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Cardiovascular effects of free or complexed linalool with β-cyclodextrin: a focus for antihypertensive action

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LITERATURE REVIEW

ABSTRACT

Investigating the cardiovascular effects of natural compounds, such as linalool, has aroused interest due to the potential impact on cardiovascular health. Linalool, a component present in several essential oils, has demonstrated promising pharmacological properties, including antihypertensive activity. However, its bioavailability and efficacy can be influenced by complexation with β-cyclodextrin, a strategy frequently used to improve the solubility and stability of bioactive substances. This study aimed to carry out a systematic review of the literature, exploring the cardiovascular effects of free linalool and linalool complexed with β-cyclodextrin. Objective: To investigate the cardiovascular effects of free linalool and linalool complexed with β-cyclodextrin, with emphasis on the antihypertensive action, through a systematic review of the literature. Methodology: The review was conducted according to PRISMA guidelines. The PubMed, Scielo and Web of Science databases were consulted, using the descriptors "linalool", "β-cyclodextrin", "cardiovascular effects", "antihypertensive" and "complexation". The inclusion criteria covered studies published in the last 10 years, focusing on in vivo experiments, clinical trials and systematic reviews. Articles unrelated to the topic, duplicate studies and those without peer review were excluded. Results: They revealed that linalool, when complexed with β-cyclodextrin, presented greater bioavailability and stability, enhancing its antihypertensive action. In vivo studies have demonstrated a significant reduction in blood pressure in hypertensive animal models. Furthermore, the complexation positively influenced the gastrointestinal absorption of linalool. These findings suggest that the complexed formulation may represent an effective approach to improving the cardiovascular effects of linalool. Conclusion: The systematic review highlights the relevance of complexing linalool to β-cyclodextrin as a strategy to enhance its antihypertensive effects. Understanding these mechanisms can contribute to the development of more effective pharmaceutical formulations in the management of hypertension, promoting advances in cardiovascular therapy.

Keywords: "linalool", "β-cyclodextrin", "cardiovascular effects", "antihypertensive" and "complexation".

RESUMO

A investigação dos efeitos cardiovasculares de compostos naturais, como o linalol, tem despertado interesse devido ao potencial impacto na saúde cardiovascular. O linalol, um componente presente em diversos óleos essenciais, demonstrou propriedades farmacológicas promissoras, incluindo atividade anti-hipertensiva. No entanto, sua biodisponibilidade e eficácia podem ser influenciadas pela complexação com β-ciclodextrina, uma estratégia frequentemente utilizada para melhorar a solubilidade e estabilidade de substâncias bioativas. Este estudo se propôs a realizar uma revisão sistemática da literatura, explorando os efeitos cardiovasculares do linalol livre e complexado à β-ciclodextrina. Objetivo: Investigar os efeitos cardiovasculares do linalol livre e complexado à β-ciclodextrina, com ênfase na ação anti-hipertensiva, por meio de uma revisão sistemática da literatura. Metodologia: A revisão foi conduzida conforme as diretrizes do PRISMA. As bases de dados PubMed, Scielo e Web of Science foram consultadas, utilizando os descritores "linalol", "β-ciclodextrina", "efeitos cardiovasculares", "anti-hipertensivo" e "complexação". Os critérios de inclusão abrangeram estudos publicados nos últimos 10 anos, com foco em experimentos in vivo, ensaios clínicos e revisões sistemáticas. Foram excluídos artigos não relacionados ao tema, estudos duplicados e aqueles sem revisão por pares. Resultados: Revelaram que o linalol, quando complexado à β-ciclodextrina, apresentou maior biodisponibilidade e estabilidade, potencializando sua ação anti-hipertensiva. Estudos in vivo demonstraram redução significativa da pressão arterial em modelos animais hipertensos. Além disso, a complexação influenciou positivamente a absorção gastrointestinal do linalol. Esses achados sugerem que a formulação complexada pode representar uma abordagem eficaz para melhorar os efeitos cardiovasculares do linalol. Conclusão: A revisão sistemática destaca a relevância da complexação do linalol à β-ciclodextrina como estratégia para potencializar seus efeitos anti-hipertensivos. A compreensão desses mecanismos pode contribuir para o desenvolvimento de formulações farmacêuticas mais eficazes no manejo da hipertensão, promovendo avanços na terapêutica cardiovascular.

Palavras-chave: "linalol", "β-ciclodextrina", "efeitos cardiovasculares", "anti-hipertensivo" e "complexação".

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INTRODUCTION:

Research into the cardiovascular effects of natural compounds has stood out as a promising area in the search for effective therapeutic strategies for the management of hypertension. In this context, linalool, a component present in several essential oils, emerges as an agent of interest, mainly due to its potential antihypertensive activity. Recent studies have been dedicated to elucidating the direct impact of linalool on reducing blood pressure, revealing its role as a promising candidate in the field of cardiovascular health.

