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Peptides and Lysine: New Therapeutic Frontiers in the Fight Against Alzheimer's Disease

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Abstract- Alzheimer's Disease (AD) is a prevalent neurodegenerative condition, affecting millions of people globally, particularly in an aging population. It is characterized by the aggregation of beta-amyloid and tau proteins, leading to the progressive loss of cognitive functions. This study investigates the therapeutic potential of peptides and the amino acid lysine in modulating the pathological processes of AD. The methodology included a systematic review of articles published between 2010 and 2024, focusing on experimental and observational studies addressing the efficacy of these compounds.

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Peptides and Lysine: New Therapeutic Frontiers in the Fight Against Alzheimer's Disease

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Abstract- **Alzheimer's Disease (AD) is a prevalent neurodegenerative condition, affecting millions of people globally, particularly in an aging population. It is characterized by the aggregation of beta-amyloid and tau proteins, leading to the progressive loss of cognitive functions. This study investigates the therapeutic potential of peptides and the amino acid lysine in modulating the pathological processes of AD. The methodology included a systematic review of articles published between 2010 and 2024, focusing on experimental and observational studies addressing the efficacy of these compounds. The results indicate that specific peptides can destabilize amyloid plaques, while lysine contributes to neuroprotection and the reduction of neuroinflammation. Despite the promising findings, the efficacy and safety in humans still require validation through robust clinical trials. The discussion emphasizes the importance of understanding the underlying molecular mechanisms and the need for new therapeutic interventions. It is concluded that, although peptides and lysine show significant potential, continued research is crucial to develop effective strategies for treating AD, aiming to improve the quality of life for patients.**

Keywords: alzheimer's disease, lysine, neuroinflammation, neuroprotection, peptides.

I. Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder, currently without a cure, that predominantly affects elderly individuals (Alzheimer's Association, 2024). It is characterized by a progressive decline in memory and other cognitive functions, significantly impacting occupational and social abilities. Initially, AD impairs processes such as learning and information retrieval, leading to a gradual deterioration in the capacity to acquire new knowledge. As the disease progresses, there is a further worsening, culminating in the inability to preserve remote memories (Souza *et al.*, 2023).

Alzheimer's Disease (AD) is a complex condition whose causes are not yet fully understood, but it is believed to result from an interaction between genetic, environmental, and lifestyle factors. Genetic predisposition is significant, especially in cases with mutations in the APP, PSEN1, and PSEN2 genes, as well as the presence of the APOE-ε4 allele, which increases the risk of developing the disease. Environmental factors, such as exposure to pollutants and heavy metals, have also been linked to a higher risk of AD. Additionally, lifestyle factors, including physical inactivity, poor diet, smoking, and chronic diseases like hypertension and diabetes, can contribute to the development of AD. Aging, the primary risk factor, is associated with chronic inflammation and the accumulation of neurotoxic proteins, which are directly related to the pathogenesis of AD (Scheltens *et al.*, 2021).

The neurodegenerative disease presented by Alzheimer's is the most prevalent in the world, affecting approximately 18 to 25 million people globally. It is the leading cause of dementia, accounting for between 50% and 56% of diagnosed cases (Souza; Santos; Silva, 2021). The impact of dementias extends beyond affected individuals, reaching their families and society as a whole, mainly due to the high socioeconomic burden these conditions impose (Neves, 2021). According to the World Health Organization (WHO), dementia is responsible for 11.9% of the years lived with disability caused by non-communicable diseases, with a global cost estimated at $604 billion in 2010 (Santos; Bessa; Xavier, 2020).

In Brazil, population aging has contributed to the increased prevalence of AD, highlighting the urgent need for more effective therapeutic strategies for managing this condition. Until recently, therapeutic approaches focused on symptomatic relief. Cholinesterase inhibitors, such as donepezil and rivastigmine, were widely used to improve cognitive function, although without significant effect on disease progression. However, recent advances in understanding the pathophysiological mechanisms of AD have driven the development of innovative therapies aimed not only at symptom relief but also at modifying the course of the disease (Bretas, 2023).

Currently, the use of peptides and lysine has been explored as a promising approach in the treatment of AD, due to their potential to modulate pathological processes associated with the disease. Synthetic peptides have shown the ability to interfere with beta-amyloid aggregation, one of the main markers of AD, promoting its destabilization and preventing the formation of neurotoxic amyloid plaques. On the other hand, lysine, an essential amino acid, has shown beneficial effects in controlling neuroinflammation and

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inhibiting the formation of cross-links in beta-amyloid and tau proteins. These mechanisms may contribute to reducing the accumulation of protein aggregates in the brain and preserving neuronal function (Singh *et al.*, 2023).

