatment of Dementia - A review of their Pharmacology, Efficacy, and Tolerability. CNS Drugs 13, 201-213.
McCaffrey, R., Thomas, D.J., Kinzelman, A.O., 2009. The effects of lavender and rosemary essential oils on test-taking anxiety among graduate nursing students. Holist Nurs Pract. 23, 88-93.
Mimica-Dukic, N., Bozin, B., Sokovic, M., Simin, N., 2004. Antimicrobial and antioxidant activities of Melissa officinalis L. (Lamiaceae) essential oil. J Agric Food Chem. 52, 2485-2489.

Miroddi, M., M., N., Quattropani, M.C., Calapai, F., Gangemi, S., Calapai, G., 2014. Systematic review of clinical trials assessing pharmacological properties of Salvia species on memory, cognitive impairment and Alzheimer's disease. CNS Neurosci Ther. 20, 485-495.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, T.P., 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine 6, e1000097.
Mohs, R.C., Marin, D., Green, C.R., Davis, K.L., 1997. The Alzheimer's Disease Assessment Scale: Modifications That Can Enhance its Use in Future Clinical Trials, in: Becker, R., Giacobini, E., Barton, J.M., Brown, M. (Eds.), Advances in Alzheimer Disease Therapy. Birkhäuser Boston, pp. 407-411.
Moss, L., Rouse, M., Wesnes, K.A., Moss, M., 2010. Differential effects of the aromas of Salvia species on memory and mood. Hum Psychopharmacol. 25, 388-396.
Moss, M., Cook, J., Wesnes, K., Duckett, P., 2003. Aromas of rosemary and lavender essential oils differentially affect cognition and mood in healthy adults. Int J Neurosci. 113, 15-38.
Moss, M., Oliver, L., 2012. Plasma 1,8-cineole correlates with cognitive performance following exposure to rosemary essential oil aroma. Ther Adv Psychopharmacol. 2, 103–113.
National Institute on Aging US, 2011. Understanding Alzheimer's Disease - what you need to know. Silver Spring NIH publication.
O'Bryant, S.E., Waring, S.C., Cullum, C.M., Hall, J., Lacritz, L., Massman, P.J., Lupo, P.J., Reisch, J.S., Doody, R., Consortium, T.A.s.R., 2008. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. Arch Neurol. 65, 1091-1095.
Olsen, R.W., 2000. Absinthe and gamma-aminobutyric acid receptors. Proc Natl Acad Sci U S A. 97, 4417-4418.
Orhan, I., Kartal, M., Kan, Y., Sener, B., 2008. Activity of essential oils and individual components against acetyl- and butyrylcholinesterase. Z Naturforsch C. 63, 547-553.
Ozarowski, M., Mikolajczak, P.L., Bogacz, A., Gryszczynska, A., Kujawska, M., Jodynis-Liebert, J., Piasecka, A., Napieczynska, H., Szulc, M., Kujawski, R., Bartkowiak-Wieczorek, J., Cichocka, J., Bobkiewicz-Kozlowska, T., Czerny, B., Mrozikiewicz, P.M., 2013. Rosmarinus officinalis L. leaf extract improves memory impairment and affects acetylcholinesterase and butyrylcholinesterase activities in rat brain. Fitoterapia 91, 261-271.
Pengelly, A., Snow, J., Mills, S.Y., Scholey, A., Wesnes, K., Butler, L.R., 2012. Short-term study on the effects of rosemary on cognitive function in an elderly population. J Med Food 15, 10-17.
Perry, N., Court, G., Bidet, N., 1996. European herbs with cholinergic activities: potential in dementia therapy. Psychiatry 11, 1063-1069.
Perry, N., Perry, E., 2006. Aromatherapy in the management of psychiatric disorders: clinical and neuropharmacological perspectives. CNS Drugs 20, 257-280.
Perry, N.S., Bollen, C., Perry, E.K., Ballard, C., 2003. Salvia for dementia therapy: review of pharmacological activity and pilot tolerability clinical trial. Pharmacol Biochem Behav. 75, 651-659.
Petersen, M., Simmonds, M.S.J., 2003. Rosmarinic acid. Phytochemistry 62, 121-125.
Porres-Martínez, M., González-Burgos, E., Carretero, M.E., Gómez-Serranillos, M.P., 2015. Major selected monoterpenes α-pinene and 1,8-cineole found in Salvia lavandulifolia (Spanish sage) essential oil as regulators of cellular redox balance. Pharm Biol. 53, 921-929.
Raal, A., Orav, A., Arak, E., 2007. Composition of the essential oil of Salvia officinalis L. from various European countries. Nat Prod Res. 21, 406-411.

Raskin, J., Cummings, J., Hardy, J., Schuh, K., Dean, R.A., 2015. Neurobiology of Alzheimer's Disease: Integrated Molecular, Physiological, Anatomical, Biomarker, and Cognitive Dimensions. Curr Alzheimer Res. 12, 712-722.
Rasoolijazi, H., Mehdizadeh, M., Soleimani, M., Nikbakhte, F., Eslami Farsani, M., Ababzadeh, S., 2015. The effect of rosemary extract on spatial memory, learning and antioxidant enzymes activities in the hippocampus of middle-aged rats. Med J Islam Repub Iran. 29, 187.
Ready, R.E., Ott, B.R., 2003. Quality of Life measures for dementia. 1, 11.
Roberti di Sarsina, P., Alivia, M., Guadagni, P., 2012. Traditional, complementary and alternative medical systems and their contribution to personalisation, prediction and prevention in medicine-person-centred medicine. EPMA J. 3, 15.
Rosen, J., Burgio, L., Kollar, M., Cain, M., Allison, M., Fogleman, M., Michael, M., Zubenko, G.S., 1994. A user-friendly instrument for rating agitation in dementia patients. Am J Geriatr Psychiatry 2, 52-59.
Rosen, W.G., Mohs, R.C., Davis, K.L., 1984. A new rating scale for Alzheimers' disease. American Journal of Psychiatry 141, 1356-1364.
Rusted, J.M., Newhouse, P.A., Levin, E.D., 2000. Nicotinic treatment for degenerative neuropsychiatric disorders such as Alzheimer's disease and Parkinson's disease. Behav Brain Res. 113, 121-129.
Santos, C.D., Cabot, J.C., 2015. Persistent effects after camphor ingestion: a case report and literature review. J Emerg Med. 48, 298-304.
Sarason, I.G., 1984. Stress, anxiety, and cognitive interference: reactions to tests. J Pers Soc Psychol. 46, 929-938.
Savelev, S.U., Okello, E.J., Perry, E.K., 2004. Butyryl- and acetyl-cholinesterase inhibitory activities in essential oils of Salvia species and their constituents. Phytother Res. 18, 315-324.
Scholey, A., Gibbs, A., Neale, C., Perry, N., Ossoukhova, A., Bilog, V., Kras, M., Scholz, C., Sass, M., Buchwald-Werner, S., 2014. Anti-stress effects of lemon balm-containing foods. Nutrients 6, 4805-4821.
Scholey, A.B., Tildesley, N.T., Ballard, C.G., Wesnes, K.A., Tasker, A., Perry, E.K., Kennedy, D.O., 2008. An extract of Salvia (sage) with anticholinesterase properties improves memory and attention in healthy older volunteers. Psychopharmacology (Berl). 198, 127-139.
Shakespeare, W., 2015. Hamlet. Penguin, London.
Shekarchi, M., Hajimehdipoor, H., Saeidnia, S., Gohari, A.R., Hamedani, M.P., 2012. Comparative study of rosmarinic acid content in some plants of Labiatae family. Pharmacogn Mag. 8, 37-41.
Shen, Y., Sun, Z., Guo, X., 2015. Citral inhibits lipopolysaccharide-induced acute lung injury by activating PPAR-γ. Eur J Pharmacol. 747, 45-51.
Snow, L.A., Hovanec, L., Brandt, J., 2004. A controlled trial of aromatherapy for agitation in nursing home patients with dementia. J Altern Complement Med. 10, 431-437.
Thomas Gualtieri, C., 2004. Computerized neurocognitive testing and its potential for modern psychiatry. Psychiatry (Edgmont) 1, 29-36.
Tildesley, N.T., Kennedy, D.O., Perry, E.K., Ballard, C.G., Savelev, S., Wesnes, K.A., Scholey, A.B., 2003. Salvia lavandulaefolia (Spanish sage) enhances memory in healthy young volunteers. Pharmacol Biochem Behav. 75, 669-674.
Tildesley, N.T., Kennedy, D.O., Perry, E.K., Ballard, C.G., Wesnes, K.A., Scholey, A.B., 2005. Positive modulation of mood and cognitive performance following administration of acute doses of Salvia lavandulaefolia essential oil to healthy young volunteers. Physiol Behav. 83, 699-709.

