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Evaluation of the potential of N-acetylcysteine in Alzheimer's disease

Avaliação do potencial da N-acetilcisteína na doença de Alzheimer

Evaluación del potencial de la N-acetilcisteína en la enfermedad de Alzheimer

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ABSTRACT

Objective: This review aims to show the studies related to the acetylcysteine molecule in Alzheimer's disease, the glutamatergic hypothesis, and to show the difference of this drug in the use of medications and food supplements. **Methods:** The integrative review was performed in 6 detailed steps, the articles for the construction of the research were obtained from the databases Scopus; Scielo; MEDLINE, available at the Universidade Federal de Paraná-UFPR, through CAFe access. By the Boolean operators "AND" and "OR", the terms defined for data collection were obtained through the Descriptors in Health Sciences (DeCS/MeSH). **Results:** A total of 68 studies were found, divided among the authors; and using the inclusion and exclusion criteria, only 7 studies remained, in which were added to the search after being read in full; the studies that showed better affinity in the use of the acetylcysteine molecule associated with Alzheimer's in vivo or in vitro tests were narrated in full. **Final considerations:** In the research it was possible to verify that the use of N-acetylcysteine off label can be a target molecule for Alzheimer's disease, but to prove this action further studies are recommended to ensure its effectiveness.

Keywords: Alzheimer's disease, Acetylcysteine, Cysteine, Glutamic Acid.

RESUMO

Objetivo: Essa revisão tem como objetivo mostrar os estudos relacionados com a molécula de acetilcisteína na doença de Alzheimer, a hipótese glutamatérgica, e a mostrar diferença deste fármaco no uso de medicamentos e suplementos alimentares. **Métodos:** A revisão integrativa foi realizada em 6 etapas detalhados, os artigos para construção da pesquisa foram obtidos a partir das bases de dados Scopus; Scielo; MEDLINE, disponível na Universidade Federal de Paraná-UFPR, através do acesso CAFe. Pelos operadores booleanos "AND" e "OR", os termos definidos para a recolha de dados foram obtidos através dos Descritores em Ciências da Saúde (DeCS/MeSH). **Resultados:** Foi encontrado um total de 68 estudos, divididos entre os autores; e utilizando os critérios de inclusão e exclusão, restaram apenas 7 estudos, no qual foram

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adicionados à pesquisa após terem sido lidos por completo; os estudos que demonstraram melhor afinidade no uso da molécula acetilcisteina associada com Alzheimer em teste *in vivo* ou *in vitro* foram narrados na integra. **Considerações finais:** Na pesquisa foi possível verificar que a utilização de N-acetilcisteína *off label* pode ser uma molécula alvo para a doença de Alzheimer, mas para provar está ação recomenda-se a realização de mais estudos para garantir a sua eficácia.

Palavras-chave: Doença de Alzheimer, Acetilcisteína, Cisteína, Ácido Glutâmico.

RESUMEN

Objetivo: Esta revisión tiene como objetivo mostrar los estudios relacionados con la molécula de acetilcisteína en la enfermedad de Alzheimer, la hipótesis glutamatérgica, y para mostrar la diferencia de este fármaco en el uso de medicamentos y suplementos alimentícios. **Métodos:** La revisión integradora se realizó en 6 pasos detallados, los artículos para la construcción de la investigación se obtuvieron de las bases de datos Scopus; Scielo; MEDLINE, disponible en la Universidad Federal de Paraná-UFPR, a través del acceso CAFe. Mediante los operadores booleanos "AND" y "OR", los términos definidos para la recogida de datos se obtuvieron a través de los Descriptores en Ciencias de la Salud (DeCS/MeSH). **Resultados:** Se encontró un total de 68 estudios, divididos entre los autores; y utilizando los criterios de inclusión y exclusión, sólo quedaron 7 estudios, en los cuales fueron añadidos a la búsqueda después de ser leídos en su totalidad; los estudios que mostraron mejor afinidad en el uso de la molécula de acetilcisteína asociada a la prueba de Alzheimer in vivo o in vitro fueron narrados en su totalidad. **Consideraciones finales:** En la investigación fue posible verificar que el uso de N-acetilcisteína fuera de etiqueta puede ser una molécula de ayuda para la enfermedad de Alzheimer, pero para probar esta afirmación se recomienda la realización de más estudios para garantizar su eficacia.