Lysine, an essential amino acid indispensable for protein synthesis and metabolic processes, is not produced by the human body and is obtained exclusively through diet. Peptides, on the other hand, are short chains of amino acids that play crucial biological roles, such as cellular signaling and the regulation of various physiological activities. In the context of Alzheimer's disease (AD), lysine and specific peptides have garnered attention for their potential in modulating neurodegenerative processes. Studies suggest that lysine may interfere with the aggregation of pathological proteins, such as the beta-amyloid peptide, while bioactive peptides demonstrate the ability to mitigate neuroinflammation, promote synaptic plasticity, and enhance cognitive functions (Yu *et al.*, 2021; Fonseca-Gomes *et al.*, 2024).

In this context, these advances suggest that lysine-based compounds and peptides may be promising in future therapeutic approaches for this debilitating condition. The progress in understanding the molecular mechanisms of AD has opened new therapeutic possibilities, with peptides and lysine standing out for their potential to modify the course of the disease. Despite significant advances, the search for more effective interventions remains a crucial challenge for medicine. Thus, exploring these approaches represents not only a scientific promise but also an essential step to address the growing prevalence and impact of AD in an aging global population.

Thus, this study aims to provide a comprehensive overview of AD, highlighting the urgent need for more effective therapeutic strategies. Additionally, it seeks to demonstrate the innovative therapeutic potential of peptides and lysine, emphasizing their ability to modulate pathological processes of AD, such as the aggregation of beta-amyloid and tau proteins, and their promising properties in controlling neuroinflammation.

II. Materials and Methods

The present study is a systematic review of a qualitative nature, conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The studies were independently selected by three reviewers from the databases: PubMED, Cochrane, Scopus, LILACS, and SciELO. The controlled descriptors of Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS) were standardized using the terms: “Peptides”, “Lysine”, “Treatment”, "Alzheimer Disease", combined using the Boolean operator “AND”.

The central question of the article was developed according to the PICO strategy (Table 1), in which the eligible components of the study were defined as follows: population (P): Patients diagnosed with Alzheimer's Disease; intervention (I): The use of peptides and the amino acid lysine as a therapeutic approach for the treatment of Alzheimer's Disease; comparison (C): Patients diagnosed with Alzheimer's disease who do not use peptides and the amino acid lysine as a therapeutic approach; outcome (O): Peptides and lysine assisting in the inhibition of protein aggregation, possessing neuroprotective properties, antioxidant and anti-inflammatory effects, in addition to improving cognitive function. In finalizing the method, the guiding question for the study was formed: "What is the impact of using peptides and the amino acid lysine as a therapeutic approach for Alzheimer's Disease?", which will be answered in the results and discussion of the article.

The inclusion criteria established were original articles, experimental and observational studies available in full text, those that addressed peptide therapy and the amino acid lysine in the treatment of Alzheimer's Disease, conducted in animals and humans, available for free, published between 2010 and 2024, and those in Portuguese and English. The search for articles was conducted in October 2024. The exclusion criteria were incomplete articles, duplicates, and those that did not fit within the following guiding question of the study defined by the PICO strategy.

The selection for identifying relevant studies was carried out in three stages: first, the article titles were examined to determine if they were aligned with the topic of interest. Next, the abstracts of the articles that passed the initial screening were read to verify if they met the inclusion criteria. Finally, the full texts of the selected articles were thoroughly reviewed to ensure they truly met all the established criteria for the research. The documents were organized using the Mendeley Reference Manager tool. Additionally, in cases of disagreement about inclusion, the studies were excluded. To assess the quality of the selected articles, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used. This information was organized in a chart and subsequently discussed.

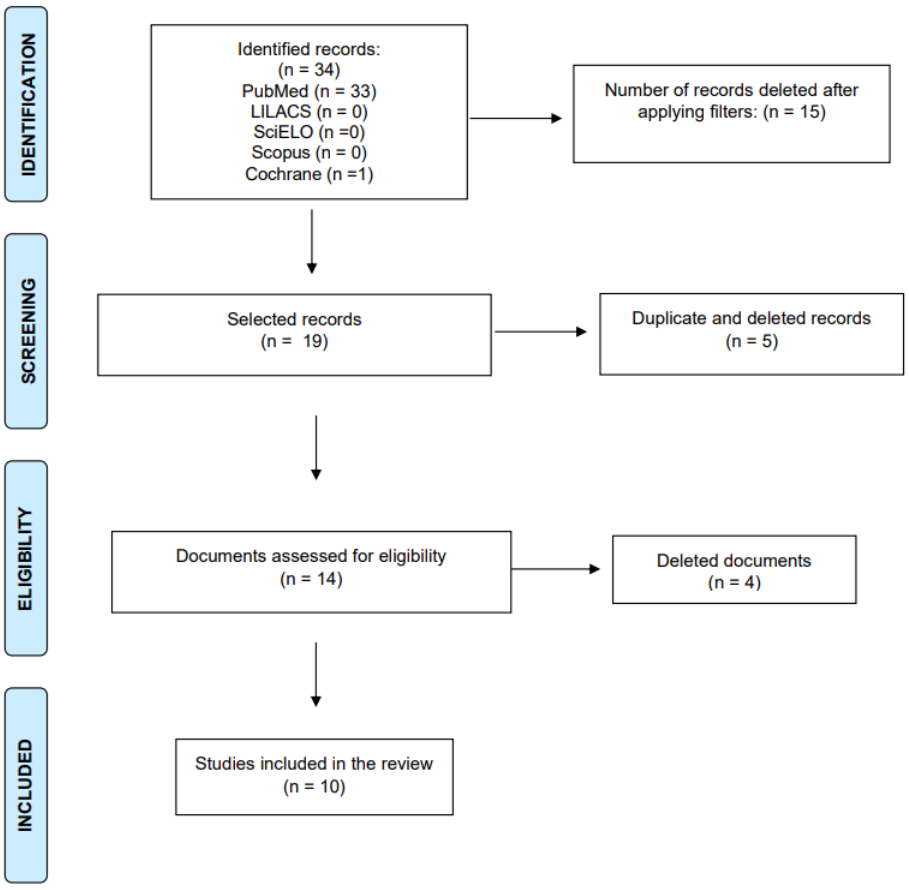
Thirty-four documents were found with the keywords, of which 15 did not meet the inclusion criteria of the study. After verifying duplicates, selecting titles and abstracts for reading, 5 more were excluded. Of the remaining 14 records, 4 were not eligible after full reading, totaling 10 selected articles (Table 2).

