ANALYSIS OF THE EFFECT OF NANOPARTICLES CONTAINING ALFA HUMULENE AND CURCUMIN ON NEUROINFLAMMATION: A SYSTEMATIC REVIEW

Giovanna Tardem Oliveira[1], Isabella Cristina Chiamolera[2], João Alfredo Schiewe[3], Livia Hoyer Garcia Miranda[4], Daniele Eurick[5], Jaine Alessandra Korchak Alves[6], André Alexandre Pezzini[7] and Ivo Ilvan Kerppers[8].

[1] Laboratory of Neuroanatomy and Neurophysiology, Medical Student
State University of the Midwest (UNICENTRO)
Email: giovanna.tardem@gmail.com
ORCID: https://orcid.org/0009-0005-5154-5224
LATTES: http://lattes.cnpq.br/5841550160666508
[2] Laboratory of Neuroanatomy and Neurophysiology, Medical Student
State University of the Midwest (UNICENTRO)
E-mail: bella.chiamolera@gmail.com
ORCID: https://orcid.org/0009-0007-7835-6794
LATTES: http://lattes.cnpq.br/5989698389186472
[3] Laboratory of Neuroanatomy and Neurophysiology, Undergraduate in Medicine
State University of the Midwest (UNICENTRO)
E-mail: jschiewepriv@gmail.com
ORCID: https://orcid.org/0000-0003-3942-5746
LATTES: http://lattes.cnpq.br/5014605095768040
[44] Laboratory of Neuroanatomy and Neurophysiology, Medical Student
State University of the Midwest (UNICENTRO)
E-mail: livia.hoyer@hotmail.com
ORCID: https://orcid.org/0000-0002-0051-7005
LATTES: http://lattes.cnpq.br/0021879377701826
[5] Laboratory of Neuroanatomy and Neurophysiology, Graduated in Physical Therapy
State University of the Midwest (UNICENTRO)
E-mail: eurickdaniele@gmail.com
ORCID: https://orcid.org/0009-0008-5158-8971
LATTES: http://lattes.cnpq.br/9330766585607775
[6] Laboratory of Neuroanatomy and Neurophysiology, Graduated in Physical Therapy
State University of the Midwest (UNICENTRO)
E-mail: korchakjaine@gmail.com
ORCID: https://orcid.org/0009-0003-1081-5254
LATTES: http://lattes.cnpq.br/0972370307887375
[7] Professor of the Dentistry Course at the State University of Western Paraná - UNIOESTE
State University of Western Paraná – Unioeste
Email: www.pezzini@hotmail.com
ORCID: https://orcid.org/0000-0002-0437-1031
LATTES: http://lattes.cnpq.br/1790432663943586
[8] Professor of the Physiotherapy course at the State University of the Center - UNICENTRO, Professor of the Master's program in Nanosciences and Biosciences - Unicentro. Professor of the Master's Program in Veterinary Sciences - Unicentro. State University of the Midwest (UNICENTRO)
Email: ikerppers@unicentro.br
ORCID: https://orcid.org/0000-0002-5901-4007
LATTES: http://lattes.cnpq.br/2107257822885032

ABSTRACT

Objective: To analyze the available evidence about nanoparticles containing alpha humulene and curcumin, and their possible therapeutic effects on neuroinflammation. Methodology: Systematic review of the literature, carried out from December 2023 to July 2024, covering publications from 2014 to 2024, in the Cochrane and PubMed electronic databases, based on the following descriptors: "curcumin", "Alzheimer disease", "Alzheimer", "cytokines", "humulene" and "nanoparticles", with the aid of the Boolean operator "AND". Results: A total of 672 articles were found, of which 10 met the inclusion and exclusion criteria. They addressed topics such as inflammatory changes in cerebrospinal fluid and blood, effects of curcumin and alpha-humulene on inflammatory markers, action on ß-amyloid and hyperphosphorylated tau proteins, modulation of insulin resistance, cognitive decline, in addition to the challenges of bioavailability and formulation of compounds, highlighting the relevance for prevention and intervention in Alzheimer's. Discussion: The review identified variables on the effects of α-humulene and curcumin on neuroinflammation and highlighted the need for further studies on their efficacy in Alzheimer's.

Keywords: Beta Amyloid. Humulene. Neuroinflammation. Cytokines. Alzheimer's disease.

