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Review

Cinnamaldehyde and its derivatives, a novel class of antifungal agents

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ABSTRACT

The last few decades have seen an alarming rise in fungal infections, which currently represent a global health threat. Despite extensive research towards the development of new antifungal agents, only a limited number of antifungal drugs are available in the market. The routinely used polyene agents and many azole antifungals are associated with some common side effects such as severe hepatotoxicity and nephrotoxicity. Also, antifungal resistance continues to grow and evolve and complicate patient management, despite the introduction of new antifungal agents. This suitation requires continuous attention. Cinnamaldehyde has been reported to inhibit bacteria, yeasts, and filamentous molds *via* the inhibition of ATPases, cell wall biosynthesis, and alteration of membrane structure and integrity. In this regard, several novel cinnamaldehyde derivatives were synthesized with the claim of potential antifungal activities. The present article describes antifungal properties of cinnamaldehyde and its derivatives against diverse classes of pathogenic fungi. This review will provide an overview of what is currently known about the primary mode of action of cinnamaldehyde. Synergistic approaches for boosting the effectiveness of cinnamaldehyde and its derivatives have been highlighted. Also, a keen analysis of the pharmacologically active systems derived from cinnamaldehyde has been discussed. Finally, efforts were made to outline the future perspectives of cinnamaldehyde-based antifungal agents. The purpose of this review is to provide an overview of current knowledge about the antifungal properties and antifungal mode of action of cinnamaldehyde and its derivatives and to identify research avenues that can facilitate implementation of cinnamaldehyde as a natural antifungal.

Contents

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1. Introduction

Fungi are ubiquitous and feed on decaying organic matter. Many fungal species are non-pathogenic to humans. Of the pathogenic fungi, several species are mainly responsible for superficial infections of the skin, nails, hair and mucous membranes [1], whereas, some species of fungi are known to cause life-threatening infections particularly in immuno-compromised patients [2–5]. The past decade has witnessed a steady increase in the number of immunocompromised patients, *e.g.*, individuals with hematologic diseases, malignancy, AIDS and those undergoing organ transplantation or with inflammatory auto-immune conditions. This has resulted in a drastic increase in the incidence of opportunistic fungal infections [6–9], which is now a severe public health problem [10,11].

Candida spp., *Cryptococcus* and *Aspergillus* spp. are the most frequently isolated species, whereas *Zygomycetes*, *Scedosporium*, *Fusarium*, and *Penicillium* are the increasingly observed species in clinical practice [12–16] (Table S1). Common causes of fungal infections, particularly *Candida* infections, include more aggressive surgeries, prosthetic devices, broad-spectrum antibiotics, and use of antineoplastic and immunosuppressive drugs [17–21]. The patients with HIV, cancer, neutropenia, burns, pancreatitis and hematopoietic stem cell transplant recipients are highly prone to invasive fungal infections [21,22]. Yeasts mostly *Candida* are increasingly being reported as leading causes of infections in burn patients [23,24]. The fungal infections of hematopoietic stem cell transplant recipients are caused due to candidiasis, zygomycosis, aspergillosis and filamentous fungal infections [22,25–27]. Invasive infections of candidiasis, aspergillosis, cryptococcosis, and zygomycosis are a major problem in solid organ transplant recepients [26,28], whereas hematologic malignant patients develop zygomycosis over time [29,30].

Treating fungal infections is a challenging task due to the limited number of effective antifungal drugs, the emergence of drug resistance and elevated renal and liver toxicities [31–35]. Current treatments include the synthetic azoles (*e.g.* fluconazole and flucytosine) or the natural polyene amphotericin B (AmB). However usage is becoming limited by resistance development to the azoles, and acute toxicity of AmB [31–35]. Also, the burden of antifungal resistance is becoming a major concern, and has thus intensified the search for new, safer, and more efficacious agents to combat serious fungal infections.

Cinnamaldehyde (Fig. 1) is a yellow oily liquid with a cinnamon odor and sweet taste. From a long time ago, cinnamaldehyde has been used as a flavoring agent in chewing gums, ice creams, candies, beverages, and sweets. Also, it has been widely used to give a cinnamon flavor to medical products, cosmetics, and perfumes [36–40]. Cinnamaldehyde is an active inhibitor of bacterial growth [41–43], yeast, and filamentous molds [44–46]. It exerts inhibitory effects by the inhibition of ATPases activity [47], cell wall biosynthesis [48], and alteration of the membrane structure and integrity [49]. As a consequence of these facts, cinnamaldehyde and its derivatives (Fig. 1) were screened against several pathogenic fungi, and shown to possess potential antifungal activity against several fungal isolates.

2. Review background

The currently available synthetic antifungal drugs are structurally less diverse (only a few structure activity relationships are available), are prone to resistance by several fungal strains, and produce severe adverse effects when administered systemically [50–55]. The complete information of synthetic antifungal agents and their mode of action, and mechanisms of resistance is summarized in supplementary tables (Tables S2–S3) [56–60]. Researchers working with natural products have

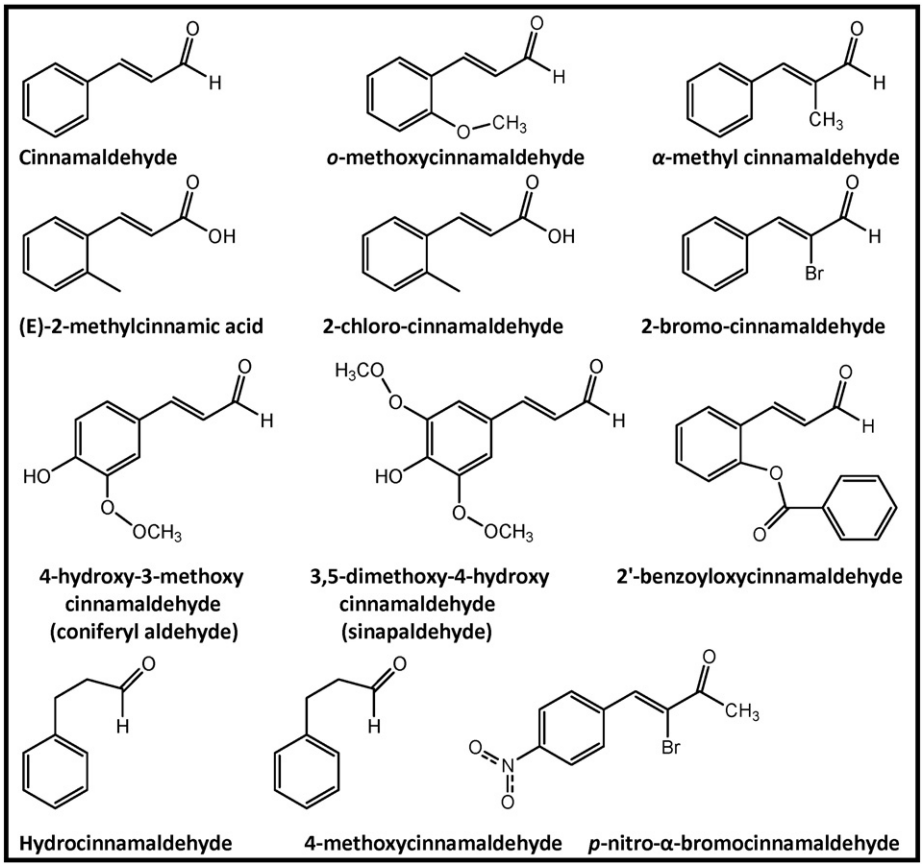

Fig. 1. The chemical structure of cinnamaldehyde and its biologically active derivatives.