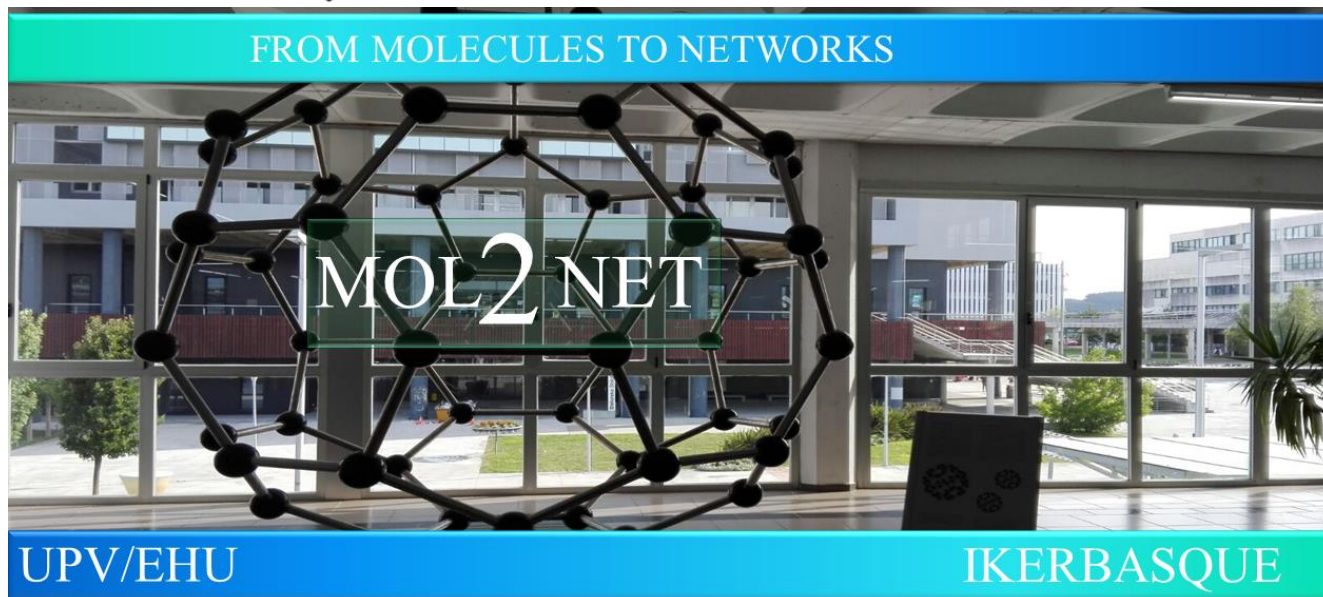




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Alpha-pinene toxicity correlations