INTRODUCTION

Alzheimer's disease is a progressive, incurable, multifactorial and slow-developing brain disease, whose incidence has increased worldwide (TWAROWSKI; HERBET, 2023). Its pathophysiology is complex, with the production and aggregation of β-amyloid peptides (Aβ) playing a major role, as well as the formation of intracellular neurofibrillary tangles of tau, both processes occurring in an unbalanced manner in the face of the elimination rate of metabolites from the Central Nervous System (CNS) (MAISAM et al., 2023).

As a consequence, there is the secretion of mediators by inflammatory cells present in neuroinflammation and an oxidation process triggered, from which neuronal losses, gliosis occur (MAISAM et al., 2023) and synaptic changes (GRIFFITHS; GRANT, 2023). Thus, the characterization of the clinical picture of Alzheimer's disease is described as memory loss, cognitive and behavioral changes, and progression of the disease to neuronal death (MAISAM et al., 2023).

Curcumin It is a polyphenolic compound found in turmeric and known for its antioxidant and anti-inflammatory properties (KNIGHT et al., 2023). Its therapeutic potential encompasses degenerative diseases due to its ability to inhibit pro-inflammatory pathways and modulate the immune system. In the context of Alzheimer's disease, this substance interferes with the formation of amyloid plaques and influences epigenetic changes associated with the disease, such as DNA methylation and histone modifications, impacting the progression of Alzheimer's disease (ABDUL-RAHMAN et al., 2024).

Curcumin's properties range from its effects neuroprotective to the reduction of oxidative stress and inflammatory response in the brain. This compound destabilizes the structures of Aβ and tau, influences the expression of proteins related to the elimination of tau, is able to increase the levels of acetylcholine in the brain and has the ability to cross the blood-brain barrier and modulate pathways of other neurotransmitters related to the pathology of Alzheimer's disease, such as serotonin and dopamine. In addition, curcumin regulates gene expression and, in the context of modulating the immune response, it increases Aβ uptake by macrophages (ABDUL-RAHMAN et al., 2024). As a negative factor, however, it has been shown that its bioavailability to act in the CNS is low (KNIGHT et al., 2023).

There are several studies to investigate possible treatments for Alzheimer's disease and there are many potential compounds, but it is necessary to elucidate both the pathophysiology mechanisms and the real impact of the substances studied in the course

of this disease. Curcumin shows promise (MAISAM et al., 2023), as well as another phytochemical compound, humulene, or α-humulene. This compound is characterized as a monocyclic sesquiterpene, naturally present in hop essential oil and other plant sources. α-humulene also has strong potential for the treatment of chronic inflammation, such as those present in neurodegenerative diseases, as it modulates the activity of NF-κB, a crucial pathway in inflammation, and results in reduced release of pro-inflammatory cytokines, such as IL-6 and TNF-α, in differentiated THP-1 cells in macrophages. Despite possible therapeutic effects, α-humulene needs to have its anti-inflammatory and antioxidant mechanism better understood, as there remains a gap in the knowledge of its properties related specifically to Alzheimer's disease, as well as a paucity of research covering this issue. In addition, it is reported that this compound in high concentrations can lead to toxic effects (BECKER; HOLTMANN, 2024).

Nanotechnology can also offer possible benefits in the treatment of Alzheimer's disease, through nanoparticle technology, which allows the delivery of drugs to the brain. Through these developed materials, it is possible to achieve greater biocompatibility and ability to cross the blood-brain barrier. Nanoparticles such as liposomes, polymeric nanoparticles, gold nanoparticles and solid lipid nanoparticles can be combined with phytochemical compounds, such as curcumin and humulene, to achieve potential for the treatment of Alzheimer's disease, with the possibility of increasing the safety and bioavailability of the compounds offered (MAISAM et al., 2023).

In this systematic review of the literature, we sought to identify, evaluate and summarize the available evidence on the effects of nanoparticles of α-humulene and curcumin in neuroinflammation, especially with a focus on their possible therapeutic effects for Alzheimer's disease. Thus, this review highlights two main topics to be discussed: Do curcumin and α-humulene have effects on neuroinflammation?; Would curcumin and α-humulene be possible alternatives for the treatment of Alzheimer's disease?

