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Review Article

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

Efeitos cardiovasculares de linalol livre ou complexado à β-ciclodextrina: um foco para ação anti-hipertensiva

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ABSTRACT: Introduction: The monoterpene linalool (LIN) has several pharmacological activities, including as an antihypertensive, but it has solubility problems due to its lipophilic character. Thus, stabilization strategies and improvement of pharmacokinetic and pharmacodynamic parameters have been studied, such as the formation of inclusion complexes with cyclodextrins (CDs). **Objective**: The purpose of this review is to gather information about the cardiovascular effects of LIN and to evaluate the possibility of using CDs to improve the biological properties of LIN. **Methodology:** This literature review covered articles between 1998 and 2022, collected in the PUBMED, SciELO, LILACS and MEDLINE databases. **Results:** In normotensive rats, LIN induced hypotension associated with tachycardia while in hypertensive rats, it reduced blood pressure without changing heart rate. LIN has a direct action on the vasculature promoting vasorelaxation and improving cardiac function. Interestingly, complexation of LIN with β-CDs improved the antihypertensive activity of the monoterpene. **Conclusion**: It was evidenced in this review the pharmacological potential of LIN as a hypotensive, vasorelaxant and antihypertensive agent. Furthermore, there is evidence that it is possible to improve the antihypertensive effect of LIN with the use of inclusion systems with CDs, but additional studies on this topic should be carried out.

KEYWORDS: Hypertension; Cardiovascular diseases; Linalool; Beta-Cyclodextrins; Cyclodextrin.

RESUMO: Introdução: O monoterpeno linalol (LIN) apresenta várias atividades farmacológicas, inclusive como anti-hipertensivo, porém, apresenta problemas de solubilidade devido ao seu caráter lipofílico. Dessa forma, estratégias de estabilização e melhoria de parâmetros farmacocinéticos e farmacodinâmicos vem sendo estudadas, como a formação de complexos de inclusão com ciclodextrinas (CDs). **Objetivo:** O objetivo desta revisão é reunir informações sobre os efeitos cardiovasculares do LIN e avaliar a possibilidade do uso de CDs para melhorar as propriedades biológicas do LIN. **Metodologia:** Esta revisão de literatura abrangeu artigos no período entre 1998 e 2022, coletadas nas bases de dados PUBMED, SciELO, LILACS e MEDLINE. **Resultados:** Em ratos normotensos, o LIN induziu hipotensão associada à taquicardia, enquanto em ratos hipertensos, reduziu a pressão arterial sem alterar a frequência cardíaca. O LIN tem ação direta sobre a vasculatura promovendo relaxamento vascular e melhora da função cardíaca. Interessantemente, a complexação de LIN com β-CDs melhorou a atividade anti-hipertensiva do monoterpeno. **Conclusão:** Foi evidenciado nesta revisão o potencial farmacológico do LIN como agente hipotensor, relaxante vascular e anti-hipertensivo. Além disso, há evidências que é possível melhorar o efeito anti-hipertensivo do LIN com a utilização de sistemas de inclusão com CDs, porém, estudos adicionais sobre este tema deverão ser realizados.

PALAVRAS-CHAVE: Doenças Cardiovasculares; Hipertensão arterial; Linalol; Ciclodextrina; Beta- Ciclodextrinas.

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INTRODUCTION

Cardiovascular diseases (CVD) are among the leading causes of death worldwide. In 2019, it is estimated that 17.9 million people died from CVD[1]. Arterial Hypertension (AH) is a main risk factor for CVD. AH stage 1 is clinically defined by systolic blood pressure (SBP) values between 130-139 mmHg or diastolic blood pressure (DBP) between 80-89 mmHg, and AH stage 2 by SBP ≥ 140 mmHg or DBP ≥ 90 mmHg after repeated examinations[2], according to the guidelines of the American College of Cardiology and the American Heart Association ACC/AHA.