Table 1: Description of the PICO strategy to formulate the guiding research question: "What is the impact of using peptides and the amino acid lysine as a therapy for Alzheimer's Disease?"

Acrônimo	Definição	Descrição
P	Patients	Patients diagnosed with Alzheimer's Disease.
I	Intervention	The use of peptides and the amino acid lysine as a therapy for the treatment of Alzheimer's Disease.
C	Controls	Patients diagnosed with Alzheimer's disease who do not use peptides and the amino acid lysine as therapy.
O	Outcome	Peptides and lysine assist in inhibiting protein aggregation, possessing neuroprotective properties, antioxidant and anti-inflammatory effects, as well as improving cognitive function.

Source: Prepared by the authors (2024)

Table 2: PRISMA Flowchart



Source: Prepared by the authors (2024

III. Results

Out of the total of 10 articles analyzed, as shown in Table 3, the highest frequency of publication occurred in 2022 (n = 4), where "n" is the number of articles that meet the selected criteria, indicating a recent growing interest in the topic discussed. Regarding the Qualis classification of the journals in the sample, all 10 studies are allocated between the excellence ranges A1 to A3, according to the CAPES evaluation, reflecting the scientific relevance and high editorial quality of the publications. In terms of methodological approach, the majority of the articles used experiments as a basis for theoretical foundation and hypothesis testing (n = 9), demonstrating a preference for empirical methods to strengthen the evidence presented. Additionally, one study opted for a theoretical approach, contributing an analytical and integrative perspective on the available data.

Table 3: Studies Analyzing the Impact of using Peptides and the Amino Acid Lysine as Therapeutics for Alzheimer's Disease

ID	Autoria/Ano	Periódico (Qualis)	Métodos	Objetivos	Resultados
01	Pan *et al.* (2022)	Cell Metabolism **(A1)**	Experimental	Understanding how a positive feedback loop involving histone lactylation and PKM2 activation in microglia contributes to disease progression.	The enzyme PKM2 is elevated in microglia near β-amyloid plaques in Alzheimer's models, promoting histone lactylation (H4K12la) and activation of glycolytic genes, which exacerbates neuroinflammation. Inhibition of PKM2 reduces lactate, glycolytic genes, IL-6, TNF-α and may improve cognitive function, suggesting a promising therapeutic target.
02	Bai *et al.* (2022)	Cell Reports **(A1)**	Experimental	Investigate how SIRT2 modulates the acetylation of amyloid precursor protein (APP) and its impact on cognitive function and the pathology of Alzheimer's disease (AD) in APP/PS1 transgenic mice.	SIRT2 inhibition leads to an increase in the acetylation of amyloid precursor protein (APP) at lysines K132 and K134, resulting in greater production of the neuroprotective peptide sAPPa and promoting non-amyloidogenic processing of APP. Furthermore, SIRT2-deficient APP/PS1 mice showed significant improvements in cognitive function, evidenced by superior performance in spatial learning tests and a reduction in amyloid plaque burden in the brain, suggesting that modulation of APP acetylation by SIRT2 may be a promising therapeutic strategy for Alzheimer's disease.
03	Li *et al.* (2022)	Journal of Biological Chemistry **(A1)**	Case-control	Investigate the impact of TFEB acetylation on lysosomal biogenesis and β-amyloid (Aβ) clearance in APP/PS1 mice, analyzing the effect of Trichostatin A (TSA) on TFEB acetylation, its nuclear translocation, reduction of Aβ plaques, and cognitive improvements, aiming at new therapies for neurodegenerative diseases.	Treatment with Trichostatin A (TSA) in APP/PS1 mice reduced β-amyloid (Aβ) plaques by 62.8% in the cortex and 71.3% in the hippocampus, increased the expression of genes related to lysosomal biogenesis and autophagy, and improved learning and memory in behavioral tests. The results suggest that HDAC inhibition and TFEB acetylation may be promising strategies for treating Alzheimer's and neurodegenerative diseases.
04	Yu *et al.* (2021)	Journal of the American Society for Mass Spectrometry **(A2)**	Retrospective Experimental	Identify structural changes, post-translational modifications, and molecular interactions that influence lysine accessibility, elucidating the pathological mechanisms of the disease and its implications on brain function.	Alterations in lysine accessibility were identified in 17% of the proteome associated with Alzheimer's disease, identifying differentially exposed peptides in tau proteins and RNA splicing complexes, markers of the pathology. The native TMT methodology quantified changes in the structure of proteins related to transcription, mitochondrial, and synaptic functions. The