Based on the analysis of the available literature, this review aims to cooperate with future research in the area and to enhance the available collection on the relationship between curcumin nanoparticles and curcumin. α-humulene with the neuroinflammation triggered in Alzheimer's disease. In addition, the content of this study also aims to identify the gaps in knowledge on this topic and indicate the need for further research on both compounds and the pathophysiology of Alzheimer's disease.

METHODOLOGY

This study is characterized as a systematic review of the literature, which involves a process of evaluation of evidence based on a well-established scientific criterion, with organized and systematized methods of search, application of critical thinking and synthesis of the selected information, with the objective of cooperating with future investigations (DONATO; DONATO, 2024).

To conduct this systematic review Regarding the effects of nanoparticles containing α-humulene and curcumin on neuroinflammation, articles were selected, from December 2023 to February 2024, through searches in the Cochrane and PubMed electronic databases. The chosen platforms have notoriety in the scientific community and have a comprehensive collection of relevant and up-to-date texts. No language restrictions were applied, but only those published between 2014 and 2024 were selected.

The following descriptors in English were used to perform the search process: "curcumin", "alzheimer disease", "alzheimer", "cytokines", "humulene" and "nanoparticles", with the help of the Boolean operator "AND", in order to combine the terms and refine the searches. In addition, articles that met the defined inclusion criteria were selected: clinical trials, whose design was not characterized as a pilot study. The study was supposed to be related to the effects of curcumin and the α-humulene in neuroinflammation or in the course of Alzheimer's disease, and the selected articles were limited to publications from the last 10 years, in order to delimit studies of a relevant and current nature for the objectives of this review.

At the end of the search process, the selected articles were screened, first removing the duplicates and then choosing them according to the reading of their title and abstract. Texts with distance from the theme proposed by this research were excluded. After reading the full articles, all those that did not meet the inclusion criteria or that were characterized as a systematic review and had been erroneously selected were also excluded, and 10 studies were finally included.

After completing the article selection stages, the analysis and extraction of relevant information from each study was carried out, in order to make the subsequent data synthesis stage more effective and assertive. The information identified was: title of the article, year and place of publication, database, authors, objective of the study and main results found. Then, these data were gathered and organized, as shown in Table 1.

From the data collected, it was possible to synthesize the information found and analyze it, so that it could be organized in order to answer the questions that concern the objective of this systematic review. The studies and their results were compared, looking for the presence of agreements and disagreements between them, as well as the analysis of their outlines, strengths and limitations. This step was recorded in a descriptive way, focusing on clarifying the effect of curcumin and α-humulene nanoparticles on neuroinflammation and its possible repercussions on Alzheimer's disease. In addition, the lack of studies on the subject and the need for in-depth research that addresses the implications of nanoparticles of both compounds on the neurodegeneration and neuroinflammation characteristic of Alzheimer's disease was also highlighted.

Figure 1. Flowchart for capturing studies.
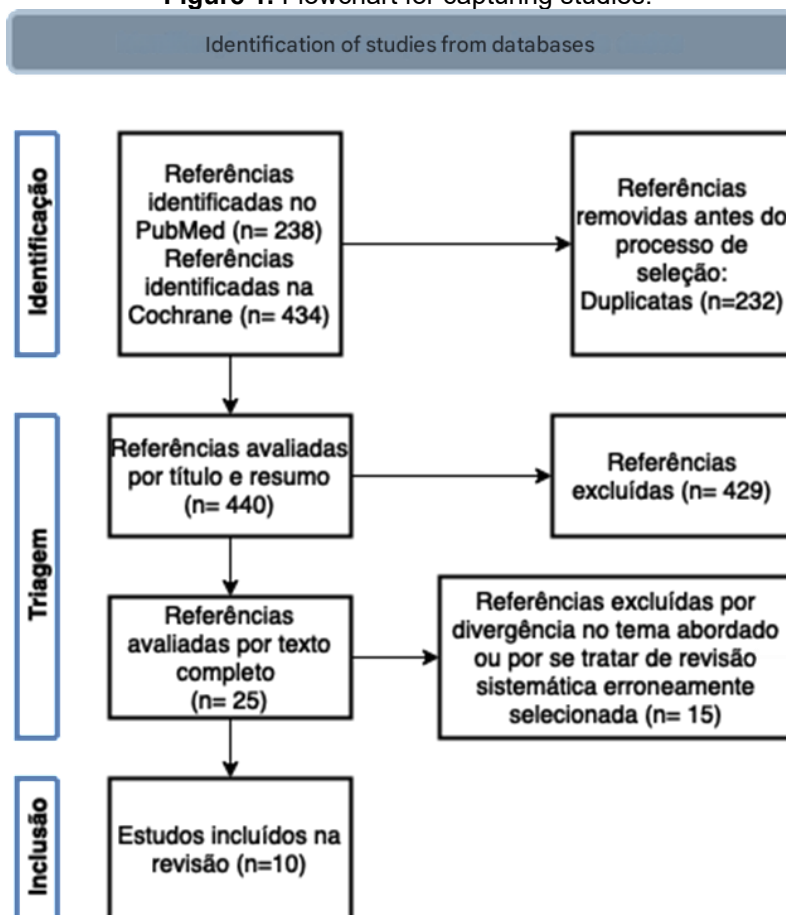
Source: OLIVEIRA, G. T. et al. (2024)

