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Research Article

The Effect of A-Bisabolol on Alzheimer Disease

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Abstract

Alzheimer's disease is a condition that causes permanent effects due to damage in memory cells, leading to the inability to meet basic life needs and eventually resulting in loss of life. The increasing lifespan of individuals, particularly in advanced and developing cells, has raised the risk of developing this disease among people aged 65 and older. α-Bisabolol is a molecule derived from the essential oil of hemp. It is found in various plants, such as chamomile, similar to its presence in hemp. Due to its molecular structure, α-Bisabolol is considered to have strong effects against Alzheimer's disease. In this systematic review, clinical animal and cell line studies investigating α-Bisabolol for Alzheimer's disease have been examined. Given that α-Bisabolol is a newly discovered compound and there is a lack of sufficient clinical and experimental studies, there are still uncertainties. With further research in the future, the effects of α-Bisabolol on Alzheimer's disease can be determined conclusively.

Keywords: alzheimer; aβ; α-bisabolol; treatment

Introduction

Alzheimer's disease is a debilitating condition that results in permanent effects due to damage to memory cells, ultimately leading to the inability to meet basic life needs and, in some cases, loss of life (1). The increasing lifespan of individuals, particularly in advanced and developing cells, has raised the risk of developing this disease among people aged 65 and older.

Alzheimer's disease begins with the formation of amyloid plaques and neurofibrillary tangles between brain cells (2). The increasing plaques and tangles lead to a gradual decline in communication between cells. Consequently, the diminishing level of information and skills can provide insights into the progression of the disease.

Casdellani et al. (2020) described the cognitive and functional impairments that develop in Alzheimer's patients, including memory decline, difficulties in understanding and perceiving routine everyday questions, decreased responsiveness, loss of skills such as dressing, and deficiencies in tasks like bathing or shopping (3). Furthermore, the U.S. Department of Health and Human Services (HHS) has provided various information about Alzheimer's, emphasizing the importance of not confusing it with dementia and Parkinson's disease.

The treatment options for Alzheimer's disease currently remain uncertain. Existing clinical treatments aim to reduce the formation of amyloid plaques. The drugs developed for this purpose aim to slow down the progression of the disease, but the extent of their effectiveness is still a subject of debate.

Numerous studies are being conducted to develop therapeutic agents based on newly obtained information.

Mintun et al. (2021) reported that Donanemab halted the formation of amyloid plaques after 12 months of treatment (4). Bouter et al. (2015) found that Solanezumab, Crenezumab, and Bapineuzumab react with amyloid plaques and dissolve amyloid β (Aβ), allowing it to pass from neuronal cells into the plasma (5). McDade et al. (2022) reported that Lecanemab reduced amyloid plaques and slowed down clinical deterioration (6). Jun et al. (2023) demonstrated that a carbamate JNK3 inhibitor restored cognitive functions to their previous state in a transgenic mouse model (7).

Most of the current research aims to prevent the production or reduce the formation of amyloid plaques. However, the exact causes of the disease's onset are not fully understood.

Therefore, research continues to explore different molecules that could potentially prevent the disease. Particularly, molecules that can be naturally supplemented through daily diet would be beneficial for protecting against neurocognitive disorders in advanced age.

α-Bisabolol is a molecule derived from the essential oil of hemp. It is found in various plants, including hemp and chamomile (8). Due to its molecular structure, α-Bisabolol is believed to have effects against Alzheimer's disease.

In our study, we aimed to systematically evaluate the clinical, animal, and cell line studies that investigate the effects of α-Bisabolol on Alzheimer's disease.

Materials and Methods

Type of Research

This study is a systematic review prepared according to the PRISMA checklist and Cochrane guideline (9, 10).

