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Chapter

Learning and Memory Impairment Induced by Amyloid Beta Peptide and Effects of Thymol on Hippocampal Synaptic Plasticity in Rats Fed a High-Fat Diet That Received Amyloid Beta

Masoumeh Asadbegi (Hamedi), Alireza Komaki, Parsa Amiri, Seyed Asaad Karimi, Parichehreh Yaghmaei, Azadeh Ebrahim-Habibi and Iraj Salehi

Abstract

Thymol is a natural phenolic compound that is present in various plants; the significant antioxidant activities of Thymol may be helpful in preventing the progress of various oxidative stress-related diseases. Recent studies have confirmed that antioxidant-rich foods play a vital role in the disease prevention of neurodegenerative diseases, including Alzheimer’s disease (AD). We examined the protective and therapeutic effects of Thymol on the Aβ-induced long-term potentiation (LTP) impairments in rats fed a high-fat diet. LTP is a type of synaptic activity that has been thoroughly studied in the hippocampus and is thought to be the neural correlate of learning and memory. If Thymol is protective against AD-related impairments, then natural therapeutic agents based on the structure of Thymol could be used to protect against oxidative stress-related illnesses, such as AD.

Keywords: learning and memory, hippocampal synaptic plasticity, rat, amyloid beta, long-term potentiation, Thymol, high-fat diet

1. Introduction

Turning to a growing public health issue, Alzheimer’s disease (AD) is raising concerns worldwide with an increasing rate of occurrence [1, 2]. As the sixth leading cause of all deaths and the fifth in people over 65, AD is an irreversible neurodegenerative disorder marked by a progressive decline in cognition, function, and behavior [3–6].
The contributing factor to this increased prevalence seems to be the global aging population [7]. The number of deaths resulting from AD in Americans over 65 reached 700,000 in 2017. The estimated cost of healthcare and hospice services for those over 65 inflicted with AD or other forms of dementia is expected to exceed $250 billion [3–8].

Neuronal and synaptic loss, progressive memory loss, personality changes, and dementia are among the pathological manifestations of AD, believed to be primarily caused by the accumulation of extracellular beta-amyloid peptides (Aβ) and the intracellular hyperphosphorylated tau proteins [1, 3, 4]. Aβ aggregation is linked with ROS (reactive oxygen species) generation and metabolism disturbance, leading to synaptic dysfunction and neuronal death due to membrane lipid peroxidation [2, 3, 8].

Environmental and genetic factors are also pathogenic contributors, along with nutrition, inflammation, and oxidative stress; however, the AD pathophysiology is not yet fully comprehended. Although a high-fat diet (HFD) is among the risk factors for AD, few studies have been devoted to the link between nutrition and neurodegeneration. It is noteworthy that growing evidence indicates obesity and HFD are associated with cognitive function reduction among the elderly population [1, 9–16].

The dramatic rise in the prevalence of obesity is a grave danger to global healthcare, considering its association with neurodegenerative diseases [17]. One in three American adults is dealing with obesity. Reduced physical activity and diet changes are the outcomes of the modern lifestyle. The cognitive deterioration mechanisms caused by the interaction of aging and obesity are still unclear [16, 18].

Animal studies have shown a connection between a high-fat diet and higher cytokine levels, resulting in a general inflammatory state, increased Aβ aggregation, and behavior impairment [19–22]. The increased AD-like pathogenesis of obesity and HFD, regardless of sex, highlights long-term memory loss and cognitive impairment due to neuronal damage [11, 19]. Addressing obesity and its inflammatory effects could be an invaluable practical method to control the disease [11, 20, 21, 23].

Several complications, such as AD, Parkinson’s disease (PD), and aging, are associated with the elevation of oxidative stress, potentially damaging DNA, lipids, sugars, and proteins within cells [1, 7, 23]. The detrimental effects of oxidative stress in AD pathogenesis are well established [24, 25]. Maintaining a balance between oxidation and anti-oxidation through antioxidants can promote neuroprotection and heal the biological system. Thus, oxidative stress and subsequent inflammation are an underlying mechanism in AD pathogenesis, contributing to the Aβ formation. Obesity can generate systemic micro-inflammation, elevated oxidative stress, and reduced hippocampal neurogenesis and function, leading to cognitive deficit [1, 7, 23, 24, 26, 27].