					results indicate that these alterations may be associated with post-translational modifications and protein aggregate formation, contributing to understanding the disease's molecular mechanisms.
05	Fonseca-Gomes *et al.* (2024)	Molecular Therapy **(A1)**	Experimental	Evaluate the efficacy and safety of the peptide TAT-TrkB as a therapy for Alzheimer's disease (AD), aiming to restore the function of BDNF and its receptor TrkB.	The peptide TAT-TrkB prevented the loss of rapid synaptic functions of BDNF induced by beta-amyloid (Ab) and restored long-term potentiation (LTP) in the hippocampus, suggesting the reactivation of TrkB-FL signaling. Additionally, TAT-TrkB prevented the excessive accumulation of the TrkB-ICD fragment, associated with dendritic spine loss and neuronal hyperactivity, and reduced the pathology of hyperphosphorylated tau, linked to deficits in neurogenesis and cognitive function. These results suggest that TAT-TrkB has potential as a disease-modifying agent, with the ability to prevent and reverse cognitive deficits in Alzheimer's patients.
06	Long *et al.* (2024)	Pharmacological Research **(A1)**	Experimental	Investigate the role of Kallistatin in cognitive function and glutamate homeostasis, focusing on transgenic mice (KAL-TG).	Transgenic mice for Kallistatin (KAL-TG) exhibited cognitive deficits in tests such as the Morris water maze and the Y-maze. They showed elevated basal glutamate levels and increased frequency of miniature excitatory postsynaptic currents (mEPSCs) in the CA1 region of the hippocampus, indicating dysfunction in glutamate homeostasis. The expression of glutamine synthetase (GS) in hippocampal astrocytes was reduced, while the EAAT2 transporter remained unchanged. Kallistatin promoted the degradation of GS through a proteasome-mediated mechanism involving acetylation and ubiquitination of the protein. Fenofibrate improved memory in KAL-TG mice, suggesting therapeutic potential against the effects of elevated Kallistatin.
07	Puris *et al.* (2021)	Scientific Reports **(A1)**	Case-control	To explore the effects of LPS-induced systemic inflammation on the plasma and brain metabolome and lipidome in APdE9 transgenic mice, a model of Alzheimer's disease.	The administration of LPS in transgenic APdE9 mice induced significant changes in the brain metabolome and lipidome, particularly in the cysteine and methionine metabolism pathways, arginine and proline, and fatty acids. These changes, more pronounced in LPS-treated APdE9 mice, indicate that systemic inflammation

					accelerates biochemical disturbances linked to Alzheimer's. In contrast, wild-type mice showed minimal changes, suggesting that inflammation impacts Alzheimer's models more than healthy organisms, reinforcing the role of infections in the metabolic worsening of the disease.
08	Song *et al.* (2023)	The Journal of Clinical Investigation **(A1)**	Prospective Experimental Study	Investigate the impact of tau protein acetylation at lysine 280 on pathological tau aggregation and the progression of tauopathies.	The monoclonal antibody Y01 has proven effective in preventing the progression of tauopathy induced by tau acetylated at lysine 280, significantly reducing tau aggregation and cell death in cell and mouse models. The results suggest that Y01 can protect neurons from the characteristic dysfunction of tauopathies, highlighting the importance of understanding tau modifications to develop specific therapies against neurodegenerative diseases such as Alzheimer's.
09	Rubey (2010)	Neuropsychiatric Disease and Treatment **(A3)**	Literature Review	Explore the hypothesis that lysine supplementation can prevent or delay the development of Alzheimer's disease (AD), particularly in relation to the reactivation of the herpes simplex virus type 1 (HSV-1), which has been implicated in the pathogenesis of AD.	Data indicate that HSV-1 is present in 90% of the brains of elderly individuals, including those with AD, and that its replication can be inhibited in environments rich in lysine and poor in arginine. It is suggested that lysine-rich diets, such as the Mediterranean diet, may be related to a lower risk of AD. Although definitive prospective studies are lacking, lysine supplementation is presented as a possible safe and economical strategy to prevent or mitigate AD, highlighting the need for future research to validate this hypothesis.
10	Bellver-Sanchis *et al.* (2022)	ChemMedChem **(A1)**	Experimental	Identifying new inhibitors of G9a, a lysine methyltransferase essential for the repression of genes linked to learning and memory, with the potential to treat neurodegenerative diseases.	The new G9a inhibitors demonstrated efficacy in reducing levels of the repressive marker H3K9me2, similar to the positive control UNC0638, indicating that they target G9a activity. They also significantly reduced amyloid β aggregate deposition in the transgenic C. elegans model, with up to a 25% reduction observed with UNC0638. Some compounds exhibited promising pharmacokinetic properties, although with lower blood-brain barrier permeability compared to UNC0638, possibly due to lower lipophilicity. These results highlight the potential of G9a inhibitors as therapeutic candidates for Alzheimer's.

