

● REVIEW

Essential oils and functional herbs for healthy aging

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Abstract

As total life expectancy increases, the prevalence of age-related diseases such as diabetes and Alzheimer's disease is also increasing. Many hypotheses about Alzheimer's disease have been developed, including cholinergic neuron damage, oxidative stress, and inflammation. Acetylcholine is a major neurotransmitter in the brain and cholinergic deficits leads to cognitive dysfunction and decline. Recent studies have linked diabetes as a risk factor in developing Alzheimer's disease and other types of dementia. The incidence of patients with type II diabetes and increased levels and activity of α -amylase is higher in patients with dementia. It has been shown that aromatherapy with essential oils from the mint family can improve cognitive performance in Alzheimer's disease patients. Selected monoterpenoids from these essential oils are reported to inhibit acetylcholinesterase, both *in vitro* and *in vivo*. Terpenoids are small, fat-soluble organic molecules that can transfer across nasal mucosa if inhaled, or penetrate through the skin after topical application, enter into the blood and cross the blood-brain barrier. Recent evidence supports the idea that the common constituents of essential oils also inhibit α -amylase, a starch digestive enzyme that plays an important role in the control of diabetes. The mint family is a fragrant plant family that contains most of the culinary herbs found in the Mediterranean diet. The Mediterranean diet is considered to be one of the healthiest diets in the world, and is found to be beneficial not only for the heart but also for the brain. Herbs used in this diet are rich in antioxidants that can prevent oxidative damage caused by free radicals. However, our study shows that they also contain biologically active compounds with potent α -amylase and acetylcholinesterase inhibitory activities. Consumption of fresh herbs can help boost memory and reduce sugar levels in the body. The use of herbs as a functional food could lead to significant improvements in health. Cognitive stimulation with medical food and medical herbs could delay development of cognitive decline, and improve the quality of life of Alzheimer's disease patients. This effect can be enhanced if combined with aromatherapy, topically or by inhalation, and/or by ingestion. Terpenes and terpenoids, the primary constituents of these essential oils are small, lipid soluble organic molecules that can be absorbed through the skin or across nasal mucosa into the systemic blood circulation. Many terpenes can also cross the blood-brain barrier. Therefore, topical application or inhalation of essential oils will also produce a systemic effect.

Key Words: functional herbs; essential oils; dementia; mediterranean diet; diabetes; acetylcholinesterase; α -amylase; mint family

Alzheimer's Disease and an Aging Population

As total life expectancy is increasing globally, the prevalence of age-related diseases such as diabetes and Alzheimer's disease (AD) is increasing due to poor diets and unhealthy lifestyles. AD, the most common form of dementia, is an age-related progressive neurodegenerative disease of the central nervous system. As the disease progresses, the brain goes through biological and chemical changes, atrophy (shrinking) of certain brain areas as the neuronal cells die, brain inflammation, and cognitive impairment. Microscopic examinations of affected brain tissue show two neuropathological hallmarks: abnormal accumulations of extracellular protein segments known as amyloid-beta plaques and intracellular neurofibrillary tangles. The formation of the plaques and tangles is associated with the increased acetylcholinesterase (AChE) expression and metabolic disorders. Increased activity of AChE leads to reduced levels of neurotransmitter, acetylcholine and synaptic alterations. Acetylcholine is essential for processing memory and learning (Francis, 2005). Some studies suggest that AChE may directly interact with

amyloid-beta in a manner that increases the deposition of this peptide into insoluble plaques and promote its aggregation (De Ferrari et al., 2001). Three of the five medication treatments for AD that are approved by the US. Food and Drug Administration, donepezil, galantamine and rivastigmine are cholinesterase inhibitors. Memantine acts on the glutamatergic system by blocking N-methyl-D-aspartate receptors that are also important for learning and creating new memory (Rowland et al., 2005). The fifth medication is a combination of donepezil (a cholinesterase inhibitor) with memantine. Delivery of these drugs to the brain is limited by the presence of the blood-brain barrier. Recent studies suggest that the brain uptake for donepezil (Kim et al., 2010) and rivastigmine (Lee and Kang, 2010) is decreased due to saturable carrier mediated transport involved in the penetration of these drugs across the blood-brain barrier. Galantamine, on the other hand, being a plant alkaloid, is less lipophilic than the other two cholinesterase inhibitors and hence exhibits a very low brain-to-blood concentration ratio (Maelicke, 2015). We have performed a PubMed and Scifinder Scholar literature search of articles published in

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the period January 1995–June 2018 on the beneficial health effects of herbs in treating and preventing the onset of AD. In particular, their possible role in altering AChE and α -amylase activity in patients with AD and diabetes.