AD severely affects the hippocampus, entorhinal cortex, amygdala, neocortex, and some subcortical areas, damaging synapses and neurons due to high concentrations of plaques and tangles. The hippocampus is crucial in learning and memory, emotion regulation and response, anxiety, stress, and fear [1, 9].

Long-term potentiation (LTP), a sort of long-lasting synaptic plasticity investigated comprehensively in the hippocampus, is a significant study model for learning and memory [28, 29]. Learning and memory are formed through the constant alteration of synaptic communication in the central nervous system. The dentate granule neurons of the hippocampal dentate gyrus (DG), one of the few regions in the rat brain with post-birth neurogenesis, are responsible for learning and memory formation. With the stimulation reaching the perforant pathway (PP), field excitatory postsynaptic potential (EPSP) is produced in the neuron population [29, 30].
Thyme essential oil obtained from Thymus vulgaris L. contains the main monoterpene phenol Thymol (2-isopropyl-5-methyl phenol). Listed in GRAS (generally recognized as safe) as a non-toxic molecule, the compound has antibacterial, anti-inflammatory, antihyperglycemic, hyperlipidemic, and antioxidant properties, beneficial for glycoprotein metabolism regulation in HFD-induced diabetic mice [1, 31].

With 35 million people suffering from AD, a rapidly growing number of afflicted individuals, and no decisive therapy available, more effective therapeutic targets are needed since the existing AD treatment concentrates on the progression delay [32, 33]. On the one hand, limited understanding of risk factors and potential therapeutic targets for neurodegenerative diseases such as AD and, on the other hand, the absence of an effective remedy for obesity-associated brain dysfunction may bring about serious public health ramifications, further emphasizing the identification of relevant preventive and medicinal strategies [2, 17].

In this chapter, we will summarize the current understanding of the AD pathogenesis associated with obesity, recent findings on the cross-link between the two, and their risk factors, which lead to the aggregation of Aβ peptides, synaptic plasticity impairment, and neuronal death. In addition, the potential neuroprotective effects of Thymol, as an option for AD treatment, in rats given HFD will be discussed. We hope to provide significant insights into the development of novel therapeutics for such memory impairments.

2. AD: a significant health problem worldwide

AD, described first in 1906 and named after Alois Alzheimer, is a progressive neurodegenerative disorder and the most prevalent form of dementia associated with old age. Accounting for 50–60% of dementia cases, AD predominantly affects the elderly population over 65 years old. There is an exponential rise with age in afflicted individuals, ranging from 3.0% in 65- to 74-year-olds to 47.2% in those over 85 [12, 34]. The complications involve progressive memory decline, increased apathy, deterioration of intellectual functions, decreased speech function, gait irregularities, and disorientation [34, 35].

The stereotypical characteristic abnormalities include the loss of neurons and synapses, brain atrophy, neurotic plaques or senile plaques (SPs) created due to extracellular Aβ aggregation, the formation of neurofibrillary tangles (NFTs) within neurons in the hippocampus and cortex caused by tau-protein hyperphosphorylation, impaired energy metabolism, mitochondrial dysfunction, elevated activity of prodeath genes and signaling pathways, chronic oxidative stress, and DNA damage [36–40].

It is well established that Aβ results in neurotoxicity and neuronal death; however, the endogenous defense mechanism activated due to Aβ insult is less studied [41]. Early onset of AD affects the medial temporal lobes, hippocampus, and cholinergic neurons of the basal forebrain. The cognitive symptoms in the central nervous system are believed to arise from the loss of cholinergic function, marking a prominent deficit in AD [38, 40].

The increased age-related mortality rate of AD poses a striking social and economic risk to the ever-growing population of AD patients. Although the exact pathogenesis mechanisms remain unclear, oxidative stress and inflammation are hypothesized as the causal mechanisms of AD pathology [12, 34, 39, 40]. Furthermore, apart from age, which seems to be the primary risk factor, diabetes,
stroke, atherosclerosis, obesity, and consumption of a high-fat diet are among the risk factors for AD [12, 13].

