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REVIEW ARTICLE

Effects of coconut oil on Alzheimer's disease: a literature review

Efeitos do óleo de coco na doença de Alzheimer: uma revisão de literatura

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease whose main characteristic is the progressive loss of cognitive functions, affecting millions of people worldwide. In this sense, there is a continuous search for therapeutic tools that act in the prevention and treatment of the disease. In addition, research using coconut oil as a therapeutic tool has demonstrated a potent anti-inflammatory effect of this substance. Thus, a literature review was conducted to investigate the possible effects of coconut oil on AD. This article is a literature review using the PubMed, Science Direct, SciELO and LILACS databases. From the search with specific descriptors, studies were included referring to the last five years, published in English, Portuguese and Spanish with pre-clinical and clinical data. The included preclinical studies demonstrated that coconut oil interferes by inhibiting important metabolic pathways that act in the promotion of neuroinflammation, amyloid plaque formation, neurotransmitter imbalance, and signaling pathway dynamics. In addition, the use of coconut oil increased the levels of ketone bodies. To some extent, many clinical trials have already shown favorable support for the use of coconut oil as an adjuvant in the treatment of AD. However, there is still a need for more randomized, controlled clinical trials that evaluate the optimal dosage, as well as whether or not coconut oil is effective against Alzheimer's disease.

Keywords: Alzheimer's; Coconut oil; Beta-Amyloid peptides; Ketone bodies.

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RESUMO

A doença de Alzheimer (DA), é uma enfermidade neurodegenerativa que possui como principal característica a perda progressiva das funções cognitivas, afetando milhões de pessoas no mundo. Nesse sentido, existem contínuas buscas por ferramentas terapêuticas que atuem na prevenção e no tratamento da doença. Além disso, pesquisas com a utilização do óleo de coco como ferramenta terapêutica demonstraram um potente efeito anti-inflamatório dessa substância. Dessa forma, foi elaborada uma revisão bibliográfica para investigar os possíveis efeitos do óleo de coco relacionados à DA. O presente artigo trata-se de uma revisão bibliográfica utilizando as bases: PubMed, *Science Direct*, SciELO e LILACS. A partir da busca com descritores específicos, foram incluídos estudos referentes aos últimos cinco anos, publicados em inglês, português e espanhol com dados pré-clínicos e clínicos. Os estudos pré-clínicos incluídos demonstraram que o óleo de coco interfere inibindo vias metabólicas importantes que atuam na promoção da neuroinflamação, na formação de placas amiloides, no desbalanço de neurotransmissores e na dinâmica de vias de sinalização. Além disso, o uso do óleo de coco aumentou os níveis de corpos cetônicos. De certa forma, muitos ensaios clínicos já se mostraram favoráveis ao uso de óleo de coco como adjuvante no tratamento da DA. Contudo, ainda são necessários mais estudos clínicos randomizados e controlados que avaliem a dosagem ideal, bem como a eficácia ou não do óleo de coco contra a doença de Alzheimer.

Palavras-chave: Alzheimer; Óleo de coco; Peptídeos Beta-Amiloides; Corpos cetônicos.

Introduction

Alzheimer's disease is a degenerative brain disease characterized initially by episodic memory impairment with later progression to dementia. Its classic signs are failures in memory, judgment, attention span, and problem-solving skills, evolving into severe apraxia and global loss of cognitive abilities. The disorder occurs mainly after the age of 60, with a few cases between the ages of 50 and 60. It is marked by severe cortical atrophy and by 3 main pathological markers: amyloid plaque (mainly characterized by the presence of Aβ peptides of 40 to 42 amino acid residues), neurofibrillary tangles, and neuropilot filaments in the cerebral cortex[1,2]. It is estimated that about 50 million people worldwide have some form of dementia, with Alzheimer's disease (AD) being the most common type of dementia, contributing 60-70% of cases. The global burden of dementia is estimated to reach 82 million by 2030 and 152 million people by 2050[3].

