**Academic Journal of Science and Technology**
ISSN: 2771-3032 | Vol. 15, No. 3, 2025

# Advances on the Antimicrobial Activity of Hinokitiol and Its Derivatives

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**Abstract:** Hinokitiol is a monoterpenoid secondary metabolite with a broad spectrum of biological activities, serving as a lead compound in novel drug discovery. This review briefly summarizes the recent progress in the antibacterial properties of hinokitiol and its derivatives. Furthermore, it discusses their potential for development and application, aiming to provide a valuable reference for the design of new natural-origin antibacterial agents based on hinokitiol.

**Keywords:** Hinokitiol; derivatives; antibacterial activity.

## 1. Introduction

Hinokitiol (1, Figure 1) is a monoterpenoid secondary metabolite featuring a tropolone skeleton, widely distributed in plants of the Cupressaceae family. It exhibits diverse biological activities, including anticancer, anti-inflammatory, antibacterial, insecticidal, and acaricidal effects. Among these, its broad-spectrum and remarkable antibacterial properties have attracted considerable attention [1–3]. Studies have demonstrated that hinokitiol can significantly inhibit the growth and proliferation of various pathogenic fungi and bacteria through multiple modes of action and mechanisms [1, 2]. Moreover, owing to its unique and well-defined molecular framework, hinokitiol serves as a promising lead compound for novel drug development. This review focuses on the antibacterial activity of hinokitiol, summarizing recent advances regarding hinokitiol and its derivatives in this field. The aim is to provide a reference for the development of new natural-origin antibacterial agents based on hinokitiol.

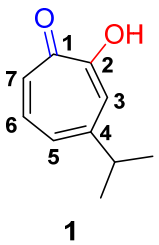


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**Figure 1.** Chemical structure of hinokitiol (1)

## 2. Antifungal Activity

Hinokitiol exerts antifungal effects by interfering with the RAS signaling pathway in Candida albicans [4]. It can also chelate intracellular iron ions, thereby disrupting mitochondrial respiration in C. albicans and inhibiting fungal growth [5]. In addition, hinokitiol has been shown to effectively suppress the formation of biofilms by various Candida species that exhibit resistance to fluconazole. This highlights its potential application in the treatment of biofilm-associated candidiasis and in addressing antifungal drug resistance [6]. Notably, hinokitiol also displays strong inhibitory activity against the wood-decay fungus Daedalea dickinsii IFO-4979, with a minimum inhibitory concentration (MIC) as low as 0.2 μg/mL [7]. In addition, hinokitiol exhibits marked inhibitory activity against the growth of several phytopathogenic fungi, including Sclerotinia sclerotiorum (causal agent of stem rot in rapeseed), Phytophthora capsici (responsible for Phytophthora blight in pepper), and Colletotrichum coccodes (the pathogen of potato anthracnose), at a concentration of 50 μg/mL [8]. Interestingly, hinokitiol also exhibits both protective and therapeutic effects against postharvest diseases in crops, such as grape gray mold and banana anthracnose. Its antifungal activity involves disrupting the integrity of the cell membranes of Botrytis cinerea and Colletotrichum musae, which leads to enhanced lipid peroxidation and leakage of intracellular contents, ultimately resulting in fungal cell death. Moreover, hinokitiol downregulates the expression of pathogenicity-related genes in B. cinerea, further contributing to its antifungal efficacy [9,10]. Hinokitiol exhibits significant inhibitory effects against Fusarium species, which cause taro rot, and Lasiodiplodia theobromae, a major pathogen associated with cocoa decay. It effectively suppresses both mycelial growth and spore germination of these fungi. The underlying mechanism involves intensified lipid peroxidation of the hyphal membranes and disruption of the subcellular structures within the hyphae [11]. Zhang Xuhuan et al. reported that hinokitiol exhibits notable inhibitory activity against Fusarium oxysporum f. sp. niveum, the causative agent of Fusarium wilt in watermelon. Under in vitro conditions, the median effective concentrations (EC50) for inhibiting mycelial growth and spore germination were 31.1 μg/mL and 45.2 μg/mL, respectively. In vivo assays further demonstrated that hinokitiol provides effective control of Fusarium wilt in watermelon. Subsequent studies confirmed that hinokitiol not only significantly suppresses fungal growth but also inhibits the biosynthesis of certain toxins or promotes their degradation, thereby reducing the pathogenicity of the fungus [12].

In 2016, Fotopoulou et al. designed and synthesized a series of Mannich base derivatives of hinokitiol. Among them, compound 2 (Figure 2) exhibited strong antifungal activity against two Penicillium species—Penicillium funiculosum and Penicillium ochrochloron—with minimum inhibitory concentrations (MICs) of 9.0 μmol/mL for both strains. This activity was significantly stronger than that of the parent

compound hinokitiol, whose MICs were 24.3 μmol/mL and 18.3 μmol/mL, respectively [13]. Encouragingly, structural modification at the C2 hydroxyl group of hinokitiol to form its sodium and potassium salts (compounds 3 and 4, Figure 2) not only greatly improved its water solubility but also retained its antifungal efficacy against wood-decaying fungi. These findings offer valuable insights for the development of novel wood preservatives [14,15].