2.1 Oxidative stress as a trigger of AD

The late-onset sporadic AD, the most common form, is supposed to rise from a combination of genetic susceptibility factors and environmental triggers, with oxidative damage and a slow inflammatory process accepted widely as possible involved mechanisms [42].

Oxidative stress is the imbalance between ROS production and the antioxidant defense system. It is known that oxidative stress increases in parallel with age, smoking, hyperhomocysteinemia, and insulin resistance, thus causing an insulin action impairment in type 2 diabetics, probably due to membrane fluidity alterations, decreased availability of nitric oxide, and increased intracellular calcium content [43].

Furthermore, oxidative stress is assumed to be a primary risk factor and a trigger for AD pathology. Whether preceding oxidative damage is directly responsible for the accumulation of intracellular beta-amyloid 1–42 (Aβ 1–42) remains unclear. Concerning the studies, mitochondria are among the first affected organelles by oxidative stress and Aβ 1–42 toxicity. These organelles serve as accumulation sites for Aβ 1–42, promoting mitochondrial dysfunction and hindering energy metabolism [44].

2.2 AD and inflammation

Numerous amyloid plaque proteins are involved in an inflammatory response in AD, such as pro-inflammatory cytokines, acute-phase proteins, and activated complement factors, most having pleiotropic effects depending on their concentrations, making it hard to assess their contribution to the amyloid formation. In addition, neurons have been shown to play an active role in the neuroinflammatory process of AD [45].

Damage signals such as infection, trauma, redox iron, oxidative agents, and t and b-amyloid oligomers induce neuroinflammation response. Regarding the relationship between the inflammatory process of the brain and neuronal damage, the over-production of pro-inflammatory agents is linked with the progressive activation of microglial cells and astrocytes [8].

Neuroinflammation and microglia–neuron cross-talks present promising therapeutic targets for the treatment of AD. Studies have demonstrated that long-term treatment with anti-inflammatory drugs decreases AD progression via the disruption of the inflammatory response and t protein self-aggregation. Also, the reduced incidence of AD in patients subjected to anti-inflammatory prescription supports the neuroinflammatory hypothesis [8].

2.3 AD and cholinergic deficit: cholinergic deficit as a consistent and early finding in AD

The neuropeptide/neurotransmitter systems are significantly affected by metabolic status [46]. The established evidence supports the association of cholinergic deficit with the pathogenesis of AD. Acetylcholinesterase inhibitors (AChEIs) have been used to treat AD symptoms through their acetylcholine-mediated boost of neuron-to-neuron transmission. AChEIs also promote antioxidant production against free radical toxicity and β-amyloid-induced injury and suppress cytokine release from monocytes and microglia through the cholinergic anti-inflammatory pathway [47].
Although the cholinergic hypothesis has garnered substantial support and led to the production of the first licensed medication for AD symptoms, it targets a consequential symptom of AD, not the underlying pathological cause, and amyloid neurotoxicity intensifies in the presence of AChE. Regardless, donepezil, rivastigmine, and galantamine are licensed in the UK [47].

The study of AChEI drugs has shown that cholinergic pathways in the cerebral cortex and basal forebrain are compromised in AD, resulting in cholinergic deficit and cognitive impairment; however, growing evidence suggests more of an anti-inflammatory role for AChEIs through the inhibition of cytokine release from activated microglia, leaving the door open to further research. Multiple cholinesterase inhibitors (ChEI) are being developed, including ChEIs, naturally derived ChEIs, hybrids, and synthetic analogs. AD also affects many other neurotransmitters, with their clinical importance not fully clarified [42, 47–49].

3. Obesity: one of the most severe global health problems

High-fat diet consumption continues to increase human obesity, affecting 2 billion worldwide. Aside from the association with overweight pathology, obesity is considered a risk factor for dementia and neurodegenerative disorders and is associated with cognitive impairment, with some deeming the relation controversial [11, 15, 38, 50].

Few from the field of nutrition have turned their attention to neurodegenerative diseases [39].

Gustafson et al. considered obesity at older ages (ages seventy nine to eighty eight) as a risk factor for dementia, notably AD. A high-fat diet consumption reduces hippocampal neurogenesis, impairing attention and visual memory even in the short term. Although the underlying causes are not elucidated, a high-fat diet results in cognitive deficits and reduced hippocampal function [11, 12, 18].