Source: Prepared by the authors based on data obtained throughout the study (2024)

IV. Discussion

The use of peptides and the amino acid lysine as therapeutic strategies for Alzheimer's Disease (AD) has gained prominence due to their potential in modulating molecular mechanisms associated with the pathology. Studies suggest that specific peptides can interfere with the aggregation of toxic proteins, such as beta-amyloid, preventing or reducing the formation of senile plaques characteristic of AD. Lysine, in turn, plays an important role in regulating protein metabolism and stabilizing cellular structures, potentially contributing to neuroprotection and the improvement of synapses affected by neurodegeneration. Although these compounds show promising results in experimental models, their efficacy and safety in humans still need to be confirmed by robust clinical trials (Zhao *et al.*, 2020).

Pan *et al.* (2022) investigated the lactylation of histone H4K12 in microglia of Alzheimer's models, elucidating how this epigenetic modification contributes to microglial dysfunction and disease progression. The research demonstrated that H4K12 lactylation promotes an increase in the transcription of glycolytic genes, establishing a cycle that intensifies neuroinflammation. Inhibition of pyruvate kinase M2 (PKM2) was identified as a promising strategy to restore microglial function and reduce Aβ peptide load, pointing to new therapeutic perspectives for the treatment of Alzheimer's disease.

Various lysine modifications in histones have been analyzed, highlighting lysine 5 in histone H4 (H4K5la), associated with the regulation of gene expression; lysine 8 in histone H4 (H4K8la), involved in transcriptional regulation; and lysine 12 in histone H4 (H4K12la), the main focus of the study due to its direct relation to microglial dysfunction in Alzheimer's. Other relevant modifications include lysine 18 in histone H3 (H3K18la), with potential influence on chromatin structure, and lysine 23 in histone H3 (H3K23la), associated with the regulation of gene expression (Pan *et al.*, 2022).

Lysines present in histones are common targets for epigenetic modifications, such as lactylation, which directly affect chromatin structure and transcriptional activity. Among these alterations, lactylation of lysine 12 on histone H4 (H4K12la) has been identified as a critical factor in stimulating the expression of glycolytic genes, contributing to the activation and subsequent microglial dysfunction in Alzheimer's disease. Understanding these modifications is essential for advancing the knowledge of gene regulation mechanisms and investigating the pathogenesis of the disease (Pan *et al.*, 2022).

Bai *et al.* (2022) investigated the acetylation of the amyloid precursor protein (APP) and its impact on Alzheimer's disease pathology, aiming to understand how this epigenetic modification influences APP processing and the production of amyloid peptides associated with the disease's development. For this, two specific peptides were analyzed: APP-K132-AC and APP-K134-AC.

The peptide AAP-K132-AC, with the sequence ac-SDALLVPDK(ac)CKFLHQERMD-NH2, represents APP with lysine at position 132 acetylated, a relevant modification for studying cellular interactions and the function of APP, especially in the context of Alzheimer's disease. This acetylation may alter the structure and biological activity of the protein (Bai *et al.*, 2022).).

Similarly, the peptide AAP-K134-AC, with the sequence ac-LVPDKCK(ac)FLHQERMD-NH2, presents the APP with lysine at position 134 acetylated, a modification that affects the processing of APP and the production of amyloid peptides. The acetylation of lysines at positions K132 and K134 modifies the structure and function of APP, impacting its processing and the formation of amyloid aggregates, critical factors in the progression of Alzheimer's disease (Bai *et al.*, 2022).

To analyze these modifications, various experimental techniques were utilized. Immunocytochemistry was employed to visualize the localization and colocalization of APP and SIRT2 in primary neurons. Western Blot allowed for the detection and quantification of APP acetylation and the levels of its cleavage products. Streptavidin Pull-Down assays quantified APP on the cell surface in N2a-sw cells, while mass spectrometry identified the acetylated lysine residues on APP. Finally, ELISA assays measured the levels of sAPPa and sAPPb in brain tissue lysates, providing a detailed analysis of the implications of APP acetylation in disease pathology (Bai *et al.*, 2022). These findings highlight the relevance of epigenetic modifications in the regulation of APP and in understanding the molecular mechanisms underlying Alzheimer's disease, contributing to the identification of potential therapeutic targets.