Palabras clave: Enfermedad de Alzheimer, Acetilcisteína, Cisteína, Ácido Glutámico.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative pathology that has several hypotheses such as the β-amyloid (Aβ) hypothesis, the acetylcholine hypothesis, the tau protein hypothesis, and the glutamatergic hypothesis, among several others. Alzheimer's has as its main symptom the memory loss that presents itself in the course of the disease (KNOPMAN DS, et al., 2021).

According to Falco AD, et al. (2016) the amino acid glutamate is the main neurotransmitter present in the central nervous system that has its activity exerted through N-methyl-Aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA) and cyanate. The emergence of the glutamatergic hypothesis is related to alterations in the NMDA receptor; problems related to this receptor may trigger alterations in calcium entry in the intracellular medium, which causes cell death (apoptosis). The authors also claim that the release of glutamate in large proportion has affinity for activation of the AMPA receptor and cyanate, which would trigger the entry of Na+ and Ca2+ ions, which would cause depolarization of the plasma membrane and cause excitotoxicity.

Acetylcysteine (NAC) consists of two molecules of acetylcysteine and L-cysteine responsible for pathophysiological processes, available as a medicine or dietary supplement sold without a prescription. Acetylcysteine is a product used worldwide, and its purpose goes beyond its use as an expectorant syrup and as an antidote for paracetamol intoxication. There is evidence in clinical research that acetylcysteine (NAC) has a purpose in articulating neurological disorders of Alzheimer's disease in the neurotransmitter of glutamate (SLATTERY J, et al., 2015).

Glutamate is a significant neurotransmitter in the central nervous system (CNS) is an amino acid developed by neurons and glial cells (contained in the CNS that participate in neurological activities in the isolation and nutrition of neurons) through glucose and oxoglutarate widely distributed throughout the brain, glutamate is

the predecessor of gamma-aminobutyric acid (GABA) And under normal conditions it is released by various stimuli that promote action on neurodevelopment, learning, memory (VALLI, LG 2014) But in neuroinflammatory conditions of Alzheimer's disease (AD) the release of the amino acid is in a disordered manner that impairs various receptors, causing neuronal excitotoxicity and neurodegenerative symptoms in AD (SLATTERY J, et al., 2015; CZAPSKI GA and STROSZNAJDER JB, 2021).

Due to glutamatergic excitotoxicity several cells are damaged and the disordered stimulation of neurotransmitters can trigger neurological diseases, hence the importance of investigating drugs capable of transmuting the effect of toxicity, and the molecule acetylcysteine available in the oral precursor form of L-cysteine, a key molecule for the creation of glutamate, has aptitude as a modulator of several neurological pathways, especially the dysregulation of the amino acid glutamate (OOI SL, et al., 2018). Therefore, this review aims to discuss the role of acetylcysteine in Alzheimer's disease in off-label use.

METHODS

According to the authors Ercole FF, et al. (2014) The integrative literature review is a review that aims to embody the results achieved in research on the subject under discussion, in a systematic, organized and broad manner. It is entitled integrative because it offers more extensive investigations on the designated subject in question, thus developing new material.

In this way the researcher is able to elaborate an integrative review with several purposes, directing to determine concepts, this method grants in the search of results in experimental articles, fomenting findings of theoretical literatures, attributing more in the more precise comprehension of the theme.

For the development of the integrative review, it is necessary to establish six steps to answer the "question" of the article, such as the choice of theme; inclusion and exclusion criteria; information that will be extracted; characteristics of the search; method of evaluation of the findings; vision of the results and presentation of the data (RAGHY G, et al., 2021).

