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# Perspectives on the use of Terpenoids, Monoterpenes, and their Derivatives in the Development of Treatments for Sepsis†

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**Abstract**

Sepsis, characterized by a generalized systemic inflammatory response, has become an increasingly challenging global health issue. This situation is exacerbated by the growing antimicrobial resistance to existing drugs. In light of this, the search for alternatives to combat these microorganisms, such as the use of natural compounds, has become necessary. In this regard, essential oils are promising for combating various microorganisms due to the presence of compounds such as terpenoids and monoterpenes in their composition. This study aims to elucidate the evidence regarding the antimicrobial activity of terpenoids and monoterpenes through a literature review.

For this purpose, the PICo strategy was employed, and searches were conducted in the PubMed, VHL (Virtual Health Library), and Science Direct databases using the descriptors "sepsis," "monoterpene," "polymicrobial sepsis," and "terpenoids," combined with the Boolean operators AND and OR. After applying exclusion criteria, eight articles were selected and analyzed in their entirety. The antibacterial and antifungal effects of compounds such as carvacrol, thymol, and 1,8-cineole were demonstrated, showing satisfactory MIC (Minimum Inhibitory Concentration), MBC (Minimum Bactericidal Concentration), and MFC (Minimum Fungicidal Concentration) values in most studies against various bacterial and fungal species. The tests primarily involved species such as Staphylococcus aureus, Escherichia coli, and Candida albicans. This analysis highlighted the role of these compounds as antimicrobial agents, not only when used in isolation but also in synergy with last-resort antibiotics for treating certain infections, such as polymyxin. The data obtained underscore the promising potential of terpenoids and monoterpenes in tackling antimicrobial resistance, offering a relevant alternative in the context of sepsis. These findings can provide a foundation for future research aimed at developing new drugs based on natural compounds, thereby expanding the therapeutic options for complex infections.

**Keywords:** Sepsis; Monoterpenes; Antimicrobial Activity; Microorganisms; Terpenoids; Monoterpenes

## Introduction

Sepsis is a critical medical condition resulting from a systemic inflammatory response to infection, leading to an exacerbated immune response and multiple organ dysfunction, which often culminates in death. The World Health Organization (WHO) estimates that approximately 50 million people are affected by sepsis annually, of which around 11 million dies. The traditional approach to treating sepsis involves the use of antibiotics from different classes; however, the uncontrolled rise of antimicrobial resistance has become a major obstacle to resolving this issue [1]. Given this scenario, the search for new alternatives to treat microbial infections has emerged as an urgent need to overcome this growing challenge, which makes sepsis increasingly difficult to manage effectively.

In this context, the therapeutic potential of medicinal plants and essential oils as antimicrobial agents has gained attention through studies investigating their actions against bacterial, fungal, and even viral infections [2,3]. Several investigations have enabled the discovery of secondary metabolites, especially those present in the essential oils of various plants, whose antimicrobial actions have been demonstrated [4]. In general, most essential oils contain monoterpenes and terpenoids as key constituents with antibacterial activity. Their mechanisms of action include destabilizing bacterial cell membranes and inhibiting efflux pumps-resistance mechanisms developed by bacteria-thus facilitating the control of these microorganisms [3]. Therefore, as the demand for alternative treatments against multidrug-resistant pathogens increases, so does the need to explore the therapeutic potential of these natural sources [4]. However, the number of studies assessing their efficacy, whether in vitro or in vivo, remains scarce. Thus, this study aims to contribute to the scientific literature by reviewing the actions of secondary metabolites against different microorganisms, highlighting their promise in addressing the challenges posed by sepsis.

## Methodology

### Study Design

This research is a narrative literature review, qualitative and descriptive-exploratory in nature. It aimed to gather and analyze scientific publications on the use of terpenoids and monoterpenes in the context of sepsis. To guide the review, the PICo strategy was applied to formulate the following research question: "What are the perspectives on the use of monoterpenes and their derivatives (I) in the development of new treatments (Co) for sepsis (P)?".

### Literature Search Strategy

#### Databases and Search Period

The literature search was conducted between November and December 2024 using the following electronic databases: PubMed, VHL (Virtual Health Library), and ScienceDirect.

#### Descriptors and Search Query

The descriptors were defined based on the Health Sciences Descriptors (DeCS) and included: "sepsis," "monoterpene," "polymicrobial sepsis," and "terpenoids." Boolean logic operators AND and OR were applied to structure the search, resulting in the following combination: "sepsis" AND "monoterpene" AND "terpenoids" AND "polymicrobial sepsis.".

### Study Selection Criteria

#### Inclusion Criteria

The following criteria were used for the inclusion of articles in the review: Studies that evaluated the use and efficacy (positive or not) of monoterpenes and their effects against microbial pathogens. Articles available in full text. Publications from 2019 to 2024. Languages: Portuguese, English, or Spanish.