Furthermore, an innovative approach has been explored to improve the efficacy of linalool: complexation with β-cyclodextrin. This strategy aims to overcome challenges related to the compound's solubility and stability, two critical aspects that can directly influence its bioaccessibility. β-cyclodextrin, in turn, acts as a kind of molecular vehicle, interacting with linalool to form a more stable and soluble structure. This molecular interaction not only preserves the therapeutic properties of linalool, but also optimizes its delivery to the body, standing out as an innovative approach in the quest to improve the effectiveness of bioactive compounds.

In this scenario, the combination of the potential antihypertensive action of linalool with the β-cyclodextrin complexation strategy raises relevant questions regarding the synergistic impacts of these elements on cardiovascular health. This review aims to explore in detail the cardiovascular effects of linalool, both in its free and complexed forms, highlighting the nuances of these interactions and providing a comprehensive overview of the therapeutic potential of these innovative approaches in the management of hypertension.

The search for innovative strategies in the field of cardiovascular health has led to the investigation of the effects of linalool, a component present in several essential oils, on reducing blood pressure. In addition to this intrinsic antihypertensive property, studies indicate that the complexation of linalool to β-cyclodextrin plays a crucial role in improving its bioavailability. However, it is in the practical expression of these phenomena that fascinating nuances emerge.

The enhanced bioavailability of linalool, when complexed with β-cyclodextrin,

becomes evident in in vivo experiments, especially in hypertensive animal models. Consistent results reveal that this formulation promotes a significant reduction in blood pressure, suggesting superior efficacy compared to linalool in its free form. This phenomenon is not limited only to antihypertensive effects, extending to the gastrointestinal absorption of complexed linalool, where an optimization is observed that potentially favors its cardiovascular efficacy.

These findings highlight the relevance of the complex interaction between linalool and β-cyclodextrin in the context of cardiovascular health. The improved absorption and efficacy demonstrated in hypertensive animal models suggest that complexation represents a promising strategy to optimize the delivery of linalool to the body, enhancing its beneficial effects. This study, by exploring these aspects in detail, aims to offer a comprehensive view of the synergistic impacts of complexation and linalool in the management of hypertension, thus contributing to the advancement of scientific knowledge in this area.

To investigate, through a systematic review of the literature, the cardiovascular effects of linalool, both in its free form and complexed with β-cyclodextrin, focusing on the antihypertensive action. Analyze studies published in the last 10 years in the PubMed, Scielo and Web of Science databases, using the descriptors "linalool", "β-cyclodextrin", "cardiovascular effects", "antihypertensive" and "complexation". Comprehensively explore the results of these studies, highlighting enhanced bioavailability, effects in hypertensive animal models, and influence on gastrointestinal absorption, to provide in-depth insight into the potential contribution of this approach to the effective management of hypertension.

METHODOLOGY

The systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist, using the descriptors "Linalol", "Ciclodextrin", "Cardiovascular Effects", "Anti-Hypertensive" and "Complexation". The databases selected for the bibliographic search were PubMed, Scielo and Web of Science, with a time frame of studies published in the last 10 years (2012-2023). The inclusion criteria included studies that addressed the cardiovascular

effects of linalool, both in its free form and complexed with β-cyclodextrin, with a focus on peer-reviewed articles. In vivo experiments, clinical trials and systematic reviews were considered, as long as they were available in full text.

On the other hand, the exclusion criteria aimed to eliminate duplicate studies, research not related to the scope of the review, publications without peer review and works without access to the full text. Furthermore, studies published before the determined period of 10 years (before 2013) were excluded.

The selection process involved an initial search in databases with the specified descriptors, followed by screening according to the inclusion and exclusion criteria. The detailed analysis of the selected articles, aligned with the objectives outlined by the PRISMA checklist, provided relevant information for the systematic review on the cardiovascular effects of linalool.

RESULTS

15 articles were selected. Linalool, a monoterpene widely found in essential oils from plants such as lavender and basil, has attracted considerable interest due to its antihypertensive potential. Clinical studies and in vivo experiments indicate that linalool exerts vasodilatory effects, promoting a reduction in peripheral vascular resistance and, therefore, a reduction in blood pressure. This phenomenon is associated with linalool's ability to modulate the activity of adrenergic receptors and influence the release of nitric oxide, a key mediator in the regulation of vascular tone.

In the clinical context, the application of linalool as an antihypertensive agent may represent a valuable alternative, especially in patients seeking more natural therapeutic approaches. Furthermore, the relative safety of the compound, derived from plant sources, contributes to its attractiveness as a potential medication for controlling hypertension. However, it is imperative that future research explore the precise mechanisms by which linalool exerts its antihypertensive effects, as well as establish clinically effective administration and dosing protocols.

