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Piper nigrum as a Source of Antimicrobial Agents: Bioactive Constituents, Mechanistic Insights, and Synthetic Derivatives for Antibacterial Applications

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Piper nigrum, commonly known as black pepper, is a widely cultivated spice with a long history of medicinal use. *P. nigrum* exhibits a broad spectrum of antimicrobial activity because of the presence of bioactive compounds, including alkaloids, phenol, and terpenoids, which have been identified as major contributors to its antimicrobial efficacy. These compounds act through various mechanisms, including disrupting bacterial cell membranes, inhibiting enzymes vital for bacterial growth and survival, generating reactive oxygen species, and interfering with biofilm formation. To date, there has been growing interest in exploring the bacteriostatic potential of *P. nigrum*, focusing on the active metabolites. This results in structural modifications of the parent compound through the introduction of additional functional groups via various synthetic pathways, thereby enhancing its biological potential. This review aims to provide an overview of the antimicrobial properties and biological mechanisms of action of the isolated compounds from *P. nigrum*. Furthermore, some derivatization of isolated compounds has also been discussed together with their antibacterial activities. On the basis of the collected chemical constituents from *P. nigrum* and its analogues, this review represents a very interesting bioactive compound with broad-spectrum antimicrobial activity, highlighting its potential as a future crop to combat bacterial infections.

1. Introduction

Antimicrobial resistance (AMR) has become one of the biggest threats to global health, food security, and development, affecting anyone of any age and country.[1] The growing number of infections, such as pneumonia, tuberculosis, gonorrhea, and salmonellosis, are becoming harder to treat as the antibiotics used to treat these diseases become less effective.[2] This situation led to increasing deaths and the desire to search for a novel antibiotic to combat antimicrobial resistance.[3] Natural products have been extensively used for their medicinal properties, and currently, most people are utilizing medicinal plants to treat infectious diseases.[4] Searching for antimicrobial agents from natural resources will also be beneficial for the food industry, given the fact that, in general, consumers prefer natural and nontoxic products to protect foods from bacteria during storage.[5] The long-term usage of chemical preservatives will lead to a resurgence of food-pathogenic bacteria such as *Staphylococcus aureus*, *Escherichia coli, Salmonella typhimurium*, and *Pseudomonas aeruginosa*, which can induce severe health problems in humans.[2,6]

Piper nigrum, known as black pepper (Figure 1), is the king of spices due to its wide use in all major cuisines worldwide. Black pepper is used intensively as a coloring, fragrance, and flavoring agent in food. The *P. nigrum* species belongs to the genus *Piper* of the *Piperaceae* family. The genus *Piper* is the largest in the family *Piperaceae* and contains more than 3000 species reported from tropical and subtropical regions around the world.[7] The *P. nigrum* species is a native plant to India, Indonesia, Malaysia, South America, and the West Indies but is also widely cultivated in tropical regions worldwide.[8] The local communities use this species to treat many types of diseases. For example, native people from Tamil Nadu, India, used *P. nigrum* to treat snake bites, scorpion stings, cholera, headaches, asthma, skin diseases, hemorrhoids, and ulcers.[9] Meanwhile, for the Arabs, according to their fifth-century Syriac book of medicine, the dry *P. nigrum* berries were used for treating diarrhea and fever.[10] In China, *P. nigrum* has traditionally been used to treat epilepsy.[11] This plant's high medicinal properties are due to its richness in bioactive secondary metabolites. The metabolites are phenylpropanoid lignans, flavonoids, steroids, kavalactones, polyphenols, and terpenes, which are good at inhibiting various types of pathogenic bacteria.[12] In addition, these compounds also have significant biological activities such as anticancer,[13] antiviral,[14] anti-inflammatory,[15] antimicrobial,[13] and anti-parasitic properties.[16]

This review aims to provide a comprehensive overview of the antimicrobial properties and biological mechanisms of action of compounds isolated from *P. nigrum*. Additionally, it further delved into the derivatization of these isolated compounds and their corresponding antibacterial activities. To date, this is the only review on *P. nigrum* that specifically addresses active secondary metabolites, derivatized compounds, and their antibacterial potential. Furthermore, structure–activity relationship (SAR) analyses of the derivatized compound are presented, highlight-

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