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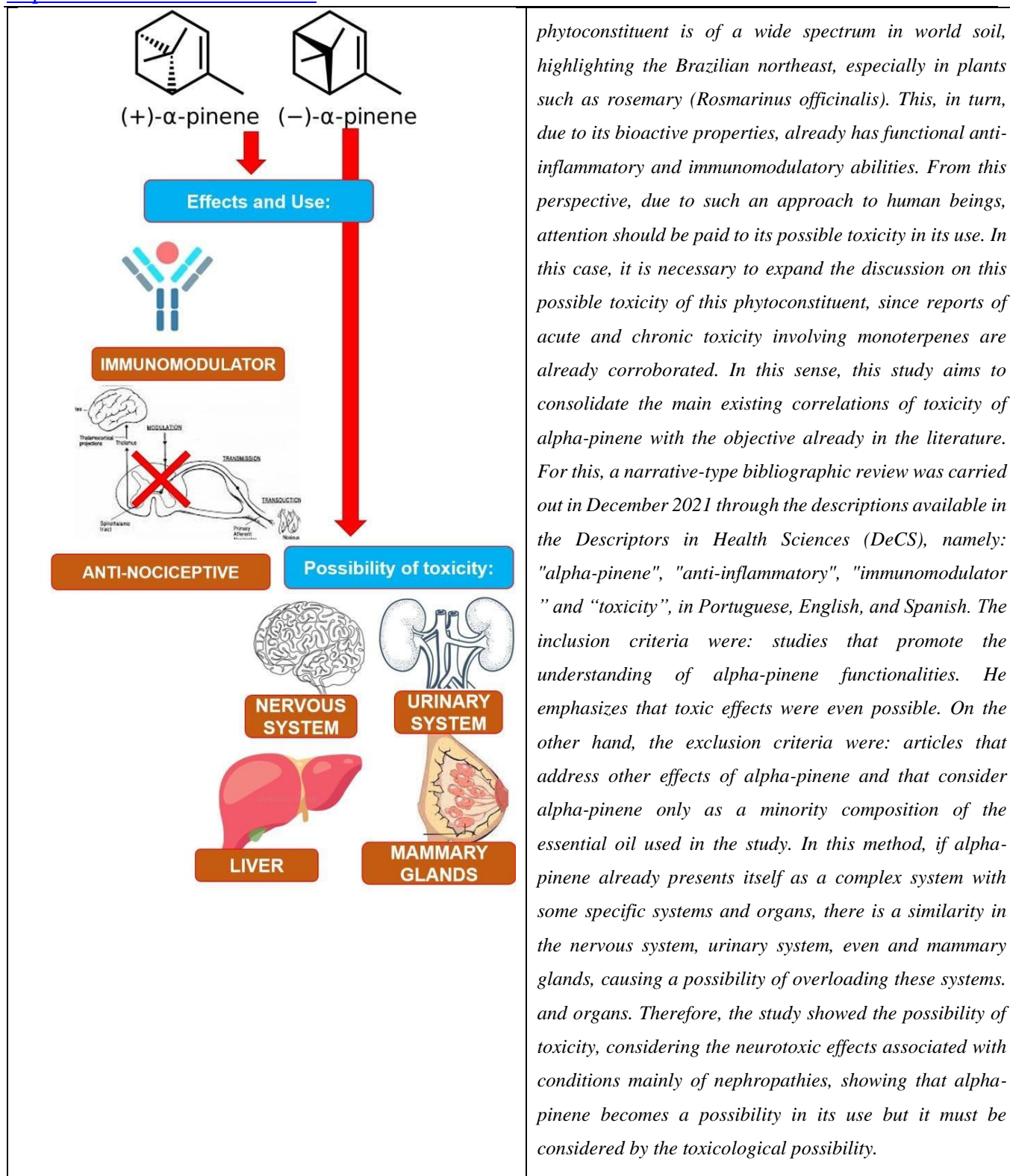
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Graphical Abstract

Abstract.

With the development of the chemical industry, phytoconstituents have become bioactive targets with pharmacological functionalities, highlighting the use, of herbicide and aromatherapy. In this spectrum, alpha-pinene stands out, an organic compound of the terpenoid class and subclass of monoterpenes. The presence of this



phytoconstituent is of a wide spectrum in world soil, highlighting the Brazilian northeast, especially in plants such as rosemary (*Rosmarinus officinalis*). This, in turn, due to its bioactive properties, already has functional anti-inflammatory and immunomodulatory abilities. From this perspective, due to such an approach to human beings, attention should be paid to its possible toxicity in its use. In this case, it is necessary to expand the discussion on this possible toxicity of this phytoconstituent, since reports of acute and chronic toxicity involving monoterpenes are already corroborated. In this sense, this study aims to consolidate the main existing correlations of toxicity of alpha-pinene with the objective already in the literature. For this, a narrative-type bibliographic review was carried out in December 2021 through the descriptions available in the Descriptors in Health Sciences (DeCS), namely: "alpha-pinene", "anti-inflammatory", "immunomodulator" and "toxicity", in Portuguese, English, and Spanish. The inclusion criteria were: studies that promote the understanding of alpha-pinene functionalities. He emphasizes that toxic effects were even possible. On the other hand, the exclusion criteria were: articles that address other effects of alpha-pinene and that consider alpha-pinene only as a minority composition of the essential oil used in the study. In this method, if alpha-pinene already presents itself as a complex system with some specific systems and organs, there is a similarity in the nervous system, urinary system, even and mammary glands, causing a possibility of overloading these systems. and organs. Therefore, the study showed the possibility of toxicity, considering the neurotoxic effects associated with conditions mainly of nephropathies, showing that alpha-pinene becomes a possibility in its use but it must be considered by the toxicological possibility.

