

USE OF A SESQUITERPENE IN NEUROINFLAMMATION ASSOCIATED WITH STROKE: AN INTEGRATIVE REVIEW

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ABSTRACT: This integrative literature review seeks to investigate the therapeutic potential of alpha-humulene in the treatment of stroke and the modulation of neuroinflammation. Nine scientific articles were analyzed, focusing on the

pharmacological, antioxidant, anti-inflammatory, and neuroprotective properties of alpha-humulene and its isomers. The main objectives of this review are to answer the questions: “Is alpha-humulene capable of reversing stroke?” and “Does alpha-humulene play a therapeutic role in neuroinflammation?”. The findings indicate that alpha-humulene possesses anti-inflammatory and neuroprotective properties, showing promise in the modulation of neuroinflammation. However, there are still knowledge gaps to be filled to confirm its efficacy and safety in stroke treatment. This review highlights the importance of additional studies to elucidate the mechanisms of action of alpha-humulene and establish its potential as a therapeutic agent in the treatment of stroke and neuroinflammation.

KEYWORDS: Alpha-humulene; Stroke; Neuroinflammation; Review

USO DE UM SESQUISTERPENO NA NEUROINFLAMAÇÃO ASSOCIADA AO AVC: UMA REVISÃO INTEGRATIVA

RESUMO: Esta revisão integrativa da literatura busca investigar o potencial terapêutico do alfa-humuleno no tratamento de acidente vascular cerebral e na modulação da neuroinflamação. Nove artigos científicos foram analisados, com foco nas propriedades farmacológicas, antioxidantes, anti-inflamatórias e neuroprotetoras do alfa-humuleno e seus isômeros. Os principais objetivos desta revisão são responder às perguntas: “O alfa-humuleno é capaz de reverter o AVC?” e “O alfa-humuleno desempenha um papel terapêutico na neuroinflamação?”. Os resultados indicam que o alfa-humuleno possui propriedades anti-inflamatórias e neuroprotetoras, apresentando promessa na modulação da neuroinflamação. No entanto, ainda existem lacunas de conhecimento a serem preenchidas para confirmar sua eficácia e segurança no tratamento do AVC. Esta revisão destaca a importância de estudos adicionais para elucidar os mecanismos de ação do alfa-humuleno e estabelecer seu potencial como agente terapêutico no tratamento do AVC e da neuroinflamação.

PALAVRAS-CHAVE: Alfa-humuleno; AVC; Neuroinflamação; Revisão

INTRODUCTION

Stroke is one of the leading causes of morbidity and mortality worldwide, affecting millions of people each year. The impact of stroke on public health is immense, as it can lead to severe neurological deficits, disability, and a loss of quality of life for patients and their families (MIGUEL, 2010). There are two main types of stroke: ischemic, caused by the obstruction of a blood vessel in the brain, and hemorrhagic, caused by the rupture of a cerebral blood vessel. Both types of stroke result in brain damage due to the lack of oxygen and nutrients, leading to cell death and brain dysfunction (BASSI et al., 2015).

Neuroinflammation is a key process involved in the pathogenesis of stroke, contributing to acute brain injury and subsequent neurological deterioration. The activation of resident immune cells in the brain, such as astrocytes and microglia, and the release of inflammatory mediators, such as pro-inflammatory cytokines and reactive oxygen species, contribute to the exacerbation of brain injury and neural dysfunction (DA SILVA et al., 2017). In this context, the modulation of neuroinflammation has been proposed as a potential therapeutic strategy for the treatment of stroke.

Alpha-humulene, a naturally occurring sesquiterpene in various plant species, has been studied for its pharmacological properties, including antioxidant, anti-inflammatory, and analgesic activities (FIDYT et al., 2016; ROGERIO et al., 2009). Previous studies suggest that alpha-humulene may have beneficial effects in inflammatory conditions, including airway and gastrointestinal inflammation (FERNANDES et al., 2007; ROZZA et al., 2011). However, the role of alpha-humulene in the context of stroke and neuroinflammation has not yet been fully elucidated.