Type II Diabetes is a Risk Factor for AD

Type II diabetes involves the dysfunctional use of pancreatic insulin by the body. Insufficient insulin availability or defective cells response/sensitivity to insulin, results in high glucose levels in blood, irregular protein synthesis and other metabolic disorders that might lead to diabetic complications. These complications and uncontrolled diabetes ultimately lead to cardiovascular disease, kidney disease, neuropathy, and diabetic retinopathy. Recent studies have linked diabetes to AD, suggesting that there is a clinical relationship between type II diabetes and AD (Nicolls, 2004). Both dementia and diabetes are complex disorders related to age and lifestyle. Both disorders share certain systematic pathways which include neuro-inflammation, increased amyloid beta plaques and neurofibrillary tangles, abnormal levels of AChE and butyrylcholinesterase, insulin resistance, and reduced glucose metabolism (Mushtaq et al., 2014). The incidence of patients with type II diabetes is significantly higher in patients with dementia when compared to age-related non-AD patients. Although AD patients show reduced gene expression for α -amylase there are increased levels and activity of α -amylase when compared with non-demented control patients. These findings suggest that α -amylase is expressed and active in the human brain, and that altered α -amylase enzyme activity may play an important role in the neurodegenerative pathology of AD (Byman et al., 2018). It has been demonstrated that antidiabetic medications affect AD markers, such as neuritic plaques and vascular integrity (Kravitz et al., 2013), and therefore could be associated with improved cognitive functioning. Beeri et al. reported that the use of both insulin and other hypoglycemic medication resulted in a substantially lower number of senile neuritic plaques (Beeri et al., 2008).

The Benefits of Aromatherapy and the Consumption of Herbs in Treating AD

Essential oils have been used for generations to ease the symptoms of AD and other dementias. Current knowledge of the biological effects of essential oils is based mainly on qualitative observations, rather than rigorous quantitative scientific studies. However, there has been recent work that has helped to explain their biological activity, with the volatile component compounds shown to have numerous therapeutic properties. Thus, it is no surprise that there is a recent increased interest in the use of essential oils, in alternative medicine such as aromatherapy. Aromatherapy with essential oils of chamomile, lavender, marjoram and rosemary can significantly reduce agitated behavior in AD patients (Ayaz et al., 2017). Selected monoterpenoids from thyme (*Thymus vulgaris*) essential oil, thymol, carvacrol, and linalool (minor component), have been found to inhibit AChE *in vitro*

(Jukic et al., 2007), while the essential oil of Spanish sage (*Salvia lavandulaefolia*) and its individual monoterpenoids were found to inhibit AChE both *in vitro* and *in vivo* (Perry et al., 2001). Terpenes are small, fat-soluble organic molecules that can transfer quickly across the single epithelial cell layer in nasal mucosa, into systemic blood circulation, and cross the blood-brain barrier. Inhibitory effects have also been observed for lavender, where different concentrations of lavender extract were shown to inhibit the AChE enzyme in *in vitro* tests using cell lines (Perry et al., 1996). Major anticholinesterase monoterpenoids from essential oils have been shown to act synergistically to inhibit AChE. However, when given individually as pure compounds, monoterpenes have significantly less anticholinesterase activity than when combined in an essential oil (Perry et al., 2003). Recent evidence supports the idea that the common constituents of essential oils also inhibit α -amylase to a significant degree. Inhibition of starch digestive enzymes, such as α -amylase, might play an important role in the control of diabetes. However, synthetic hypoglycemic agents that inhibit α -amylase, currently in clinical use, like acarbose and miglitol, have their limitations. They are non-specific, may fail to diminish diabetic complications, and have several side effects. There are an increasing number of studies investigating the effect of essential oils on α -amylase activity. Different commercially available lemon balm essential oils (*Melissa officinalis*, from the mint family) were found to increase glucose consumption and exhibit an antidiabetic effect. Gas chromatography-mass spectrometry profiles suggested that mixtures of citrals and some other minor compounds from essential oils may be responsible for this effect (Yen et al., 2015). However, other essential oils, such as orange and lemon, which are well known to possess abundant amounts of citrals, are inactive. Therefore, the compositions of other minor compounds with or without citrals in the lemon balm essential oils may be involved in α -amylase inhibition.

