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TECHNOLOGIES USED IN THE TREATMENT OF ALZHEIMER'S DISEASE: A LITERATURE REVIEW

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ABSTRACT

The objective of this work is to present current technologies for the treatment of Alzheimer's disease. The methodology used is based on searching for articles in an online database to obtain reliable results. The most common pathologies found in Alzheimer's disease include the accumulation of beta-amyloid (Aβ) protein in the brain, damage caused to tau protein, and oxidative stress-induced damage. The results demonstrate advancements in the technologies used in the last decade, with a notable emphasis on nanobiotechnology. Nanotechnology facilitates research on the delivery of medications across the blood-brain barrier through various nanostructures. Additionally, artificial intelligence (AI) serves as a valuable tool for predicting Alzheimer's disease based on magnetic resonance images, achieving accuracy rates exceeding 90%.

Keywords: Bio, Technologies, Nano, AI.

RESUMO

O objetivo deste trabalho é apresentar tecnologias atuais para o tratamento da doença de Alzheimer. A metodologia utilizada baseia-se na busca de artigos em uma base de dados online para obtenção de resultados confiáveis. As patologias mais comuns encontradas na doença de Alzheimer incluem o acúmulo de proteína beta-amilóide (Aβ) no cérebro, danos causados à proteína tau e danos induzidos por estresse oxidativo. Os resultados demonstram avanços nas tecnologias utilizadas na última década, com notável ênfase na nanobiotecnologia. A nanotecnologia facilita a pesquisa sobre a distribuição de medicamentos atravessando a barreira hematoencefálica por meio de nanoestruturas. Além disso, a inteligência artificial (IA) é considerada uma ferramenta valiosa para prever a doença de Alzheimer com base em imagens de ressonância magnética, alcançando taxas de precisão superiores a 90%

Palavras-chave: Bio, Tecnologias, Nano, IA.

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1. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease that primarily affects the elderly, leading to a gradual loss of cognitive function, memory, and thinking skills. It is classified as the most common form of dementia (Ren *et al.*, 2022).

Alzheimer's disease is characterized by two primary abnormalities in the brain: the first involves the abnormal accumulation of amyloid beta protein (Aβ), which forms insoluble plaques between nerve cells. These plaques disrupt communication between neurons, ultimately leading to cell death. The second abnormality pertains to neurofibrillary tangles, composed of tau proteins, which typically play a crucial role in maintaining the structure of nerve cells. However, in individuals with Alzheimer's, these tau proteins become abnormally distorted and entangled within brain cells. This phenomenon hinders the transport of nutrients and vital information within nerve cells. The consequence of these two pathological processes is the progressive buildup of Aβ plaques and neurofibrillary tangles, resulting in substantial brain atrophy and, consequently, the gradual loss of cognitive functions (Li *et al.*, 2018).

Recently, there has been growing interest in treatment methods associated with Aβ overproduction and aggregation. However, the discontinuation of several related clinical trials has revealed that simply targeting Aβ does not seem to be effective enough to offer a cure for Alzheimer's disease (Loera-valencia *et al.*, 2019). Critical factors, such as glial cell-mediated oxidative stress, play a pivotal role in the onset and advancement of diseases. Oxidative stress is a significant factor in the pathogenesis and progression of Alzheimer's disease. Consequently, the control of the pathological environment within lesions by mitigating the oxidative stress cascade has emerged as a promising new approach for Alzheimer's disease treatment (Shalabalija et al., 2021).

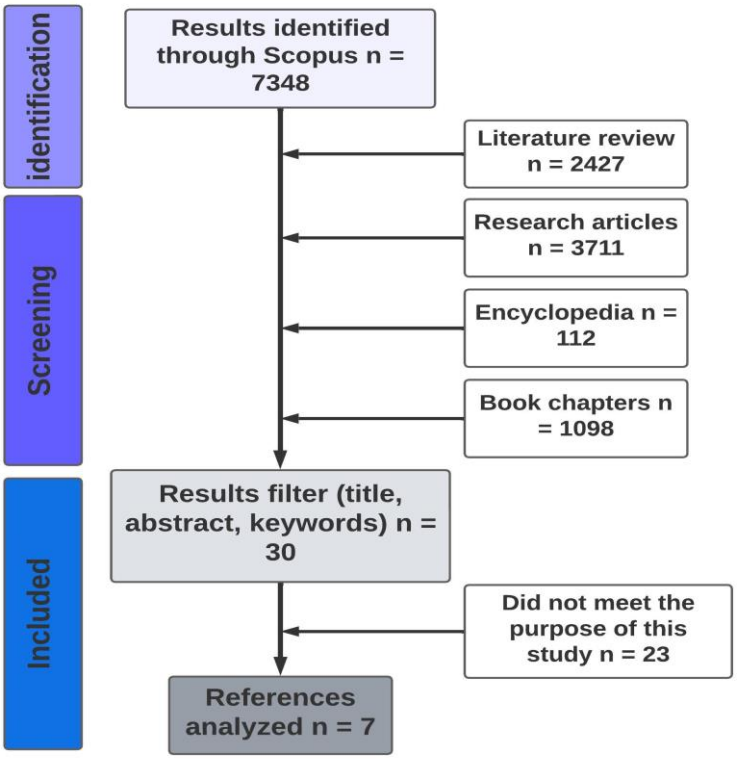
Nanotechnology plays a critical role in advancing the treatment of Alzheimer's disease, as it is essential for overcoming the blood-brain barrier during drug administration. Artificial intelligence also plays a significant role in identifying disease markers in human patients. All of these aspects will be comprehensively explored and illustrated in the discussion and results sections of this work. Our primary objective is to present modern technologies employed in the treatment of Alzheimer's disease.

