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Review Article

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From Traditional Use to Modern Pharmacology: A Review of Cinnamomum Bark Bioactive

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Abstract

The traditional medicinal use of Cinnamon bark, primarily derived from Cinnamomum verum and Cinnamomum cassia, is based on its well-established antimicrobial, antioxidant, and anti-inflammatory properties. As a result, the rising global challenge of drug-resistant fungal infections has sparked a renewed and urgent interest in investigating new natural therapeutic options. Cinnamon bark emerges as a promising candidate, offering a rich source of secondary metabolites. Its strong pharmacological profile is due to key bioactive compounds such as cinnamaldehyde, eugenol, and a variety of polyphenols, which together demonstrate significant inhibitory effects against common pathogenic fungi. Preclinical studies have shown broad-spectrum effectiveness against well-known genera, including Candida species, Aspergillus species, Cryptococcus neoformans, and various dermatophytes. This comprehensive review systematically examines the bark's complex phytochemical makeup and explains the proposed mechanisms of antifungal action. Additionally, we critically assess the existing in vitro and in vivo evidence, explore the potential for synergistic interactions with conventional antifungal drugs, discuss important safety considerations, and highlight the critical research gaps that need to be addressed to enable its clinical application.

Introduction

Fungal infections are increasingly becoming a major threat to global public health, especially among vulnerable groups such as the elderly and those with weakened immune systems. Infections from opportunistic fungi significantly contribute to illness and death worldwide, creating a substantial clinical challenge. The current therapeutic options, which have traditionally depended on a limited range of antifungal drugs like azoles, amphotericin B, and echinocandins, are now in a critical state. The widespread and often careless use of these traditional treatments has led to the rapid development of drug-resistant fungal strains, making standard therapies ineffective and highlighting the urgent need for new treatment strategies[1]. This global issue has sparked significant interest in exploring diverse sources for new pharmacological agents, with a strong focus on natural products from plants. Among these, cinnamon bark, primarily obtained from cinnamomum species, is particularly noteworthy. As one of the oldest and most historically significant commodities, cinnamon has played a crucial role in human civilization, not only as a spice but also as a medicinal remedy. Traditional medical systems, such as Ayurveda, Siddha, and Traditional Chinese Medicine, have long utilized the bark for its effectiveness in treating a variety of conditions, including infections, respiratory problems like bronchitis, inflammatory diseases, and digestive issues[2,3]. Modern ethnopharmacological studies now support these historical uses. Recent scientific research has confirmed that the bark is rich in bioactive compounds, including powerful volatile essential oils and polyphenolic components, which provide significant antimicrobial properties. The evidence for its strong antifungal capabilities is particularly persuasive, making cinnamon bark a highly relevant and promising resource in the search for next-generation treatments that can overcome established antifungal resistance[4,5].

Botanical Overview

2.1 Taxonomy

Cinnamon bark is sourced from various species within the Lauraceae family, genus Cinnamomum. The most commercially significant species are *cinnamomum verum J. Presl* (formerly *C. zeylanicum*), commonly known as ceylon *cinnamon*, and *cinnamomum cassia (L.) J. Presl*, often referred to as Cassia or Chinese Cinnamon; another species, *cinnamomum burmannii* (Nees & T.Nees) Blume, or Indonesian Cinnamon, is also economically important, particularly for its volatile oil yield[6].

Table 1: Taxonomy classification

Kingdom	Plantae
Order	Laurales
Family	Lauraceae
Genus	Cinnamomum
Species	*C. verum, C. cassia, C. burmannii*

2.2 Morphological and Chemical Characteristics of bark:

Cinnamomum trees are evergreen and feature rigid, leathery leaves that contain glands for secreting essential oils the medicinal benefits are predominantly found in the dried bark during the harvesting and processing stages, the inner bark is meticulously peeled and dried, which causes it to form the unique tubular shapes known as quills[7,8]. This particular morphological process is crucial because the bark holds the highest levels of volatile oils, which are the main contributors to its distinctive pungent scent and strong medicinal effects[9].