In Brazil, AH is a chronic disease that most affects the population. The Longitudinal Study of Adult Health (ELSA-Brazil), conducted between 2008-2010, evaluated 15.105 employees of teaching and research institutions in six Brazilian cities, aged between 35-74 years, demonstrating that 35.8% of the participants were classified as hypertensive, with a higher prevalence among men[3]. Black populations are more prone to resistant and nocturnal hypertension; even more, they develop hypertension and target organ damage at an earlier age. Such differences are attributed to genetic factors, but socioeconomic and lifestyle-related factors may be associated[4].

Blood pressure (BP) regulation is multifactorial and involves different mechanisms. For instance, there is coordinated action among the cardiovascular, endocrine, renal, and neural systems, which collectively modulate the determinants of BP, including cardiac output and peripheral vascular resistance[5]. CVD mortality increases progressively with elevated and sustained BP levels starting from 115/75 mmHg, following a linear and continuous manner[6]. Therefore, taking measures to prevent the progression of hypertensive conditions is crucial. This involves raising awareness among the population about the significance of disease management and risk factors to prevent potential complications in target organs, such as heart, kidney, or brain diseases in the future[7].

According to the most recent guidelines on hypertension and antihypertensive therapy by the International Society of Hypertension (2020), specifically the Global Hypertension Practice Guidelines, pharmacological treatment is recommended for individuals with BP in the range of 140-159/90-99 mmHg for high-risk patients, and for those with BP ≥160/100 mmHg. For patients with BP in the range of 140-159/90-99 mmHg and low to medium risk, pharmacological treatment should be considered if BP remains uncontrolled after 3-6 months of lifestyle changes. The first-line drug classes for hypertension treatment include thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists[4].

Despite the wide array of drugs available to control BP, resistant hypertension is reported in approximately 10% of the hypertensive population[4]. Resistant hypertension is defined as BP that remains uncontrolled (≥140/≥90 mmHg) despite treatment with three or more antihypertensive drugs or as hypertension that is controlled (<140/90 mmHg) but requires four or more antihypertensive drugs[8]. Therefore, the pursuit of new therapeutic alternatives for the treatment of AH is essential.

Plants are important sources of biologically active compounds, many of which have been used as a basis for the development of new drugs. Among the plant-derived compounds, we emphasize the essential oils with diverse biological actions[9]. Terpenes are the main constituents of essential oils, comprising mainly monoterpenes (about 90% of volatile oils) and sesquiterpenes, each with a wide range of structures and functions. Monoterpenes can be divided into three subgroups: acyclic (e.g., linalool), monocyclic (e.g., α-terpineol), and bicyclic (e.g., camphor). Additionally, each subgroup can be classified into unsaturated hydrocarbons, alcohols, aldehydes, ketones, lactones, and tropolones[10].

Monoterpenes have several pharmacological properties, such as anti-inflammatory, antinociceptive[11,12], vasorelaxant[13], anxiolytic[14,15], antidepressant[16,17], sedative[18,19] and antihypertensive[20,21] actions.

The scientific literature has a large number of studies about the biological effects of different monoterpenes on the cardiovascular system, for example, carvacrol[20], citronellol[22], cineole[23], linalool[21], menthol[24], rotundifolone[13], thymol[25], and limonene[26]. Some experimental studies have evaluated the cardiovascular effects of monoterpenes *in vivo*. For example, intravenous administration of (+)-alpha-pinene, (-)-beta-pinene, (+/-)-citronellol, and (+/-)-linalool (1, 5, 10, and 20 mg/kg, i.v.) was able to induce hypotension and tachycardia in normotensive and non-anesthetized rats[27].