Many of the herbs from the *Lamiaceae* or *Labiatae* family (commonly known as the mint family), like peppermint, basil, oregano, rosemary, sage, thyme, lavender, have a long history of medicinal applications (Table 1). They are common to Mediterranean countries and widely used as culinary herbs.

Rosmarinic acid, which is found in many plants from the *Lamiaceae* family exhibits important biological activities. Evaluation of a standardized extract from sage leaves (*Salvia officinalis*) indicated that its main ingredient, rosmarinic acid, has protective effects against amyloid-beta-amyloid peptide-induced neurotoxicity, generation of reactive oxygen species, lipid peroxidation, DNA decomposition, tau protein hyperphosphorylation and protein kinase activation (Iuvone et al., 2006). In a mouse model, a 0.25 mg/kg dose of rosmarinic acid protected against the memory impairment by the amyloid peptide, leading to the conclusion that daily consumption of culinary herbs containing rosmarinic acid may provide a chemoprotective effect against dementia (Alkam et al., 2007). Nuclear magnetic resonance spectroscopic techniques have indicated that rosmarinic acid binds

Table 1 Investigated Lamiaceae species and their biological activities and potential uses

Common name	Species	Genus	Biological activities	Used parts
Oregano	<i>Origanum vulgare</i> L.	<i>Origanum</i>	Antioxidant and antimicrobial (Dorman and Deans, 2004); for colds, digestive, and respiratory problems (Ličina et al., 2013); antibacterial (Alexopoulos et al., 2011)	Leaves
Rosemary	<i>Rosmarinus officinalis</i> L.	<i>Rosmarinus</i>	Antiseptic, anti-inflammatory, antispasmodic, hepatoprotective, anti-diabetic, anti-ulcerogenic, antidepressant, and antioxidant (Lagouri and Alexandri, 2013; Yosr et al., 2013); antimicrobial (Toroglu, 2011)	Aerial parts
Sage	<i>Salvia officinalis</i> L.	<i>Salvia</i>	Antimicrobial (Rota et al., 2004); antibacterial, allelopathic, and antioxidant (Bouajaj et al., 2013); gastroprotective, antidiabetic, anti-obesity, anti-inflammatory, antispasmodic, virucidal, fungicidal, and bactericidal (Jug-Dujaković et al., 2012)	Leaves and flowers
Lavender	<i>Lavandula angustifolia</i> Mil.	<i>Lavandula</i>	Anti-inflammatory and analgesic (Hajhashemi et al., 2003); antioxidant (Blažeković et al., 2010); antimicrobial (Rota et al., 2004)	Leaves, petals, and flowering tips

to amyloid-beta ligomers (Airoldi et al., 2013) and inhibits amyloid-beta oligomerization and deposition (Hamaguchi et al., 2009). A thioflavin T assay (Levine III, 1993), a commonly used probe to monitor *in vitro* amyloid fibril formation, has confirmed that rosmarinic acid, methyl caffeate, and methyl cinnamate, natural products present in many herbs, could have multiple neuroprotective therapeutic effects against AD.