Introduction

With the unbridled advance of antimicrobial resistance, as well as the difficulty of indiscriminate use of antimicrobials, phytoconstituents become a pharmacological alternative due to their structural variety and physicochemical properties (1). In addition, herbicidal, anti-inflammatory, analgesic, and aromatherapy activities are also mentioned in this diversified set of functionality (2). However, it is still

corroborated to understand the beneficial and harmful benefits of these compounds in the long term, since their interaction with the human organism is not fully understood (3).

In this context, the use of alpha-pinene, from the terpenoid class and monoterpene subclass, stands out. This, in turn, presents itself as an important non-biological alternative, since its bioactive reactions permeate the possibility of exploring actions that may be an alternative benefit of benefit to the general population (3). It is noteworthy that the prominence of Brazilian plants is not only in its isolated biochemical properties but also in its abundance as a component of its several main sources in Brazilian soil in a heterogeneous way, mainly in the northeast, such as rosemary officinalis (*Rosmarinus officinalis*) (4).

In this sense, alpha-pinene gains notoriety given the need to understand its repercussions, highlighting a possible picture of structural damage at the cellular and genetic level, inferring changes in the homeostasis of the organism. This is exalted in the face of the applicability of essential oils to understand the molecular effects they may present, since such phytoconstituents may project a permanence of up to five days in the body (2). Furthermore, reports are considered that monoterpenes, alpha-pinene class, have already conditioned some degree of acute and/or chronic toxicity (6).

Thus, alpha-pinene activities may be an alternative in the treatment of several aspects, however, it is necessary to elucidate the toxic impacts at the cellular level that this molecule can cause (7) (8). From this perspective, it is essential to understand how such substances may interact with the organism and its possible repercussions, especially at the neurological level, since alpha-pinene contains such an affinity (9).

Therefore, this narrative review aims to demonstrate the functionality of alpha-pinene as a possible pharmacological aspect and its correlation with its toxic effects.

Materials and Methods

This study is a bibliographic review of the narrative type of qualitative approach with a descriptive objective from a bibliographic procedure. This method is based on the need to report the already known functionalities of alpha-pinene and relate them to their possible toxic effects.

The research took place in December 2021 through the following databases: Virtual Health Library (BVS) and PubMed. For this, descriptors relevant to the theme were selected from the Descriptors in Health Science (DeCS) database, namely: “alpha-pinene”, “anti-inflammatory”, “immunomodulator” and “toxicity” in Portuguese, English, and Spanish. . It is noteworthy that to format the search formula, Boolean operators were used, considering AND, OR and parentheses. Then, the articles were selected in the following sequence: articles available in full and indexed, without a time frame, and in Portuguese, English, and Spanish, respectively.

Inclusion criteria were: studies that promote the understanding of alpha-pinene functionalities, specifically anti-inflammatory and immunomodulatory effects related to pharmacological potentials. It is noteworthy that research that referred to possible toxic effects was also included. On the other hand, articles that addressed other effects of alpha-pinene and that considered it only with a minority composition of the essential oil used in the study, as well as opinion articles and duplicate studies, were excluded.

The titles and abstracts were read, and the articles classified as eligible were considered in their entirety, in which the data characterized as essential to meet the objective of this investigation were extracted. The results were grouped into two categories: biochemical possibilities of alpha-pinene and reported toxicity in specific systems and organs with the use of this phytoconstituent. Finally, it is noteworthy that there was no need for submission to the Research Ethics Committee because it is not private data or data with living beings.

