



RECENT ADVANCES IN DEVELOPMENT OF CAMPHOR BASED FUNGICIDES

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Abstract

In face of large-scale diseases, the control of chemical agrochemicals remained a fast, economical, and effective method. However, the long-term and widespread use of chemical agrochemicals have led to increase of plant pathogen resistance and the effect on crop quality and ecological environment. The search for novel bioactive agrochemicals has long been a priority in crop protection. Camphor is a forest derived natural product extracted from camphor trees, which has attracted much attention due to its wide range of medicinal and pesticide biological activities. In recent years, many reports have been published on the modification synthesis and investigation of the fungicidal activity of camphor scaffolds, but there was a lack of a comprehensive classified review on camphor derivatives. Considering this issue, here we have reviewed the published articles on the fungicidal activity of the camphor derivatives.

Keywords: Camphor, Natural product, Plant pathogen, Fungicides, Scaffolds.

1. Introduction

For a long time, crops in China have often been severely threatened by plant pathogen diseases, resulting in significant economic losses.^I The emergence and evolution of diseases are influenced by various external factors,^{II} such as fungi, oomycetes, bacteria, viruses and certain specific hosts. Among them, fungi are one of the main infectious factors that affect the normal growth of crops, and their main harm is to reduce crop yield and quality.^{III} Several pathogen *Rhizoctonia solani*, *Fusarium graminearum*, *Phytophthora capsici*, *Botryosphaeria dothidea* would cause severe vegetables and fruits disease, which

significantly reduce the great losses of yield.^{IV-XII} Facing with the large-scale plant diseases, the control of chemical pesticide still remains a fast, economical and effective method. The use of modern fungicides can not only reduce the harm caused by various pathogens, but also improve crop yield and quality.¹⁴ However, the long-term and widespread use of chemical fungicides has led to many potential problems becoming increasingly apparent. For example, long-term use of fungicides can lead to a decrease in the number of harmful microorganisms in the soil, thereby disrupting ecological balance.^{XIV,XV} Therefore, it is imperative to develop novel fungicides with novel mechanisms, which are also efficient and low toxic.

Due to the diverse chemical structures, significant biological activity and low toxicity to none target organisms, natural products have been used in the development of pesticides in recent years. Among them, as an important branch of natural products, natural products derived from forest refer to bioactive substances from forestry resources. It has always held a pivotal position in natural product resources of China. Camphor is an important forest derived natural product extracted from camphor trees, which has attracted much attention due to its wide range of medicinal and pesticide biological activities, such as antifungal,^{XVI} anti-inflammatory,^{XVII} antibacterial,^{VXIII} and insecticidal.^{XIX} Camphor is a bicyclic monoterpene with the molecular formula $C_{10}H_{16}O$. Its IUPAC name is 1,7,7-trimethylbicyclo[2.2.1]hept-2-one, and its structural formula is shown in Figure 1. It is a waxy, transparent solid extracted and isolated from *Cinnamomum camphora* (Linn) Presl with a strong odor and flammable properties. Camphor contains two chiral centers and exists in two enantiomeric forms (natural camphor is right-handed, synthetic camphor is racemic).^{XX} At present, camphor is mainly used in the following fields: pharmaceuticals,^{XXI,XXII} adjuvants and ligands for asymmetric synthesis reactions^{XXIII,XXIV} and sanitary pesticides.^{XV} In China, the main planting areas of camphor trees are Jiangxi, Zhejiang, Yunnan, Guangdong, Fujian, Taiwan, and Hunan provinces. In general, the older the camphor tree, the higher the proportion of natural camphor it contains.^{XXVI} In recent years, due to the continuous expansion of camphor application fields and other reasons, the production of natural camphor can no longer meet the growing market demand.^{XXVII} Therefore, the method of synthesizing camphor by using α -pinene as a raw material has emerged.^{XXVII} At present, although some commercially available camphor products are derived from synthetic camphor,^{XXIX} natural camphor is still popular among consumers. Therefore, by modifying the structure of these forest derived natural products, novel camphor derivatives can be screened to control and delay the problem of agrochemicals resistance in plant pathogens. The key scientific problem to solve this project is to explore the mechanism of action between candidate of camphor derivatives and the new target. From mentioned above, here we have reviewed the published articles on the fungicidal activity of the camphor derivatives in recent years.