RESULTS

Table 1. Articles identified in the Cochrane and PubMed databases, according to their titles, year of publication, journal, authors, objective, and main results.

Article Title, Year and Place of Publication	Database	Authors	Objective of the Study	Key results
Micellar Curcumin: Pharmacokinetics and Effects on Inflammation Markers and PCSK-9 Concentrations in Healthy Subjects in a Double-Blind, Randomized, Active-Controlled, Crossover Trial. 2022. *Molecular Nutrition & Food Research.*	Cochrane	Grafeneder, J. *et al.*	To investigate and compare the bioavailability of micellar curcumin versus native curcumin and to verify the anti-inflammatory and concentration-lowering effects of proprotein convertase subtilisin/kexin type 9 (PCSK9).	Micellar curcumin has better oral bioavailability, but has no anti-inflammatory effects in this model, and achieved a possible reduction in plasma concentrations of PCSK9.
Curcumin and cognition: a randomised, placebo-controlled, double-blind study of community-dwelling older adults. 2016. *British Journal of Nutrition.*	Cochrane	Rainey-Smith, S. R., *et al.*	To investigate the ability of dietary supplementation for 12 months with curcumin to prevent cognitive decline in healthy older adults.	The curcumin-treated group did not show cognitive decline at 6 months, as did the placebo group. There were no other differences between the groups on clinical and cognitive measures.
Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial. 2018. *The American Journal of Geriatric Psychiatry.*	Cochrane	Small, G. W., *et al.*	Understand the implications of curcumin on the memory of non-demented adults and how it influences the accumulation of amyloid and tau protein in the brain.	Curcumin in its bioavailable and oral form led to significant memory and attention benefits, associated with decreased plaque buildup and protein tangles in brain regions related to mood and memory. This may be a result of curcumin's anti-inflammatory and anti-amyloid effect.
Systemic inflammatory regulators and risk of Alzheimer's disease: a bidirectional	Cochrane	Yeung, C. H. C.; Schooling, C. M.	To evaluate the effect of systemic inflammatory regulators on the development of Alzheimer's	Five specific systemic inflammatory regulators have been related to Alzheimer's

Mendelian-randomization study. 2021. *International Journal of Epidemiology.*			disease.	Disease, namely: Basic Fibroblastic Growth Factor, Granulocyte Colony-Stimulating Factor, Interferon gamma, Interleukin-13 and Interleukin-7. Another 41 inflammatory regulators were not associated with Alzheimer's disease.
Anti-inflammatory effects of α-humulene on the release of pro-inflammatory cytokines in lipopolysaccharide-induced THP-1 cells. 2024. *Cell biochemistry and biophysics.*	PubMed	Becker, L.; Holtmann, D.	To evaluate the possible anti-inflammatory effect of sesquiterpene α-humulene on the induction of lipopolysaccharides (LPS), focusing on the release of pro-inflammatory cytokines, such as IL-6, TNF-α and IL-1β, in human THP-1-derived macrophages.	α-humulene may be a promising natural alternative to established pharmaceuticals for the treatment of elevated IL-6 levels and chronic inflammation in humans.
CSF Cytokines in Aging, Multiple Sclerosis, and Dementia. 2019. *Frontiers in Immunology.*	PubMed	Hu, W. T., *et al.*	To analyze the levels of cytokines associated with innate immunity and different subtypes of T-helper cells in the cerebrospinal fluid (CSF) of healthy individuals of different age groups. In addition, to investigate how these cytokine levels change with aging and whether they are influenced by neurological disorders such as multiple sclerosis (MS) and Alzheimer's disease (AD).	Cytokine levels in CSF can be useful markers of brain inflammation and aging, and some neurological conditions can accelerate the change in inflammatory cytokines associated with aging.
Definition and quantification of six immune- and neuroregulatory	PubMed	Schipke, C.G., *et al.*	Quantify biomarkers related to immune and neuroregulatory	Under standardized conditions, concentrations of