Epidemiologic studies also argued that diets rich in saturated fats (especially in midlife) are a primary risk factor for AD development [51]. HFD-induced obesity may impact synaptic plasticity via insulin resistance and altered glucose metabolism, affecting learning, memory, and neuronal survival [14]. HF diet can also have detrimental effects on the brain independent of the explained factors, such as inducing Aβ deposition in the brains of mice or increased expression of amyloid precursor protein (APP) in humans [22].

A greater prevalence of AD is observed in countries with a higher intake of high-fat or high-calorie diets. Studies on transgenic AD mice on a high-fat diet show heightened disease neuropathology and behavioral deficits [12, 13]. Aside from the increased accumulation of the toxic Aβ, animal models show increased susceptibility to HFD-induced bodyweight gain following AD [19, 52].

Investigations in genetically obese animal models indicated impaired spatial memory and hippocampal synaptic plasticity. Since the consumption of HFD in humans is the common cause of obesity, animal models of HFD-induced obesity imitate the pathological obesity changes better [18].

3.1 HFD and oxidative stress

Oxidative stress is caused either by excessive ROS production or by antioxidant defense deficiency [53]. HFD has been shown to induce oxidative stress, mitochondrial dysfunction, inflammation, and adipokine dyshomeostasis, leading to
neurodegeneration [54]. As a worldwide epidemic, obesity is characterized by excessive fat deposition, increased cardiovascular risk factors, and high oxidative stress. The early phases of being overweight involve increased ROS production, reduced NO bioavailability, and endothelial dysfunction. Unlike synthetic antioxidant supplementation, diets enriched in natural antioxidants help regulate blood pressure, serum lipid composition, and oxidative stress [55].

3.2 HFD and inflammation

An essential component of neurodegenerative diseases is neuroinflammation. Neuroinflammation caused by the infiltration of inflammatory immune cells and activation of microglial cells, stress response, and the disruption of the blood–brain barrier (BBB) are probable outcomes of the increased metabolic flux in the brain as a result of obesity [17]. HFD consumption can also contribute to autoimmune encephalomyelitis (EAE), highlighting its significant effects on neuroinflammation further [56].

The increased cross-talk between the peripheral system and neuroinflammation is another consequence of HFD consumption, exhibiting an increased induction of pro-inflammatory cytokines in peripheral tissues and the hypothalamus, including interleukin (IL-1β), IL6, and tumor necrosis factor α (TNFα). Investigations show a connection between AD and the impairment of cognition and memory with HFD-induced neuroinflammation. The mechanisms through which obesity promotes neuroinflammation require further investigations [16, 17].

3.3 HFD impairs learning, memory, and synaptic plasticity

Unlike the hypothalamus, few studies investigated the effects of HFD on the hippocampus. Several articles have shown the impacts of obesity and HFD consumption on increased memory impairment, AD, and dementia [2]. The activation of NADPH oxidase activity caused by carbohydrate-enriched HFD consumption was shown to impair learning, memory, and synaptic plasticity [11]. Neurodegeneration is the neuronal loss of structure, function, and death within the regions associated with learning, memory, and emotion, such as the hippocampus and basal forebrain. The progressive nature of neurodegenerative diseases will eventually result in short-term memory loss, mood changes, and cognitive impairment. Memory formation depends on long-term potentiation (LTP), a form of synaptic plasticity. AD patients also suffer from LTP impairment [2]. AD development and reduction of spatial learning skills and hippocampal plasticity have been linked to HFD-induced obesity in rodents, with the promoted brain dysfunction considered a consequence of stress and neuroinflammation [17, 39]. Systemic inflammation and oxidative stress in obesity worsen with age, disrupting the BBB even further. In another study, the neuroinflammation and oxidative stress in aged obese animals contributed to a significant cognitive decline and learning and memory impairment [11, 16].

4. Oxidative stress and AD

4.1 The production of free radicals

A free radical is a highly reactive molecule with an unpaired electron. The free radical binds to another molecule to acquire an electron, thus changing or breaking it
biochemically into another free radical or an altered chemical structure. A free radical can damage any molecule, including proteins, carbohydrates, lipids, and nucleic acids, resulting in apoptosis and cell death [26, 57].