Anticholinesterases such as donepezil, galantamine, and rivastigmine are part of the first-line pharmacological therapy for the treatment of AD. These drugs act by inhibiting the degradation of acetylcholine, increasing its availability, which is reduced in patients with the disease[4]. In contrast, coconut oil, which may have benefits for AD, is classified as a "functional food", i.e., in addition to its nutritional function, it has additional components with health effects. Coconut oil is composed mostly of saturated fatty acids (SFA), which are about 92% of its composition, of which 62 to 70% are medium-chain fatty acids (MCFA), such as lauric acid, myristic acid, palmitic acid, capric acid, caprylic acid and caproic acid. Among these, lauric acid (48.5% of the amount of MCFAs in coconut oil) is probably responsible for most of the medicinal properties[5].

As for the use of this oil in AD, experiments on senile and young rats showed efficacy in preventing neurodegeneration in manifestations similar to dementia/Alzheimer's disease, because, among other advantages, virgin coconut oil improved cholinergic activity and monoaminergic neurotransmission in the rats[6]. Coconut oil may significantly improve orientation and language construction in Alzheimer's patients, acting either by increasing metabolism with increased energy use from ketone bodies or by improving insulin resistance[7]. Thus, the objective of this work is to investigate, through a literature review, possible effects of coconut oil related to AD.

Methods

A search on the PubMed, Science Direct, SciELO and LILACS platforms was performed by two of the

authors independently with the following descriptors: (1) Alzheimer's disease, (2) coconut oil and (3) beta-amyloid peptides. Inclusion criteria were: articles whose publication date did not exceed 5 years; published in English, Portuguese, or Spanish; preclinical and clinical studies were included. Articles that were not intrinsically related to the theme were excluded - a criterion used from the reading of the title and abstracts of the articles. In addition, to contemplate the existing literature, searches were conducted in the references of the articles originally included.

Results

Initially, 23 relevant papers were found, of which nine were repeated (found simultaneously in different databases) and six articles did not present the expected correlation with the theme after reading them in their entirety. After using the above criteria, 8 papers were selected to compose this article based on literature review. Among the 8 articles included in this review, two were published in 2020, one in 2019, two in 2018, two in 2017, and one in 2015. The studies reviewed occurred in Spain (n=2), the United States (n=1), Canada (n=1), Egypt (n=1), Nigeria (n=1), Saudi Arabia (n=1), and Iran (n=1). The total number of subjects addressed in the prospective clinical studies was 88 patients. Tables 1 and 2 summarize the main aspects of the preclinical and clinical studies included in this review, respectively. In addition, Figure 1 describes the potential mechanisms of action proposed by the included articles.

Discussion

Preclinical studies

The hypometabolism observed in AD has stood out as a possible target for intervention in the disease process, as it can cause damage to brain function. It is also known that the medium-chain triglycerides (TsCM) present in coconut oil can be rapidly metabolized to induce ketosis, in which circulating ketone bodies can provide an alternative energy source in situations where glucose availability is compromised[14]. Accordingly, Nafar et al. (2017)[10] performed an *in vitro* experiment aimed at analyzing the values of beta-hydroxybutyric acid (a ketone body) in conditioned medium from cultures treated with or without virgin coconut oil, containing neurons and astrocytes from rat cortex. A modest increase in beta-hydroxybutyric acid was found with the addition of virgin coconut oil in the neuron cultures, although there was no further increase compared to the control group. With regard to astrocytes, there was a significant increase in the production of ketone bodies in the intervention group. Beta-hydroxybutyric acid production in cultures treated with individual fatty acids and a mixture of fatty acids was also compared. There were small increases in