Vladimir-Knežević, S., Blažeković, B., Kindl, M., Vladić, J., Lower-Nedza, A.D., Brantner, A.H., 2014. Acetylcholinesterase inhibitory, antioxidant and phytochemical properties of selected medicinal plants of the Lamiaceae family. Molecules 19, 767-782.
Wang, H.F., Provan, G.J., Helliwell, K., 2004. Determination of rosmarinic acid and caffeic acid in aromatic herbs by HPLC. Food Chemistry 87, 307-311.
Williamson, E.M., 2001. Synergy and other interactions in phytomedicines. Phytomedicine 8, 401-409.
Wortmann, M., 2012. Dementia: a global health priority - highlights from an ADI and World Health Organization report. Alzheimers Res Ther. 4, 40.
Yoo, D.Y., Choi, J.H., Kim, W., Yoo, K.Y., Lee, C.H., Yoon, Y.S., Won, M.H., Hwang, I.K., 2011. Effects of Melissa officinalis L. (lemon balm) extract on neurogenesis associated with serum corticosterone and GABA in the mouse dentate gyrus. Neurochem Res. 36, 250-257.
Zgórka, G., Głowniak, K., 2001. Variation of free phenolic acids in medicinal plants belonging to the Lamiaceae family. J Pharm Biomed Anal. 26, 79-87.
Zhang, M., Yan, H., Li, S., Yang, J., 2016. Rosmarinic Acid Protects Rat Hippocampal Neurons from Cerebral Ischemia/Reperfusion Injury via the Akt/JNK3/Caspase-3 Signaling Pathway. Brain Res pii: S0006-8993, 30807-30801.

Figure Legends

Figure 1. PRISMA flow diagram of the bibliographic review of *S. officinalis* and *S. lavandulaefolia*. Records screened (n = 235). Records assessed for eligibility and included in qualitative synthesis (n = 8).

Figure 2. PRISMA flow diagram of the bibliographic review of *R. officinalis*. Records screened (n = 112). Records assessed for eligibility and included in qualitative synthesis (n = 5).

Figure 3. PRISMA flow diagram of the bibliographic review of *M. officinalis*. Records screened (n = 177). Records assessed for eligibility (n = 10) and included in qualitative synthesis (n = 8).

Figure 4. Volatile constituents of the three Lamiaceae members. Common and unique essential oil constituents (Table 2) are graphically presented.

Figure 1

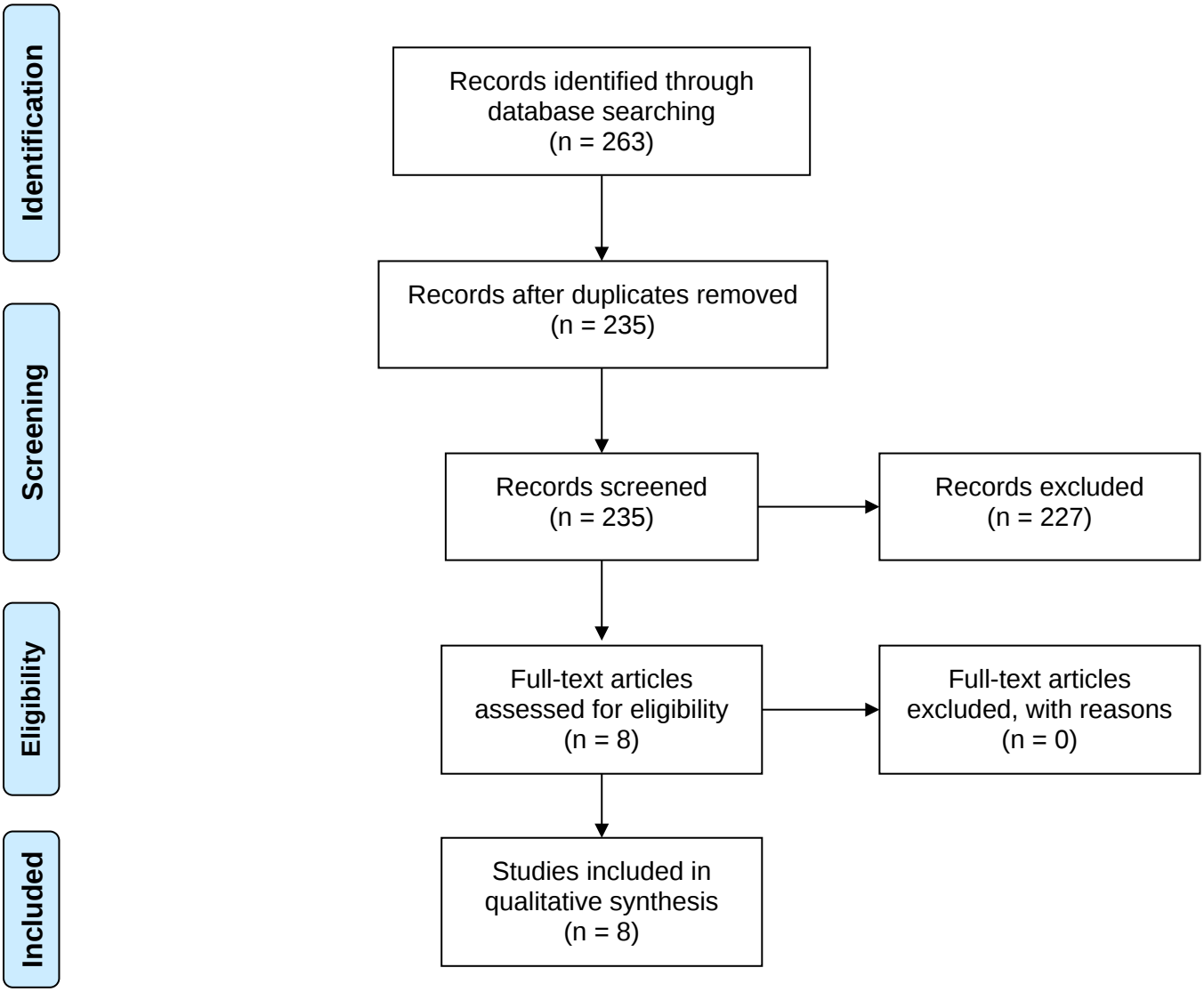
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 263)
Records after duplicates removed (n = 235)
Records screened (n = 235)
Records excluded (n = 227)
Full-text articles assessed for eligibility (n = 8)
Full-text articles excluded, with reasons (n = 0)
Studies included in qualitative synthesis (n = 8)