2. METHODOLOGY

This study falls into the exploratory category of integrative literature review. The search was conducted using Boolean descriptors and operators, with the following English keywords: 'Alzheimer; treatment; nano; technologies.' The search period encompassed the months from July to September 2023 and was performed within the Scopus electronic database.

For the selection of articles, inclusion criteria were applied that included the availability of complete articles and their publication in the last decade. In addition, the selected articles should have titles, abstracts and/or keywords related to the research context.

Figure 1. Flowchart with the article selection strategy



Source: Author construction

After searching the selected databases, titles and abstracts were analyzed, resulting in the selection of articles that met the criteria established in this study for full reading. The following information was recorded about the publications: year of

publication, name(s) of the author(s) and types of technologies aimed at treating Alzheimer's disease.

The search conducted in the selected databases yielded a total of 7.756 articles, out of which 7 met the established criteria and were consequently included in the study. The selection process for these articles is illustrated in Figure 1.

3. RESULTS AND DISCUSSIONS

This study presents current research on technologies used in the treatment of Alzheimer's disease. Additional details can be found in Table 1.

Table 1. publications that made up the study.

Year	*Authors*	*Technologies*
2023	YU et al.	Micelles with oridonin and Phillyrin
2022	Haeberlein et al.	Human monoclonal antibody
2023	Mycroft-West et al.	Clycosaminoglycan
2020	BI et al.	Deep Learning (Artificial Intelligence)
2018	Kheradmand et al.	Hesperetin and nano-hesperetin
2022	LI et al.	Melantonin-trientine conjugate
2022	HE et al.	Blood-brain barrier targeting nano-missiles

Source: Author construction

In an approach to the treatment of Alzheimer's disease, as reported by *Yu et al.* (2023), orodonin and phyllin nanomicelles were utilized to overcome the blood-brain barrier, guided by a peptide called 'ApoE,' specifically targeting the brain. This approach led to an increase in the drug's concentration and its therapeutic effectiveness. Nanotechnology combined with the medicinal plants can be a valuable tool in disease research. Nanostructures called micelles with encapsulated drugs were tested with the goal of overcoming the blood-brain barrier and delivering the compounds to the brain to combat Alzheimer's. Encouraging results were presented, demonstrating an encapsulation efficiency of 80% for the micelles within 21 days, showing good biocompatibility and targeting neuronal cells. The results also showed that ApoE-Ori/Phi-Ms inhibited astrocytes and microglia, reduced inflammatory factors

such as TNF-α, IL-1β, and IL-6, hindered the deposition of Aβ plaques, and reduced oxidative stress.

In the study conducted by *Haeberlein et al.* (2022), the effectiveness and safety of aducanumab in early-stage Alzheimer's disease were assessed. Aducanumab is a human monoclonal antibody targeting both aggregated and soluble as well as insoluble forms of amyloid beta. The EMERGE trial, a pioneering phase 3 study, establishes a link between the reduction in biological markers of Alzheimer's pathology and a clinically significant slowing of decline, suggesting that the removal of Aβ from the brain, coupled with changes in subsequent disease indicators, may be associated with clinical improvements in individuals with early-stage Alzheimer's. However, due to issues encountered in some assessments, the clinical efficacy of aducanumab will be further examined in an upcoming clinical trial.