Following this method, we obtained the following characteristics:

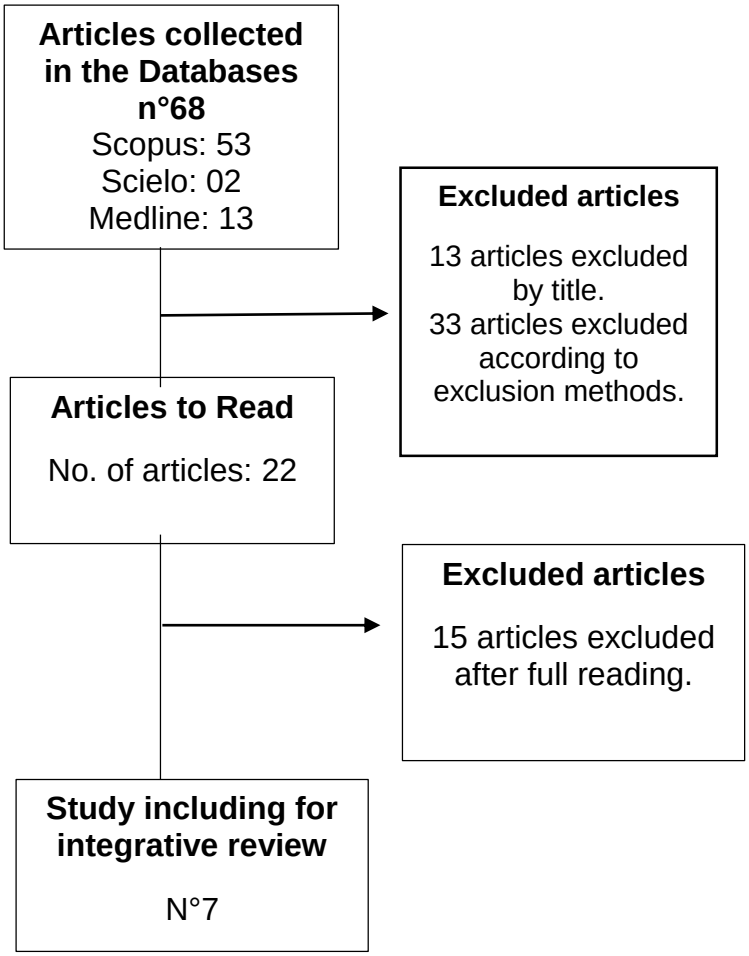
First stage choice of topic; Second stage inclusion criteria: *In vitro* and *In vivo* studies, related to acetylcysteine, Alzheimer's and glutamate, complete studies showing result of NAC use, research in Portuguese and English in the period of 23 years; exclusion criteria:

Research that does not fit the "inclusion criteria", systematic and narrative reviews, incomplete research, studies that do not relate to Alzheimer's disease; Third step information to be collected (Clinical results of the articles); Fourth step characteristics of the searches, the searches were performed by the Boolean Operators method "AND" and "OR", the terms defined for data collection was obtained by the Descriptors in Health Sciences (DeCS/MeSH) - Alzheimer's disease; Acetylcysteine; Glutamic acid, Cysteine.

Terms used in the Boolean operator: ("glutamic acid"[MeSH Terms] OR ("glutamic"[All Fields] AND "acid"[All Fields]) OR "glutamic acid"[All Fields] OR "glutamate"[All Fields] OR "glutamates"[MeSH Terms] OR "glutamates"[All Fields]) AND ("alzheimer disease"[MeSH Terms] OR ("alzheimer"[All Fields] AND "disease"[All Fields]) OR "alzheimer disease"[All Fields] OR "alzheimer"[All Fields]) AND ("acetylcysteine"[MeSH Terms] OR "acetylcysteine"[All Fields] OR "acetylcysteine"[All Fields]). Terms used in Portuguese: "Alzheimer" "Acetylcysteine" "Glutamate".

Fifth step method of evaluating the findings reading and interpreting the clinical data; sixth step presentation of the results that will be exposed in table form detailing the authors' research method. The articles were obtained from the databases Scopus; Scielo; MEDLINE, available from the Federal University of Paraná-UFPR, through CAFe access. As shown in **figure 1**.

Figure 1 - Flowchart of the research.



Source: Fernandes IC, et al., 2023.

Detail of the stages of the studies after the survey of the data collection in the databases.