Screening for Therapeutic Activity in Essential Oils and Herbs

In an effect-directed analysis conducted by our group, the health benefits of essential oils from lavender, peppermint, sage, lemon myrtle, oregano and rosemary and extracts obtained from fresh oregano, basil, lavender, rosemary, sage and thyme were investigated. The effects of essential oils and fresh herbs on mental health, aging and cognitive function were evaluated through their antioxidant potential, α -amylase inhibition and AChE inhibition. For that purpose, high-performance thin-layer chromatography (HPTLC) as an enhanced form of thin-layer chromatography (TLC), was hyphenated with biochemical (α -amylase and acetylcholine enzymatic) derivatizations for effect-directed analysis of biologically active molecules on chromatograms. TLC is compatible with enzymatic bioassays as it is an open system. This enables elimination of the mobile phase before bioassay application and plate neutralization. In contrast, column chromatography while allowing higher separation efficiency, when combined with bioassays, requires time consuming steps including fraction collection, drying or lyophilization, and re-suspension in an appropriate solution (Järvinen et al., 2016). Furthermore, the use of column chromatography with these techniques requires the use of long reaction coils and dilution with reagents, which results in extra peak broadening (Järvinen et al., 2016). In contrast TLC chromatography requires minimal sample preparation (crude extracts can be applied without losing components), and enables parallel profiling of samples on the same plate, or a parallel performance of different effect-directed assays (Figure 1).

α -Amylase inhibition assays were carried out using the method developed by our group (Agatonovic-Kustrin and

Morton, 2017) and involved using a starch test and iodine solution as an indicator. Starch produces a dark-blue color on the chromatographic plate in the presence of iodine, with a blue zone around the bands indicating reduced α -amylase activity in the sample. The blue color comes from the starch-iodine complex formed with starch not hydrolyzed because of α -amylase inhibition by the compounds in the sample (Figure 2A).

The AChE inhibitory assay is based on the α -naphthyl acetate and fast blue B system for the detection of AChE activity. Enzyme activity was detected by the conversion of α -naphthyl acetate into naphthol, which then reacts with Fast Blue B to form an intensely purple coloured diazonium dye compound. Inhibitors of cholinesterases produce white spots on a purple coloured background on the TLC plates due to the presence of the diazonium dye and Fast Blue B (Figure 2B).

In the case of essential oils, the highest α -amylase inhibitory activities were produced by oregano leaf and lemon myrtle. The highest AChE inhibitory activity was produced by sage, and was significantly higher from the rest of the essential oils. Lemon myrtle and rosemary exhibited moderate AChE activity, significantly higher than lavender, peppermint and oregano. The nutraceutical potential(s) of fresh herbs that are commonly used in the Mediterranean diet (basil, lavender, oregano, rosemary, sage and thyme) were compared by assessing their antioxidant, antidiabetic and neuroprotective activities. The highest antioxidant activity was found in extract from fresh oregano leaves, while the highest α -amylase and AChE inhibition were found in lavender leaves extract, followed by the lavender flowers extract and sage extract. α -Amylase inhibitory activities were correlated to AChE inhibition. Similar R_f values on chromatograms for bands showing positive α -amylase and AChE inhibition have indicated that similar compounds might be responsible for inhibition of both α -amylase and AChE (Figure 2). The colour reaction with p-anisaldehyde and ultraviolet spectral analysis of the bands suggest a diterpenoid structure for these compounds. Diterpenoids are secondary plant metabolites containing 20 carbon atoms, with their structures derived from the condensation of four isoprenyl