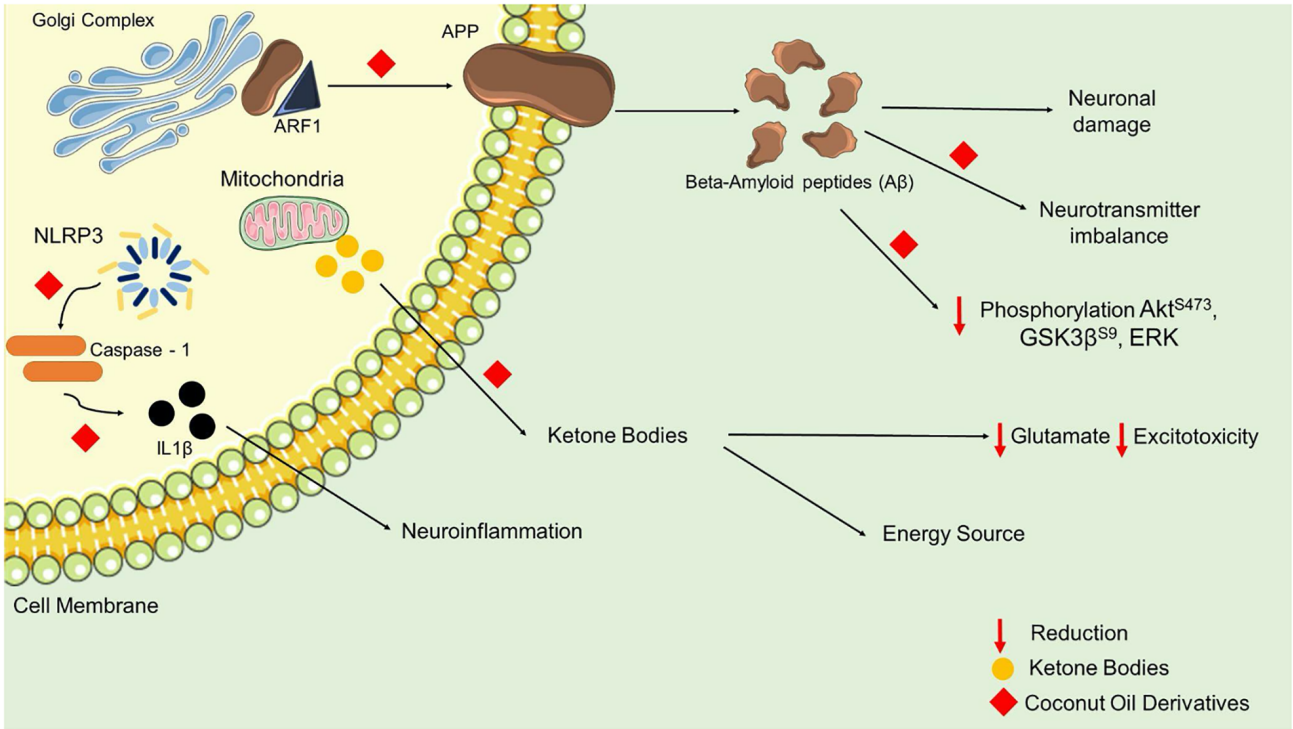

Figure 1. Molecular aspects related to coconut oil derivatives.

Amyloid Precursor Protein (APP). ADP Ribosylation Factor (ARF1). NOD-like Receptor Family containing the Pyrine Domain 3 (NLRP3). Interleukin 1 Beta (IL1β). Protein Kinase B (Akt). Glycogen synthase kinase 3 Beta (GSK3β). Extracellular Signal Regulated Kinase (ERK). This figure was created using illustrations from Servier Medical Art (https://smart.servier.com/), which has a Creative Commons Attribution 3.0 Unported license (https://creativecommons.org/licenses/by/3.0/).

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ketone body production with octanoic and decanoic acids (C10) and the mixture of both. The lauric acid condition showed a modest increase only at the 2 hour time point.

As for Aβ peptides, present in amyloid plaques, it is known that they are proteolytic fragments of the β-amyloid precursor protein (APP). When APP is highly expressed on the cell surface, it is cleaved by β- and γ-secretases, which leads to the formation of Aβ[2]. APP is synthesized in the endoplasmic reticulum and transported by the Golgi complex via ARF1, a protein belonging to the ARF class I group[15].

The co-localization of AFR1 and APP in the Golgi complex was studied by Bansal et al. (2019)[8] by immunostaining and confocal microscopy. The authors aimed to reduce the expression of APP, and consequently decrease the formation of Aβ peptides. For this, they analyzed the effect of 0.1% coconut oil on mammalian cells (N2a/APP695) with APP overexpression. In the presence of the oil, a 55% reduction of ARF1 and a 40% reduction of APP was observed by densitometry, and using RT-PCR examination, a 30% decrease of ARF1 mRNA was verified. Consequently, there was also a statistically significant reduction of Aβ 42 ($p \leq 0.05$) and Aβ40 ($p \leq 0.05$) compared to the control group.