RESULTS AND DISCUSSION

Off label

According to the Agência Nacional de Vigilância Sanitária ANVISA (2022a) when a drug is approved for a certain therapeutic purpose, nothing prevents it from being used only for that situation, it can appear in the package insert; however, a marketed drug and its new indications have not been approved by the regulatory agencies for lack of evidence of efficacy and it does not appear in the package insert and the prescribed will write for a certain physio pathological situation is performed with the risk of the prescribed and can be indicated as medical error, however, in most cases it is the correct indication, just not approved. The term off label refers to the use of a pharmaceutical drug that is not indicated for that purpose, that is, its use is different from that indicated in the package insert and approved by the regulatory agencies in force in each country, which in Brazil is the National Health Surveillance Agency (ANVISA, 2022b).

N-acetylcysteine (NAC) in off-label use, contributes to the synthesis of glutathione (GSH) that has its level increased in a disordered manner during oxidative stress, it is synthesis of GSH, and together with glutathione reductase (GR) recovers the oxidized glutathione amino acid and with age GSH levels decrease, Thus, the use of oral NAC can increase GSH levels by providing the addition of cysteine which stimulates glutathione

development, reducing oxidative stress and maintaining normal GSH levels in the brain (VAN HECKE O and LEE J, 2020).

Glutamatergic Hypothesis of Alzheimer's Disease

The neurotoxicity provided by the amino acid glutamate has been observed in Alzheimer's disease, this amino acid is an important neurotransmitter present in the mammalian nervous system and is related in various brain functions. Glutamate is signaled by a variety of receptors, for example, ionotropic and metabotropic receptors (MDSYSTEMS, 2022). The glutamatergic hypothesis called Alzheimer's excitotoxicity emerged in the 1980s, the amino acid glutamate being essential in excitatory neurotransmission in the central nervous system (CNS), the glutamatergic hypothesis assumes that under certain conditions, for example, activation of N-methyl-D-aspartate (NMDA) receptors cause alterations in calcium homeostasis, causing an increase in its concentration in the brain triggering cell and neural death processes, NMDA receptors have a difficult structure with multiple binding sites for the amino acid glutamate, it is also possible that the relationship in glutamate release initially triggers the action of alpha-amino-3-hydroxy-5-4-isoxazolpropionic acid (AMPA) and cyanate (calcium receptors) receptors, which although having little binding favor rapid cell degradation due to Na+ and Ca2+ entry, which would cause the depolarization of the plasma membrane, removing the blockade of Mg2+ ions in the NMDA receptor, providing the binding of glutamate in certain subunits, contributing to the excitatory activity. In pathophysiological situations, depolarization present in neural cell membranes triggering Mg2+ blockade of NMDAR increasing Ca 2+ concentration, this increase can cause excitotoxic necrosis, research on neurological diseases such as AD has shown that neurodegeneration through 1-Glu pathways occurs in Alzheimer's with similar characteristics as tangles (HYND MR, et al., 2004).

Acetylcysteine

According to the Administrative Rule 344 of May 12, 1998, a drug is defined as a pharmaceutical product, technically obtained or elaborated, for prophylactic, curative, palliative, or diagnostic purposes. Medicines are pharmaceutical forms that contain active substances capable of alleviating or curing pathologies, causing permanent or temporary relief and well-being, and can be presented in solid, liquid, or gaseous form (SAUDE, 1998).

According to legislation number 6.360, dated September 23,1976, the drugs are available in three categories: similar drugs that contain the same active ingredient, the same concentration, posology, administration and indication, changing only some similarities, such as box marketing, drug size, among others; generic drugs equivalent to the original drug, scientifically proven with bioequivalence and bioavailability tests; reference drugs, innovative products, the first to appear, also known as "brand names", registered in the National Health Surveillance Agency (ANVISA) (PLANALTO, 1998).