#### Exclusion Criteria

The exclusion criteria were as follows: Studies with incomplete results. Duplicate publications. Studies outside the defined scope of the review.

### Data Synthesis and Analysis

Publications that met the study's objectives were compiled and critically analyzed. The results were organized and presented in a discursive format, linking the findings from the selected articles directly to the research question to provide a current and comprehensive overview of the topic.

## Results and Discussion

Terpenoids and monoterpenes-classified as a subclass of terpenoids- are natural compounds produced by a wide range of organisms, from terrestrial plants to marine bacteria and fungi. They are bioactive molecules with demonstrated antioxidant, antitumoral, and antimicrobial activities [3,5-7]. In this review, 41 articles were initially selected; after screening, 8 publications were retained for analysis, which evaluated or reported the antimicrobial actions of monoterpenes and/or terpenoids.

p-cymene [8] investigated the antimicrobial activity of essential oils from Satureja sahendica and Satureja spicigera. The main constituents were carvacrol (36.88% and 32.58%), p-cymene (12.33% and 8.23%), $\gamma$-terpinene (14.76% and 16.27%), and thymol (10.28% in S. spicigera), all monoterpenes. Antimicrobial assays against *Staphylococcus aureus* (ATCC 6538P), *Escherichia coli* (ATCC 8739), *Bacillus subtilis* (ATCC 6633), *Pseudomonas aeruginosa* (ATCC 27853), and *Candida albicans* (ATCC 10231) showed greater efficacy for *S. sahendica* oil, with MIC, MBC, and MFC values particularly effective against *P. aeruginosa* (MIC 96 $\mu$g/mL; MBC and MFC 192–384 $\mu$g/mL). P. aeruginosa was the most resistant strain, while *C. albicans* was the most sensitive, with MIC, MBC, and MFC values as low as 24 $\mu$g/mL.

Complementarily, Fan et al. [9] identified significant antimicrobial activity in indole alkaloids/monoterpenes isolated from the bark of *Tabernaemontana corymbosa*, particularly tacamine derivatives. MIC values were 6.25 $\mu$g/mL against S. aureus and 62.5 $\mu$g/mL against *C. albicans*. Structural analysis showed that functional group stereochemistry, such as $COOCH_3$ groups, directly influenced bioactivity, underscoring the therapeutic potential of monoterpenes.

Vaz et al. [10] evaluated the essential oil (EO) of *Zingiber officinale* (ginger) as an alternative against multidrug-resistant (MDR) bacteria. Chromatographic analysis revealed that 89.2% of its composition was oxygenated monoterpenes (54.2%), hydrocarbon monoterpenes (16.2%), sesquiterpene hydrocarbons (11.8%), and oxygenated hydrocarbons (6.9%), with geranial, neral, and 1,8-cineole as major components. *In vitro*


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tests demonstrated strong inhibition of planktonic bacterial cells (72 mg/mL), though biofilm formation was unaffected. *In vivo*, EO treatment of carbapenem-resistant Klebsiella pneumoniae-infected mice significantly reduced mortality: no deaths occurred in treated groups versus 50% mortality in controls. Treated animals also showed reduced bacterial loads in pleural fluid (~4 log10 CFU/mL vs. ~6 log10 CFU/mL in controls). These results were comparable-and in some cases superior-to polymyxin, highlighting EO of *Z. officinale* as a promising therapeutic option.

Wang et al. [11] investigated bakuchiol (BAK), a monoterpene isolated from *Psoralea corylifolia* fruit, in a murine model of polymicrobial sepsis induced by cecal ligation and puncture (CLP). Male C57BL/6 mice received doses of 5, 15, and 45 mg/kg of BAK one hour before CLP. Treatment significantly reduced bacterial load in blood and kidneys, attenuated inflammatory response, decreased oxidative stress, and improved renal histology, ultimately increasing 7-day survival rates.

Tariq et al. [3] further demonstrated that terpinen-4-ol from *Melaleuca alternifolia* oil synergistically enhanced the activity of traditional antimicrobials against methicillin-resistant *S. aureus* (MRSA). Similarly, Gozari et al. [12] reported that marine terpenoids showed cytotoxic (61%) and antibacterial (16%) activities, underscoring both their therapeutic potential and toxicity concerns.

Overall, these findings reinforce the potential of monoterpenes and terpenoids as stand-alone agents or as adjuvants in antimicrobial therapy. Evidence from both *in vitro* and *in vivo* studies highlights their promise in combating antimicrobial resistance and severe infections, including sepsis.

## Conclusion

This study highlights terpenoids, monoterpenes, and their derivatives as strong candidates for the treatment of severe microbial infections, particularly bacterial sepsis. The reviewed evidence demonstrates their antimicrobial, anti-inflammatory, and additional therapeutic properties, emphasizing the need for further *in vivo* and *in vitro* studies to provide more conclusive evidence for their clinical application in sepsis management.

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