serum proteins in healthy and demented elderly. 2019. *Neurodegenerative Disease Management.*			processes, and compare their concentrations between patients with Alzheimer's disease and healthy controls.	the biomarkers BDNF, IGF-1, TGF-β1, MCP-1, and IL-18 in blood serum differ significantly between patients with Alzheimer's disease and healthy controls, with the exception of VEGF. The analysis of the six biomarkers can be a useful tool for diagnosing dementia in Primary Care.
Dietary Supplementation with Curcumin Reduce Circulating Levels of Glycogen Synthase Kisane-3β and Islet Amyloid Polypeptide in Adults with High Risk of Type 2 Diabetes and Alzheimer's Disease. 2020. *Nutrients.*	PubMed	Thota, R. N., *et al.*	To investigate the effects of dietary supplementation with curcumin on key peptides related to insulin resistance in individuals at high risk of developing type 2 diabetes (T2D).	Curcumin supplementation reduced circulating levels of GSK-3β and IAPP compared to the placebo group. There was also a significant reduction in insulin resistance in the group that received curcumin. This suggests a novel mechanism by which curcumin may be used to lower the risk of type 2 diabetes and Alzheimer's disease by acting on markers related to insulin resistance.
Anti-Inflammatory Effects of Nanoparticles Containing Alpha-Humulene in a Model of Alzheimer's Disease. 2024. *Journal of Advances in Medicine and Medical Research.*	PubMed	Wendler, S. A., *et al.*	To evaluate the anti-inflammatory effect of treatment with nanoparticles containing alpha-humulene on pro- and anti-inflammatory cytokines, and also on markers of neuroinflammation such as Tau and GAPF.	Treatment with the nanoparticles containing alpha-humulene was effective in reducing inflammation associated with AD, indicating a therapeutic potential for this approach in the treatment of the disease.
Effects of	PubMed	Zahedi, H., *et al.*	To investigate the	Curcumin

| curcuminoids on inflammatory and oxidative stress biomarkers and clinical outcomes in critically ill patients: A randomized double-blind placebo-controlled trial. 2021. *Phytotherapy Research.* | | | impacts of curcuminoid supplementation on inflammatory and oxidative stress biomarkers, clinical outcomes, and nutritional status in patients with severe traumatic brain injury. | supplementation may have beneficial effects on inflammation, clinical outcome, and nutritional status of critically ill head injury patients. |

Source: OLIVEIRA, G. T. et al. (2024)

DISCUSSION

Uncontrolled inflammation participates in the pathology of Alzheimer's disease (ZAHEDI et al., 2021). However, senescence creates a naturally pro-inflammatory environment, making it difficult to separate the specific impact of Alzheimer's disease on cytokine increases (HU et al., 2019). The study by Hu et al. analyzed the cerebrospinal fluid (CSF) of 105 individuals between the ages of 23 and 86 years and found that inflammatory aging and Alzheimer's disease are associated with increased IP-10 and IL-10 in CSF.

Schipke et al. (2019) addressed the relevance ofThe aim of this study is to analyze the prevalence of blood biomarkers for early diagnosis and monitoring of Alzheimer's disease, since peripheral inflammation may precede symptoms. Biomarkers such as BDNF, IGF-1, TGF-β1, MCP-1, IL-18, and VEGF, identified by ELISA, are useful for early diagnosis and disease delay. However, systemic biomarkers such as FGF, G-CSF, IFN-γ, IL-13, and IL-7 are more related to after-effects rather than primary risk factors. Systemic inflammation may be a response to brain damage or to factors that trigger both inflammation and Alzheimer's pathology (YEUNG; SCHOOLING, 2021).