Figure 2

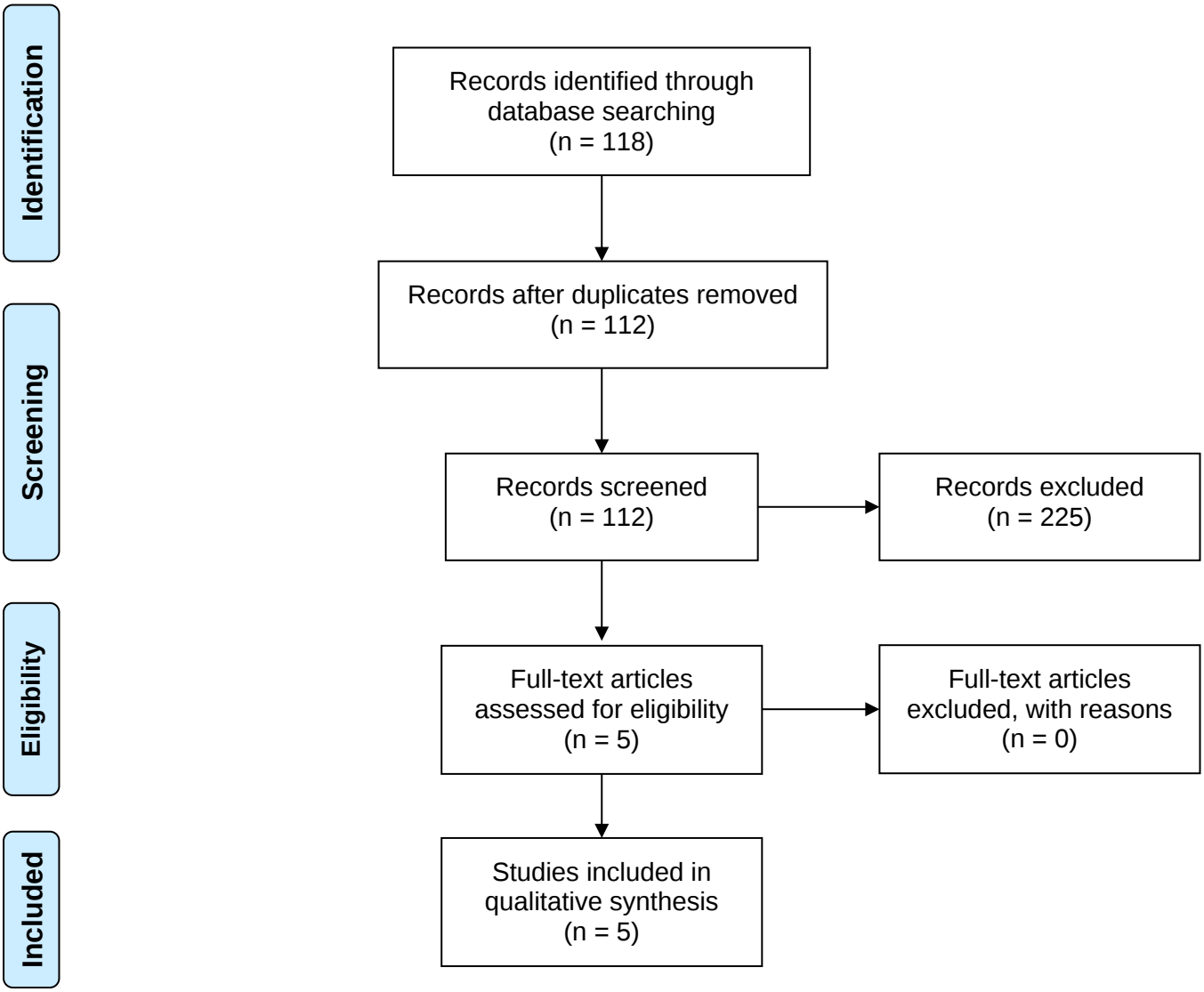
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 118)
Records after duplicates removed (n = 112)
Records screened (n = 112)
Records excluded (n = 225)
Full-text articles assessed for eligibility (n = 5)
Full-text articles excluded, with reasons (n = 0)
Studies included in qualitative synthesis (n = 5)