Oxidative stress is responsible for the pathogenesis of several diseases, including memory deficits caused by oxidative damage in rats and humans. The brain undergoes severe damage under oxidative stress due to the abundance of unsaturated fatty acids, lower antioxidant protection, redox-active metals (Fe, Cu), and high oxygen concentrations [7, 23, 29].

Aging contributes to increased oxidative stress, probably playing a crucial role in the pathogenesis of AD [7]. The neuron capacity to regulate redox imbalance decreases with age, which might lead to irreversible impairment such as neurodegenerative diseases. MDA, HNE, carbonyls, and other indicators of oxidative stress increase in aging and neurodegenerative diseases; however, a quantifiable method to identify relevant complications is not developed [26].

Studies have recently emphasized the crucial role of oxidative stress in the pathogenesis of various neurodegenerative diseases, such as AD, PD, and amyotrophic lateral sclerosis. Several common indicators are observed, including glutathione loss, DNA, and protein damage [7].

4.2 Antioxidant systems

Antioxidants have shown a promising effect on Aβ-induced neurotoxicity and cell death, improving impaired cognition and memory in AD. Antioxidants protect cells against damage induced by free radicals, preventing neuronal injury due to oxidative stress. The oxidative injury seems to be the factor initiating the neurodegeneration, not merely a byproduct or an end product of the process. However, AD treatment via antioxidants is met with great suspicion, as most of them can hardly cross the BBB. Accordingly, smaller antioxidant molecules or non-toxic carriers can provide favorable modifications for the current complications [25, 26, 29].

ROS substances, antioxidants, and non-enzymatic molecules can be used to assess oxidative stress status. The accepted evaluation method involves the total antioxidant status (TAS) and total oxidant status (TOS) measurements [58].

5. Hippocampus synaptic plasticity and LTP

Hippocampal synaptic plasticity is the principal means of information processing and memory formation [59]. The hippocampus goes through synaptic reorganization and neurophysiological changes in response to stimuli [60]. In the hippocampal input region, the DG is crucial to memory formation, converting the cortical inputs to new output, which then travels to the CA3 [61, 62].

Neurogenesis is preserved in various parts of the adult brain, especially the subventricular zone of the lateral ventricles and the subgranular zone of the DG. The process is induced under different physiological or pathological circumstances, ranging from exercise and environmental adaptations to seizures or injuries [63].

LTP is a continuous increase in synaptic strength, mainly through stimulation. Analyzing LTP in the hippocampus is a widely used cellular and molecular method to evaluate learning and memory. Coordinated gene transcription, protein synthesis, and degradation are needed for long-lasting synaptic plasticity [7, 64]. LTP induction
relies on several mechanisms, such as the activation of AMPA and NMDA receptors, changes in the number and shape of the spines, and the enhancement of transmitter release [30, 64].

5.1 Synaptic plasticity and AD

Aβ1–42 has a central role in the development of AD and its cognitive impairment, considerably inhibiting the hippocampal LTP at a cellular level [7, 65]. Reduced LTP and enhanced long-term depression (LTD) have been shown in acute exposure to Aβ, keeping the basal synaptic transmission unchanged. Studies suggest a shared molecular pathway between apoptosis and non-apoptotic functions, including synaptic plasticity. The activation of caspase-3 is essential for LTD and Aβ-induced inhibition of LTP [9, 66].

5.2 Synaptic plasticity and HFD

HFD-induced obesity has several detrimental effects on the hippocampal structure and function, affecting the normal growth of the CNS; impairing LTP, cognitive function, and learning; and disrupting neurogenesis [62, 67].

6. Thymol and potential to treat AD

Thymol obtained from thyme essential oil is a translucent crystal and a monoterpenic aromatic alcohol with a boiling point of 232°C. It also has an herbaceous, sweet-medicinal, warm odor and a pleasant taste. The vast biological properties of Thymol include larvicidal, nematicidal, acaricidal, antifungal, antibacterial, anti-inflammatory, and antioxidant activities [68, 69].