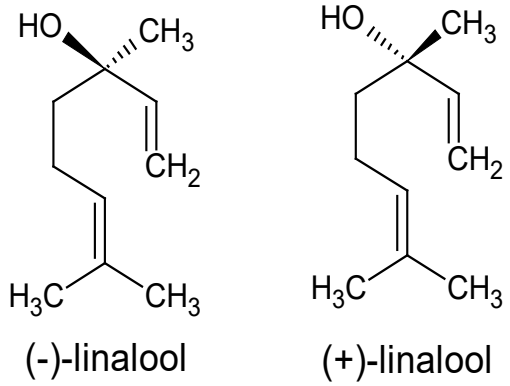
Linalool (LIN) is primarily found in plants widely used in Brazilian cuisine, such as bergamot (*Citrus bergamia*), jasmine (*Jasminum auriculatum*), basil (*Ocimum gratissimum*), and cilantro (*Coriandrum sativum*)[28]. Chemically named 3,7-dimethyl-1,6-octadien-3-ol, LIN is an open-chain tertiary alcoholic monoterpene[29], with a molecular weight of 154.25 g/mol, a density of 0.862 g/mL, and molecular formula $C_{10}H_{18}O$. It has a boiling point of 199º C and water solubility of 1.589 g/L[30].

This monoterpene exhibits promising pharmacological activities, such as antinociceptive and anti-inflammatory actions, and it reduces allodynia in neuropathic pain models[31–33]. Additionally, it demonstrates sedative activity through central mechanisms involving glutamatergic modulation[34]. LIN is naturally found in two stereoisomers, 3R-(-)-LIN and 3S-(+)-LIN, each with distinct odors, chemical properties, and biological effects[33,35]. Its chemical structure can be seen in Figure 1.

LIN is a widely used substance in the pharmaceutical and food industries, where it serves as a fixative for

fragrances and a component in perfumery products. Additionally, it has a long history of consumption in infusions and decoctions of natural products within traditional medicine for its anti-inflammatory, antinociceptive, and antihypertensive properties[29,31,36].

While the properties of LIN are well-documented, it does have limitations due to its high volatility and liposolubility[9]. For this reason, controlled release systems have been used for decades to improve the biological properties of many substances and compounds, often utilizing cyclodextrins (CDs). A CD-based formulation is expected to improve drug release at the active site, ensure controlled release, and reduce potential side effects[37]. In light of these considerations, this review aims to conduct a literature survey on LIN's therapeutic potential in the cardiovascular system and explore possible enhancements in its biological activities when combined with CDs.



Font: Camargo; de Vasconcelos, 2015[28].
Figure 1 - Chemical struture of (-) -linalool and (+) -linalool

METHODOLOGY

This literature review, covering 1998 to 2022, was conducted through electronic searches in the databases PUBMED, SciELO, LILACS, and MEDLINE. The search employed these keywords: linalool AND cardiovascular AND biological activities, linalool AND vasorelaxant, linalool AND antihypertensive, linalool AND hypotensive, linalool AND cardiovascular AND cyclodextrins, linalool AND cardiovascular AND inclusion-linalool complex, linalool AND vascular, linalool AND heart attack, linalool AND cyclodextrins, in both English and Portuguese. Original articles that assessed the use of pure and complex linalool in treating hypertension and other related biological effects were selected.

RESULTS

We initially found 179 articles across PUBMED, MEDLINE, SciELO, and LILACS using the specified descriptors. To ensure the relevance of the selected articles, we excluded reviews and those unrelated to the research theme based on a review of their titles and abstracts. Additionally, we removed any duplicated articles found across the platforms. Ultimately, this process led to the selection of 14 articles for a comprehensive review. The process of searching for articles is shown in Figure 2.

Table 1 presents the description of the 14 articles selected for analysis regarding the type of study, tissue and/or species used, optical isomers of LIN and/or LIN-β-CD used, and biological effects observed.