Figure 3

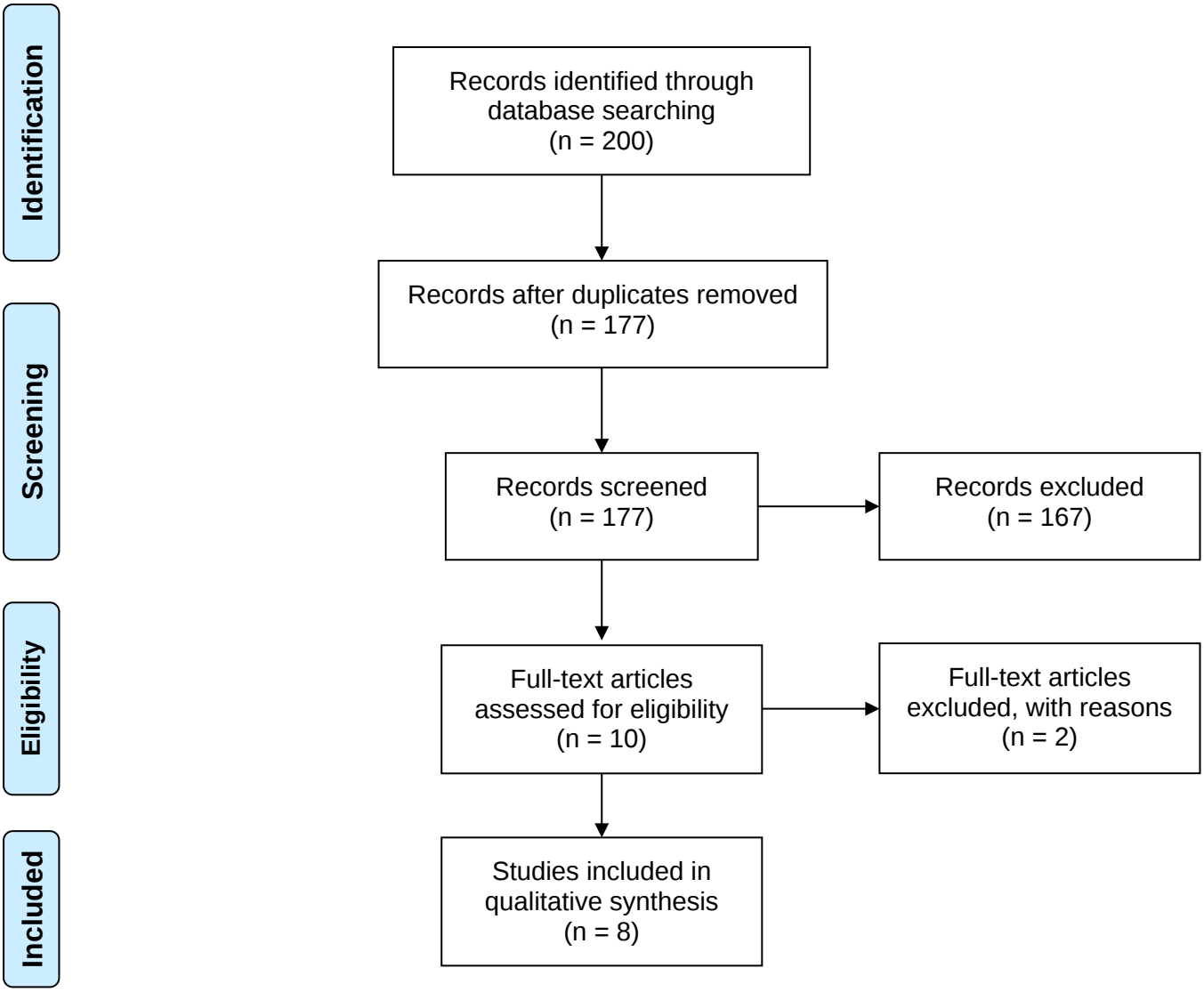
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 200)
Records after duplicates removed (n = 177)
Records screened (n = 177)
Records excluded (n = 167)
Full-text articles assessed for eligibility (n = 10)
Full-text articles excluded, with reasons (n = 2)
Studies included in qualitative synthesis (n = 8)

Figure 4

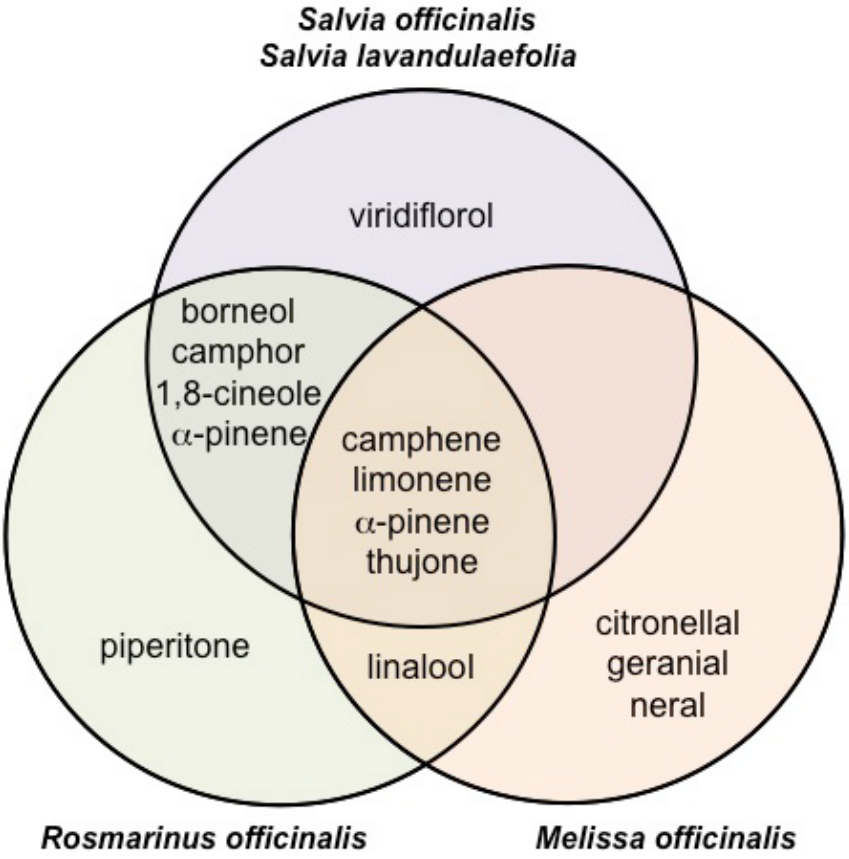
Salvia officinalis
Salvia lavandulaefolia
viridiflorol
borneol
camphor
1,8-cineole
α-pinene
camphene
limonene
α-pinene
thujone
piperitone
linalool
citronellal
geranial
neral
Rosmarinus officinalis
Melissa officinalis

Table 1: Rosmarinic acid contents in Lamiaceae species

	Rosmarinic acid (mg/g)				
	Zgórka & Głowniak 2001 #	Wang *et al*. 2004 *	Kivilompolo & Hyötyläinen 2007 #	Shekarchi *et al*. 2012 §	Benedec *et al*. 2015 **
Lavandula angustifolia Mill.	0.4	2.0		1.7 ± 0.2	
Melissa officinalis L.	9.9	27.4		36.5 ± 0.8	7.84 ± 0.07
Mentha x *piperita* L.	0.9				
Mentha spicata L.		7.1 – 14.3	5.62	58.5 ± 1.4	
Ocimum basilicum L.	11.8		3.08		
Origanum majorana L.	4.3				
Origanum vulgare L.			5.98	25.0 ± 0.1	12.4 ± 0.08
Prunella vulgaris L.		21.7			
Rosmarinus officinalis L.	6.5	10.0 – 11.0	9.16	7.2 ± 0.1	1.33 ± 0.01
Salvia officinalis L.	5.2	8.5 – 14.1	9.96	39.3 ± 0.9	2.12 ± 0.02
Satureja hortensis L.	12.2				
Thymus vulgaris L.	5.5	4.5 – 8.7	9.96	23.5 ± 0.5	

Methanol extract
* Ethanol:water (30:70) extract
§ Water:methanol:2-propanol (80:10:10) extract
** Ethanol:water (70:30) extract