6.1 Thymol and antioxidant activity

In the aerobic environment, reactive oxygen species are the most lethal by-products of metabolism that mediate many human diseases including AD, Parkinson’s disease, diabetes mellitus, atherosclerosis, and aging processes [70, 71].

Antioxidants protect cell membranes against free radicals and accelerate the excretion of cellular wastes [69]. An oxidant and antioxidant balance is crucial for optimal physiological conditions. Therefore, oxidative stress can be described as redox signaling and control disruption. Such a devised definition can lead to new treatments for oxidative stress-related diseases. Several pieces of research have been devoted to replacing synthetic chemicals with natural substances, like natural antioxidants. Due to significant phenolic content, Thymol has a remarkable reducing power and great ferric-reducing ability. It also shows superb antioxidant properties through extensive scavenging activity. Its total amount of phenol is 0.36 ± 0.06 μg/ml. As a folkloric medicine, it might be helpful to prevent the progression of various diseases related to oxidative stress [24, 69–71].

DPPH radical scavenging activity was used to determine the antioxidant activity. The method represents a strong absorption maximum based on the reduction of DPPH at 517 nm. A hydrogen donor acts as a free radical scavenging antioxidant to pair with the odd electron and decrease absorption strength. Considering the number of captured electrons, Thymol presence shows a stochiometric de-colorization. The
reducing properties are demonstrated to be generally associated with the reductones, exerting antioxidant action by breaking the FR chain through the donation of a hydrogen atom. FRAP assay was also used to evaluate the ability of phytochemicals to reduce ferric ions. Thymol displayed a good reducing ability of ferric tripyridyl triazine complex into ferrous-(TPTZ) complex.

The results of the experiments approved a good antioxidant power and a free radical scavenging activity for Thymol. Hence, it can be a basis for herbal medicine development to prevent and treat disorders related to oxidative stress, such as Alzheimer’s disease [70].

6.2 Thymol and anti-inflammatory activity

As a natural monoterpene, it has considerable biological influences on cells, mainly through its antioxidant and anti-inflammatory effects. Airway inflammation in ovalbumin-induced mouse asthma was ameliorated by inhibition of NF-κB activation. Via the interference with the activation of nuclear factor kappa (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways, the compound exerted its anti-inflammatory properties in lipopolysaccharide-stimulated mouse mammary epithelial cells. The results indicate the anti-inflammatory effects of Thymol through the suppression of several biomarkers involved in inflammation. Thymol is suggested to have significantly ameliorated inflammatory responses through protective antioxidation, anti-inflammation, and anti-lipid peroxidation effects. Therefore, it is a promising compound to cure inflammatory processes [72].

6.3 Thymol and anticholinesterase activity

The inhibition of AChE, the predominant enzyme involved in the hydrolysis of acetylcholine (ACh), is a developed therapeutic strategy for AD treatment. Regarding traditional medicine, several plants are reputed to enhance cognitive function and alleviate other symptoms of AD, including depression. T. vulgaris essential oil indicates neuroprotective effects. With a small molecular size and lipophilicity, volatile constituents of essential oils and aglycones from glycosides are likely to cross the BBB. Thymol, carvacrol, and their derivatives, such as thymoquinone and thymohydroquinone, can be used as inhibitors of AChE, though their possible application in Alzheimer’s treatment or other cognitive disorders needs further investigation. The probable link between the antioxidant and the AChE inhibitory activity of the mentioned compounds could also be interesting to study [73].

6.4 Thymol and anti-obesity activity

Thymol anti-hyperglycemic and anti-hyperlipidemic activities are yet to be explored [74]. As mentioned, obesity has become a worldwide health problem, and most synthetic anti-obesity drugs have failed to address the issue due to their ineffectiveness or adverse effects. Thymol prevents HFD-induced obesity in the murine model through several mechanisms, including the attenuation of visceral fat accumulation, lipid-lowering action, improvement of insulin and leptin sensitivity, and enhanced antioxidant potential [75].