Research Strategy

We aimed to evaluate the effect of α-bisabolol in Alzheimer's disease. It has been evaluated that α-bisabolol affects Alzheimer's by preventing the formation of amyloid plaque, by dissolving the formed plaques or by acting in another mechanism. Science Direct, Web of Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Pubmed, Cochrane Library, Proquest databases were made by searching English articles published between January 2000 and June 2024. The abstracts of 173 studies published between January 2000 and June 2024 for the words α-bisabolol and Alzheimer's disease were systematically reviewed, and then 6 studies suitable for the purpose of the study constituted the sample of the study.

Although the entire research was done by a single researcher, full-text review and data abstraction were done in duplicate.

When the articles were scanned, only clinical, experimental animal models and cell line studies showing the effect of α-bisabolol were included.

The effect of other therapeutic agents on Alzheimer's disease or other diseases in which bisabolol acts are not included.

Inclusion criteria

•Full text accessible,

•In the field of Alzheimer,

•About α-bisabolol,

•Studies published in the Science Direct, Web of Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Pubmed, Cochrane Library, Proquest database center between January 2000 since June 2024 were included.

In this study, PICOS;

- (P: Population): People with Alzheimer's disease.
- (I: Intervention): People using α-bisabolol
- (C: Comparison): People who do not use α-bisabolol
- (M: Results): Consequences of α-bisabolol use and Alzheimer's disease.
- (Q: Study design): Clinical, experimental animal model and cell line study treatment was included.

Limitation of the study

The compilations that were not included in the Science Direct, Web of Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Pubmed, Cochrane Library, Proquest databases and were not saved in the system could not be accessed. Investigating the effects of α-bisabolol treatment on Alzheimer's disease, accessing the same reviews with different keywords, and the small number of accessed articles are the limitations of the study. Effects of other molecules for Alzheimer's disease are not included.

Ethical aspect of research

Ethical permission was not obtained because reviews were open to access were used in this systematic review. Reviews were selected by the researchers considering the PRISMA checklist.

Analysis of data

The data were evaluated using the data summary form prepared by the researchers. The data summary form includes the article name, authors, year, aim and results of the study. Data summary forms were evaluated independently by the researchers and filled with consensus.

Results

Using the search strategy, PRISMA checklist and Cochrane guideline, 173 articles were identified in the Science, SCOPUS, Springer Link, Networked Digital Library of Theses & Dissertations, Ovid, CINAHL, Pubmed, Cochrane Library, Proquest databases data. Duplicate studies were weeded out. Only 6 (3.4%) of the articles were related to Alzheimer's disease and α-Bisabolol. Other studies include the efficacy of α-Bisabolol in different diseases (8%), different molecules trying to treat Alzheimer's disease (69%), full text not available (12%), presence of disease other than Alzheimer's disease (4.6%), and α-Bisabolol. It was not included because it was used in other different molecules. (Figure 1).