Table 2: Major constituents (%) in essential oils

	S. officinalis		*S. lavandulaefolia*		*R. officinalis*		*M. officinalis*	
	Bozin 2007	Ali 2015	Porres-Martinez 2013		Bozin 2007	Gachkar 2007	Nimica-Dukic 2004	de Sousa 2004
borneol	5.4	1.5	0.3	0.1	6.2	3.7		
camphene	0.7	1.0	5.2	7.1	3.9	3.3	0.2	
camphor	18.9	6.4	14.4	23.9	21.6	5.0		
1,8-cineole	4.2	4.4	31.9	13.5	2.1	7.5		
citronellal							13.7	
geranial							23.4	47.3
limonene	1.0				21.7		2.2	
linalool					1.1	14.9		0.8
menthol/isomenthol							2.9	2.9
neral							16.5	39.3
α-pinene	1.5	1.9	9.0	11.7	13.5	14.9	0.3	
piperitone						23.7		
α-thujone	19.9	25.8	0.1	0.1			0.2	
β-thujone	3.8	5.7			0.2		0.8	
viridiflorol	17.5	20.4						

Table 3: Clinical trials – *S. officinalis* and *S. lavandulaefolia*

1st Author & Year	Target population & Intervention	Design & outcome measures	Results	Summary
Kennedy, 2011	Population: Healthy volunteers N=36 (26 women and 10 men, aged 23.8±4.38) Intervention: 1. Treatment: capsules containing *S.lavandulaefolia* essential oil 50µL in olive oil 2. Control: Placebo capsules with olive oil only	Design: Single dose, double-blind, placebo-controlled, balanced crossover Outcome measures: Pre-dose and 1 and 4h post-dose 1. Computerised Mental Performance Assessment System (COMPASS) (cognition and mood) 2. Cognitive Demand Battery: Serial 3s (speed/accuracy) and mental fatigue 3. Bond-Lader mood scales and State-trait anxiety inventory (STAI) subscale (mood/ well-being)	1. Improved performance of secondary memory and attention (pronounced at 1h) 2. Reduced mental fatigue and increased alertness (pronounced at 4h)	Herbal preparation, dosage and administration method: *S.lavandulaefolia* essential oil, 50µL, acute oral Overall outcomes: Improved performance, attention, alertness; Reduced fatigue
Moss, 2010	Population: Healthy volunteers N=45 (37 women aged 21.3±3.6, 8 men aged 22.4±3.0) for *S.officinalis* group; N=45 (36 women aged 21.3±4.9, 9 men aged 23.1±3.8) for *S.lavandulaefolia* group Intervention: 1. Treatment: Aroma of *S.officinalis* or *S.lavandulaefolia* essential oils for 5 min (5 drops in 5mL water, diffused in the testing cubicle) 2. Control: No aroma Acute olfactory* administration	Design: Single dose, single-blind, one factor, independent group Outcome measures: 1. A tailored Cognitive Drug Research computerised assessment battery (Assessed factors: quality of memory, speed of attention, accuracy of attention, speed of memory) 2. Bond-Lader mood scales (mod)	1. *S.officinalis* improved quality of memory**. 2. Both *S.officinalis* and *S.lavandulaefolia* enhanced alertness (subjective).	Herbal preparation, dosage and administration method: *S.officinalis* or *S.lavandulaefolia* essential oils, acute, aroma Overall outcomes: Improved quality of memory by *S.officinalis.* Enhanced alertness by *S.officinalis* and *S.lavandulaefolia*
Scholey, 2008	Population: Healthy older volunteers N=20 (9 women and 11 men, Aged 65-90) Intervention: Treatment: Standardised 70% ethanolic extract of *S.officinalis* dried leaf, lyophilised and powdered (167, 333, 666, and 1332mg extract). Acute oral administration	Design: Single dose, placebo-controlled, double-blind, balanced crossover Outcome measures: Cognitive Drug Research computerised assessment battery (Assessed factors: working memory, speed of memory, accuracy of attention, and speed of attention)	1. Significant enhancement of secondary memory performance* and improvements in accuracy of attention following 333mg-dose**. 2. No significant effect on working memory.	Herbal preparation, effective dosage and administration method: 70% ethanolic extract of *S. officinalis* dried leaf, 333mg, acute oral Overall outcomes: Enhanced memory performance and improved accuracy of attention only at 333mg (not at 167, 666, and 1332mg)

Kennedy, 2006	Population: Healthy volunteers N=30 (17 men and 13 women, Aged 24.4±4.4,) Intervention: 1. Treatment: Opaque capsules containing dried leaf of *S.officinalis* 300 or 600mg 2. Control: Inert placebo with the same appearance Acute oral administration	Design: Single dose, placebo-controlled, double-blind, balanced crossover Outcome measures: 1. Mood assessment at pre-dose and at 1 and 4h post-dose using Bond-Lader mood scales and State Trait Anxiety Inventory (STAI) after stress*. 2. Task performance was assessed by DISS.	1. Improved mood: reduced anxiety by 300mg **; increased alertness, calmness, and contentedness by 600mg. 2. Improved task performance: higher Stroop Colour-word score by 600mg. (No difference in math, highest number tap, and memory search.)	Herbal preparation, dosage and administration method: *S. officinalis* dried leaves, 300 and 600mg, acute oral Overall outcomes: Reduced anxiety at 300mg, increased alertness and calmness at 600mg, improved task performance at 600mg
Tildesley, 2005	Population: Healthy volunteers N=24 (16 women and 8 men, aged 18-37) Intervention: 1. Treatment: Capsules of 25 or 50µL of *S.lavandulaefolia* essential oil in sunflower oil 2. Control: Placebo capsules with sunflower oil only Acute oral administration	Design: Single dose, placebo-controlled, double-blind, balanced crossover Outcome measures: 1. Tailored version of Cognitive Drug Research computerised assessment battery (cognition) 2. Bond-Lader visual analogue scales (mood) 3. Numeracy (Serial Sevens test) Pre-dose and post-dose (at 1, 2.5, 4, or 6h) measurement	1. 'Speed of memory' improvement by 25 and 50µL. 2. 'Secondary memory' improvement by 25µL. 3. Mood enhancement: alertness, calmness, and contentedness by 50µL; calmness by 25µL	Herbal preparation, dosage and administration method: *S.lavandulaefolia* essential oil, 25 and 50µL, acute oral Overall outcomes: Speed of memory improvement at 25 and 50µL, secondary memory improvement at 25µL, enhanced alertness and contentedness at 50µL, enhanced calmness at 25 and 50µL
Tildesley, 2003	Population: Healthy volunteers Trial 1: N=20 (18 women and 2 men, aged 18-31) Trial 2: N=24 (16 women and 8 men, aged 18-37) Intervention: 1. Treatment: Capsules containing *S.lavandulaefolia* standardised essential oil (25, 50, 100, 150µL) and sunflower oil 2. Control: Placebo capsules containing sunflower oil alone Acute oral administration	Design: Single dose, placebo-controlled, double-blind, balanced crossover Outcome measures: Tailored version of Cognitive Drug Research computerized assessment battery - Simple word recall (cognition) Pre-dose and post-dose (at 1, 2.5, 4, or 6h) measurement	50µL dose improved immediate word recall when administered 1 or 2.5h before test. No effect at 25, 100, and 150µL.	Herbal preparation, dosage and administration method: *S.lavandulaefolia* essential oil, 50µL, acute oral Overall outcomes: Improved cognition only at 50 µL (not at 25, 100, and 150µL)
Perry, 2003	Population: Mild to moderate Alzheimer's disease N=11 (10 women and a man, aged 76-95)	Design: An open-label pilot study Outcome measures: Cognitive Drug Research computerised	1. Trends for improved memory and attention. 2. Statistically significant reduction	Herbal preparation, dosage and duration: *S.lavandulaefolia* essential oil, 50µL, increased dosage 1-3