N-acetylcysteine (NAC) C5H9NO3S, was discovered in 1961 and patented by researcher Mead Johnson in 1965; its expectorant benefit was reviewed by author Ziment (1986) (SCRIABINE A and RABIN DU, 2009; PUBCHEM, 2022a]. The acetyl molecule belongs to an acetyl functional acid group of acetic acid, and is present in many organic and inorganic compounds. In biological functions, the acetyl molecule participates in the formation of the neurotransmitter acetylcholine, and is also responsible for cellular respiration and cellular metabolization and energy production for the human body (NORTH BJ and VERDIN E, 2004). The acetyl group is constantly present in histones, changing their properties, such as in DNA in acetyltransferases (HATs), making gene transcription possible; if acetyl is extracted by histone deacetylases (HDACs), transcription function is compromised (KOIDE K, et al., 2011).

The cysteine molecule was first reported in 1980 by Wollaston, who isolated a crystalline element present in urinary calculus and called it cystic oxide, which we now call cystine; cysteine in the form of cystine made its detection impossible for many years, certainly because initially amino acid methods were not compatible with sulfur-containing analysis (NORTH BJ and VERDIN E, 2004). Cysteine is an important amino acid for proteins, in drug detoxification, metabolic activities, skin texture, and in the development of the amino acid taurine. Cysteine is an important antioxidant element, glutathione, which performs essential activity in the biotransformation of chemical compounds such as coenzyme A, heparin, and biotin (PUBCHEM, 2022b).

Acetylcysteine is also classified as a food supplement by NORMATIVE - MS No. 28, OF JULY 26, 2018 (GOV, 2020) food supplements are products with complementary action to the diet such as vitamins, minerals, enzymes, etc. Supplements are in the form of capsules, tablets, liquids, powders, among others, such as supplements for sports (NABUCO HCG, et al., 2016). Food supplements are different from medicines because they do not have the function of treating, preventing or curing pathologies, supplements are designed for healthy people, their activity is to provide nutrients for the body, this category was formed in 2018 to ensure the quality of the supplement and the use of the product in the population, its composition can only be used as ingredients authorized by ANVISA (National Health Surveillance Agency) (NABUCO HCG, et al., 2016).

Acetylcysteine and glutamate in Alzheimer's disease

The ability of the acetylcysteine molecule to provide glutathione restitution and maintain glutamate levels in the nervous system may cause good benefits for brain health, the amino acid glutamate is an important excitatory neurotransmitter present in the central nervous system of mammals, widely distributed in the brain, when it is at rest its amount is 0. 6 μM, in the course of synaptic transport the amount of glutamate tends to increase to 10 μM at certain extracellular sites, this amino acid is synthesized by various metabolic pathways and removed by the uptake/transport system, receptors for this enzyme are known as ionotropic glutamate receptors (iGluRs), which assist in large parts of mammalian neurotransmitter activities, In addition to playing an important role in synaptic plasticity, memory, and learning in humans, blocking or disrupting the normal functions of iGluRs can trigger several neurological pathologies, including Alzheimer's disease (AD), Parkson's disease (PD), and multiple sclerosis (MS) (CHANG CH, et al., 2020).

For decades Alzheimer's has been growing and its diagnosis is still undefined, since then several researches have demonstrated hypotheses about the cause of AD, for example "insoluble beta-amyloid (Aβ) plaque formation hypothesis", "tau protein neurofibrillary tangles" and "cholinergic hypothesis", among others that are discovered during research on the pathology, AD has characteristics due to the instability of neural synaptic signals, decreased blood flow, mitochondrial dysfunction and glutamatergic signaling, which designates another "hypothesis", this hypothesis appears at the beginning of the pathology by the decreased uptake of the amino acid glutamate, which gives rise to excitotoxicity. Several studies have shown that during the aging process there is a significant reduction in glutamatergic signaling, and due to the formation of beta-amyloid plaques in the disease, glutamate uptake and astrocytes are compromised, and these astrocytes (cells) respond in a very arduous way with Aβ plaques, which characterizes homeostatic changes and to obtain glutamate requires high energies and changes in these cells may also be linked to insufficient uptake of the amino acid, so decreased glutamate levels in the brain may be related to significant loss of glutamatergic neurons and/or astrocytes, both of which have an important purpose in glutamate uptake (ANDERSEN JV, et al., 2021; BENNETT ML and VIAENE AN, 2021).