From this perspective, according to Li *et al.* (2022), treatment with Trichostatin A (TSA), an HDAC inhibitor used in APP/PS1 mice, a model of Alzheimer's disease, showed significant effects on both pathology and cognitive function. The functionality of TSA lies in its ability to increase the expression of genes related to lysosomal biogenesis and autophagy, helping to reduce the accumulation of β-amyloid, one of the main markers of Alzheimer's Disease.

With this, a substantial reduction of β-amyloid (Aβ) plaques was observed, with decreases of 62.8% in the cortex and 71.3% in the hippocampus compared to vehicle-treated mice (saline) as part of the control group. Additionally, TSA increased the expression of genes associated with lysosomal biogenesis and autophagy, highlighting the crucial role of transcription factor EB (TFEB) acetylation in the activation of these processes (Li *et al.*, 2022).

In the context of cognitive function, mice treated with TSA showed significant improvements in learning

and memory tests, such as the Morris Water Maze, exhibiting less time to locate the platform and a higher frequency of crossings in the platform area compared to controls. The study also emphasized the importance of TFEB acetylation for its nuclear translocation and activation, highlighting the relevance of acetylation regulation in lysosomal biogenesis. These findings suggest that HDAC inhibition and the promotion of TFEB acetylation may constitute promising therapeutic strategies for Alzheimer's disease and other neurodegenerative diseases (Li *et al.*, 2022).

The study by Yu *et al.* (2021) on lysine accessibility and structural changes of proteins in brain samples from Alzheimer's patients identified 103 differentially exposed (DE) peptides, originating from 97 human proteins, with most being more abundant in the Alzheimer's samples. These data indicate an increase in lysine accessibility in proteins associated with neurofibrillary tangles and RNA splicing dysfunctions, hallmark features of the studied pathology.

Yu *et al.* (2021) investigated structural changes in proteins associated with Alzheimer's disease (AD), a condition characterized by protein misfolding and aggregation. The study aimed to understand how the lysine accessibility in protein peptides, such as tau and RNA splicing components, influences the disease pathology. A total of 15,370 peptides were identified, including those derived from tau proteins and 10 RNA splicing proteins, selected due to their relevance to cellular function and AD progression.

These peptides are crucial for understanding protein misfolding and RNA splicing dysfunction, which are central characteristics of the disease, and they can support the development of therapeutic strategies. To achieve this, the proteins were extracted under native conditions and subjected to Tandem Mass Tag (TMT) labeling, trypsin digestion, and analysis by liquid chromatography and mass spectrometry LC/LC-MS/MS (Yu *et al.*, 2021).

The large-scale analysis of lysine accessibility using TMT labeling revealed an increase in lysine accessibility in 9 out of 10 RNA splicing proteins in AD brain samples, indicating greater exposure of these regions, possibly related to misfolding and RNA splicing dysfunction. On the other hand, in the tau protein, a decrease in lysine accessibility was observed, corroborating its aggregation and misfolding, which have already been established as pathological features of AD (Yu *et al.*, 2021).

Alterations in lysine accessibility were also detected in proteins involved in mitochondrial and synaptic functions, suggesting that these structural changes affect multiple cellular processes and contribute to disease progression. These variations in accessibility reflect conformational changes and molecular interactions critical for understanding the underlying mechanisms of AD pathology, offering insights for new therapeutic approaches (Yu *et al.*, 2021).

Fonseca-Gomes *et al.* (2024) investigated synaptic dysfunction associated with Alzheimer's disease (AD), focusing on the cleavage of TrkB receptors. The study assessed the efficacy of TAT-TrkB peptides, a peptide that combines the TAT domain with the TrkB receptor sequence, in preventing BDNF receptor cleavage and restoring synaptic physiology in murine models of Alzheimer's, using cell-permeable peptides.

TAT-TrkB peptides were selected due to their ability to cross cell membranes and restore TrkB receptor function, which is compromised in AD. These peptides have been shown to prevent TrkB cleavage, promote BDNF signaling, and enhance synaptic plasticity, factors that can mitigate the cognitive deficits characteristic of the disease. The lysine in the TAT-TrkB peptide sequence played a key role, acting as a positive residue that facilitates interaction with cell membranes. This positive charge allowed overcoming the lipid barrier of the membrane, enabling the peptide's cellular translocation. Additionally, lysine contributed to the stability and solubility of the peptide in solution, enhancing its functionality (Fonseca-Gomes *et al.*, 2024).

The experimental protocol included the administration of TAT-TrkB in 5XFAD transgenic mice, followed by assessments of synaptic plasticity, analysis of TrkB cleavage, and measurements of cognitive performance. This approach allowed for the examination of the peptide's impact on preventing receptor cleavage and restoring synaptic function, contributing to the understanding of the underlying molecular mechanisms in AD and the development of promising therapeutic interventions (Fonseca-Gomes *et al.*, 2024).