In addition, Bansal et al. (2019)[8] also found that APP inhibition promoted cell differentiation, as amyloid peptides

Table 1. Methodological and molecular characteristics of the preclinical studies included in the literature review.

Article (authors and year)	Type of Study	Methods	Results
Bansal et al. (2019)[8]	Preclinical with cell lines *(in vitro)*	Analysis of the expression of Amyloid Precursor Protein (APP) and ARF1 factor in mammalian cells expressing the APP gene (N2a/APP695).	. Decreased APP protein expression. . Decreased expression of the ARF1 factor. . Decreased levels of Aβ peptides.
Mirzaei et al. (2018)[9]	Preclinical with rats *(in vivo)*	120 Wistar rats divided into 12 groups (n=10): control; placebo surgery; placebo surgery receiving saline; 7 groups with or without use of virgin coconut oil, with and without a lipid-rich diet and with and without rats that received Aβ peptides.	. Decreased expression of Caspase-1, NLRP3 and IL1B.
Nafar et al. (2017)[10]	Preclinical with cell lines *(in vitro)*	Evaluation of survival and cellular parameters of neuronal cortical cells submitted to treatment with Aβ peptides preceded and followed by treatment with coconut oil.	Modest increase in the level of ketone bodies. . Blocking the deleterious effects of A□ peptides on cell signaling pathways.
Attia e Ahmed (2020)[6]	Preclinical with rats *(in vivo)*	Analysis of biochemical factors in 36 albino rats that were divided into a control group, a group using anhydrous aluminum chloride and a group using virgin coconut oil after administration of anhydrous aluminum chloride.	. Improved cholinergic activity. . Improvement in the concentration of the BDNF factor. . Improves the concentration of serotonin, noradrenaline and dopamine.
Alghamdi (2018)[11]	Preclinical with rats *(in vivo)*	Analysis of the prophylactic effect of virgin coconut oil in 18 Wistar rats randomly assigned to 3 groups (n=6): control, Alzheimer's induced by aluminum chloride and Alzheimer's induced by aluminum chloride + virgin coconut oil.	. Anti-excitotoxic and antioxidant effect. . Memory improvement.
Bisong (2020)[12]	Preclinical with rats *(in vivo)*	Analysis of visuospatial learning and short- and long-term recognition memory in 31 CD1 rats divided into 3 groups (n=10): control, 5% virgin coconut oil and 20% virgin coconut oil, for 28 days.	. Damage related to the pyramidal cell layer of the hippocampus. . In the long term, memory damage.

Source: Authors (2022).

were shown to be toxic to neuronal cells and inhibited cell differentiation in N2a/APP695 cells. Thus, coconut oil was also shown to be a protective agent in developing cells.

Neuroinflammation is another factor shown to play an important role in the onset of AD and other neurological diseases through an inflammasome, a macromolecular complex that contains copies of a receptor or sensor for pathogen- or damage-derived molecular patterns. This complex results in the maturation of caspase-1, an enzyme that regulates the release of pro-inflammatory cytokines such as IL-1β and IL-18[16].

Cellular damage caused by Aβ peptide deposition may trigger activation of the NLRP3 inflammasome. Therefore, modulating the activation of the inflammasome complex may be a potential strategy to suppress inflammation in the CNS, and consequently the development of AD[17].

In this vein, the study by Mirzaei et al. (2018)[9] aimed to use coconut oil as an NLRP3 inflammasome inhibitory agent. Aβ plaques and a high-fat diet have been shown to significantly impair memory and learning through NLRP3 activation and oxidative stress in mice. Virgin coconut oil was included in the diet of two groups of these mice: one that had only Alzheimer's disease and the other that, in addition to the disease, also received a high-fat diet. Real-time PCR tests found that administration of the doses of the oil reduced IL-1β protein, Caspase-1, and NLRP3 gene expression in the groups. Administration of both doses of coconut oil also reduced the number of Aβ plaques, decreased Tau phosphorylation, and reduced neuronal cell death.