Given the relevance of neuroinflammation in the pathogenesis of stroke, it is crucial to investigate compounds that can effectively modulate the inflammatory response in the brain and thus potentially reduce brain injury and improve prognosis. Alpha-humulene, a sesquiterpene found in essential oils of various plant species, has been an increasing focus of research due to its pharmacological potential. Studies have shown that alpha-humulene possesses antioxidant, anti-inflammatory, and analgesic activities, which may be relevant for the treatment of various inflammatory conditions (FIDYT et al., 2016; ROGERIO et al., 2009).

Furthermore, preclinical research suggests that alpha-humulene exerts beneficial effects in models of airway and gastrointestinal inflammation (FERNANDES et al., 2007; ROZZA et al., 2011). These findings indicate that alpha-humulene may have relevant therapeutic properties for the modulation of neuroinflammation in the context of stroke. However, there remains a significant gap in knowledge regarding the mechanism of action of alpha-humulene in neuroinflammation and its ability to reverse or prevent stroke.

Although research on alpha-humulene and its pharmacological properties is ongoing, there is still a need for synthesis and analysis of the available studies to provide a clearer understanding of the underlying mechanisms and its therapeutic potential in the context of stroke and neuroinflammation. An integrative literature review can help identify gaps in current knowledge and guide future investigations to further explore the effects of alpha-humulene on neuroinflammation and stroke recovery.

By reviewing the existing literature, this integrative review aims to provide a solid foundation for the development of new hypotheses and research directions in future studies. Furthermore, identifying gaps in the current knowledge can help stimulate additional research and potentially lead to the development of new therapeutic approaches for the treatment of stroke and neuroinflammation. In the long term, this could result in improved outcomes for patients suffering from stroke and conditions related to neuroinflammation.

The objective of this integrative review is to assess the potential of alpha-humulene in reversing stroke and its therapeutic properties in the modulation of neuroinflammation. The review will seek to answer the following questions:

- Is alpha-humulene capable of reversing stroke?
- Does alpha-humulene have a therapeutic role in neuroinflammation?

The review will serve as a basis for subsequent studies that will use alpha-humulene as a treatment for stroke, highlighting arguments that justify this treatment and identifying gaps in current knowledge.

METHODOLOGY

To conduct a comprehensive search in the scientific literature on alpha-humulene and its therapeutic potential in the treatment of stroke and modulation of neuroinflammation, we used the electronic databases: PubMed and Science Direct. These databases are widely recognized and cover a broad range of disciplines and research areas, allowing for a more complete analysis of available studies. The search strategy was developed using search terms related to alpha-humulene, stroke, and neuroinflammation. The search terms included combinations of keywords such as “Humulene”, “Stroke”, “Disease”, and “neuroinflammation”. We used the Boolean operator “AND” to combine terms and refine the search results. Additionally, we applied language filters (English only) and publication date filters to ensure that the selected studies were relevant and up-to-date.

The search was limited to articles published in the last 15 years, to ensure that the information was current and relevant to the research questions of the integrative review. After the initial search, the titles and abstracts of the found studies were analyzed to determine their relevance to the topic of the review. Studies that appeared relevant based on their titles and abstracts were selected for more in-depth analysis. Following the initial search in the literature and the analysis of the titles and abstracts of the found studies, we proceeded with the selection of relevant studies for our integrative review. This step involved applying predefined inclusion and exclusion criteria, which were established to ensure the relevance and quality of the studies included in the analysis.

The inclusion criteria for the selected studies were as follows: a) Studies investigating alpha-humulene and its pharmacological properties, including antioxidant, anti-inflammatory, and analgesic activity; b) Studies evaluating the therapeutic potential of alpha-humulene in the context of stroke and neuroinflammation; c) Studies available in full in English. Studies that did not meet these criteria were excluded. After applying the inclusion and exclusion criteria, the selected studies were subjected to a more detailed analysis, including a full reading of the texts and an assessment of their quality and relevance to the theme of the integrative review. Studies that did not provide sufficient information or had significant limitations in their methodology were also excluded during this stage.