According to *Mycroft-West et al.* (2023), the clinically significant anticoagulant heparin, a member of the carbohydrate glycosaminoglycan family, has been shown in studies to inhibit Beta-Site Amyloid Precursor Protein Cleavage Enzyme 1 (BACE-1). BACE-1 is a secreted enzyme that acts by cleaving the amyloid precursor protein (APP) at a specific location, generating fragments that contribute to neuronal issues and exacerbate Alzheimer's disease. In addition to its BACE-1 inhibitory effects, heparin exerts favorable biological activities by influencing various pathophysiological factors such as inflammation, oxidative stress, and tau phosphorylation. However, the primary limitation in the use of heparin lies in its anticoagulant potency. The solution proposed in this study involves a sulfated glycosaminoglycan extract of marine origin obtained from the Atlantic scallop, Placopecten magellanicus. This extract demonstrates a high inhibitory potential against BACE-1 (IC50 = 4.8 μg/mL·1), while exhibiting significantly lower anticoagulant activity, approximately 25 times less potent than heparin.

According to *Bi et al.* (2020), a study focused on the application of deep learning technologies to aid in Alzheimer's disease prediction using magnetic resonance images (MRI) yielded promising results, with an accuracy rate exceeding 90%. The study utilized data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) online database. The primary objective of this research is to identify sensitive and specific markers for the early stages of Alzheimer's disease progression, aiding researchers

and clinicians in the development of new treatments and monitoring their effectiveness. A total of 1075 examinations from individuals categorized into three groups: AD (Alzheimer's disease), NC (Normal Cognition), and MCI (Mild Cognitive Impairment) were employed. The results demonstrated that a fully unsupervised method can autonomously predict Alzheimer's disease patients solely based on MRI images.

According to a study conducted by *Kheradmand et al.* (2018), hesperetin (Hst) has been identified as an antioxidant and anti-inflammatory agent. The study evaluated both the regular form of hesperetin and nano-hesperetin in the hippocampal region of rats within an experimental model for Alzheimer's disease. Behavioral tests showed improvements in memory retrieval and recognition memory. The use of Hst and nano-Hst led to increased activity levels of antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GRx), catalase (CAT), and glutathione (GSH). These findings suggest a therapeutic potential for addressing Alzheimer's.

Li et al. (2022) developed a compound known as melatonin-trientine (TM), which was covalently synthesized using the antioxidant melatonin trientine. The study involved testing mice that expressed amyloid-β protein and presenilin (APP/PS1), a protein complex involved in the processing of amyloid precursor protein (APP). Normally, APP undergoes controlled processing in a series of steps. However, in individuals with Alzheimer's disease, this processing can lead to the formation of beta-amyloid protein fragments that tend to accumulate in amyloid plaques in the brain, exacerbating the disease. Encouragingly, the results showed a reduction in Aβ deposition and a decrease in neuronal degeneration associated with PS1. Several positive outcomes were observed following the use of the compound, including reduced tau protein phosphorylation, decreased neuroinflammation, and reduced oxidative stress, all of which are considered key factors in Alzheimer's disease treatment. These findings suggest that the TM compound may enhance therapeutic effectiveness by targeting multiple mechanisms associated with Alzheimer's disease pathology.

According to *He et al.* (2022), a co-delivery system was developed for encapsulated drugs consisting of ibuprofen and FK506 in response to high levels of reactive oxygen species and the receptor for advanced glycation end products (RAGE)

in Alzheimer's disease. Cellular uptake efficiency confirmed that the compound targeted diseased cells in the blood-brain barrier and improved nanoparticle internalization. Results from tests on rats with AD demonstrated a reduction in Aβ plaques, and the compound treated AD through anti-neuroinflammation and neuroprotection.

4. CONCLUSION

In summary, the pathogenesis of Alzheimer's disease has been a persistent challenge that has intrigued scientists and affected patients for many years. In this study, we highlight three key pathological features associated with Alzheimer's disease: the accumulation of amyloid beta protein in the brain, damage to tau protein, which affects communication between neurons, and oxidative stress, playing a significant role in the progression of Alzheimer's disease. Understanding these mechanisms is essential for developing more effective therapeutic strategies for this complex neurodegenerative condition.

The blood-brain barrier is also a challenge faced by scientists, but it has been easily overcome through tools employing nanotechnology, utilizing nanostructures to transport encapsulated medications across this barrier, and directing them to specific targets. Therefore, finding solutions to these issues remains a priority.

Despite the complexity of multiple pathogenic processes and intricate hypotheses related to Alzheimer's disease, oxidative stress and its detrimental effects on neurons are central factors that play significant roles in all of these mechanisms. Oxidative stress acts as a bridge that connects the various pathogenic aspects of Alzheimer's disease, representing an inevitable step in all these processes. Finally, we have an ally in the process of identifying early-stage Alzheimer's patients: Artificial Intelligence, which can greatly assist doctors and patients in treatment and the prospects of a cure.

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