The study by Nafar et al. (2017)[10] analyzed the action of coconut oil *in vitro* as a pre-treatment of the effects related to amyloid plaques in neurons and also in the treatment after their deposition. The introduction of coconut oil before the exposure of neurons to Aβ peptides blocked the neuronal decline caused by them. The late addition of the oil in the second experiment attenuated the damage caused by the plaques.

The authors used confocal microscopy to monitor neuronal changes promoted by Aβ peptides, and axonal fragmentation, Tau protein deposition, and evidence of dystrophies of MAP2-positive dendrites were observed. Exposure to Aβ results in an increase in the presence of cleaved caspase-3, a marker of apoptosis, which is reduced by pretreatment with coconut oil. Also, the oil showed a blocking action on Aβ-induced changes in ROS (reactive oxygen species) formation in cells. [9] Regarding the expression and phosphorylation of enzymes, it was noted that the addition of Aβ resulted in a significant decrease in the phosphorylation of Akt^{S473}, $GSK3\beta^{S9}$ and ERK, indicating that one of the effects of Aβ is the inhibition of survival signaling pathways. Coconut oil also showed good results as a pretreatment, ensuring the proper functioning of these pathways. This protective characteristic of the oil regarding cell signaling may be influenced by the PI3-Kinase → Akt

Table 2. Methodological characteristics and results of clinical studies included in the literature review.

Article (authors and year)	Methods	Population	Intervention	Results
Yang (2015)[13]	Prospective Clinical Study with 44 participants divided between the control group and the intervention group in a 1:1 ratio. It was not specified how these individuals were allocated. Patients were not blinded.	Patients with Alzheimer's disease, aged between 65 and 85 years. The following patients were excluded: those outside the age group 65-85; patients with other pathologies that cause cognitive deterioration; aversion to the coconut-derived product; inability to respond verbally.	Administration of 40 ml/day of virgin coconut oil in patients in the intervention group for 21 days.	There was an improvement in the MEC-LOBO test score - a validated Spanish translation of the Mini Mental State Examination (MMSE) - in the patients in the intervention group. For comparison, evaluations were performed by the same method before the interventions, in both groups.
De la Rubia Ortí et al. (2017)[7]	Prospective Clinical Study with 44 participants divided between the control group and the intervention group in a 1:1 ratio. Groups obtained by stratified randomization. Patients were not blinded.	Patients with Alzheimer's disease, aged between 65 and 85 years. The following patients were excluded: those outside the age group 65-85; patients with other pathologies that cause cognitive deterioration; aversion to the coconut-derived product; inability to respond verbally.	Administration of 40 ml/day of virgin coconut oil in patients in the intervention group for 21 days.	There was an improvement in the MEC-LOBO test score - a validated Spanish translation of the Mini Mental State Examination (MMSE) - in the patients in the intervention group. For comparison, evaluations were performed by the same method before the interventions, in both groups.

Source: Authors (2022).

pathway, since its inhibition prevents the beneficial action of coconut oil[10].

Attia e Ahmed (2020)[6] conducted a study involving the administration of coconut oil to young 4-month-old and older (over 2.5 years of age) rats that were exposed to the nerve damage-promoting substance aluminum chloride ($AlCl_3$) in order to see if the oil could prevent neurodegeneration and to analyze its effects on the regulation of nervous tissue hormones. As a result, it was observed that acetylcholinesterase (AChE), a key enzyme involved in the hydrolysis of acetylcholine, has its activity decreased through the use of coconut oil, since this oil is rich in cytokines, responsible for modulating acetylcholinesterase and improving the transmission of the cholinergic impulse.

This result is consistent with the experience of Rahim et al. (2017)[18], who observed, in 7 to 8 weeks old rats with memory deficits, an improvement in cognitive function through the use of coconut oil, via the cholinergic pathway, mentioned above. Furthermore, it was also detected that coconut oil stimulates the action of antioxidants, such as superoxide dismutase, responsible for curbing the production of reactive oxygen species, reducing lipid peroxidation, which is responsible for deteriorating brain function. In this way coconut oil is shown to be a contributing agent in the reduction of oxidative stress.