Long *et al.* (2024) investigated the relationship between glutamate homeostasis and cognitive function in Alzheimer's models, with a focus on the dysfunction of the glutamatergic system in neurodegeneration and disease progression. The study examined the role of Kallistatin in glutamine synthesis, glutamate homeostasis, and its influence on cognitive function in transgenic mice (KAL-TG) that reproduce characteristics of Alzheimer's disease.

The analyzed peptides included Kallistatin, hydrocortisone, and fenofibrate. Kallistatin was the primary focus, while hydrocortisone and fenofibrate were used as complementary therapeutic agents. Glutamate was investigated due to its relevance as a central excitatory neurotransmitter in the nervous system. The research explored how dysfunction in glutamate homeostasis, often associated with excitotoxicity, contributes to cognitive decline in Alzheimer's models. The potential of Kallistatin to regulate glutamate levels and protect against its toxicity,

promoting improvements in cognitive function, was also evaluated (Long *et al.*, 2024).

The results demonstrated that Kallistatin can reduce glutamate toxicity, improve glutamine synthesis, and protect cognitive function. Hydrocortisone and fenofibrate also showed efficacy in mitigating the effects of neurodegeneration, with a positive impact on cognition (Long *et al.*, 2024).

Experiments were conducted on KAL-TG mice, subjected to behavioral tests such as the Morris water maze and the Y-maze for cognitive function assessment. Blood samples were collected for analysis of Kallistatin and glutamate levels, while the expression of proteins related to glutamine synthesis was evaluated in brain tissue (Long *et al.*, 2024).

The findings indicated that the regulation of Kallistatin is associated with improved glutamate homeostasis and the preservation of cognitive function in transgenic mice. Furthermore, treatments with hydrocortisone and fenofibrate demonstrated therapeutic potential for reducing the effects of neurodegeneration, suggesting that Kallistatin is a promising target for interventions in the treatment of Alzheimer's disease (Long *et al.*, 2024).

The results of the study conducted by Puris *et al.* (2021) on the effects of systemic inflammation in APdE9 transgenic mice demonstrated several significant alterations. The analyses revealed modifications in the levels of lipids in the cortex and hippocampus of mice treated with lipopolysaccharide (LPS). Specifically, a reduction was observed in certain phospholipids, such as PE ae C40:7 and PC aa C35:3/PE aa C38:3, while others, including PC ae C36:6 and PC ae C36:5, showed an increase in levels.

It was found that Aβ deposition was associated with the degradation of white matter, indicating that the molecular mechanisms involved in these metabolic and lipid alterations have complex and cell-specific characteristics. The statistical analysis in the study was conducted rigorously, using t-tests and ANOVA to evaluate the differences in cytokine and metabolite levels between the experimental groups. Bonferroni correction was applied to ensure statistical significance (Puris *et al.*, 2021).

The most altered biochemical pathways were identified using the pathway analysis module of MetaboAnalyst 4.0, allowing the comparison of the main characteristics of the metabolites analyzed. These results highlight the relevance of investigating metabolic changes in the context of Alzheimer's disease and the potential impact of systemic inflammation on these dynamics (Puris *et al.*, 2021).

Song et al. (2023) in their study demonstrated that the monoclonal antibody Y01 has a high specific affinity for the acetylated residue K280 of the tau protein, with the ability to inhibit tau aggregation induced by acetylation. Fluorescence assays using thioflavin T (ThT) showed that the addition of Y01 significantly reduced the aggregation of tau treated with the p300 enzyme in a concentration-dependent manner.

The modification of lysine 280 (K280), carried out to investigate its role in tau protein acetylation and subsequent aggregation, showed that by substituting K280 with alanine (K280A), researchers were able to assess how this alteration affects tau release and toxicity, as well as to better understand the contribution of K280 acetylation to the progression of tauopathies. The monoclonal antibody Y01, effective in detecting the tau-acK280 residue in brain tissue samples from P301L transgenic mice and human cerebrospinal fluid, revealed an interaction through hydrogen bonds and electrostatic complementarities between the antibody and tau protein residues, indicating its clinical potential in the neutralization and removal of pathological protein aggregates (Song *et al.*, 2023).

Rubey (2010) presents in his study highly relevant results about the relationship between herpes simplex virus type 1 (HSV-1) and Alzheimer's disease (AD), as well as the potential of lysine supplementation. HSV-1 DNA was detected in a high percentage (90%) of the brains of elderly individuals, including those diagnosed with AD, indicating that the virus can persist in the brain for long periods and reactivate itself, contributing to the pathogenesis of the disease.

Lysine is proposed as a potential inhibitor of HSV-1 activation, as diets high in lysine and low in arginine can suppress viral replication. Furthermore, the Mediterranean diet, characterized by high levels of lysine and low levels of arginine, may be associated with a lower prevalence of AD. This hypothesis is supported by studies indicating a reduced risk of AD in individuals who regularly consume fish, a food with a high lysine-to-arginine ratio (Rubey, 2010).

