Research on the mechanism and application of plant essential oils in improving Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease, mainly caused by brain cell aging , impaired autophagy function , and reduction of nicotinic acetylcholine receptors . Amyloid-β (Aβ) peptide aggregation and Tau protein hyperphosphorylation, as well as memory impairment and cognitive dysfunction , are hallmarks of the disease . Clinical current traditional anti-AD drugs have shortcomings such as ineffective efficacy and large side effects. Therefore, the research of new effective therapeutic drugs has a very broad space for development and value significance. Plant essential oil (EO) has very obvious advantages in the treatment of neurodegenerative diseases such as Alzheimer's disease. Because of their lipophilicity, small molecular weight, easy to cross the blood-brain barrier (BBB), and rich active ingredients, they have significant effects on regulating AD-related neurotransmitters and hormone release, and regulating the expression of brain-derived neurotrophic factors and pro-inflammatory cytokines. This article describes the pathogenesis of AD, summarizes recent studies on the anti-Alzheimer's disease effects and mechanisms of essential oils, and provides a review of therapeutic AD chemical constituents in plant essential oils. The article provides a theoretical basis for research on plant essential oils for alleviating and treating Alzheimer's disease.

1. Introduction

The most common medical manifestation of dementia symptoms is usually considered to be Alzheimer's disease (AD), which is an irreversible condition that is progressive and characterized by inter-individual differences. The causes and course of the disease are complex and varied, and it usually progresses from mild cognitive impairment and memory loss to dementia, though there are many different ways in which this can happen. [1] Alzheimer's disease (AD) is the sixth leading cause of mortality in the United States, and currently, it is the only disease among the ten leading causes of death for which there is no available cure, prevention method, or method for slowing its progression.[2] It is important to note that Alzheimer's disease (AD) can present in two distinct forms: early-onset familial and late-onset sporadic. It appears that synaptic dysfunction, including loss, may be closely related to cognitive impairment in patients with Alzheimer's disease (AD).

Clinical drugs can be used to treat patients with mild to severe AD and relieve the symptoms of AD patients to a certain extent. However, these drugs have been unable to demonstrate efficacy in halting or slowing the progression of AD. Furthermore, the clinical trials conducted thus far have yielded only limited beneficial effects. Additionally, all of these drugs are associated with gastrointestinal side effects, and aducanumab has been linked to the potential for cerebral hemorrhage. In recent years, there has been a growing interest in the potential of medicinal plants and their main components as a means of treating various diseases. These medicinal plants, which can often be obtained through artificial cultivation, are cheaper and safer than chemically synthesized drugs, and are therefore gradually becoming a new option for the treatment of neurological disorders.

Essential oils (EO) are a type of aromatic substance that is thought to have beneficial properties. They are thought to be extracted from the flowers, leaves, stems, roots or fruits of plants by refining and extracting them through a number of different processes, including water vapor distillation, extrusion, cold infusion or solvent extraction. It has many functions, such as providing a unique fragrance, stress relief, improving sleep, anti-inflammatory and anti-allergy.[4] The effects of essential oils (EOs) on the central nervous system (CNS) are primarily analgesic, sedative, antidepressant, anticonvulsant, antiepileptic, and neuroprotective. Due to

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their insolubility in water and solubility in lipids, as well as their smaller molecular structure and lower molecular weight, which facilitate crossing cell membranes and the blood-brain tissue barrier, some plant EOs may also enter the brain by binding to carrier molecules or utilising specific transport mechanisms. Therefore, EO can better exert its anti- AD effect. Essential oils have some unique advantages over chemical drugs. Firstly, essential oils are usually derived from natural plants, and they may contain a variety of biologically active components that may act synergistically to achieve multi-targeted treatments for AD, resulting in a more integrated effect. Second, some people believe that plant essential oils are relatively mild and may have fewer side effects on the body. Furthermore, essential oils are applicable in numerous ways, such as in aromatherapy and massage therapies.[5].

The aim of this review is to elucidate the pathogenesis of Alzheimer's disease in vivo, to delineate the types and compound components of natural plant essential oils used to treat AD, and to further elucidate the mechanism of action of volatile oils in natural medicines. The combination of the medicinal properties of plant essential oils to identify more appropriate routes of administration is anticipated to facilitate the development of novel anti-Alzheimer's drugs. Further exploration of the use of plant essential oils, either alone or in combination with other drugs or therapeutic approaches, may yield improvements in therapeutic efficacy and the minimisation of side effects

2. Pathogenesis of Alzheimer’s disease

2.1. Brain cell aging

There is a close connection between the aging of brain cells and Alzheimer's disease. As we age, brain cells will undergo the aging process, and the synaptic connections between them may weaken or disappear. [6] This may lead to impaired information transmission between neurons, affecting cognitive and memory functions. In Alzheimer's disease, synaptic decline may be more pronounced and closely related to symptoms of the disease. Concurrently, with the progression of age, the functionality of in vivo immunity may diminish, resulting in a diminished capacity to eliminate aberrant proteins and pathogens. This, in turn, may facilitate the accumulation of detrimental substances, such as beta-amyloid, within the cerebral cortex, thereby promoting the development of Alzheimer's disease. In addition, brain cell aging may lead to changes in neurotransmitter synthesis, release, and receptor function. This may affect signaling between neurons, thereby affecting functions such as cognition and emotion.