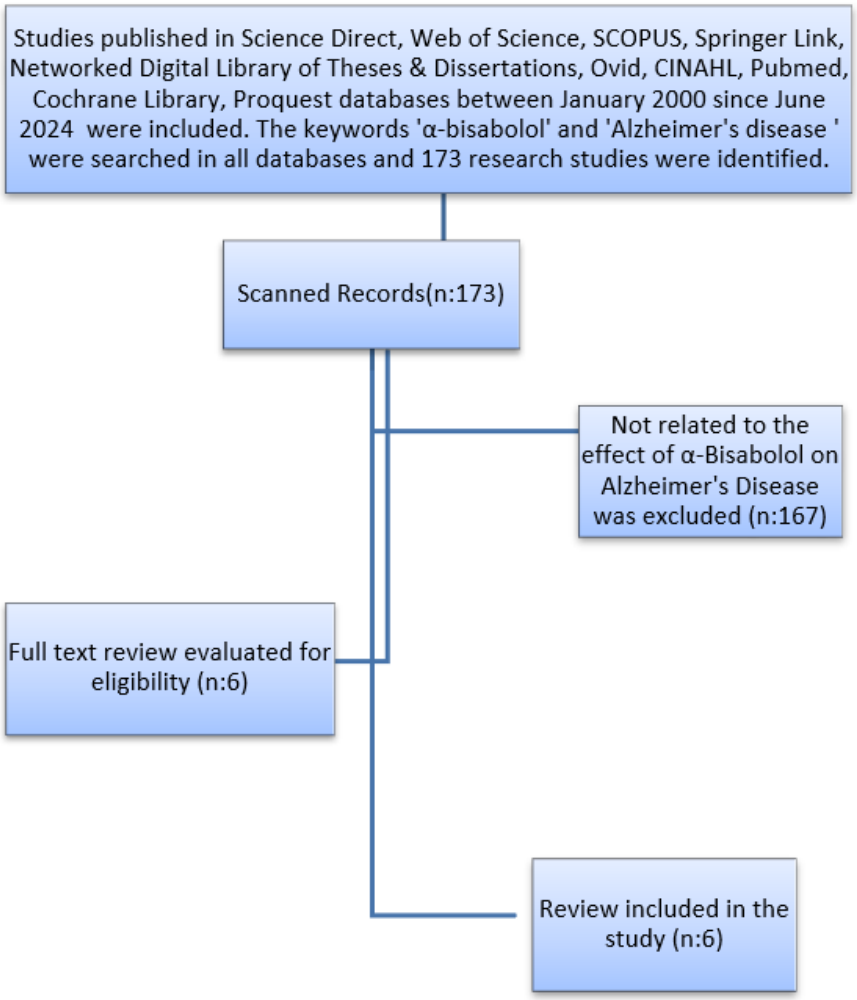

Figure 1. Prisma flow chart

Article Name	Year and Author	Aim	Results
α-Bisabolol Protect Mice Of Neuronal Loss And Cognitive Deficitis İn Sporadic Alzheimer's Disease Animal Model İnduced By Streptozotocin	2019;Jéssica Rabelo Bezerr	Evaluation of the effect of α-Bisabolol in an animal model of sporadic Alzheimer's disease induced by streptozotocin.	It was reported that α-bisabolol treatment significantly improved impairments in working memory, avoidance memory, recognition memory and spatial memory, and did not affect motor activity. It has been stated that α-bisabolol treatment is not sufficient to reduce the increase in nitrite concentration in the prefrontal cortex and hippocampus, but significantly reduces the increase in malondialdehyde (MDA) concentration in the prefrontal cortex, prevents neuronal damage and the decrease in synaptophysin expression in the hippocampus, and increases synaptophysin expression(11).