The study by Zahedi et al. (2021) investigated the effects of curcumin on biomarkers of inflammatory stressOxidative and oxidative in patients with traumatic brain injury (TBI), an inflammatory condition. Research has revealed a significant reduction in serum levels of IL-6, TNF-α, MCP-1, and CRP, suggesting that curcumin may modulate the inflammatory response in a beneficial way. Improvements in APACHEII and NUTRIC scores also indicated a positive impact of curcumin on inflammation and oxidative stress.

Grafeneder et al. (2022) confirmed that curcumin reduces cytokines pro-inflammatory by inhibiting the NF-kB pathway, corroborating the results of Zahedi et al. (2021). Although curcumin may also inhibit inflammation by binding to the TNF-α receptor, this effect was not observed in the study by Grafeneder et al., possibly due to the low dose and health status of the volunteers. The lack of effect on IL-6 has been attributed to these reasons.

Although oxidative stress is important in Alzheimer's disease (RAINEY-SMITH et al., 2016), Zahedi et al. (2021) found no effect of curcumin on the activity of antioxidant enzymes such as Glutathione peroxidase (GPx) and Superoxide Dismutase (SOD). These divergent results may be due to variations in curcumin formulations and dosages, analytical methods, or deficiency of cofactors such as zinc and copper (ZAHEDI et al., 2021).

Curcumin Shows Benefits Regarding β- Proteinsamyloid (Aß) and insoluble hyperphosphorylated tau (RAINEY-SMITH et al., 2016; SMALL et al., 2018), both by its direct action and by intestinal routes (SMALL et al., 2018). Thota et al. (2020) indicate that curcumin reduces the accumulation of Aß and tau in the brain by modulating insulin resistance, decreasing islet amyloid peptide levels and hyperactivity of Glycogen synthase kinase 3, resulting in reduced Aß aggregation and tau hyperphosphorylation.

Rainey-Smith et al. (2016) demonstrated that curcumin protects against declsuggesting a function of attenuating decline, rather than cognitive improvement. Small et al. (2018) corroborated that curcumin can prevent and slow neurodegeneration by improving verbal memory, short-term and long-term memory, and sustained attention with daily use. Future studies should consider longer follow-up periods and cohorts with greater cognitive decline to better assess the effect of curcumin (RAINEY-SMITH et al., 2016).

It is suggested that curcumin may also have antidepressant and anxiolytic effects, stabilizing mood. Scans with FDDNP-PET protocol showed a decrease in plaques and protein tangles in brain regions related to mood and memory, such as the amygdala and hypothalamus (SMALL et al., 2018).

Curcumin It is rapidly metabolized in the gut and liver, which reduces its oral absorption and bioavailability. The various formulations of curcumin vary in pharmacokinetics, leading to inconsistent results. The dose, the administration schedule, and factors such as the stage of neurodegeneration of the volunteers and differences in education between groups also influence the results (RAINEY-SMITH et al., 2016; SMALL et al., 2018).

Or α-humulene, in turn, has an anti-inflammatory effect by inhibiting the release of IL-6 in THP-1 cells, and may be a natural alternative to conventional anti-inflammatory drugs (BECKER; HOLTMANN, 2024). Although it reduced IL-6, it did not affect other pro-inflammatory cytokines and had a dose-dependent effect. In animal models of Alzheimer's disease, α-humulene reduced IL-6, IFN, and IL-12, and increased IL-10, suggesting potential to reduce neuroinflammation and improve disease symptoms (WENDLER et al., 2024). However, further studies are needed to better understand its impact on the inflammatory cascade (BECKER; HOLTMANN, 2024).

CONCLUSION

It can be concluded that curcumin has therapeutic potential in Alzheimer's disease, especially in reducing pro-inflammatory cytokines and oxidative stress. However, its efficacy is influenced by dosage and formulation, and the identification of an optimal therapeutic concentration still requires further research. The low bioavailability of curcumin, due to rapid metabolization and poor oral absorption, results in variable results.

Although studies in animal models indicate cognitive benefits, the evidence in humans is limited and inconsistent. Curcumin may inhibit the formation of plaques of β-amyloid and hyperphosphorylated tau, as well as modulating insulin resistance and offering antidepressant and anxiolytic benefits.

Or α-humulene, has promising anti-inflammatory properties, reducing cytokines such as IL-6 and IFN, but understanding its efficacy in Alzheimer's disease and its mechanism of action requires further investigation.