	Intervention: 1. Treatment: Capsules containing 50µL *S.lavandulaefolia* essential oil plus 50µL sunflower oil. Week 1 – one capsule at 8 am Week 2 –at 8 am and 7 pm, one capsule each Week 3-6 – at 8 am, 7 pm, 12:30 pm, one capsule each 2. Control: None	assessment (cognition) and Neuropsychiatric Inventory (NPI) (psychopathology, including delusions, hallucinations, agitation, depression, anxiety, and appetite)	in neuropsychiatric disturbances.	times a day, oral, 6 weeks Overall outcomes: Trends for improved memory and attention. Reduction in neuropsychiatric disturbances
Akhondzadeh, 2003	Population: Mild to moderate Alzheimer's disease (ADAS-cog ≥ 12; CDR ≤ 2) N=42 (18 women and 24 men, aged 65 – 80 years) Intervention: 1. Treatment: *S.officinalis* 1:1 extract (dried leaves in 45% EtOH), 60 drops per day, for 4 months. 2. Control: placebo* 60 drops per day	Design: Placebo-controlled, parallel group Outcome measures: Change in Alzheimer's Disease Assessment Scale (ADAS-cog) and Clinical Dementia Rating-Sum of the Boxes (CDR-SB) over the trial.	ADAS-cog: Significant improvement over the course between 4-16 weeks. CDR-SB: Significant improvement over the course between 8-16 weeks.	Herbal preparation, dosage and duration: *S. officinalis* 1:1 extract (dried leaves in 45% EtOH), 60 drops (= 3-6mL) per day, oral, 4 months Overall outcomes: Significant improvement in cognition

ADAS-cog, cognitive subscale of the Alzheimer's disease assessment scale
CDR, clinical dementia rating
CDR-SB, clinical dementia rating–sum of the boxes

Table 4: Clinical trials – *R. officinalis*

1st Author & Year	Target population & Intervention	Design & outcome measures	Results	Summary
Lindheimer, 2013	Population: Young adult with lack of energy (Mood States-Brief Form POMS-BF) N=26 (rosemary) N=24 (placebo) (73% women, mixed ethnicity, aged 20.8±3.4) Intervention: 1. Treatment: Capsules containing 1.7g powdered mixture of *R.officinalis* and *R.eriocalyx* (rosmarinic acid content 20mg/g) 2. Control: Placebo capsules containing 3.1g rice flour Acute oral administration	Design: Single dose, randomised, placebo controlled, double blind*, crossover Outcome measures: 1. Cognition measured by Bakan Vigilance Task 2. Motivation and mood (subjective) Pre-dose and post-dose at 60 and 90min	Small, transient reductions in false alarm errors and mental fatigue	Herbal preparation, dosage and administration method: 1.7g mixture of *R.officinalis* and *R.eriocalyx*, containing rosmarinic acid 20mg/g, acute oral Overall outcomes: Transient reductions in false alarm errors and mental fatigue
Pengelly, 2012	Population: Healthy older adult, aged 65-90, recruited via local media and networking N=28 (20 women and 8 men) Intervention: 1. Treatment: Powdered dried *R.officinalis* (0.75, 1.5, 3.0, or 6.0g) in tomato juice 2. Control: Placebo – tomato juice without *R.officinalis* Acute oral administration	Design: Randomised, placebo-controlled, double blind, repeated-measures crossover Outcome measures: 1. Cognitive Drug Research test battery (cognition) 2. Bond-Lader visual analogue scales (mood)	1. Dose specific improvement in 'speed of memory' at 0.75g dose, while 6.0g had a negative impact. 2. Improved alertness (subjective) at 0.75g. 2. Negative impact on 'continuity of attention', and 'working memory' at some doses.	Herbal preparation, dosage and administration method: Powdered dried *R.officinalis* (0.75g) in tomato juice, acute oral Overall outcomes: Dose specific improvement in 'speed of memory' and subjective 'alertness' at 0.75g, while other dosages had some negative impacts.
Moss, 2012	Population: Healthy volunteers N=20 (12 women aged 23.2 ± 3.2 and 8 men aged 22.6 ± 2.9) Intervention: Treatment: Aroma of *R.officinalis* essential oil (4 drops on a diffuser pad in the testing cubicle, starting from 5 min prior to testing)	Design: Randomised, blind, parallel Outcome measures: 1. Computerised battery - serial trees, serial sevens, rapid visual information processing (RVIP) (cognition) 2. Bond-Lader Visual Analogue Scales (mood) 3. Blood test for 1,8-cineole absorption	1. A positive relationship between serum 1,8-cineole levels and correct answers on serial threes task. 2. Negative relationship between serum 1,8-cineole and the reaction time on serial threes and serial sevens task. 3. Negative relationship between serum 1,8-cineole and the reaction time on RVIP.	Herbal preparation, dosage and administration method: *R.officinalis* essential oil, aroma, acute Overall outcomes: Positive correlations between serum 1,8-cineole levels and cognitive performances.

			4. Negative relationship between serum 1,8-cineole and contentedness.	
McCaffrey, 2009	Population: Test-taking graduate nursing students N=40 Intervention: 1. Treatment: Essential oil inhaler of *R. officinalis* or *Lavandula hybrida*, prior to and during the test 2. No treatment for baseline	Design: Quasi-experimental, crossover Outcome measures: 1. Anxiety measured by Test anxiety inventory (TAS) scores (pre- and post-test) 2. Blood pressure and radial pulse 3. Stress-reduction properties assessed by post-test discussion	1. Significant reduction in post-test anxiety by both *R.officinalis* and *L.hybrida*, however *R. officinalis* was superior to *L. hybrida* 2. No effect on blood pressure 3. Significant reduction in pulse by both *R. officinalis* and *L. hybrid*.	Herbal preparation, dosage and administration method: *R.officinalis* essential oil, aroma (inhaler), acute Overall outcomes: Reduction in anxiety. Relaxing, and assisting in concentration and information recall.
Moss, 2003	Population: Healthy volunteers •Rosemary grope: N=48 (28 women aged 25.3±6.9, 20 men aged 23.8±7.8); •Lavender group: N=48 (27 women aged 23.8±6.3, 21 men aged 24.7±6.7) Intervention: 1. Treatment: Aroma of *R.officinalis* essential oil 4 drops on a diffuser pad in the testing cubicle, starting from 5 min prior to testing 2. Control: Water 4 drops instead of essential oil	Design: Randomised, blind, parallel Outcome measures: Tailored version of the Cognitive Drug Research computerised assessment system (cognition) 2. Bond-Lader visual analogue scales (mood)	1. Enhanced performance for overall quality of memory and secondary memory, but reduced speed of memory, in the treatment group 2. Improved alertness and contentedness in the treatment group.	Herbal preparation, dosage and administration method: *R.officinalis* essential oil, aroma, acute Overall outcomes: Enhancement of performance for overall quality of memory and improved alertness and contentedness.