Investigations conducted by Rubey in 2010 revealed that a rural community in India exhibits significantly reduced rates of Alzheimer's Disease (AD) incidence compared to other regions. This phenomenon may be linked to a diet rich in dairy products, characterized by a high lysine to arginine ratio. Lysine, in particular, might play a crucial role in preventing the formation of amyloid plaques and neurofibrillary tangles, which are associated with AD, by inhibiting the activity of herpes simplex virus type 1 (HSV-1) in the brain. These findings suggest that exploring the interaction between diet, lysine, and HSV-1 activation could be a promising area for developing effective preventive strategies against AD.

Bellver-Sanchis *et al.* (2022) highlight that G9a inhibitors, identified through structure-based virtual screening, demonstrated significant efficacy in experimental models. On one hand, the compounds tested in this study exhibited promising ability to cross the blood-brain barrier; on the other hand, they were effective in improving age-related paralysis in a

transgenic model of Alzheimer's disease, specifically in the CL2006 lineage of Caenorhabditis elegans. Furthermore, these inhibitors had a positive impact on reducing amyloid-β aggregation, one of the main pathological markers associated with Alzheimer's disease.

G9a, also known as lysine methyltransferase or euchromatin histone-lysine N-methyltransferase 2 (EHMT2), is an enzyme whose main function is to add methyl groups to lysine 9 of histone H3 (H3K9), resulting in mono-methylation (H3K9me1) and di-methylation (H3K9me2). This methylation of H3K9 is an epigenetic mark associated with the repression of gene transcription, silencing genes by modifying the chromatin structure and making it less accessible to the transcription machinery. Furthermore, G9a plays a crucial role in regulating gene expression, affecting important biological processes such as development, cell differentiation, and stress response. Studied as a therapeutic target in various diseases, including cancer, psychiatric disorders, and neurodegenerative diseases like Alzheimer's Disease, G9a is associated with the repression of genes involved in learning and memory, contributing to cognitive impairment in these contexts.

Given the above, recent scientific investigations point to a wide range of promising therapeutic approaches for Alzheimer's disease, encompassing dietary interventions and peptide-based strategies to the use of enzyme inhibitors and monoclonal antibodies. These strategies aim not only to mitigate the structural and functional damage associated with the pathology but also to act on key processes such as toxic protein aggregation, neuroinflammation, and metabolic dysfunction. Although results in experimental models are encouraging, more robust research and large-scale clinical trials are still necessary to validate the efficacy and safety of these approaches in humans. Thus, advancing the understanding of the molecular mechanisms underlying Alzheimer's disease and the development of targeted therapeutic interventions may, in the future, transform the treatment landscape of this condition, bringing significant benefits to patients and caregivers.

V. Conclusions

Research on peptides and the amino acid lysine as therapies for Alzheimer's Disease reveals significant potential in modulating pathological processes associated with the disease. Peptides, especially those that act on beta-amyloid aggregation, demonstrate the ability to destabilize neurotoxic amyloid plaques. In turn, lysine plays a crucial role in regulating protein metabolism and cell stabilization, promoting neuroprotection and synaptic recovery. These substances not only reduce the accumulation of protein aggregates but also control neuroinflammation, a determining factor in the progression of the disease.

Although the results are promising, further studies are necessary to validate the efficacy and safety of using peptides and lysine in humans. Rigorous clinical trials are essential to confirm the therapeutic benefits and deepen the understanding of the mechanisms of action. Moreover, the continuation of research is crucial to elucidate molecular interactions and develop effective interventions that improve patients' quality of life.

Furthermore, the systematic literature review highlights the growing evidence that these interventions can inhibit protein aggregation and exhibit neuroprotective, antioxidant, and anti-inflammatory properties. This suggests that the use of peptides and lysine may improve cognitive function in patients with the disease.

However, it is important to recognize the limitations of this study, such as the variability of the methods in the reviewed articles and the predominance of studies in animal models, which may limit the generalizability of the results. For future research, it is recommended to conduct controlled clinical trials and investigations into the molecular mechanisms underlying these therapeutic effects.

The importance of the findings of this study lies in the possibility of developing new therapeutic approaches, significantly contributing to the management of Alzheimer's Disease. The identification of therapeutic targets, such as the inhibition of PKM2 and the modulation of APP acetylation, opens new perspectives for interventions that may alter the course of the disease. Therefore, the formulation of public policies focused on the treatment of Alzheimer's Disease, which affects millions of people globally, should be encouraged.

Therefore, the search for new therapies is urgent, and peptides and lysine may represent a valuable contribution in this context. This work emphasizes the importance of continuing the investigation into the role of these compounds in the treatment of Alzheimer's Disease, highlighting the need for a collaborative effort among researchers, clinicians, and policymakers to transform discoveries into effective practices that benefit patients with this neurodegenerative disease.

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