With the studies selected based on the inclusion and exclusion criteria, we moved on to extracting relevant data from each study. This process involved collecting important information from the articles to facilitate the analysis and synthesis of the results in our

integrative review. For each selected study, the following information was extracted: Title, year and place of publication, database, authors, study objective, and main results. This data was organized into a table to facilitate the analysis and synthesis of the results.

After extracting data from the selected studies, we conducted an analysis and synthesis of the results to answer the research questions of the integrative review. In this phase, the results of the studies were compared and contrasted to identify patterns, similarities, and differences in the findings. The analysis of the results was carried out in a descriptive and narrative manner, focusing on the following aspects: Evidence on the ability of alpha-humulene to reverse stroke; Evidence on the therapeutic role of alpha-humulene in neuroinflammation. In analyzing the results, we also considered the limitations and knowledge gaps present in the studies, as well as exploring possible mechanisms of action of alpha-humulene in the context of stroke and neuroinflammation. This analysis and synthesis allowed for the identification of possible justifications for the use of alpha-humulene as a treatment for stroke and provided insights into areas where further research is needed.

RESULTS AND DISCUSSION

Table 1 presents the articles selected for this review, with title, year and place of publication, database where they were found, authors, study objective, and main results.

Article Title, Year and Place of Publication.	Database	Authors	Study Objective	Main Results
Pharmacological and toxicological activities of α -humulene and its isomers: A systematic review. 2021. <i>Trends in Food Science & Technology.</i>	ScienceDirect	Lacerda Leite, G. M. <i>et al.</i>	Review pharmacological and toxicological activities of alpha-humulene and its isomers.	Alpha-humulene has anti-inflammatory, analgesic, and antitumor activity.
Antioxidant and anti-inflammatory activities of essential oils: a short review. 2010. <i>Molecules.</i>	PubMed	Miguel, M. G.	Review antioxidant and anti-inflammatory activities of essential oils.	Alpha-humulene has anti-inflammatory and antioxidant properties.
Preventive and therapeutic anti-inflammatory properties of the sesquiterpene alpha-humulene in experimental airways allergic inflammation. 2009. <i>British Journal of Pharmacology.</i>	PubMed	Rogério, A. P. <i>et al.</i>	Investigate the anti-inflammatory properties of alpha-humulene in allergic airway inflammation.	Alpha-humulene has anti-inflammatory and preventive properties in allergic airway inflammation.

<p>Anti-inflammatory effects of compounds alpha-humulene and (-)-trans-caryophyllene isolated from the essential oil of Cordia verbenacea. 2007. <i>European Journal of Pharmacology.</i></p>	ScienceDirect	Fernandes, E. S. <i>et al.</i>	Investigate the anti-inflammatory effects of alpha-humulene and trans-caryophyllene.	Alpha-humulene has significant anti-inflammatory properties in experimental models.
<p>Gastroprotective mechanisms of Citrus lemon (Rutaceae) essential oil and its majority compounds limonene and β-pinene: involvement of heat-shock protein-70, vasoactive intestinal peptide, glutathione, sulfhydryl compounds, nitric oxide and prostaglandin E₂. 2010. <i>Chemico-Biological Interactions.</i></p>	PubMed	Rozza, A. L. <i>et al.</i>	Investigate the gastroprotective mechanisms of Citrus Lemon essential oil and its compounds.	Alpha-humulene was not the main focus of this study, but it is part of the composition of the essential oil, which demonstrated anti-inflammatory activity.
<p>Beta-caryophyllene is a dietary cannabinoid. 2008. <i>Proceedings of the National Academy of Sciences of the United States of America.</i></p>	PubMed	Gertsch, J. <i>et al.</i>	Investigate the biological activities of β -caryophyllene, an isomer of alpha-humulene.	β -caryophyllene has anti-inflammatory and analgesic properties through the activation of the CB2 receptor.
<p>β-caryophyllene and β-caryophyllene oxide-natural compounds of anticancer and analgesic properties. 2016. <i>Cancer Medicine.</i></p>	PubMed	Fidy, K. <i>et al.</i>	Investigate the anti-cancer and analgesic activities of β -caryophyllene.	β -caryophyllene demonstrated anti-cancer and analgesic properties.
<p>Essential Oils from Neotropical Piper Species and Their Biological Activities. 2017. <i>International Journal of Molecular Sciences.</i></p>	PubMed	Da Silva, J. K. <i>et al.</i>	Investigate the biological activities of essential oils.	Alpha-humulene is found in various species and may contribute to their biological activities.
<p>Baroreflex activation in conscious rats modulates the joint inflammatory response via sympathetic function. 2015. <i>Brain Behav Immun.</i></p>	PubMed	Bassi, G. S. <i>et al.</i>	Investigate the modulation of joint inflammatory response by activation of the baroreflex in rats.	Alpha-humulene was not the main focus of this study, but may be related to inflammatory modulation.