These factors affecting communication in neurological responses can cause neural death leading to consequences for Alzheimer's disease, which makes it even more difficult to develop therapeutic strategies. At this point there is still no drug that cures the pathology, but there are drugs that stop the progressive growth of Alzheimer's disease called acetylcholinesterase inhibitors (donepezil, galantamine or rivastigmine) and memantine (NMDA) that block glutamatergic passage when it is in excess in the brain, maintenance of glutamate balance in the brain by decreasing excitotoxicity, such a goal in decreasing neural toxicity is found in plants such as Celastrus paniculatus (Celastraceae) and Huperzia serrata (Lycopodiaceae) and the drug and supplement N-acetylcysteine (NAC) (CZAPSKI GA and STROSZNAJDER JB, 2021).

Acetylcysteine (NAC) and Alzheimer's disease

Long used its use as an expectorant syrup and currently as a food supplement, with its mechanism of action involving glutathione is an important antioxidant for the disease. Glutathione is composed of three amino acids with different purposes: cysteine (protection against free radicals), glutamate (neural synaptic activity) and glycine (fight against free radicals and skin firmness). The use of NAC can be considered an ally in fighting neurological disorders because it can increase the levels of glutamate and cysteine in the body, eliminating the free radicals that cause Alzheimer's disease. The effect of neurotransmission is investigated by taking

NAC, providing cystine, and research on Alzheimer's disease indicates that the use of acetylcysteine has beneficial effects on activity in the amino acid balance, as shown in **Table 1** (RAGHU G, et al., 2021; TARDIOLO G, et al., 2018).

Table 1 - Table of studies related to the use of NAC and Alzheimer's disease.

Pathology	Types of Studies	Treatments	Authors
Alzheimer's disease	*In vivo (mice)*	Drinking water or water supplemented with NAC	ROBINSON RA et al (2011).
Alzheimer's disease	*In vitro*	Nα-acetyl-L-cysteine (NAC)	NEELY DM, et al. (2000).
Alzheimer's disease	*In vivo* (adult male Wistar rats)	Sulfasalazine and NAC	ZHANG D, et al. (2016)
Alzheimer's disease	*In vivo* (Juvenile male mice Sprague-Dawley)	Synaptotoxic beta-amyloid oligomers (AβOs) and N-acetylcysteine (NAC).	MORE J et al (2018).
Alzheimer's disease	*In vivo* (male Wistar rats)	Intra hippocampal injection of Aβ and N-acetylcysteine (NAC)	SHAHIDI S, et al. (2017)
Alzheimer's disease	*In vivo* (Mice)	Acetylcysteine (NAC)	HSIAO YH, et al. (2012)
Alzheimer's disease	*In vivo* (Mice)	N-Acetylcysteine (NAC) N-Acetylcysteine amide (NACA)	Penugonda, Ercal (2011)

Source: Fernandes IC, et al., 2023.

It has long been used as an expectorant syrup, and currently as a food supplement, with its mechanism of action involving glutathione is an important antioxidant for disease. Glutathione is composed of three amino acids with different purposes: cysteine (protection against free radicals), glutamate (neural synaptic activity) and glycine (fight against free radicals and skin firmness). The use of NAC can be considered an ally in combating neurological disorders because it can increase the levels of glutamate and cysteine in the body, eliminating the free radicals that cause Alzheimer's disease. The effect of neurotransmission is investigated by consuming NAC, providing cystine, and research on Alzheimer's disease indicates that the use of acetylcysteine has beneficial effects on activity in the balance of amino acids, as shown in **Table 1**.

Robinson RA, et al. (2011) explored the antioxidant activity of using N-acetylcysteine (NAC) as a therapy for Alzheimer's disease at different disease progressions in mice; the use of NAC in mice showed increased protein ban and attenuation of cofilin in the brain, in addition to protection against oxidative stress by acting by eliminating free radicals, the investigation showed that acetylcysteine altered some brain proteins in mice, i.e., the use of acetylcysteine has significant effects as a brain protector with NAC treatment.

Neely MD, et al. (2000) research addresses most studies on the reactivation of lipid peroxidation of aldehydes is 4-hydroxy-2-nonenal (HNE) found in increased situation in the brains of people with Alzheimer's disease and the application of NAC in the study was able to block the appearance of HNE.