Amyloid-β induced neuropathological actions are suppressed by Padina gymnospora (Phaeophyceae) and its active constituent α-bisabolol in Neuro2a cells and transgenic Caenorhabditis elegans Alzheimer's model	2019; Balakrishnan Shanmuganathan, Sethuraman Sathya, Boopathi Balasubramaniam, Krishnaswamy Balamurugan, Kasi Pandima Devi	Evaluation of the neuroprotective efficacy of α-bisabolol against neurotoxicity induced by Aβ25-35 in N2a cells.	It reverses the change in intracellular protein and lipid oxidation induced by Aβ25-35, inhibits cholinesterase and β-secretase activity in Neuro2a cells, decreases the production of intracellular reactive oxygen species (ROS) and reactive nitrogen species (RNS) in Neuro2a cells, Bax and caspase- It has been stated that apoptotic proteins such as 3 reduce the expression level. In addition, it has been reported that it has a neuroprotective effect against proteotoxicity induced by Aβ, and inhibits Aβ synthesis by reducing life span, macromolecular damage and AD-related ace-1, hsp-4 and Aβ gene expression(12).
Deciphering the anti-apoptotic potential of α-bisabolol loaded solid lipid nanoparticles against Aβ induced neurotoxicity in Neuro-2a cells	2020; Sethuraman Satha,Balakrishnan Shanmuganathan, Kasi Pandima Devi	Evaluation of the protective efficacy of α-bisabolol-loaded particles against Alzheimer's against neurotoxicity induced by Aβ25-35 in N2a cells.	According to the results of in vitro studies, it has been reported that α-bisabolol prevents macromolecular damage and oxidative stress by scavenging reactive oxygen and nitrogen species, exhibits cholinergic activity, inhibits β-secretase enzyme and apoptosis-mediated cell death(13).
α-Bisabolol loaded solid lipid nanoparticles attenuates Aβ aggregation and protects Neuro-2a cells from Aβ induced neurotoxicity	2018; Sethuraman Sathya, Balakrishnan Shanmuganathan, Ganeshan Manirathinam, Kandasamy Ruckmani, Kasi Pandima Devi	Evaluation of the neuroprotective effect of α-bisabolol loaded solid nanoparticles in N2a cells	It has been reported that solid nanoparticles loaded with α-Bisabolol inhibit AChE and have antioxidant potential, protect N2a cells from Aβ-induced neurotoxicity, and inhibit Aβ aggregation(14).
α-bisabolol β-D-fucopyranoside inhibits β-amyloid (Aβ)25–35 induced oxidative stress in Neuro-2a cells via antioxidant approaches	2022; Mahalingam Jeyakumar, Sethuraman Sathya, Soniya Gandhi, Prabhakararao Tharra, Murali Aarthy, Devasahayam Jaya Balan, Chandrammohan Kiruthig, Beeraiah Baire, Sanjeev Kumar Singh, Kasi Pandima Devi	Evaluation of the protective efficacy of α-bisabolol against neurotoxicity induced by Aβ25-35 in N2a cells.	It has been reported that α-bisabolol inhibits caspase 3 production, increases anti-apoptotic protein expression, and protects it from Aβ 25-35 peptide-induced toxicity(15).
Anti-amyloidogenic and anti-apoptotic effect of α-bisabolol against Aβ induced neurotoxicity in PC12 cells	2018; Balakrishnan Shanmuganathan, Venkatesan Suryanarayanan, Sethuraman Sathya, Muralidharan Narenkumar, Sanjeev Kumar Singh, Kandasamy Ruckmani, Kasi Pandima Devi	Investigation of anti-amyloidogenic and anti-apoptotic properties of α-bisabolol against Aβ25-35-induced neurotoxicity	It has been reported that α-bisabolol has the ability to rescue PC12 cells from Aβ-induced neurotoxicity and chromosomal damage(16).

Table 1. Studies using α-Bisabolol in Alzheimer's disease research.

Studies in which α-Bisabolol was used in Alzheimer's disease studies are given in the table below (table 1). Bezerra (2019) evaluated the cognitive functions of α-Bisabolol on mice in his research. while other studies evaluated the effect of α-Bisabolol in cell line studies. No studies were found in which α-Bisabolol was evaluated clinically. The fact that α-Bisabolol is newly discovered and not enough research has been done on it limits our research. For this reason, the data obtained from the current studies are given below.

Studies using α-Bisabolol in Alzheimer's disease studies are given in table 1 (table 1).

Bezerra (2019) evaluated the cognitive functions of α-Bisabolol in mice in his research. In her research, Bezerra injected streptozotocin intracerebroventricularly to rats. She stated that the reason for using streptozotocin is that it causes deterioration in insulin signaling pathways, increase in oxidative stress parameters, neuroinflammation and neurogenesis dysfunctions. In her study, which aimed to examine the

effects of α-bisabolol on these negative effects of streptozotocin, she reported that treatment with α-bisabolol did not cause a significant change in blood glukoz, significantly improved the deficits in working memory, aversive memory, recognition memory and spatial memory, and did not change locomotor activity. In addition, she reported that after the treatment protocol with α-bisabolol, it could not stop the increase in nitrite concentration in the prefrontal cortex and hippocampus, affected the dose-dependent increase in MDA concentration in the prefrontal cortex, and prevented neuronal damage in the hippocampus by increasing the expression of synaptophysin.