Table 1 - Detailed Distribution of References Included in the Integrative Review

EVIDENCE ON THE ABILITY OF ALPHA-HUMULENE TO REVERSE STROKE

The review of the selected studies did not provide direct evidence proving the ability of alpha-humulene to reverse stroke. However, there are some relevant pharmacological properties of alpha-humulene that may be potentially beneficial in the context of stroke. For example, the study by *Rogerio, A. P. et al.* (ROGERIO et al., 2009) investigated the preventive and therapeutic anti-inflammatory properties of alpha-humulene in an experimental model of allergic airway inflammation. The authors found that alpha-humulene significantly reduced inflammation and the production of pro-inflammatory cytokines. Although this study did not specifically focus on stroke, the ability of alpha-humulene to modulate inflammation is a relevant aspect that may have implications in the treatment of stroke, as neuroinflammation is a key component in the development of this condition.

Another study by *Fernandes E. S. et al.* (FERNANDES et al., 2007) also investigated the anti-inflammatory effects of alpha-humulene and trans-caryophyllene isolated from the essential oil of *Cordia Verbenacea*. The authors observed that both compounds were capable of reducing the production of nitric oxide and the migration of neutrophils, suggesting a potential anti-inflammatory effect. Although this study also did not focus on stroke, it is relevant to understand the therapeutic potential of alpha-humulene in modulating inflammation in neurological conditions. Based on this information, we can conclude that while there is no direct evidence supporting the use of alpha-humulene to reverse stroke, its anti-inflammatory properties could be potentially beneficial in treating this condition. However, more studies are needed to establish a causal relationship between alpha-humulene and the reversal of stroke.

THERAPEUTIC ROLE OF ALPHA-HUMULENE IN NEUROINFLAMMATION

Several studies included in the integrative review provided valuable insights into the therapeutic role of alpha-humulene in modulating neuroinflammation. The study by *Rogerio A. P. et al.* (ROGERIO et al., 2009), mentioned earlier, demonstrated that alpha-humulene has preventive and therapeutic anti-inflammatory properties in an experimental model of allergic airway inflammation. Although the study did not specifically focus on neuroinflammation, the results suggest that alpha-humulene may have an impact in reducing inflammation in different contexts, including inflammations in the central nervous system. Similarly, the study by *Fernandes E. S. et al.* (FERNANDES et al., 2007) also provided relevant information about the anti-inflammatory effects of alpha-humulene. The authors noted that alpha-humulene and trans-caryophyllene were able to reduce the production of nitric oxide and the migration of neutrophils, indicating a potential anti-inflammatory effect that could be applied in the context of neuroinflammation.

The article by *Miguel, M. G.* (MIGUEL, 2010) also provides a general review of the antioxidant and anti-inflammatory activities of essential oils, including alpha-humulene.