Table 5: Clinical trials – *M. officinalis*

1st Author & Year	Target population & Intervention	Design & outcome measures	Results	Summary
Alijaniha, 2015	Population: Volunteer adult outpatients with heart palpitation •Treatment group: N=28 (17 women aged 42.4±10.7) •Control group: N=27 (18 women aged 41.1±12.3) Intervention: 1. Treatment: Capsules containing 500mg lyophilised aqueous extract of *M.officinalis* leaves, twice a day (morning and night) 2. Control: Placebo capsules with similar appearance Oral administration for 14 days	Design: randomised, double-blind, placebo-controlled Outcome measures: 1. Heart palpitation (subjective), evaluated by patient's diaries and a self-report questionnaire. 2. Psychiatric symptoms (subjective) (somatisation, anxiety and insomnia, social dysfunction and depression) evaluated by General Health Questionnaire-28 (GHQ-28)	*M.officinalis* treatment reduced frequency of palpitation, and reduced anxiety and insomnia.	Herbal preparation, dosage, administration method and duration: 500mg lyophilised aqueous extract of *M.officinalis* leaves, twice a day (morning and night), oral, for 14 days Overall outcomes: Reduced anxiety and insomnia
Scholey, 2014	Population: Healthy volunteers Study 1 (Tea-like drink): N=25 (17 women and 8 men, aged 18-39) Study 2 (Yoghurt): N=21 (8 women and 13 men, aged 21-30) Intervention: 1. Treatment: Dried aqueous extract of *M.officinalis* (rosmarinic acid > 6%) in tea-like drink or yogurt 2. Control: Tea or yoghurt without *M.officinalis* extract with artificial sweetener	Design: Double-blind*, placebo-controlled, crossover Outcome measures: 1. Cognitive Drug Research computerised assessment battery (cognition and mood) 2. State-Trait Anxiety inventory (mood) 3. Bond-Lader Visual Analogue Scales (mood) 4. Profile of Mood States (POMS) (mood) 5. Spielberger State Anxiety Questionnaire (mood) 6. Cortisol levels	1. Significant reduction in salivary cortisol levels at 1h after *M.officinalis* in drink. 2. No significant improvement in mood and cognition.	Herbal preparation, dosage, administration method: Dried aqueous extract of *M. officinalis* leaves, 0.3 or 0.6g in tea-like drink or yoghurt, oral, single dose Overall outcomes: No significant improvement in mood and cognition
Burns, 2011	Population: Older people (> 60 years) with Alzheimer disease and agitation. •*M.officinalis* group: N=32 (21 women and 11 men) •Donepezil: N=31 (20 women and 11 men) •Placebo group: N=31 (15 women and 16 men) Intervention: 1. Treatment: *M. officinalis* aromatherapy (10%	Design: Randomised, double-blind, parallel-group, placebo controlled Outcome measures: 1. Agitation assessed by Pittsburgh Agitation Scale (PAS, observational) 2. Behavioural and psychological symptoms assessed by Neuropsychiatric Inventory (NPI)	Not superior compared to placebo or donepezil in reducing agitation (PAS) and observational psychological symptoms (NPI), however effectively improved Quality of Life (Blau QOL scale).	Herbal preparation, administration method and duration: *M.officinalis* essential oil, aromatherapy (massage), 12 weeks Overall outcomes: Effective in improving QoL, however not superior to placebo in reducing agitation or

	essential oil applied to the skin 1-2min) and placebo medication 2. Donepezil medication and placebo aromatherapy (sunflower oil) 3. Control: Placebo medication and aromatherapy (sunflower oil) 4-week interventions and 12-week follow-ups.	3. Quality of life measured by the Blau QoL scale		observational psychological symptoms
Kennedy, 2004	<u>Population</u>: Healthy volunteers N=18 (8 women and 10 men, aged 29.11 ± 6.81) <u>Intervention</u>: 1. Treatment: capsules containing *M. officinalis* methanol:water (30:70) extract, dried, 300mg or 600mg 2. Control: placebo Acute oral administration	<u>Design</u>: Single dose, randomised, placebo controlled, double-blind, balanced crossover <u>Outcome measures</u>: Defined Intensity Stressor Simulation (DISS) computerised battery (cognitive and psychomotor tasks) – medium difficulty/intensity level, for cognition; Bond-Lader Visual Analogue Mood Scales for mood.	1. Reduction in DISS-induced negative mood and increased calmness and reduced alertness (self-rated) by 600mg. 2. Increase in the speed of mathematical processing by 300mg.	<u>Herbal preparation, administration method and duration</u>: *M. officinalis* methanol:water (30:70) dried extract, 300mg or 600mg, oral, single dose <u>Overall outcomes</u>: Reduction in negative mood and alertness and increased calmness at 600mg. Increased speed of mathematical processing by 300mg.
Akhondzadeh, 2003	<u>Population</u>: Patients with mild to moderate Alzheimer's disease N=42 (18 women and 24 men, aged 65-80) <u>Intervention</u>: 1. Treatment: *M.officinalis* leaf extract (1:1 in 45% alcohol, standardised > 0.5mg/mL citral) 60 drops/day 2. Control: placebo 60 drops/day Oral, for 4 months	<u>Design</u>: Randomised, placebo controlled, double-blind, parallel group <u>Outcome measures</u>: Change in Alzheimer's Disease Assessment Scale (ADAS-cog) and Clinical Dementia Rating-Sum of the Boxes (CDR-SB) over the trial.	Improvement in treatment group, while decline in placebo group, in both ADAS-cog and CDR-SB scores over the 4 months.	<u>Herbal preparation, administration method and duration</u>: *M.officinalis* leaf extract (45% alcohol), 60 drops/day, oral for 4 months <u>Overall outcomes</u>: Improved cognition
Kennedy, 2003	<u>Population</u>: Healthy volunteers N=20 (14 women and 6 men, aged 18-23) <u>Intervention</u>: 1. Treatment: capsules containing 0, 600, 1000, or 1600 mg of *M.officinalis* leaf 2. Control: placebo capsules	<u>Design</u>: randomised, placebo-controlled, double-blind, balanced crossover <u>Outcome measures</u>: 1. Cognitive Drug Research computerised assessment battery (cognition) 2. Bond-Lader visual analogue scales (mood)	1. Improved working memory and accuracy, and calmness at 1600mg. 2. Slower performance and decreased accuracy at 600 and 1000mg.	<u>Herbal preparation, administration method and duration</u>: 1.6g of *M.officinalis* leaves, oral, single dose <u>Overall outcomes</u>: Improved working memory and