Fig 1. *cinnamomum* bark

3. Phytochemical Composition

The strong antifungal properties of *cinnamomum* bark stem from its intricate and chemically varied composition, which includes a blend of volatile

essential oils and non-volatile polyphenolic secondary metabolites. The specific makeup can differ greatly depending on the species (*C. verum vs. C. cassia*), the geographic origin, and the method of extraction[10].

3.1 Major Volatile Constituents

The most pharmacologically potent part of the bark is the essential oil component. The main compound that imparts both the distinctive scent and the predominant antimicrobial properties is:

Cinnamaldehyde: This aromatic aldehyde generally makes up 80% of the essential oil content in *cinnamomum cassia*. Its alpha, beta-unsaturated aldehyde structure is crucial for its interaction with microbial membranes and enzymes.

Eugenol: A significant phenylpropanoid present in high amounts in *cinnamomum verum* oil, offering strong antimicrobial and antioxidant effects[11].

Related Monoterpenes: Other important volatile substances include cinnamic acid and its alcohol form, Cinnamyl alcohol, which are products of cinnamaldehyde metabolism. Additionally, Linalool (a monoterpene alcohol) and β-caryophyllene (a sesquiterpene) enhance the overall inhibitory range[12]. Safrole and Methyl eugenol, although usually present in small quantities, are highlighted in toxicological research for possible regulatory issues when consumed in large amounts.

Coumarins are benzopyrone compounds found naturally, with a high concentration in *C. cassia* and typically minimal levels in *C. verum*. These compounds are significant due to their potential to cause liver toxicity, making their presence a crucial topic in safety evaluations.

The ratio of cinnamaldehyde to eugenol is a key chemical distinction between *C. cassia and C. verum*, which is crucial for therapeutic use and safety evaluation.

3.2 Polyphenolic Constituents

Apart from the volatile oil, the bark contains a wealth of nonvolatile polyphenolic compounds that play a crucial role in enhancing the extract's potent antioxidant and anti-inflammatory effects through strong synergistic interactions:

Proanthocyanidins (PACs): These are oligomers and polymers of flavan-3-ols, renowned for their ability to bind proteins and scavenge free radicals[13].

Flavonoids: Notable examples include Quercetin and Kaempferol. These compounds serve as powerful antioxidants, safeguarding cellular integrity and influencing host inflammatory responses[14].

Catechins and Tannins: These substances contribute to the bark's astringency and may disrupt fungal cell wall structures by forming complexes with cell wall proteins[15].

4. Mechanisms of Anti-fungal Action

The impressive antifungal effectiveness of *cinnamomum* bark extracts is not due to a single mechanism but results from a coordinated assault on several crucial cellular targets within the fungal cells[19,20]. The main active ingredients, notably cinnamaldehyde and eugenol, work through synergistic and multifaceted processes, resulting in either fungistatic or fungicidal effects[21,22].

4.1 Disruption of Cell Membrane Integrity

The most extensively studied mechanism involves directly compromising the fungal cell membrane cinnamaldehyde lipophilic properties enable it to easily integrate into the fungal lipid bilayer, disrupting its structural and functional arrangement. Importantly, these phytochemicals have been found to hinder the production of ergosterol, a cholesterol-like compound unique to fungal cell membranes. This inhibition leads to Increased Membrane Permeability: The structural damage causes the rapid development of pores and channels within the membrane.

Leakage of Cellular Components: This weakened barrier function results in the irreversible loss of essential intracellular substances, such as ions, proteins, and nucleic acids, thereby disturbing cellular homeostasis.

Inhibition of Growth and Replication: The resulting loss of membrane potential and cellular integrity ultimately prevents fungal cell growth, reproduction, and survival.