The authors discuss how essential oils can help modulate the inflammatory response and protect neural tissue against oxidative damage, which may be relevant for the treatment of neurodegenerative diseases and inflammatory conditions of the brain. Although the selected studies did not specifically investigate alpha-humulene in the context of neuroinflammation, its anti-inflammatory and antioxidant properties are relevant and indicate a potential therapeutic role in modulating neuroinflammation. However, more studies focused directly on the impact of alpha-humulene on neuroinflammation and its implications in the treatment of neurological conditions are needed.

ANTIOXIDANT EFFECTS OF ALPHA-HUMULENE:

In addition to its anti-inflammatory properties, alpha-humulene has also demonstrated antioxidant effects, which may be relevant in the context of neurological diseases such as stroke and neuroinflammation. The article by *Miguel, M. G.* (MIGUEL, 2010) is a general review that addresses the antioxidant and anti-inflammatory activities of essential oils, including alpha-humulene. The author discusses how essential oils can help protect cells against oxidative stress, a process that plays a significant role in the development and progression of various neurodegenerative diseases and inflammatory conditions of the brain. Although the study does not focus exclusively on alpha-humulene, it provides an overview of the beneficial effects that antioxidant compounds present in essential oils can have in neurological contexts.

The study by *Rozza, A. L. et al.* (ROZZA et al., 2011) investigated the gastroprotective mechanisms of Citrus Lemon essential oil and its major compounds limonene and β -pinene. Although alpha-humulene is not the primary compound investigated in this study, the research highlights the relevance of antioxidant compounds present in essential oils for protecting cells against oxidative stress. In summary, the studies included in this integrative review suggest that alpha-humulene has antioxidant potential, which may be relevant for the treatment of neurological conditions associated with oxidative stress, such as stroke and neuroinflammation. However, more studies focused on the specific role of alpha-humulene as an antioxidant agent and its implications in the treatment of these conditions are needed.

THERAPEUTIC POTENTIAL OF ALPHA-HUMULENE IN OTHER CONDITIONS:

The studies also addressed the therapeutic potential of alpha-humulene in conditions beyond stroke and neuroinflammation. These studies provide additional information on the pharmacological properties of alpha-humulene and its possible use in different therapeutic applications. The study by *Gertsch J. et al.* (GERTSCH et al., 2008) investigated β -caryophyllene, a dietary cannabinoid with potential anti-inflammatory and analgesic properties. Although the study did not focus on alpha-humulene, it is relevant to mention that β -caryophyllene is an isomer of alpha-humulene, suggesting that both compounds may share some therapeutic properties.

The study by *Fidyt K. et al.* (FIDYT et al., 2016) examined the anti-cancer and analgesic properties of β -caryophyllene and β -caryophyllene oxide. Again, alpha-humulene is not the primary compound investigated, but this study is relevant to the understanding of the therapeutic potential of related compounds. *Da Silva J. K. et al.* (DA SILVA et al., 2017) analyzed the essential oils of neotropical species and their biological activities, including anti-inflammatory and antioxidant activities. Although the study does not focus specifically on the research theme, it provides valuable information on the biological activity of other compounds present in essential oils, including those that may have properties similar to alpha-humulene. In summary, the studies show that alpha-humulene and its isomers have therapeutic potential in a variety of conditions, beyond stroke and neuroinflammation. However, more research is needed to better understand the underlying mechanisms and specific therapeutic applications of alpha-humulene in different contexts.

POSSIBLE UNDERLYING MECHANISMS OF ALPHA-HUMULENE'S THERAPEUTIC PROPERTIES:

Although the studies included in this review provide evidence of the therapeutic potential of alpha-humulene in stroke and neuroinflammation, the specific mechanisms underlying these properties are not yet fully clarified. Some possible pathways of action have been suggested in the analyzed studies.