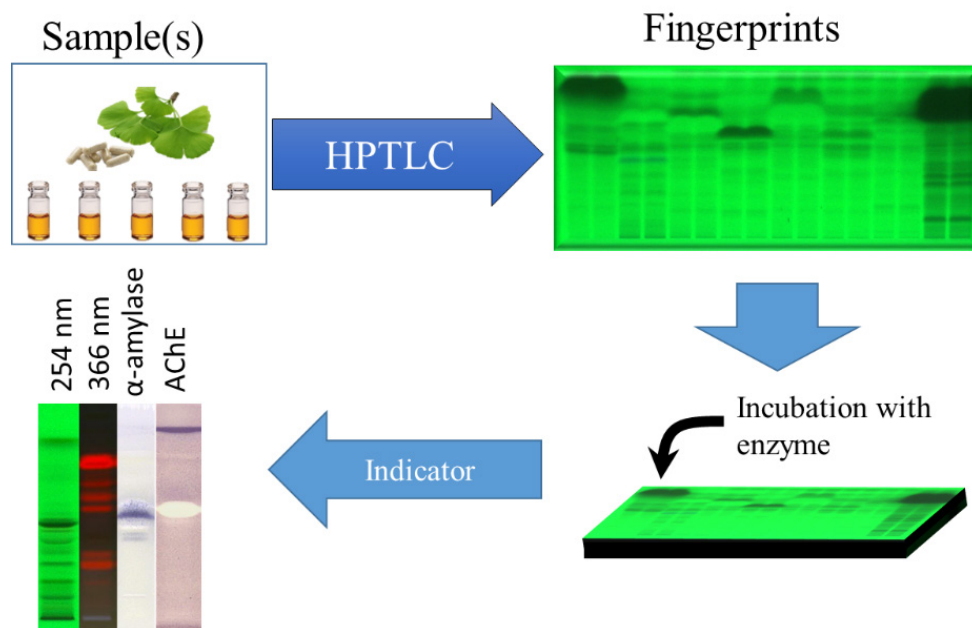


Figure 1 Direct bioautographic HPTLC as an effect-directed analysis method.

AChE: Acetylcholinesterase.

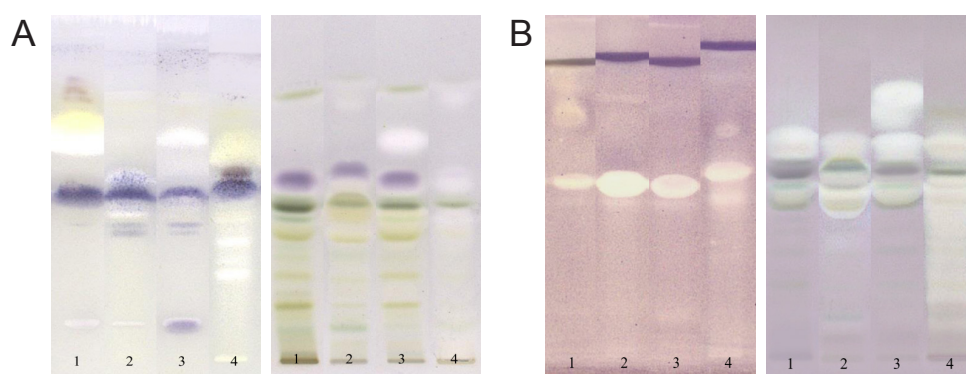


Figure 2 HPTLC of bioactive compounds from essential oils (left) and fresh herbs (right) under white light, after α -amylase assay (A) and acetylcholinesterase assay (B).

Track 1: Oregano; track 2: rosemary; track 3: sage; track 4: lavender.

units. As with other terpenoids, they are a widespread and diverse group of compounds in the plant kingdom, and include many medicinally important compounds.

Our results provide some evidence that the use of fresh herbs in the Mediterranean diet may be a contributing factor in the low incidence of diabetes mellitus and AD. It has been recognised that the Mediterranean diet, due to a low morbidity and mortality for many chronic diseases, presents a healthy eating choice and is reported to be beneficial in reducing the risk of AD (Scarmeas et al., 2006).

Conclusions and Future Work

The consumption of fresh or powdered herbs from the mint family in culinary doses can help boost memory. This effect is enhanced if combined with the use of essential oils, topically as aromatherapy, by inhalation, and/or by ingestion. Terpenes are small, lipid soluble organic molecules that can be absorbed through the skin if applied topically or transferred quickly across nasal mucosa if inhaled into the systemic blood circulation. Many terpenes can also cross the

blood-brain barrier. Therefore, topical application or inhalation of essential oils may produce an effect on the nervous system that is not purely psychological. Given the complexity of AD, involving many pathological processes, treatment with multifunctional compounds has become an important area of research. Given that the diterpenes reported here have desirable multifunctional bioactive properties, further work investigating the benefits of Mediterranean herbs in reducing the incidence and severity of AD (and other age related diseases) warrants further attention.

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