	Acute oral administration			accuracy, and calmness.
Kennedy, 2002	Population: Healthy volunteers N=20 (15 women and 5 men, aged 18-22) Intervention: 1. Treatment: Capsules containing *M.officinalis* leaf methanol:water (30:70) extract, 300, 600, or 900mg 2. Control: Placebo Acute oral administration	Design: Single dose, randomised, placebo-controlled, double-blind, balanced-crossover Outcome measures: 1. Cognitive Drug Research computerised assessment battery and serial subtraction (cognition) 2. Bond–Lader Visual Analogue Scales (mood). Measured at pre-dose, post-dose (1h, 2.5h, 4h, and 6h)	1. Improved accuracy of attention, but reduced working & secondary memory at 600mg. 2. Elevated calmness by 300mg and reduced alertness by 600mg.	Herbal preparation, administration method and duration: *M.officinalis* leaf methanol:water (30:70) extract, 300 or 600mg, oral, single dose Overall outcomes: Improved accuracy of attention, but reduced working & secondary memory and alertness at 600mg. Elevated calmness at 300mg
Ballard, 2002	Population: Severe dementia patients N=72 (36 for each group - female 20 for treatment and female 23 for control, aged 77.2±7.6 for treatment and 79.6±8.5 for control) Intervention: 1. Treatment: *M.officinalis* essential oil (aromatherapy) 2. Control: Sunflower oil Topical application to the face and both arms twice a day, total 200mg of oil (combined with base lotion), for 4 weeks	Design: Randomised, placebo-controlled, parallel Outcome measures: 1. Cohen-Mansfield Agitation Inventory (CMAI) 2. Neuropsychiatric Inventory (NPI) 3. QoL measured by Dementia Care Mapping	*M.officinalis* was Significantly more effective than control in reducing agitation and improving QoL	Herbal preparation, administration method and duration: *M.officinalis* essential oil, aromatherapy (topical administration to the face and arms), 4 weeks Overall outcomes: Reduced agitation and improved QoL

Supplementary table 1: Comparison of essential oil contents between *S. officinalis* and *S. lavandulaefolia*

	Potential toxicity and pharmacological actions	*S. officinalis* (% in essential oil)**				*S. lavandulaefolia* (% in essential oil)**		
		Savelev *et al*., 2004	Mirjalili *et al*., 2006	Darwish *et al*. 2013	Hamidpour, *et al*. 2014	Savelev *et al*., 2003	Perry *et al*., 2001	Savelev *et al*., 2004
thujone (α & β)	Toxic at high doses, $GABA_A$ and $5\text{-}HT_3$ inhibition	6.2	13.9	2 - 6	2.1-3.3	-	0.28	-
camphor	Toxic at high doses, TRPV3 activation	11.0	7.1	5 - 10	8.0-10.0	24.7	27	42.5
1,8-cineole	AChE inhibition	5.4	16.8	37 - 60	55.0-62.0	26.8	17	17.4
α-pinene (camphene*)	AChE inhibition	(1.2)	2.7 (3.4)	3 - 10	3.7-4.5 (2.6-5.0)	6.6	5	-

* Camphene can be a by-product of α-pinene during the processing

** Data adopted from Savelev *et al*. (2004)

Supplementary table 2: Assessment methods used in the trials

Test (References)	Applications	Factors assessed	Other notes
Bond-Lader Visual Analogue Scales (Bond and Lader, 1974; Hasson and Arnetz, 2005)	1. To assess subjective feelings. 2. Used for sedative drug effects etc.	Mental sedation, physical sedation, and calmness	1. Subjective measures of mood 2. 16 scales 3. Easier to use (but might be less specific/precise) compared to Likert scale
Clinical Dementia Rating scale - Sum of the Boxes (CDR-SB) (O'Bryant et al., 2008)	Diagnosis of dementia. (Not able to assess cognitive decline in the normal population)	Global cognitive function	1. Involves structured interviews to determine the presence of dementia. 2. Lacks sensitivity and precision.
Cognitive Drug Research (CDR) computerised assessment battery (Thomas Gualtieri, 2004)	1. To assess cognitive impairment related to a variety of disorders including dementia, drugs, and environmental toxins. 2. To differentiate different conditions causing dementia (AD, Huntington's disease, Parkinson's disease, mild cognitive impairment, and stroke)	Attention, executive function and working memory, episodic secondary memory, motor skill	1. Automated. 2. Yes or No. 3. Records the accuracy and reaction time. 4. Additional tests can be added to the standard battery
Cognitive subset of the Alzheimer's disease assessment scale (ADAS-cog) (Mohs et al., 1997; Rosen et al., 1984)	Diagnosis of dementia. (Not able to assess cognitive decline in the normal population)	Global cognitive function	1. Involves structured interviews to determine the presence of dementia. 2. Lacks the sensitivity and precision. 3. Administration by paper and pencil
Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield et al., 1989)	To assess the frequency of manifestations of agitated behaviours in elderly persons.	Abusive or aggressive behaviours, normal behaviours with inappropriate frequency, inappropriate behaviours according to social norm	1. Caregivers' rating questionnaire. 2. Rating 1-7 for 29 descriptors.
Computerised Mental Performance Assessment System (COMPASS) (Brain, performance and nutrition research centre)	1. To assess Mood and cognition. 2. Sensitive in nutraceutical intervention.	Mood and cognitive factors such as working memory, attention, and executive function	1. Automated. 2. Can do parallel stimuli (multi-tasking) 3. Flexible.
Dementia Care Mapping (Brooker, 2005)	To assess the well-being of dementia	Behaviours with high or low potential for well-being, personal detractions, positive events	1. Observational 2. Involves one or two trained mappers 3. Well- or ill-being (6-point scale from extreme ill-being to extreme well-being)
Neuropsychiatric Inventory (NPI) (Cummings et al., 1994; Forester and Oxman, 2003)	1. To assess the presence of psychopathology in patients with brain disorders 2. Widely used to measure the outcome of interventions, particularly anti-dementia agents	Delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour	1. Caregivers' rating questionnaire 2. Rating the frequency on a 4-point scale, the severity on a 3-point scale, and the distress on a 5-point scale
Pittsburgh Agitation Scale (PAS) (Rosen et al., 1994)	To assess agitation in patients with dementia.	Observational measures of behaviours: aberrant vocalisation, motor agitation, aggressiveness, resisting care	1. Observational rating (direct observation over 1 to 8 hours by clinical staff) 2. Measured on an intensity scale of 0-4

Test Anxiety Scale (TAS) (Sarason, 1984)	Anxiety in reaction to test-taking	Subjective anxiety	True or False judgment for about 40 descriptors
Bakan Vigilance Task (Bakan, 1959)	A state of readiness to detect and respond to environmental stimuli.	Auditory vigilance.	Primary and secondary auditory signals. (Bakan, 1959)