In 2023, Gui Kuo et al. designed and synthesized a series of hinokitiol-based carboxylic esters and ether derivatives. Among them, compound 5 (Figure 2) exhibited potent antifungal activity against Rhizoctonia solani, the causal agent of rice sheath blight, with an $EC_{50}$ value of 1.84 μg/mL. Compound 6 showed strong inhibition against Botrytis cinerea from tomato with an $EC_{50}$ of 2.47 μg/mL, while compound 7 demonstrated superior activity against Sclerotinia sclerotiorum infecting rapeseed, with an $EC_{50}$ of 1.05 μg/mL. These values indicate significantly enhanced antifungal efficacy compared to the lead compound hinokitiol [16]. Subsequently, based on this structural framework, Ye Jiuhui et al. further synthesized a series of hinokitiol-derived carboxylic esters and sulfonate esters. Most of these compounds showed considerable inhibitory activity at a concentration of 50 μg/mL against several phytopathogenic fungi, including Valsa mali (the causal agent of apple canker), Rhizoctonia solani (rice sheath blight), Botrytis cinerea (tomato gray mold), and Colletotrichum orbiculare (cucumber anthracnose). Further structure–activity relationship (SAR) analysis revealed that, overall, the carboxylic ester derivatives exhibited markedly stronger antifungal activity than their sulfonate ester counterparts [17].

## 3. Anti-oomycete Activity

In 2022, Che et al. reported a series of hinokitiol-derived sulfonate esters and evaluated their anti-oomycete activities. Among them, compound 8 (Figure 2) exhibited markedly improved activity against Phytophthora capsici with an $EC_{50}$ value of 18.64 μg/mL, compared to the parent compound hinokitiol ($EC_{50}$: 88.78 μg/mL). Mechanistic investigation revealed that the cycloheptatrienone moiety within the hinokitiol scaffold plays a critical role in its anti-oomycete efficacy [18]. In 2024, Wei et al. reported a new class of 2-acyloxy hinokitiol derivatives with potent activity against P. capsici. Among them, compound 9 (Figure 2) exhibited the strongest anti-oomycete activity, with an $EC_{50}$ value of 13.61 μg/mL [19].

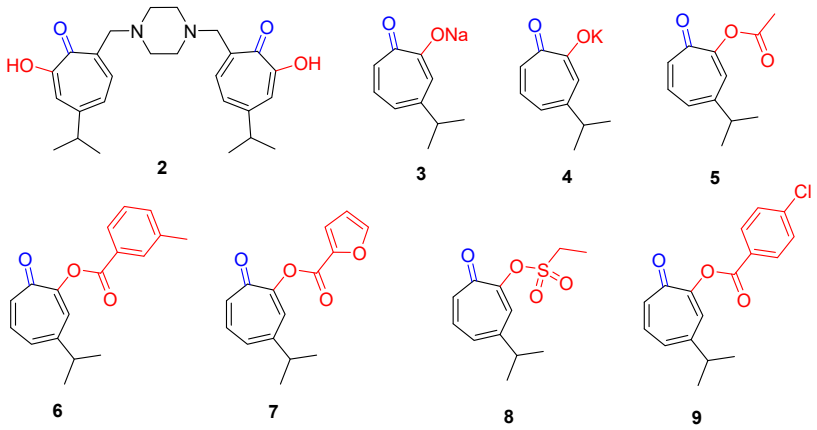


**Figure 2.** Chemical structures of hinokitiol derivatives (compounds 2–9)

## 4. Antibacterial Activity

Hinokitiol has been reported to exhibit significant inhibitory effects against a variety of bacteria, including Escherichia coli, Staphylococcus aureus, Listeria monocytogenes, Salmonella enteritidis, Porphyromonas gingivalis, and Salmonella typhimurium [1]. Additionally, hinokitiol shows notable antibacterial activity against Ralstonia solanacearum, the causative agent of bacterial wilt in plants, with a minimum inhibitory concentration (MIC) of 50 μg/mL [20].

## 5. Conclusion and Future Perspectives

This review has systematically summarized the antibacterial activities of hinokitiol and its derivatives, providing valuable insights for the development of novel antimicrobial agents. Although hinokitiol and its analogs exhibit broad-spectrum and potent antimicrobial effects, their efficacy still lags behind that of commercially available antibiotics. Therefore, rational structural optimization aimed at enhancing their antimicrobial potency warrants further investigation. Moreover, deeper studies into the underlying mechanisms of action and molecular targets are essential. Advances in this area will significantly facilitate the design of targeted drugs and accelerate the development and application of new antimicrobial agents based on hinokitiol derivatives. On the other hand, the toxicity, pharmacokinetics, and environmental toxicology profiles of hinokitiol and its highly active derivatives must not be overlooked, as these factors are critical for their safe and effective therapeutic use.

## Acknowledgement

This work was supported by the Science and Technology Planning Project of Henan Province of China (Grant No. 242102111090).

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