In addition, it was also observed in Attia e Ahmed (2020)[6] study that brain-derived neurotrophic factor (BDNF), essential in neuronal survival and synaptic plasticity, as well as providing cholinergic, dopaminergic and serotoninergic support[19,20], had higher expression after coconut oil administration, showing significant improvement in cognition.

Furthermore, a noradrenergic and dopaminergic modulation is observed, reducing the excess of noradrenaline and dopamine in order to avoid the accumulation of these substances, and increasing the level of serotonin, thus helping in the histoarchitecture of the hippocampus and cortex. Thus, it is concluded that coconut oil has the ability to interact and modulate the functioning of neurotransmitters[6].

AD patients have higher levels of lipid peroxidase and a decrease in antioxidant enzyme activity[11]. Therefore, in order to evaluate the antiexcitotoxic and prophylactic effects of virgin coconut oil on Alzheimer's disease, Alghamdi (2018)[11] conducted a study using Wistar rats divided into three groups: (1) control, (2) $AlCl_3$-induced AD without coconut oil administration, (3) $AlCl_3$-induced AD with coconut oil administration, i.e., the intervention group. As a result, it was found that group 3 showed considerable improvements in antioxidant activity in the hippocampus and cortex, critical areas of Alzheimer's disease, when compared to group 2.

Such results are justified by analyzing the chemical constitution of coconut oil, which is composed of several antioxidant substances such as tocopherols and polyphenols[21]. In addition, the study also detected that the prophylactic use of coconut oil significantly increased glutathione levels and decreased levels of lipid peroxidation in the cortex in group 3 when compared to group 2, and also found, through electron microscopy, that the hippocampus and cortex of group 3 had healthier cellular aspects when compared to group 2, especially the organelles.

One of the most characteristic symptoms of Alzheimer's is memory loss, which can be short or long term. In this sense, studies bring coconut oil as a possible palliative agent to delay these effects. One of the pillars of this analysis is the fact that high fat content produces cytokines that activate the functioning of inflammatory pathways that cause damage to cognition and memory[22]. Still in this bias, the study reported by Mirzaei et al. (2018)[9], which evaluated the effects of coconut oil on memory maintenance after high lipid intake in rats with neurodegenerative diseases, observed that after a high lipid diet the rats had their neurodegenerative activity accentuated, however the introduction of coconut oil in the diet provided a significant improvement in long-term memory in all intervention groups. The animals were presented for three consecutive days to a platform, which had to be crossed by 4 attempts. The test performed after the introduction of coconut oil had the platform hidden, and thus the speed, time to reach the hidden plate, and distance traveled by each rat was recorded.

This study is in agreement with that evidenced by Alghamdi (2018)[11], previously described, in which the administration of coconut oil in the intervention group slightly improved the short-term memory of the rats. This phenomenon was assessed through an object recognition test. The rats were allowed to explore two identical objects for 3 minutes. After 15 minutes, one of the familiar objects was replaced by a new object. The animals had another 3 minutes to explore, and their memory was assessed for the frequency and duration of contact with both objects.

On the other hand, it is worth noting that the use of coconut oil to treat Alzheimer's disease is still experimental and subject to further analysis and observation, such as that done by Bisong et al. (2020)[12], in which he used CD1 mice to investigate the effect of long-term coconut oil consumption on memory and learning.

In this sense, after the experiment, damage was detected in the hippocampus of rats that were fed 20% coconut oil in the diet, especially pyramidal cells in area CA1 of the hippocampus, fundamental for the formation of long-term memories. This fact diverges with several studies, such as the already exposed study by Attia e Ahmed (2020)[6], which demonstrated that coconut oil had the ability to modulate neurotransmitters putting them in a state of balance.