The complexation of linalool to β-cyclodextrin emerges as an innovative strategy to optimize its pharmacological properties. β-cyclodextrin, an annular cavity composed of glucose units, provides a favorable environment for the inclusion of linalool, resulting

in the formation of a stable complex. This molecular interaction has the potential to improve the solubility of linalool, a property that is often challenging in compounds of a lipophilic nature, and, therefore, increase its bioavailability.

The significant improvement in the bioavailability of linalool complexed with β-cyclodextrin may have direct implications for therapeutic efficacy, especially in the cardiovascular context. Experiments demonstrate that this complexation can modulate the controlled release of linalool, prolonging its effects and reducing pharmacokinetic variability. Furthermore, the potential to decrease gastrointestinal irritation associated with the administration of free essential oils suggests a more tolerable and clinically viable approach. In this sense, continued research into the effects of this complexation provides crucial insights for the development of pharmaceutical formulations that maximize the therapeutic potential of linalool in the cardiovascular context.

The issue of linalool bioavailability plays a central role in understanding its cardiovascular effects. Studies reveal that the complexation of linalool to β-cyclodextrin not only improves the compound's solubility, but also significantly impacts its absorption and distribution in the body. The molecular interaction between linalool and β-cyclodextrin results in the formation of a complex that, when administered, demonstrates a more controlled release of the compound, prolonging its presence in the blood circulation.

Improving the bioavailability of linalool is essential to enhance its beneficial effects on the cardiovascular system. The ability to achieve more stable therapeutic concentrations in blood plasma may be decisive in the clinical efficacy of the compound. In this sense, an in-depth understanding of the mechanisms through which complexation influences the bioavailability of linalool is essential to direct therapeutic strategies that optimize the delivery of the compound to the body, maximizing its antihypertensive effects.

Investigating the effects of linalool, especially when complexed with β-cyclodextrin, in hypertensive animal models provides valuable insights into its clinical applicability. In vivo studies consistently demonstrate a significant reduction in blood pressure in these animals when administered complexed linalool. Mechanisms such as

vasodilation and modulation of the adrenergic response have been suggested as responsible for these effects, highlighting the complexity of the underlying molecular interactions.

The efficacy observed in hypertensive animal models suggests a significant therapeutic potential of linalool, supporting the hypothesis that its complexation with β-cyclodextrin can optimize these effects. However, it is crucial to consider variations between animal models and humans, as well as the need for broader clinical investigations. In-depth understanding of the effects of linalool in hypertensive conditions provides a solid basis for future application of these findings in clinical practice, with the prospect of contributing to new hypertension treatment strategies.

The complexation of linalool to β-cyclodextrin is not limited to improving bioavailability; it exerts a notable influence on the gastrointestinal absorption of the compound. Recent research indicates that β-cyclodextrin acts as a stabilizing agent, providing a gradual release of linalool throughout the gastrointestinal tract. This characteristic is particularly relevant as it minimizes possible adverse effects associated with the rapid absorption of essential oils, often recognized for causing gastrointestinal irritation.

By optimizing the gastrointestinal absorption of linalool, complexation to β-cyclodextrin not only enhances the compound's efficacy in the cardiovascular system but also improves clinical tolerability. The controlled release of linalool throughout the digestive tract not only reduces the risk of gastrointestinal discomfort, but also offers the advantage of maintaining more stable plasma concentrations over time. This innovative approach, when considering not only therapeutic efficacy but also clinical tolerability, positions β-cyclodextrin complexation as a promising strategy in the search for more effective and well-tolerated antihypertensive treatments.

In the context of research on linalool, an in-depth analysis of the mechanisms through which this compound exerts its cardiovascular effects proves to be crucial. Scientific studies point to linalool's ability to modulate the activity of adrenergic receptors, triggering vasodilatory responses that directly impact blood pressure. Furthermore, investigations indicate the participation of linalool in regulating the production of nitric oxide, an essential mediator in vascular homeostasis.

Understanding these mechanisms provides valuable insights for the development of more targeted therapeutic strategies. The precise elucidation of the molecular and cellular events triggered by linalool contributes to the identification of specific therapeutic targets, paving the way for more effective pharmacological interventions. Therefore, continued research into the mechanisms of cardiovascular action of linalool is crucial to inform future advances in antihypertensive therapy.

Comparative investigation between linalool in its free form and when complexed with β-cyclodextrin represents an essential aspect in research into its cardiovascular effects. Scientific studies have highlighted notable differences in the pharmacokinetic and pharmacodynamic properties between the two forms of linalool. Complexation with β-cyclodextrin, in addition to improving solubility and bioavailability, influences the controlled release of the compound, standing out as a key variable in determining its physiological effects.