According to a study, rats given HFD exhibited significant enhancement of body weight gain (p < 0.001), visceral pad weight, lipids, alanine aminotransferase (ALT), aspartate amino transaminase (AST), lactate dehydrogenase (LDH), blood urea
nitrogen (BUN), glucose, insulin, and leptin levels compared to rats given a standard diet. Thymol treatment showed a significant decrease in (p < 0.001) body weight gain, visceral fat-pad weights, lipids, ALT, AST, LDH, BUN, glucose, insulin, and leptin levels in HFD-induced obese rats.

Furthermore, the treatment significantly decreased serum lipid peroxidation and increased antioxidant levels in HFD-induced obese rats, preventing HFD-induced obesity in the murine model through the discussed mechanisms. Interestingly, Thymol may also exhibit promising anti-diabetic effects [74, 75].

Recent studies have provided preliminary positive evidence for the effectiveness and safety of Thymol in alleviating cognitive impairments caused by increased Aβ levels or cholinergic hypofunction [76]. As a whole, it seems that antioxidant, anti-inflammatory, and anticholinesterase activities of Thymol might contribute to its beneficial effects. Our findings suggest that Thymol may be potentially a valuable source of natural therapeutic agents for AD treatment. However, further investigations are necessary to establish its efficacy and potential toxicity in clinical trials [76–78].

7. Conclusions

Despite the ever-increasing studies on AD, no final remedy has been developed, with palliative treatments presenting the best treatment options against AD symptoms until now. Considering the worldwide growth in obesity prevalence and the increasing number of dementia cases in an aging population, such a dual model may exhibit better results than the classical AD models.

In this case, Thymol presented a promising therapeutic potential against AD and HFD consumption that remains to be further investigated. It was hypothesized that antioxidant, anti-inflammatory, anticholinesterase, antihyperglycemic, and hyperlipidemic activities of Thymol may have contributed to its beneficial effects on learning and memory impairment, synaptic plasticity, oxidative stress, and tissue changes in HFD-induced animal models of AD.

The results stress the benefits of Thymol as a dietary antioxidant, providing preliminary evidence for its effectiveness as a remedy against LTP impairments caused by the Aβ aggregation in AD rats given HFD. The antioxidant activity of Thymol may be the reason behind its beneficial effects on hippocampal synaptic plasticity. Therefore, natural therapeutic agents based on Thymol could be used to prevent and cure complications related to oxidative stress, such as AD. Further research is required to establish its efficacy and potential toxicity in clinical trials.

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Conflict of interest

The authors declare no conflict of interest.
Acronyms and abbreviations

Aβ\textsuperscript{1} amyloid beta
AChE acetylcholinesterase
AChEIs acetylcholinesterase inhibitors
AD Alzheimer’s disease
ALT alanine aminotransferase
APP amyloid precursor protein
AST aspartate amino transaminase
BBB blood–brain barrier
BUN blood urea nitrogen
CNS central nervous system
DG dentate gyrus
EAE experimental autoimmune encephalomyelitis
EPSP excitatory postsynaptic potential
GRAS generally recognized as safe
HFD high-fat diet
IL interleukin
LDH lactate dehydrogenase
LDL low-density lipoprotein cholesterol
LTD long-term depression
LTP long-term potentiation
MAPK mitogen-activated protein kinase
MCI mild cognitive impairment
NF-κB nuclear factor kappa
NFTs neurofibrillary tangles
NMDA N-methyl-D-aspartate
Nrf2 nuclear factor
PD Parkinson’s disease
PP perforant pathway
ROS reactive oxygen species
SPs senile plaques
TAS total antioxidant status
TOS total oxidant status
TNFa tumor necrosis factor α
Author details

Masoumeh Asadbegi (Hamedi)\textsuperscript{1,4}, Alireza Komaki\textsuperscript{1}, Parsa Amiri\textsuperscript{1}, Seyed Asaad Karimi\textsuperscript{1,2,3}, Parichehreh Yaghmaei\textsuperscript{4}, Azadeh Ebrahim-Habibi\textsuperscript{4,5,6,7} and Iraj Salehi\textsuperscript{7}

1 Neurophysiology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

2 Department of Physiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

3 Neurophysiology Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

4 Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran

5 Biosensor Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

6 Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

7 Department of Neuroscience, School of Science and Advanced Technologies in Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

*Address all correspondence to: masoumehasadbegi@gmail.com
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