The study of authors Zhang D, et al. (2016) used two drugs sulfasalazine and N-acetylcysteine, the agents that obtained different actions sulfasalazine decreases the level of extracellular glutamate and intracellular GSH; on the other hand, NAC significantly increased the concentrations of intracellular glutamate and intracellular GSH and prevented Aß synaptic disruption alone or together with sulfasalazine. It can be said that both drugs may have benefits in the central nervous system, but their effects have yet to be studied and monitored in various Alzheimer's disease patients at different stages.

More J, et al. (2018). In the investigation of the use of NAC in research improved the impairment of rats injected with AβOs in the Oasis maze test; and the oral use of NAC in antioxidant action protected the redox action of the hippocampus against cognitive impairment; the use of acetylcysteine in daily doses had an increase in glutathione levels as well as the prevention of memory loss, demonstrating that the use of acetylcysteine can be an important medicine for people suffering from Alzheimer's disease.

The study conducted by researchers Shahidi S, et al (2017) evaluated the protective action in the use of acetylcysteine on learning and memory in mice, the mice obtained the induction of intrahippocampal Aβ and were evaluated in different fields, the results showed that the mice that had the application of NAC in parallel with those that did not use the drug showed improvements in Alzheimer's symptoms, which suggested that acetylcysteine may have a potential for Alzheimer's disease.

Authors Hsiao YH, et al. (2012) showed that NAC can be an effective drug for the treatment of Alzheimer's disease in a test conducted by social isolation applied to mice; the therapeutic use of NAC in the investigation decreases the activity of γ-secretase and potential action for human pathologies.

Researchers Penugonda S and Ercal N (2011), investigated the evaluation of NACA (N-acetylcysteine amide) compared to NAC (N-acetylcysteine) on the exposed oxidative action of glutamate in lead applied in mice in tests performed, both NAC and NACA increased the glutamate action and protection against the effects of lead by decreasing the levels in the bloodstream, but NACA had better antioxidant results because it is lipophilic and crosses the blood-brain barrier, and is considered as a future drug for the treatment of Alzheimer's disease.

There are still no effective drugs for a cure and/or more drug options for the treatment of Alzheimer's disease, and one of the disadvantages of this discovery is the pathological changes that appear during the course of the disease. And the currently existing drugs only have delayed activity and are beneficial in inhibiting cholinergic (donepezil, rivastigmine and galantamine) and glutamatergic receptors, since the drug called memantine this drug is clinically effective for the treatment of neurological diseases its mechanism of action is the blockade of N-methyl-aspartate (NMDA) receptors belonging to the glutamate receptor family, Even with such efficacy, memantine at high doses can impair various neurotransmitters such as serotonin and dopamine, which does not preclude further studies of Alzheimer's disease drugs (JOHNSON JW and KOTERMANSKI SE, 2006). The emergence and/or development of drugs to treat neuropathological diseases for the pharmaceutical industry and universities is something formidable, but the road ahead is quite long and financially expensive, which makes it more difficult to find more drugs for Alzheimer's disease (FORUM ON NEUROSCIENCE, 2014) this is just another setback behind Alzheimer's disease, its neurological mechanism is still poorly understood, due to its variations and hypotheses the intervention of new drugs becomes more complex (SUN D, 2022).

CONCLUDING REMARKS

Future research is needed to consider the role of L-cysteine and the use of acetylcysteine, which goes beyond an expectorant syrup. Its composition brings benefits in the daily diet, as well as being a future drug for Alzheimer's disease, where the use of N-acetylcysteine (NAC) has been demonstrated in tests that prove the action of the amino acid in neurological diseases and its purpose in the production of glutathione. It also shows that off-label use of acetylcysteine may be approved tomorrow, but for this to happen, more studies tend to prove its efficacy in a more complete way, addressing all the criteria established by ANVISA. In addition, this research serves as a basis for future discoveries with the acetylcysteine molecule and therapy for Alzheimer's disease and the use of off-label drugs for Alzheimer's disease.

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