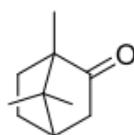


Fig. 1. The structure of camphor

2. Camphor investigation in the fungicidal field

Kong et al. reported that camphor has excellent *in vitro* fungicidal activity against on four plant pathogenic fungi *Fusarium oxysporum* G5, *Fusarium solani* G9 and *Fusarium solani* and *Fusarium graminearum*, with half of them effectively inhibiting fungi concentrations (EC_{50}) were 2.0, 2.0, 2.0, and 1.0 mg/mL, respectively.^{XXX} Bu et al modified the carbonyl adjacent methylene group of camphor and synthesized a class of camphor derivatives containing quinoline groups. Preliminary fungicidal activity tests indicated that compound **1** has an inhibitory effect against *Rhizoctonia solani* at a concentration of 50 μ g/mL. The inhibition rate is 71.4%, which is comparable to that of Chlorothalonil.^{XXXI} Huang et al has designed and synthesized new camphor derivatives with the intermediate camphoramine from D-(+)-camphor through a two-step reaction. The antifungal activity test showed that at 50 mg/L, the *in vitro* inhibition rates of compounds **2** and **3** against *Physalospora piricola* were 97.5%, and 96.4% respectively.^{XXXII} Lin et al. further synthesized camphor based phenylthiourea compounds. The fungicidal activity test showed that the target compound can effectively inhibit the growth of five plant pathogens at 50 mg/L. Among them, the inhibition rate of compound **4** against *Alternaria solani* was 82.2%.^{XXXIII}

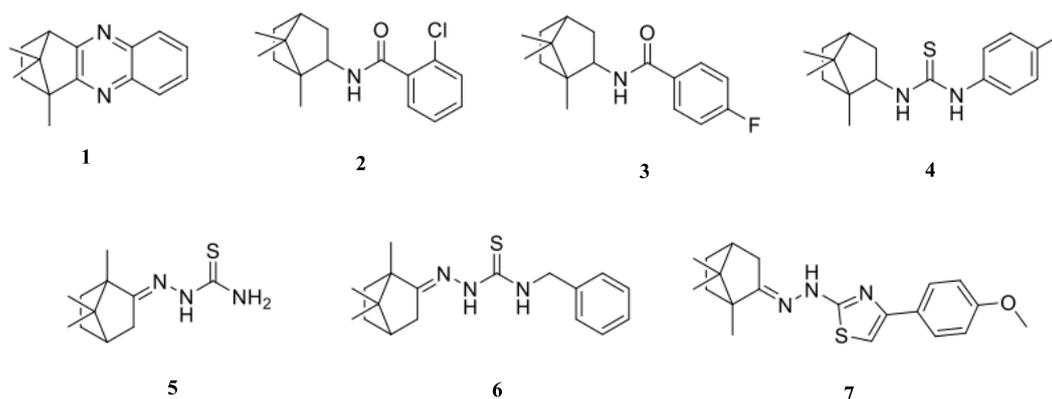


Fig. 2. The structure of camphor derivatives **1-7**

Duan et al. has synthesized three camphor derivatives containing thiourea and thiazole fragments. Compounds **5**, **6**, and **7** could effectively inhibit the growth of *Trametes versicolor*, with EC_{50} values of 0.43, 6.80, and 4.86 mg/L, respectively, which were equivalent to commercial fungicide carbendazim (EC_{50} =1.20 mg/L)^{XXXIV}(Figure 1).

Ma et al has designed and synthesized a series of camphoric acid based benzenesulfonamide compounds by using camphor as raw material. Among them, compounds **8** showed that the *in vitro* inhibition rate against tomato early blight was 86.9% at 50 mg/L.^{XXXV} In addition, he also introduced thiourea fragments into camphor scaffold. Camphor acid based thiourea compound **9** was synthesized in the matrix with 86.1% inhibition effect against *Physalospora pear* fungus at 50 mg/L.^{XXXVI} On the basis of Ma's research, Zheng et al. synthesized a series of acylhydrazone compounds based on camphoric acid scaffold and carried out fungicidal activities assay. The inhibition rates of compounds **10** and **11** against *pear cyst* fungus were 90.6% and 85.4% at 50 mg/L, respectively^{XXXVII}(Figure 3).