Shanmuganathan (2019) in his research evaluated the neuroprotective efficacy of α-bisabolol against neurotoxicity induced by Aβ25-35 in N2a cells. It showed that α-bisabolol tried to correct the differences in intracellular protein and lipid oxidation induced by Aβ25-35, and stopped cholinesterase and β-secretase activity. Reactive oxygen and nitrogen species increase in Alzheimer's disease. Shanmuganathan reported that one of the most important effects of α-bisabolol is the reduction of intracellular reactive oxygen species and reactive nitrogen species production. In other words, it can be described as one of the most important findings showing that it can be effective against Alzheimer's disease.

In their study, Sathya et al. (2020) injected Aβ25-35 into N2a cells and investigated whether α-bisabolol loaded solid lipid nanoparticles given to N2a cells could prevent the aggregation of Aβ25-35 and enhance neuronal damage repair. The research results indicated that it significantly suppressed the production of free radicals such as reactive oxygen species and nitrogen species, and it also increased the reactive oxygen species-mediated macromolecular damage and loss of mitochondrial membrane potential caused by toxic Aβ peptide. The study reported a reduction in β-secretase, caspase-3, and cholinesterase activities. Decreased expression of Bax and increased expression of Bcl-2 protein were observed, indicating that α-bisabolol loaded solid lipid nanoparticles protected against Aβ-induced apoptosis.

Sathya et al. (2018) injected Aβ25-35 into N2a cells and evaluated the neuronal protective effect of solid lipid nanoparticles loaded with α-bisabol. They reported that α-Bisabolol significantly inhibited Acetylcholinesterase, protected N2a cells from Aβ-induced neurotoxicity, and inhibited Aβ aggregation.

Jeyakumar et al. (2022), Aβ25-35 mediated neuronal damage was caused in N2a cells. The neuroprotective effect was evaluated by infusing the cells with solid nanoparticles loaded with α-bisabolol. Solid nanoparticles loaded with α-bisabolol have been reported to reduce the formation of lipid peroxides, protein carbonyls, and nitric oxides in N2a cells. It has also been reported to inhibit acetylcholinesterase. It has been reported that solid nanoparticles loaded with α-bisabolol significantly inhibit caspase 3 production in N2a cells, increase anti-apoptotic protein expression, and protect Neuro-2a cell from β-amyloid (Aβ) 25-35 peptide-induced toxicity.

Shanmuganathan et al. (2018) evaluated the effectiveness of α-bisabolol against Aβ 25–35-induced neurotoxicity in PC12 cells. According to the results of the research, it was reported that there was a decrease in the fluorescence intensity used in the detection of Aβ. It was stated that α-bisabolol breaks down mature fibrils and prevents oligomer formation.

Discussion

α-Bisabolol is a molecule that can be derived from various plants, including hemp and chamomile. Its chemical structure consists of 15 carbon, 26 hydrogen, and 1 oxygen atoms. α-Bisabolol has been evaluated for its effects on Alzheimer's disease in cell culture and animal studies. Alzheimer's disease is a progressive condition characterized by permanent cognitive impairments, and currently, there is no definitive cure for it. The available treatments aim to improve the patient's impaired quality of life or slow down the progression of the disease, but it still remains one of the most significant age-related diseases. Therefore, it remains a priority among research endeavors.

One of the fundamental characteristics that allow scientists to find faster responses to diseases is the application of newly discovered molecules in various disease models, including cell culture, animal studies, and clinical trials. In our study, we aimed to compile and systematically report the efficacy evaluations of α-Bisabolol in therapeutic approaches to Alzheimer's disease modeling.

