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Research paper

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

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ABSTRACT

Introduction: Dementia is a common, progressive disorder impairing brain function and affecting both sufferers and caregivers' wellbeing. The number 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, and has been suggested as having potential efficacy as a 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 studies for sage, five for rosemary and eight for lemon balm met the 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 [1]. 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, 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 [2–4]. 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 [5]. 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 [6,7]. Meanwhile, oxidative stress has been found to be an important culprit in the development of AD [6,7], suggesting the potentials of anti-oxidants in the prevention of the disease [7,8]. 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

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common risk factors for both types of dementia [3], 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 [9,10].

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 [11], and ACh-mediated signalling, particularly via nicotinic acetylcholine receptors, is thought to be a promising target in the symptomatic treatment of dementia [12,13]. 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 [14]. ChEIs have a modest but significant effect on the cognition, mood, and behaviour of AD patients [15]. 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' [104]. John Gerard (1545–1612) wrote 'sage is singularly good for the head and brain, it quickeneth the senses and memory' [16]. Rosemary was mentioned in Hamlet by William Shakespeare (1564–1616): 'There's rosemary, that's for remembrance' (Hamlet, act IV scene V) [17]. The historical use of rosemary as a memory enhancer dates back to ancient Greece. It was mentioned by Pedanius Dioscorides (1st century AD) [18,19], and according to Nicholas Culpeper, rosemary 'helps a weak memory, and quickens the senses' [104]. 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' [104]. According to Avicenna (Ibn-Sīnā, 980–1037), lemon balm was recognised an exhilarant [20], while Paracelsus (1493–1541) recommended it for 'all complaints supposed to proceed from a disordered state of the nervous system' [21]. 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 [22]. It is found abundantly in the members of botanical family lamiaceae, particularly in the subfamily nepetoideae [23]. Table 1 shows the levels of rosmarinic acid in lamiaceae plants [24–28]. 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 [29], rosmarinic acid is a potent inhibitor of AChE and BuChE [11,30]. In addition, rosmarinic acid protects hippocampal neurons against injuries [31,32], and can possibly enhance hippocampal functions [33]. Considering the involvement of the hippocampus in dementia development [9,10], rosmarinic acid may prevent or delay the progress of dementia through improving hippocampal functions. Furthermore, rosmarinic acid inhibits γ-Aminobutyric acid (GABA) transaminase [34], suggesting additional therapeutic benefits for accompanying symptoms such as anxiety, insomnia, and aggressive behaviour, by increasing GABA levels [35].

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 [36]. In fact, lamiaceae plants are rich in volatile constituents with potential therapeutic benefits (Table 2) [37–42]. For example, sage and rosemary are rich in volatile compounds with AChE and BuChE inhibitory properties, such as α-pinene and 1,8-cineole, [30,43–45]. 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 [46,47]. 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 [48,49]. 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 [50]. Due to impaired olfactory abilities in dementia patients, aroma alone may not be sufficiently effective [51], however those volatile components, in combination with non-volatile constituents such as rosmarinic acid, could exert an synergetic benefits [36] 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, on healthy or cognitively impaired populations, were included. Flow diagrams were generated following PRISMA format [69] (Figs. 1–3). After screening, both