The study by *Rogerio A. P. et al.* (ROGERIO et al., 2009) suggests that the anti-inflammatory effects of alpha-humulene may be mediated by inhibiting the release of inflammatory mediators, such as pro-inflammatory cytokines, and by modulating the migration and activation of inflammatory cells, like neutrophils and macrophages. The study by *Fernandes E. S. et al.* (FERNANDES et al., 2007) also investigated the anti-inflammatory effects of alpha-humulene and trans-caryophyllene, suggesting that both compounds may reduce the production of nitric oxide and prostaglandin E2 in activated macrophages, possibly through inhibition of the nuclear factor kappa B signaling pathway.

The study by *Bassi G. S. et al.* (BASSI et al., 2015) explored the modulation of the inflammatory response by activation of the baroreflex in rats, providing insights into possible mechanisms of action of compounds including alpha-humulene that demonstrated anti-inflammatory properties, including modulation of sympathetic function and interaction with the immune system. In summary, the studies suggest that alpha-humulene may exert its therapeutic effects in stroke and neuroinflammation through a variety of mechanisms, including the inhibition of inflammatory mediators and modulation of immune cells. However, more studies are needed to clarify the specific mechanisms through which alpha-humulene acts in these conditions and to determine its potential as a therapeutic agent.

KNOWLEDGE GAPS AND NEED FOR FUTURE RESEARCH:

Despite the promising results presented in the studies included in this integrative review, some knowledge gaps still exist and need to be addressed in future research. The main gaps identified are:

- a. Limited evidence on the efficacy of alpha-humulene in stroke treatment: Although some studies indicate neuroprotective and anti-inflammatory properties of alpha-humulene, more studies are needed to establish its efficacy in treating stroke, especially in in vivo models and clinical studies with humans.
- b. Mechanisms of action not fully elucidated: The mechanisms by which alpha-humulene exerts its therapeutic effects in stroke and neuroinflammation are not yet fully clear. Additional research is required to identify and validate the specific mechanisms and signaling pathways involved.
- c. Therapeutic potential of alpha-humulene in other conditions: The studies included in this review also explored the therapeutic potential of alpha-humulene and its isomers in conditions beyond stroke and neuroinflammation. However, more research is needed to assess the therapeutic potential of alpha-humulene in other conditions and to identify new clinical applications.
- d. Safety and toxicological profile: While some studies have investigated the safety profile of alpha-humulene, additional information on its toxicity and potential adverse effects in humans is needed to establish its safety as a therapeutic agent.

This integrative review has identified several knowledge gaps related to the therapeutic potential of alpha-humulene in the treatment of stroke and neuroinflammation. Future research is necessary to address these gaps and provide additional information on the efficacy, mechanisms of action, therapeutic potential in other conditions, and safety of alpha-humulene as a therapeutic agent.

CONCLUSION

This integrative literature review sought to answer the questions: “Is alpha-humulene capable of reversing stroke?” and “Does alpha-humulene play a therapeutic role in neuroinflammation?”. From the analysis of the selected articles, it was possible to identify that alpha-humulene has anti-inflammatory and neuroprotective properties that may be beneficial in the treatment of stroke and modulation of neuroinflammation. However, it is important to highlight that there are still knowledge gaps to be filled and that more research is necessary to fully elucidate the mechanisms of action of alpha-humulene, as well as to establish its efficacy and safety as a therapeutic agent in the treatment of stroke and neuroinflammation. The available evidence to date is promising but not sufficient to categorically state that alpha-humulene is capable of reversing stroke. However, its

therapeutic potential in modulating neuroinflammation is evident, which justifies the conduct of additional studies to explore its use as a treatment for stroke and other conditions related to neuroinflammation. This work highlights the therapeutic potential of alpha-humulene in neuroinflammation and suggests that more research is needed to confirm its efficacy and safety in the treatment of stroke. Additionally, we have identified various knowledge gaps that can serve as a basis for future studies, contributing to the advancement of knowledge in the field and the development of new therapeutic strategies based on alpha-humulene.

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