Results and Discussion

Natural products stand out due to their biochemical versatility. This fact aims to integrate and consolidate the pharmacological and biological benefits of these phytoconstituents present, mainly due to their complexity in the chemical constitution and, consequently, their possible action in specific molecular targets (10).

The emphasis that the use of natural products has in therapy has been understood since the dawn of humanity, especially in the field of phytotherapy. Its relevance today is perceived in the face of its range of biochemical interactions when in contact with a living organism, due to its structural chemical versatility. This fact aims to integrate and consolidate the pharmacological and biological benefits of plant secondary metabolites, also known as phytoconstituents, with investigations that aim at their possible action on specific molecular targets (10)

In this scenario, alpha-pinene is considered a phytoconstituent with therapeutic properties that could be beneficial to the pharmaceutical industry, as well as to the treatment of existing pathologies. This enantiomer is a subclass of terpenes, called monoterpenes, considered an active isomer of pinene and arising from the racemic mixture of this compound, mainly found in essential oils of pine and eucalyptus (11). In fact, in addition to its active isomerism, alpha-pinene stands out for being a bicyclic hydrocarbon, which allows considerable stability in its molecule, as well as for containing double bonds between the carbons and the cyclobutane ring.

In this aspect, some studies already corroborate the existence of antimicrobial activity, neuromodulatory and immunomodulatory effects in humans, considering its main activity in oxidative phosphorylation and/or in the electron transport chain. Furthermore, antinociceptive, antioxidant, inhibition of pro-inflammatory factors, and modulation of the expression of apoptotic factors are

considered (12) (13) (14). Screening of antibacterial activity identified growth inhibition of *Escherichia coli* ATCC 25922 by (+) – α – pinene, with an average of 16 mm of inhibition halo at a concentration of 160 μ L/mL (15).

In addition to these studies, there is a research carried out and published in volume 29 of the *Journal of Stroke & Cerebrovascular Diseases*, in 2020, which showed the decrease in the expression of pro-inflammatory cytokines, such as TNF-alpha and IL-1b, with the use of alpha-pinene. A rearrangement of molecules involved in apoptosis was also reported, highlighting the decrease in the expression of the pro-apoptotic protein BAX, which causes permeability of the mitochondrial outer membrane leading to the release of cytochrome C, and increased expression of BCL-2, an anti-inflammatory polypeptide. apoptotic that regulates the amount of oxygen free radicals, preventing oxidative stress (14).

However, despite the perceptions involved in the biochemical reactions of alpha-pinene, studies support the understanding of the toxicological effect of the administration of this compound, since there are already reports involving the acute and chronic toxicity of monoterpenes, highlighting the neurotoxic effects. for the individual (9) (2). This toxicity is based on molecular interactions with the physiological components of the organism, considering that these projections are in front of both the isolated phytoconstituent in question, as well as this compound with other phytoconstituents synergistically existing in essential oils.

In addition to these neurotoxic reactions, a study corroborates the existence of possible liver and kidney toxicity, highlighting the occurrence of hepatomegaly associated with nephropathy. To arrive at these results, researchers performed the inhalation administration of alpha-pinene in male and female mice and rats for 3 months. They also identified a significant decrease in sperm count, compared to the control group, in animals that chronically used the phytoconstituent (16).

Therefore, both by the effects already reported at the neurological level, it is considered that the effects of this possible toxicity are constituted both at the cellular and genetic level, permeating the consequences of neural categories, such as a convulsive crisis (14). It is noteworthy that this affinity to neural categories permeates irreversible consequences since the cells of the nervous system are stable cells, that is, they do not undergo renewal.

Conclusions

In this sense, alpha-pinene stands out for being involved in significant reactions in the handling of pathologies that mainly affect the nervous system and are inflammatory. However, this beneficial comes up against the ignorance of its long-term reactions, since the possibilities of interaction between this phytoconstituent and the organism are not understood. This corroborates the need to expand studies

on this topic when associated with the possible toxicity of this compound, to be highlighted in vivo, in order to optimize the benefits of this bioactivity.

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