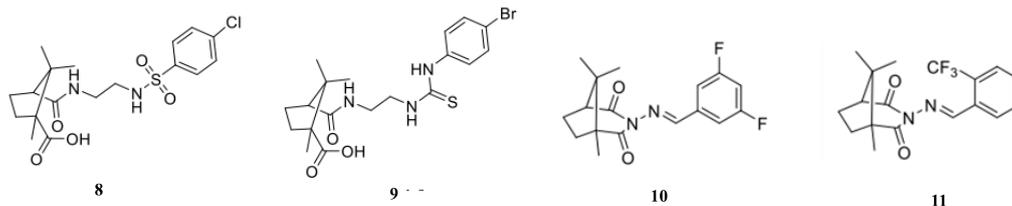


Fig. 3. The structure of camphor derivatives **8-11**

Gu's group has done a number of studies on camphor derivatives on fungicidal activity field (Figure 4). Compound **12**, **13**, **14** were synthesized with introducing sulfonyl group. Compound **12** displayed *in vitro* and *in vivo* good anti-oomycete activity against *Phytophthora capsici*.^{XXXVIII} Compound **13** demonstrated excellent anti-*Fusarium graminearum* activity on wheat leaves at 200 mg/L, which was comparable with pydiflumetofen.^{XXXIX} Compound **14** showed excellent anti-*Botryosphaeria dothidea* effect on apple fruits, which had the potential ability to control the apple ring rot disease.^{XL} For further, fungicidal mechanism investigation revealed these three camphor derivatives have been the potential fungal succinate dehydrogenase inhibitor (SDHI)^{XXXVIII-XL}. In 2023, four series of novel camphanic acid hydrazide and camphor sulfonamide derivatives were designed and synthesized. Among them, compound **15** demonstrated the most potent *in vitro* anti-*B. dothidea* activity ($EC_{50} = 1.28$ mg/L), much stronger than commercial fungicide chlorthalonil. The *in vivo* assay showed that **15** displayed significant protective effects on apple fruits infected by *B. dothidea*. Antifungal mechanism displayed that it could be potential laccase inhibitor.^{XLI}

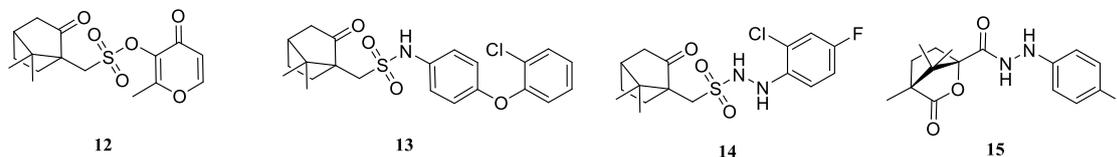


Fig. 4. The structure of camphor derivatives **12-15**

In 2024, Zhang's researching group has done several works with modifying camphor scaffold. Compound **16** was synthesized from raw material camphor, which displayed excellent anti-*R. solani* effect *in vitro* and *in vivo*. Primarily mechanism also showed that compound **16** could increase cell membrane permeability and induce abnormal mycelia and cellular morphology in *R. solani*.^{XLII} Further, this group has also synthesized a novel series of D/L-camphorhydrazide derivatives potentially targeting fungal succinate dehydrogenase (SDH). Among them, compound **17** displayed excellent *in vitro* activity against *R. solani* with EC_{50} values of 0.38 mg/L.^{XLIII} Moreover, compound **18** contained oxime ester group was synthesized from camphorsulfonic acid. Antifungal assay showed that **18** exhibited *in vitro* good anti-*R. solani* effect ($EC_{50} = 7.28$ mg/L).^{XLII}

In 2024, Liao's researching group has designed a series of camphor derivatives contained thiourea group and screening their fungicidal activity with *R. solani*. Compound **19** exhibited *in vitro* superior fungicidal activities ($EC_{50} = 6.16$ mg/L), and *in vivo* curative effects (77.5%) at 500 mg/L were significantly higher than validamycin-bacillus (66.1%). In addition, compound **19** demonstrated low cytotoxicity and acute oral toxicity for adult worker honeybees of *Apis mellifera* L.^{XLV}(Figure 5).

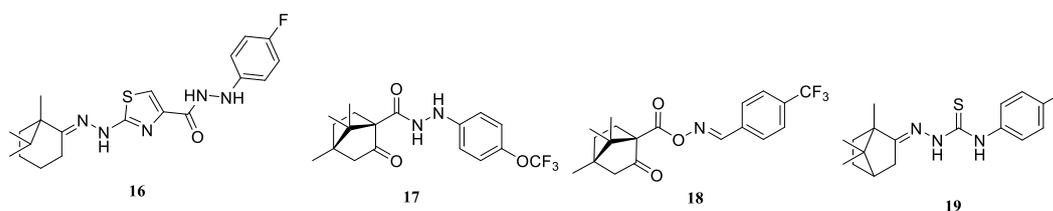


Fig. 5. The structure of camphor derivatives **16-19**

3. Summary and perspective

As a summary, camphor represents a key scaffold that is continuously investigated in the field of fungicides. In this review, a numbers of camphor derivatives have been reported with excellent anti-fungi/oomycetes activity. Some of them had accurate fungicidal target, which had the potential ability to solve the problem of plant pathogen resistance. Until now, as an important natural monoterpene from forest sources, camphor and its products are mainly used in the field of hygiene insecticides of human family. It still has a vast space on structural modification for enhancing its biological activity, which provides a theoretical basis for improving the bioavailability of natural products derived from forest sources and developing new fungicides lead compounds

Acknowledgements

This work was thankful by the doctoral research launch project of Chuxiong Normal University (BSQD2444,BSQD2400) and Student Innovation and Entrepreneurship Training Program(2025), Horizontal project(CSHX-202501, CSHX-202502),Yunnan Province Three Zones Sci-Tech Talents(2025).

Author Contribution Statement

The authors declare no competing financial interest.

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Received on 14 December 2025.