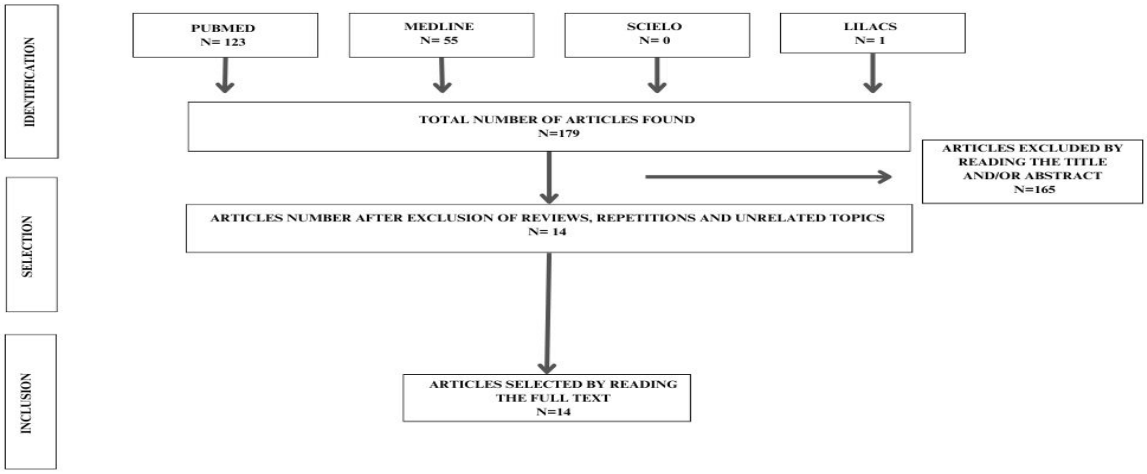


Figure 2 - Flowchart of the search and selection of articles.

Table 1 – Effects of pure or complexed LIN with β-CD.

Type of Study	Tissue and/or Species	Optical isomers of LIN and/or LIN-β-CD	Effects	References
In vivo	Human	Odor of jasmine tea and R- (-)-LIN	Bradycardia and sedative effect	[38]
In vivo	Human	R - (-) -LIN	Relaxing and soothing	[39]
In vivo	Human	S - (-) - LIN	Increased blood pressure and heart rate	[39]
In vivo	Wistar Rats	(±) -LIN	Tachycardia-associated hypotension	[27]
Ex vivo	Aortic artery of Wistar rats	(±) -LIN	Vascular relaxation	[40]
In vivo	Wistar Rats	RS - (±) -LIN	Hypotension associated with tachycardia	[29]
In vivo	Rats with renovascular hypertension 2 kidneys 1 clip (2R1C)	RS - (±) -LIN	Hypotension with no change in heart rate	[29]
Ex vivo	Mesenteric artery of Wistar rats	RS - (±) -LIN	Vascular relaxation	[29]
Ex vivo	Aortic artery of Wistar rats	(+) -LIN	Vascular relaxation via channel block for Ca^{2+}	[41]
In vivo	Wistar Rats	*A. rosaeodora* essential oil 87.7% (±) -LIN	Hypotension, bradycardia	[36]
Ex vivo	Aortic artery of Wistar rats	*A. rosaeodora* essential oil 87.7% (±) -LIN	Vascular relaxation	[36]
Ex vivo	C57BL/6 mouse aorta	(-) -LIN	Vascular relaxation	[42]
In vivo	Sprague-Dawley rats (isoproterenol-induced myocardial infarction model)	LIN	Improvement in heart function	[43]
In vitro	Fetal rat cardiomyocytes (H9c2 cells)	LIN	Decreased necrosis and cellular apoptosis	[43]
In vivo	SHR Rats	(-) -LIN	Antihypertensive	[21]
In vivo	SHR Rats	(-) -LIN- β-CD	Prevention of hypertension and reduction of blood pressure	[21]
In vivo	Wistar rats (Uremia-induced vascular calcification)	LIN	Reduction of calcium and potassium deposition in the aorta	[44]
In vivo	Sprague-Dawley rats (LAD ligation-induced myocardial infarction)	LIN	Antiarrhythmic effect	[45]
In vitro	Thoracic aortic smooth muscle cells of rats (A7r5)	LIN	Reduction of cell proliferation and migration induced by angiotensin II	[46]
In vivo and ex vivo	Wistar rats (isoproterenol-induced infarction model)	LIN	Cardioprotective effect in an infarction model	[47]

DISCUSSION

Among the main cardiovascular actions of LIN described in the evaluated studies, we can highlight the following: vascular relaxing effect[29, 36, 40-42], bradycardic action[36], hypotensive effect[27,29,36], and antihypertensive effect[21] (Table 1).