The relationships between these forms of ageing and the development of Alzheimer's disease are multifaceted and complex.

2.2. Impaired autophagy function

There is a certain connection between impaired autophagy function and Alzheimer's disease. Autophagy represents a self-protection mechanism at the cellular level. It has the capacity to remove and degrade abnormal proteins and organelles within cells, thereby maintaining cellular homeostasis. In Alzheimer's disease, studies have revealed that the autophagy function of neurons may be affected. The aggregation of aberrant proteins (such as β-amyloid) may impede the autophagy pathway, preventing neurons from effectively eliminating these detrimental substances. This may further exacerbate neuronal damage and death, and accelerate the progression of the disease. Impaired autophagy function may also be related to other pathological processes of Alzheimer's disease, such as phosphorylation of tau protein, synaptic dysfunction, etc.

2.3. Decreased nicotinic acetylcholine receptors

In individuals diagnosed with Alzheimer's disease, it is common for the acetylcholine system to be impaired, which can result in aberrant neuronal signalling and subsequent cognitive and memory impairments.The available evidence suggests that the number and function of nAChRs may be reduced in the brains of those diagnosed with Alzheimer's disease. This reduction may result in impaired communication between neurons, which could potentially impact memory, learning, and other cognitive functions. Additionally, acetylcholinesterase (AChE) is an enzyme that plays a crucial role in the breakdown of acetylcholine. In Alzheimer's disease, the activity of AChE may increase, leading to accelerated degradation of acetylcholine. Therefore, some drugs to treat Alzheimer's disease aim to target the acetylcholine system to increase acetylcholine levels or enhance nAChR function. For example, acetylcholinesterase inhibitors can reduce the breakdown of acetylcholine, thereby improving cognitive function. [9]

3. This study explores the potential applications of plant essential oils

Many of the active ingredients found in plant essential oils possess antioxidant properties that enable them to scavenge free radicals from the body. This process plays a crucial role in protecting the nervous system from potential damage. In the brain free radicals are not scavenged in a timely manner, nerve cells are damaged, and amyloid plaques in the brain are an important cause of Alzheimer's disease. In the next section, we briefly explain the types of essential oils associated with neurological disorders, their mechanisms of action, and so on. As show in table 1.

Table 1. Active ingredients of natural plant essential oils and their mechanisms of action

Essential oil name	Main active ingredients	Main indications	Mechanism	references
Lavender	Linalyl acetate, linalool, (E)-β-stilbene, limonene	Alzheimer's disease	↓: NMDA receptor	Mahdavikian et al. (2020) [10]

			↓: Serotonin transporter (SERT)	Kim M, et al. (2021) [11]
bergamot	Monoterpene limonene, monoterpene esters, linalyl acetate and linalool	depression, Parkinson's Disease Alzheimer's disease	↑: synaptic transmission ↑: Neuroprotective effect ↓: Monoamine oxidase	Kong Y et al. (2017)[13] Catalano R et al (2 022) [14]
lemon	Citral, citronellal, linalool, geraniol and beta - caryophyllene oxide	Alzheimer's disease	↑: Hippocampal synaptic density ↓: Acetylcholinease ↓: Oxidative stress, inflammation	Liu B et al. (2020)[15] .
sea buckthorn	Quercetin , Kaempferol , Isorhamnetin	Alzheimer's disease	↑: Neuroprotection ↑: synaptic transmission ↓: Oxidative stress, inflammation	Rösch D et al. (2003) [16]
oregano	Thymol, carvacrol, paracymene, γ-terpinene and linalool	Alzheimer's disease	↓: Apoptosis ↓: Acetylcholinease ↓: Oxidative stress, inflammation	Aykac A et al. (2022) [18]
pine needles	α-Pinene, terpinolene, camphene and (+)-limonene	Alzheimer's disease	↓: Acetylcholinease ↓: Oxidative stress ↓: Oxidative stress, inflammation	Postu P A et al (2 022)
Mint	Menthol , menthone β-Caryophyllene Limonene	Alzheimer's disease	↑: Amino acid metabolism ↓: Oxidative stress, inflammation	Lv X et al. (2022) [20]
Rose	β-Citronellol Geraniol	Alzheimer's disease	↓: Acetylcholinease ↓: Oxidative stress, inflammation	Zhu S et al. (2017) [21]
Thyme	Linalool Thymol, carvacrol	Alzheimer's disease	↓Acetylcholinesterase ↓: Oxidative stress, inflammation	Jukic M(2007)