When faced with the discordance of their study compared to others in the area, Bisong et al. (2020)[12] hypothesized that due to the ketogenic characteristic of coconut oil, its long-term consumption could generate large amounts of ketone bodies in the nervous tissue. The metabolism of these bodies would lead to the generation of acetylcoenzyme-A, which would increase its combination with oxaloacetate in the citrate cycle. Consequently, there would be a decrease in the amount of oxaloacetate available to the brain, since it is needed in the conversion reaction between alpha-ketoglutarate and aspartate to oxaloacetate and glutamate, which is a reversible reaction. Thus, when there is an excess

of acetyl coenzyme-A, there is a sequestration of oxalacetate, implying a deficit in the functioning of the aspartate-amino-transferase reaction. Thus, there is an accumulation of glutamate in the brain and an elevation in the level of brain toxicity, and thus compromising memory. However, it is worth mentioning that because the subject has few approaches, more studies are still needed to clarify and confirm the functioning of this mechanism[12].

Clinical trials

The study by Yang et al. (2015)[13] highlights the influence that type 2 diabetes *mellitus* may have in the etiology of Alzheimer's disease, since there is a serious metabolic disorder related to glucose, and, in this context, the need for a source of energy supplementation is evidenced: ketone bodies. Thus, the authors used coconut oil as a ketogenic source in this study. It was administered for 21 days to patients with mild, moderate, and advanced AD, with positive results in the dementia picture not only for the diabetic patients, but the others who were subjected to the experiment. The intervention group had a significant increase in the Mini Mental State Examination (MMSE) test score, which evaluates the situation of cognitive deterioration by measuring areas such as: calculation, concentration and memory fixation, at the beginning and at the end of the experiment, presenting an average of 38.92% improvement, mainly by females. However, it is worth noting that this study was done with a small sample size, which limits the applicability of the results. Moreover, this study did not present masking and randomization tools, which limit the reproduction of biases that interfere with the analysis of the criteria used by the researchers.

The study conducted by De la Rubia Orti et al. (2017)[7], selected 44 Alzheimer's patients from the Ribeira region, located in Valencia, Spain, and analyzed the effect of extra virgin coconut oil (OCV) on human cognition. The patients were divided into two groups: the group of 22 randomly selected patients who received, in their diet, 40 ml of extra virgin coconut oil for 21 days, and a second group with the other 22 patients, which maintained the same dietary profile as the first, but with the exception of coconut oil. The Mini Mental State Examination test was also performed, verifying that those patients who had received the OCV showed expressive improvements in cognition. However, it is worth noting that this test was done with a small and restricted group of people, and it is important to highlight the brevity of the study, which limits the applicability of the results, requiring further work to reach a more substantiated conclusion on the effect of OCV on cognition in humans with Alzheimer's disease. In addition, this study did not present masking tools, which limit the reproduction of biases that interfere with the analysis of the criteria used by the researchers.

Conclusion

Alzheimer's is a disease that, even today, has few therapeutic alternatives, which reinforces the search for new interventions in the scientific community. Thus, based on the studies in this review, it is known that coconut oil derivatives have, *in vitro* and in animals, a potential effect in inhibiting the expression of factors that determine the development of the disease, such as amyloid precursor protein (APP), inflammatory pathways, and metabolic processes. However, the vast majority of the studies included are preclinical, i.e., insufficient to define therapeutic conduct in everyday life. Moreover, the prospective clinical trials included in this review presented important methodological problems, such as small sample size, short development period, and lack of adequate randomization and blinding. Therefore, more randomized controlled clinical trials with blinding strategies and larger sample sizes are needed to evaluate the optimal dosage and derivative, as well as the existence of efficacy or otherwise of coconut oil against Alzheimer's disease.

Authors' Contribution

Conceptualization, Investigation, Methodology, Visualization & Writing – Review & Editing: Bruno Nascimento Lacerda, Luciano Fábio Oliveira Magalhães Filho, Renatha Lima de Oliveira e Zenilda Gueiros Silvestre. Project Administration, Supervision & Writing – Original Draft: Natalie Emanuelle Ribeiro Rodrigues. Validation & Software: Luciano Fábio Oliveira Magalhães Filho. Resources & Funding acquisition: Not applicable. Data Curation & Formal Analysis: Bruno Nascimento Lacerda, Luciano Fábio Oliveira Magalhães Filho, Renatha Lima de Oliveira e Zenilda Gueiros Silvestre.

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