Studies evaluating the cardiovascular activity of (±) LIN at doses of 1, 5, 10, and 20 mg/kg i.v. demonstrated hypotensive and tachycardic effects induced by LIN in non-anesthetized normotensive rats[27,29]. In rats with renovascular hypertension, specifically the 2 kidneys 1 clip (2R1C) model, (±) LIN reduced BP without affecting heart rate. In the superior mesenteric artery of rats, LIN appears to exert its effect by reducing the influx of Ca^{2+} and the release of Ca^{2+} from intracellular stores sensitive to inositol triphosphate (IP_3) and caffeine. This suggests that vascular relaxation results from a direct effect of LIN on vascular smooth muscle[29].

In isolated mouse aortic preparations, (-)-LIN (500 μM) was able to relax arteries precontracted with PGF2α (3 μM). This effect involves different mechanisms of action, dependent and independent of the endothelium, such as activation of soluble guanylate cyclase, activation of potassium channels, and inhibitory action on calcium influx[42] (Table 1). (+)-LIN also inhibited contractile responses by blocking L-type voltage-gated calcium channels and raised nitric oxide levels in aortic segments of rats contracted with phenylephrine, as well as reducing hypercontraction of these segments when pre-exposed to arsenic and mercury[41]. In addition, in preparations *ex vivo* of mesenteric artery rings of rats, the (RS)-(±)-LIN (6.4 μM - 6.4 mM) showed potent spasmolytic activity on phenylephrine-induced contractions. This action was independent of the presence of functional vascular endothelium and involved the blockade of voltage-sensitive calcium channels[29] (Table 1).

Since long-term hypertension can lead to changes in the structure of blood vessels, compromising homeostasis, Liang et al.[46] evaluated the effect of treatment with LIN (50, 100, and 150 μM) on the proliferation and migration of smooth muscle cells induced by angiotensin II (1 nM – 1 μM). The authors demonstrated that the treatment reduced cell proliferation and migration in a concentration-dependent manner.

Some studies have demonstrated the effect of LIN on myocardial ischemia. Zheng et al.[43] observed that the LIN (10, 20, and 40mg/Kg) promoted cardioprotection in an acute myocardial infarction model. Similar results were observed with LIN at 50 mg/kg or 100 mg/kg47 doses. In addition, the LIN (50 mg/kg or 100 mg/kg) was able to decrease the incidence of arrhythmias in this model[45]. When evaluating the cell death of cardiomyocytes in the ischemia/reperfusion model, treatment with LIN promoted a decrease in necrosis and cellular apoptosis[43].

Clinically, LIN has already been used in human studies to evaluate the influence of chirality on its effects. These studies demonstrated that S-(-)-LIN caused an increase in blood pressure and heart rate, while R-(-)-LIN induced punctual bradycardia when inhaled[39] (Table 1).

The (-)-LIN administration showed antinociceptive and anti-inflammatory effects in different experimental models, attenuating pain induced by different stimuli. Its antinociceptive effect seems to involve the inhibition of glutamatergic, dopaminergic, and opioid transmission without excluding the participation of potassium channels, since the antihyperalgesic effect may result from the indirect stimulation of these three families of receptors, which are coupled to proteins capable of inducing the opening of potassium channels[32].

Other effects have also been described for LIN, such as anti-leishmaniasis action[48] and antimicrobial, and can be used to combat microorganisms that cause nosocomial infections[35,49]. In addition to these properties, hypothermic and sedative actions were observed when the LIN was inhaled for about 1h. These effects did not impair motor function, demonstrating that olfactory stimulation by inhalation of jasmine tea, rich in LIN, induces bradycardia and a sedative effect in humans[38]. Other studies have also demonstrated an anxiolytic and sedative effect of inhalation of 1% and 3% of (±)-LIN in mice, suggesting efficient biological properties by inhalation[15,50].