Note: ↑Improvement ↓Suppress

4. Protective mechanism of plant essential oils

4.1. Antioxidation

Reactive oxygen species (ROS), or free radicals, are capable of reacting with a variety of biomolecules within the cell, ultimately leading to oxidative damage. Antioxidant enzymes are vital for maintaining ROS levels within healthy ranges, although therapeutic effectiveness might be limited by the difficulty of certain compounds in crossing the blood-brain barrier and effectively reaching the site of ROS production. The blood-brain barrier represents an important protective mechanism for the brain. Nevertheless, this also presents a significant challenge for numerous compounds in successfully reaching the brain, even if they are able to traverse the blood-brain barrier. Furthermore, even if a compound is able to cross the blood-brain barrier, reaching the mitochondrial site of ROS production may present a significant challenge. This presents a significant challenge in the treatment of brain disorders, such as neurodegenerative diseases. [23] Plant essential oils are small molecule lipophilic compounds that are more likely to cross BBB [22] and reduce the production of ROS by targeting mitochondria. For example, exposure to lavender and rosemary EO was found to reduce free radical activity (FRSA), further preventing the adverse effects of oxidative stress [17]. Xu Pan and others proved through mouse experiments that lavender essential oil and its main component aramidol significantly improved the cognitive impairment caused by D-gal and AlCl3 in mice. These changes are related to the reduction of oxidative stress in the Nrf2/HO-1 signaling pathway, the enhancement and weakening of AChE activity and tactile plasticity.

4.2. Inhibit cell apoptosis

Endogenous apoptosis represents a highly regulated process with a pivotal function in the maintenance of cellular homeostasis and normal development. Mitochondria play a central role in this regulatory mechanism. The formation of apoptotic bodies is an important feature of apoptosis, which marks the entry of the cell into an irreversible stage of death. Caspase-9 activation triggers a series of cascade reactions that ultimately lead to the activation of effector cysteine asparaginases. The entire process is regulated by the BCL-2 protein family and the caspase protein family.[7]. Once essential oil molecules have entered cells, they exert a number of effects. Firstly, they reduce the expansion of mitochondria, which is a key component of the cell's energy production. Secondly, they slow down the process of mitochondrial irritation. Thirdly, they increase the permeability of the cell membrane. Fourthly, they inhibit the conduction of the cell apoptosis pathway. Fifthly, they

reduce the release of cytochrome C. Sixthly, they reduce the formation of apoptotic bodies, which are composed of the Bcl-2 family and Caspase family. Once the apoptotic pathways have been antagonised, they in turn inhibit the depolarisation of mitochondria and prevent the production of reactive oxygen species, thereby enhancing the production of ATP energy.

4.3. Protect synapses

Impairment of synaptic plasticity may be one of the causes of cognitive and memory dysfunction. When synaptic plasticity is compromised, a number of adverse effects ensue. The number of nerve cells declines, the pathways through which information is transmitted are disrupted, the branching and density of dendritic and axonal projections diminish, and the ability to acquire information is impaired. This ultimately leads to the onset of neurodegenerative diseases. [8] .In their study, Xia Chenxi and colleagues employed a range of cellular models, including the cultured PC12 cell line, the SH-SY5Y cell line, and primary neurons, to investigate the effects of SBF on neuronal cell differentiation. And this differentiation activates the PI3K/Akt and ERK pathways that are blocked by inhibitors [3]. The activation of AKT is capable of preventing its negative regulation of Rheb through the phosphorylation of TSC1/2, thus activating mTORC1. The mammalian target of rapamycin (mTOR) pathway plays a pivotal role in regulating a multitude of cellular functions, including protein synthesis, energy metabolism, and autophagy. Its involvement in these processes makes the pathway a crucial player in various essential biological processes, including neuronal development, synaptic plasticity and memory storage in vivo at the central nervous system level. Additionally, SBF interacts with brain-derived neurotrophic factor (BDNF) at the neuronal synapses of neurons. The principal constituents of SBF are flavonoids, which may be responsible for the neurotrophic activity of SBF. It was observed that essential oils (EOs) increased the phosphorylation of phosphatidylinositol 3-kinase (PI3K) and Akt in CORT-induced mouse hippocampal neurons and PC12 cells. Furthermore, EOs were also found to promote nuclear transcription of nuclear factor erythroid 2-related factor 2 (Nrf2) in CORT-induced PC12 cells. It was demonstrated that EOs exert anti-apoptotic effects on hippocampal neurons through the PI3K/Akt/Nrf2 signalling pathway. The results of the in vitro mouse experiment demonstrated that EOs treatment attenuated CORT-induced hippocampal neuronal damage. Furthermore, the study demonstrated that EOs inhibited CORT-induced apoptosis and increased the proliferation and viability of PC12 cells. Furthermore, network analysis revealed that PI3K-Akt may be a principal signalling pathway of EOs in counteracting CORT-induced apoptosis in hippocampal neurons.