Bezerra (2019) evaluated the effects of α-Bisabolol in an Alzheimer's disease animal model induced by streptozotocin. Streptozotocin, also used by Salkovic-Petrisic et al. (2013) and Chen et al. (2014), is a commonly used model in Alzheimer's disease research (17, 18). There are also other Alzheimer's models induced by chronic exposure to $AlCl_3$ and D-galactose (1, 19). Bezerra (2019) reported that α-Bisabolol treatment significantly improved impairments in working memory, avoidance memory, recognition memory, and spatial memory, without affecting motor activity. The study indicated that α-Bisabolol treatment did not sufficiently prevent the increase in nitrite concentration in the prefrontal cortex and hippocampus. However, it significantly reduced the increase in malondialdehyde (MDA) concentration in the prefrontal cortex, prevented neuronal damage and the decrease in synaptophysin expression in the hippocampus, and increased synaptophysin expression (11). Although it did not prevent the increase in nitrite as required, the reduction in MDA expression and improvement in memory impairments suggest that long-term α-Bisabolol exposure could yield better results.

Shanmuganathan et al. (2019) attempted to induce cellular damage in N2a neuronal cell line using Aβ25-35 and treated the induced damage with α-Bisabolol and acetone extract of Padina gymnospora. The study reported that the treatment reversed the changes in intracellular protein and lipid oxidation induced by Aβ25-35, inhibited cholinesterase and β-secretase activity in N2a cells, reduced the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), decreased the expression of apoptotic proteins such as Bax and caspase-3, and exhibited neuroprotective effects against Aβ-induced proteotoxicity. The study also found that α-Bisabolol extended lifespan, reduced macromolecular damage, and lowered the expression of ACE-1, HSP-4, and Aβ genes associated with Alzheimer's disease, thereby inhibiting Aβ synthesis (12).

Sathya et al. (2020) and Sathya et al. (2018) reported that α-Bisabolol cleared ROS and RNS, inhibited β-secretase enzyme and apoptotic cell death, inhibited AChE, protected N2a cells from Aβ-induced neurotoxicity, and inhibited Aβ aggregation (13, 14).

Jeyakumar et al. (2022) reported that α-Bisabolol inhibited caspase-3 production, increased the expression of anti-apoptotic proteins, and protected against Aβ25-35 peptide-induced toxicity (15).

Shanmuganathan et al. (2018) demonstrated that α-Bisabolol had the ability to rescue PC12 cells from Aβ-induced neurotoxicity and chromosomal damage (16).

Although Bezerra (2019) did not report a reduction in RNS levels with α-Bisabolol, Shanmuganathan et al. (2019) demonstrated this effect in their cell study. It is possible that the visible effect is due to the presence of Padina gymnospora extract. The reduction in ROS and RNS levels may contribute to the alleviation of apoptotic effects by decreasing the expression of Bax and caspase-3. MacLachlan et al. (2022) reported an increase in ACE-1 activity in the early stages of Alzheimer's disease (20),

while Pereira et al. (2019) found an increase in HSP-4 in Alzheimer's disease. With these perspectives, it can be stated that α-Bisabolol may assist in the treatment of Alzheimer's disease.

Conclusion

In this study, we examined the research conducted on α-Bisabolol's effects on Alzheimer's disease, and it was observed that α-Bisabolol eliminated the factors involved in the onset and progression of Alzheimer's disease in the early stages. α-Bisabolol's ability to reduce ROS, RNS, Bax, caspase-3, ACE-1, and HSP-4 expression may contribute to its effects on the disease. However, as α-Bisabolol is a newly discovered molecule and has been investigated in only one animal study using an Alzheimer's disease model, and with limited cell line studies, its safe use cannot be fully assured. Moreover, the absence of studies specifically investigating the toxic effects of α-Bisabolol in Alzheimer's disease further complicates the decision-making process. Further research with a larger number of studies in the future is necessary for a reevaluation of α-Bisabolol's effects.

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