It is important to note that previous studies have evaluated the toxicity of oral LIN in ten rats (5/sex). The lethal 50% oral dose (LD50) administered by intubation was observed to be 2,790 mg/kg. Deaths occurred between 4 and 18 h after administration, and the main clinical sign observed was ataxia, observed soon after treatment[30,51]. In addition, the effects of LIN administration by gavage were evaluated in pregnant Sprague-Dawley rats. The authors concluded that LIN is not toxic to the development of rats when used at doses up to 1000 mg/kg/day[52]. The studies selected in this review used a very low dose compared to the lethal dose and the dose capable of causing toxicity to fetal development.

However, a major general limitation in relation to the evaluation of the biological effects of LIN is the marked volatility and liposolubility of this compound[9]. Complexation with CDs is an important strategy to increase the solubility and protection of the host molecules from the degradation of the external environment. CDs can increase the dissociation rate, physicochemical stability, and bioavailability, optimizing activity and therapeutic properties and reducing side effects and adverse reactions[53–55]. In addition, CDs are considered safe and virtually toxic-free[56].

Studies comparing the antinociceptive activity of (-) - LIN and β-CD complexed LIN (LIN-β-CD) showed antinociceptive activity in mice with chronic inflammatory muscle hyperalgesia at all doses tested. However, LIN-β-CD showed prolonged activity in relation to the isolated substance, suggesting that complexation significantly

improved therapeutic action[11,57].

Our research group evaluated the antihypertensive activity of (-) - LIN and (-) - LIN- β-CD at a dose of 50mg/kg/day, administered orally, in spontaneously hypertensive rats (SHR). The (-)-LIN (50mg/Kg/day) showed an antihypertensive effect, and the inclusion complex (-)-LIN- β-CD (50 mg/kg) was able to delay the development of hypertension in SHR and reduced BP when compared to the vehicle group[21] (Table 1).

Although the promising properties of CD are already well described in the literature, few studies relate formulations with such complexes in cardiovascular diseases. Thus, the study of CD formulations with antihypertensive drugs is a promising field of research.

CONCLUSIONS

The present study gathered several articles in the literature that evaluated the effects of LIN on the cardiovascular system using *in vivo* and *ex vivo* techniques. The analysis of the studies indicates that LIN may be a promising molecule in the treatment of hypertension. Multiple studies have shown that LIN has vasodilator, hypotensive, bradycardic, cardioprotective, antiarrhythmic, and antiproliferative effects. Additionally, LIN exhibits anti-inflammatory activity, which can be an ally in antihypertensive therapy, reducing the inflammation involved in the pathophysiology of hypertension. Furthermore, it was observed that LIN complexed with CD has its pharmacological activity potentiated.

Given the above, we can conclude that monoterpene LIN has pharmacological potential for the treatment of hypertension. However, there is a need for further studies on the effect of LIN-β-CD as an antihypertensive agent.

Authors' Contribution: *Daniele Santana de Brito* - conception and/or design of the study, data collection, data analysis and interpretation, writing of the manuscript, approval of the final version to be published. *Raiana dos Anjos Moraes* - conception and/or design of the study, data collection, critical review of the manuscript, correction of references and final edition, approval of the final version to be published. *Rafael Leonne Cruz de Jesus*- conception and/or design of the study, data collection, critical review of the manuscript, approval of the final version to be published. *Fênix Alexandra de Araújo*- conception and/or design of the study, critical review of the manuscript, approval of the final version to be published. *Liliane Barreto da Silva*- conception and/or design of the study, critical review of the manuscript, approval of the final version to be published. *Gabriela Brandão de Carvalho Lima*- critical review of the manuscript, approval of the final version to be published. *Samuel Barbosa Camargo*- critical review of the manuscript, approval of the final version to be published. *Isnar Pereira Lima da Silva*- critical review of the manuscript, approval of the final version to be published. *Darízy Flávia Silva*- conception and/or design of the study, critical review of the manuscript, approval of the final version to be published.

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