4.4. Anti - inflammatory effect

A substantial number of results thus far indicate that the pathogenesis of AD is associated with the inflammation of nerve cells. This process involves the release of inflammatory factors by certain cells, such as microglia and astrocytes, the generation of free radicals, and the disruption of synaptic function. While these events occur, the nerves themselves remain intact, leading to cognitive dysfunction, memory loss, and dementia.[12] Alma et al. inhaled peppermint essential oil into an in vivo model of AD induced by aluminum chloride (AlCl3) and found that the essential oil reversed the increase in NF-κB and NO levels and reduced the levels of inflammatory factors in the hippocampus of mice [19] . The NF-κB signaling pathway is a classic regulatory pathway for inflammatory responses. The NF-κB signalling pathway is responsible for regulating the inflammatory response process through a number of mechanisms, including the activation of NF- κ B, the degradation of IκB, and the regulation of gene expression. Additionally, it plays a role in positive and negative feedback loops.

In conclusion, plant essential oils have the potential to modulate signalling pathways associated with the pathological process of AD. By exerting multi-target synergistic regulation of crosstalk between the pathways, they can help to maintain the balance of chronic inflammatory interactions, inhibit oxidative stress damage, protect synapses and so forth, thereby improving cognitive deficits in AD patients.

5. Discussion

Despite the growing body of evidence indicating the efficacy of essential oils in the treatment of neurodegenerative Alzheimer's disease, the clinical research in this field remains in its infancy, presenting numerous challenges to the advancement of this line of enquiry. Firstly, the variability of EO composition: essential oils are complex and unstable, and their quality and efficacy may vary greatly depending on the source of raw materials, extraction process and other factors, making it difficult to form standardised products. In addition, the difficulty of achieving therapeutic concentrations in the brain: essential oils are usually used by sniffing or skin application, and in these ways, the essential oil components need to undergo a complex process of biotransformation and distribution to reach the brain. During this process, many essential oil components may be broken down or metabolised, resulting in lower concentrations reaching the brain. Secondly, the body's blood-brain barrier makes it difficult for some beneficial substances (including certain essential oil components) to reach the brain. Thus, even if essential oil components are able to reach the bloodstream, they may not be able to enter the brain because the blood-brain barrier prevents them from doing so. In laboratory studies, higher concentrations of essential oils can be achieved in mice by intraperitoneal injection. However, in clinical applications, it is difficult to use this approach to increase the concentration of essential oils in patients due to safety and feasibility considerations.

To overcome these challenges, the following future research directions and strategies can be considered:

(1) Developing standardised EO formulations: through in-depth studies of EO components, identify their main active ingredients and establish standardised extraction and preparation methods to ensure consistent quality and efficacy of EOs.

(2) Optimising delivery methods: exploring new delivery routes and technologies, such as nanocarriers and nasal drug delivery, to improve the efficiency of EO in crossing the blood-brain barrier so as to achieve therapeutic concentration in the brain.

(3) Multimodal treatment strategy: Combine EO with other therapeutic methods, such as medication and cognitive training, to form a multimodal treatment strategy in order to improve the therapeutic effect.

(4) Individualised treatment: Considering the influence of individual differences on the therapeutic response of EO, carry out individualised treatment plan, and choose the appropriate EO and therapeutic dose according to the specific conditions of patients.

(5) Long-term follow-up and safety studies: long-term follow-up studies will be conducted to evaluate the long-term effects and safety of EO treatment, providing a more reliable basis for clinical application.

6. Conclusion

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by amyloid-β (Aβ) peptide aggregation, hyperphosphorylation of Tau protein, as well as memory impairment and cognitive dysfunction. It is mainly caused by brain cell aging, impaired autophagy, and reduced nicotinic acetylcholine receptors. Currently, chemical drugs commonly used in clinical practice have the disadvantages of ineffectiveness and high side effects. Plant essential oils are expected to provide new therapeutic modalities for the treatment of AD due to their lipid solubility, small molecular structure, high active ingredients, high safety, and ease of crossing cell membranes and blood-brain tissue barriers. However, these studies are still in their infancy, and their specific actions and effects after entering the brain vary depending on the type, concentration, and mode of use of the plant essential oils. One of the main problems is the difficulty in achieving the physiological concentrations associated with current therapeutic compounds at the site of action (i.e., the mitochondria). Scientists are currently trying to solve this problem by combining therapeutic molecules with biodegradable nanocarriers.

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