This thorough comparison is crucial to guide the choice of the most effective and safe form of linalool to be used in clinical applications. The analysis of parameters such as absorption rate, tissue distribution and biological half-life provides valuable information for informed decision making. Therefore, the comparison between the free and complexed forms of linalool not only enriches the understanding of its cardiovascular effects, but also outlines strategies to optimize its clinical applicability.

When evaluating the clinical relevance of linalool, it is imperative to consider its practical applicability in the context of cardiovascular treatment. The extent of its antihypertensive efficacy, especially when complexed with β-cyclodextrin, stands out as a crucial point. Comprehensive analysis of existing research should include assessment of the safety, long-term efficacy, and potential side effects associated with clinical administration of linalool. The integration of these aspects provides a more holistic view of the clinical relevance of linalool, supporting informed therapeutic decisions.

The search for safer and more effective antihypertensive treatments encourages investigation of the clinical relevance of linalool, especially in comparison with conventional therapeutic options. Careful consideration of available data, including results of clinical trials and epidemiological studies, is essential to determine the

positioning of linalool in the therapeutic armamentarium. Understanding its safety and efficacy profile in real clinical scenarios is a crucial step in evaluating the relevance of linalool as an antihypertensive treatment option.

The development of pharmaceutical formulations that incorporate linalool, especially when complexed with β-cyclodextrin, is an area of strategic research with direct implications for the clinical applicability of the compound. The search for efficient delivery vehicles that preserve the stability and bioavailability of linalool is crucial for translating laboratory discoveries into practical applications. The development of formulations that guarantee the controlled release of linalool over time can optimize therapeutic efficacy and minimize unwanted effects.

Pharmaceutical formulations that incorporate linalool complexed with β-cyclodextrin must be carefully designed to meet clinical administration requirements. The selection of excipients, encapsulation methods and forms of administration plays a fundamental role in the success of these formulations. Furthermore, rigorous assessment of chemical and physical stability during storage is essential to ensure compound integrity throughout the drug product's life cycle. The development of effective pharmaceutical formulations represents a critical link between scientific discoveries and their practical implementation, thus shaping the potential of linalool in cardiovascular therapeutics.

When analyzing future perspectives for research into the cardiovascular effects of linalool, it is essential to consider the continuity of investigations in several aspects. A crucial area for exploration is in precisely identifying the molecular mechanisms underlying the antihypertensive effects of linalool, both in its free and complexed forms. Understanding the signaling pathways, cellular interactions and molecular targets involved provides a solid basis for developing more targeted therapeutic strategies.

Additionally, advancement in research should direct efforts towards more comprehensive clinical studies, exploring the response of linalool in human populations under different cardiovascular health conditions. The inclusion of trials that consider variables such as age, gender, and cardiovascular comorbidities is essential to generalize findings and inform clinical practices more comprehensively. Furthermore, evaluating the potential of linalool in combination with existing therapies and its application at

different stages of hypertension represent promising avenues to maximize its clinical impact. Ultimately, future perspectives should aim for a holistic understanding of the cardiovascular effects of linalool, integrating molecular, experimental and clinical approaches to consolidate its role in the effective management of hypertension.

CONCLUSION

In summary, the studies reviewed provide a comprehensive understanding of the cardiovascular effects of linalool, especially when complexed with β-cyclodextrin. The results indicate that linalool has remarkable antihypertensive potential, exerting vasodilatory effects and modulating the adrenergic response. Complexation with β-cyclodextrin emerges as a promising strategy to improve the solubility and bioavailability of linalool, in addition to influencing its gastrointestinal absorption.

The clinical relevance of these findings is highlighted by linalool's ability to reduce blood pressure, positioning it as a potential alternative for the treatment of hypertension. The controlled release of linalool throughout the gastrointestinal tract, conferred by complexation with β-cyclodextrin, not only improves its cardiovascular efficacy, but also improves its clinical tolerability, minimizing gastrointestinal discomfort.

Investigating the mechanisms of cardiovascular action of linalool, especially its interaction with adrenergic receptors and regulation of nitric oxide production, provides a solid basis for the development of more targeted therapeutic interventions. The comparison between the free and complexed forms of linalool highlights the importance of considering pharmacokinetic variables when choosing the most effective form for clinical applications.

In conclusion, the studies analyzed contribute significantly to the understanding of the therapeutic potential of linalool, pointing to possible clinical applications in the management of hypertension. However, it is imperative to highlight the continued need for robust clinical research and more comprehensive trials to validate these findings and establish linalool as an effective and safe antihypertensive agent.

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