ACKNOWLEDGMENTS

REFERENCES

1. Abdul-Rahman, T., et al. (2024). Antioxidant, anti-inflammatory and epigenetic potential of curcumin in Alzheimer's disease. BioFactors, 50(1), 85–98. https://doi.org/10.1002/biof.2003

2. Becker, L., & Holtmann, D. (2024). Anti-inflammatory effects of α-humulene on the release of pro-inflammatory cytokines in lipopolysaccharide-induced THP-1 cells. Cell Biochemistry and Biophysics, 82(2), 1213–1224. https://doi.org/10.1007/s12013-024-01273-7

3. Donato, H., & Donato, M. (2019). Etapas na condução de uma revisão sistemática. Acta Médica Portuguesa, 32(3), 227–235. https://doi.org/10.20344/amp.11508

4. Grafeneder, J., et al. (2022). Micellar curcumin: Pharmacokinetics and effects on inflammation markers and PCSK-9 concentrations in healthy subjects in a double-blind, randomized, active-controlled, crossover trial. Molecular Nutrition & Food Research, 66(22), e2200139. https://doi.org/10.1002/mnfr.202200139

5. Griffiths, J., & Grant, S. G. N. (2023). Synapse pathology in Alzheimer's disease. Seminars in Cell & Developmental Biology, 139, 13–23. https://doi.org/10.1016/j.semcdb.2022.05.013

6. Hu, W. T., et al. (2019). CSF cytokines in aging, multiple sclerosis, and dementia. Frontiers in Immunology, 10, 480. https://doi.org/10.3389/fimmu.2019.00480

7. Knight, E., et al. (2023). The role of dietary antioxidants and their potential mechanisms in Alzheimer's disease treatment. Metabolites, 13(3), 438. https://doi.org/10.3390/metabo13030438

8. Maisam, M., et al. (2023). Alzheimer's disease: Mechanism, mutations, and applications of nano-medicine. Frontiers in Bioscience (Landmark Edition), 28(10), 258. https://doi.org/10.31083/j.fbl2810258

9. Rainey-Smith, S. R., et al. (2016). Curcumin and cognition: A randomised, placebo-controlled, double-blind study of community-dwelling older adults. British Journal of Nutrition, 115(12), 2106–2113. https://doi.org/10.1017/S0007114516001203

10. Schipke, C. G., et al. (2019). Definition and quantification of six immune- and neuroregulatory serum proteins in healthy and demented elderly. Neurodegenerative Disease Management, 9(4), 193–203. https://doi.org/10.2217/nmt-2019-0008

11. Small, G. W., et al. (2018). Memory and brain amyloid and tau effects of a bioavailable form of curcumin in non-demented adults: A double-blind, placebo-controlled 18-month trial. American Journal of Geriatric Psychiatry, 26(3), 266–277. https://doi.org/10.1016/j.jagp.2017.10.010

12. Thota, R. N., et al. (2020). Dietary supplementation with curcumin reduce circulating levels of glycogen synthase kinase-3β and islet amyloid polypeptide in adults with high risk of type 2 diabetes and Alzheimer's disease. Nutrients, 12(4), 1032. https://doi.org/10.3390/nu12041032

13. Twarowski, B., & Herbet, M. (2023). Inflammatory processes in Alzheimer's disease— Pathomechanism, diagnosis and treatment: A review. International Journal of Molecular Sciences, 24(7), 6518. https://doi.org/10.3390/ijms24076518

14. Wendler, S. A., et al. (2024). Anti-inflammatory effects of nanoparticles containing alpha-humulene in a model of Alzheimer's disease. Journal of Advances in Medicine and Medical Research, 36(1), 115–128. https://doi.org/10.9734/jammr/2024/v36i15354

15. Yeung, C. H. C., & Schooling, C. M. (2021). Systemic inflammatory regulators and risk of Alzheimer's disease: A bidirectional Mendelian-randomization study. International Journal of Epidemiology, 50(3), 829–840. https://doi.org/10.1093/ije/dyaa241

16. Zahedi, H., et al. (2021). Effects of curcuminoids on inflammatory and oxidative stress biomarkers and clinical outcomes in critically ill patients: A randomized double-blind placebo-controlled trial. Phytotherapy Research, 35(8), 4605–4615. https://doi.org/10.1002/ptr.7149