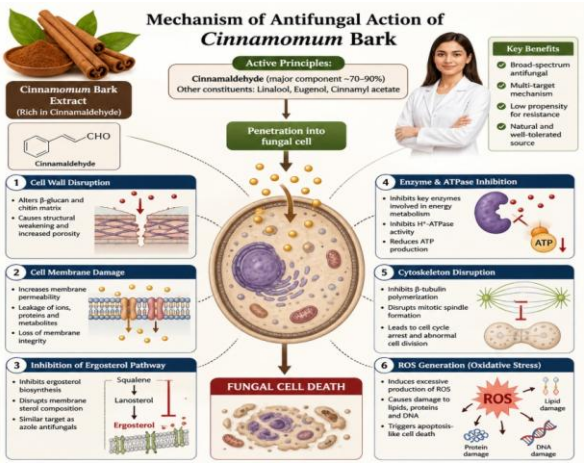

Fig 2. Mechanism of *Cinnamomum* bark (AI Generated)

4.2 Disruption of Mitochondrial Function

In addition to affecting the cell wall and membrane, cinnamon phytochemicals also disrupt the fungal energy production system. Once inside the cell, these compounds interact directly with the mitochondria, causing a significant energy imbalance:

Mitochondrial Membrane Depolarization: The compounds dismantle the proton gradient across the inner mitochondrial membrane.

Decreased ATP Production: This depolarization undermines the efficiency of the electron transport chain, drastically reducing the production of adenosine triphosphate (ATP), the main energy source for the cell.

Triggering of Oxidative Stress: The impaired electron transport chain leads to an increase in reactive oxygen species (ROS), causing substantial oxidative stress that initiates apoptotic or necrotic pathways in the fungal cell[23].

4.3 Inhibition of Spore Germination

In cases of infections caused by dermatophytes, such as Trichophyton species, which depend on dormant spores (conidia) for survival in the environment and the onset of infection, the capacity to prevent germination is crucial. Components of cinnamon exhibit specific activity in stopping the reactivation of these dormant forms, thereby preventing:

Conidial Germination: Stopping the conidia from forming the essential structures needed for growth initiation[24].

Mycelial Proliferation: Inhibiting the subsequent development of hyphal filaments, effectively halting the infection's spread at its earliest stage[25].

4.5 Antifungal Synergistic Action

One of the most promising uses of cinnamon bioactives lies in their potential for combination therapy to tackle existing drug resistance, components of cinnamon exhibit a synergistic effect by boosting the effectiveness of standard antifungal medications such as fluconazole, nystatin, and ketoconazole. This synergy is mainly achieved through two mechanisms:

Efflux Pump Inhibition: Compounds like cinnamaldehyde can inhibit the function of fungal efflux pumps (membrane transporters), which often actively expel conventional drugs from the cell, thereby restoring the drug's effective concentration within the cell[26].

Membrane Destabilization: The initial membrane damage caused by cinnamon components (Section 4.1) increases the overall permeability of the fungal cell, allowing for the passive entry of the co-administered synthetic antifungal drug. This multi-faceted approach positions cinnamon bark as a strong candidate for new single-agent or combination antifungal therapies[27,28].

5. Preclinical Evidence

5.1 *In-vitro* Studies:

Broad-Spectrum Efficacy The foundational pharmacological validation of cinnamon's antifungal capabilities is largely based on comprehensive in vitro studies, which have consistently highlighted its broad-spectrum effectiveness. These experiments repeatedly show that essential oils and various extracts from cinnamomum bark exhibit strong fungistatic and fungicidal effects against a wide range of clinically important pathogens.

Activity against key Pathogen Groups

Preclinical investigations reveal significant inhibitory effects across three primary categories of fungal pathogens:

Opportunistic Yeasts: Extensive research targets species responsible for candidiasis. Extracts and isolated compounds, especially cinnamaldehyde, have proven effective against the common pathogen Candida albicans. Importantly, this efficacy also applies to non-albicans species, such as *C. glabrata* and *C. krusei*, which are often linked to multidrug resistance and persistent infections.

Molds and Systemic Fungi: The effectiveness is not confined to yeasts; it has also been shown against filamentous molds like aspergillus niger and A.

flavus, which cause severe pulmonary infections (aspergillosis). Additionally, cinnamon bioactives inhibit the growth of the encapsulated yeast Cryptococcus neoformans, underscoring its potential in treating cryptococcosis.

Dermatophytes: Inhibition has also been noted against common agents of superficial mycoses, including Trichophyton mentagrophytes and T. rubrum. This supports the ethnobotanical use of cinnamon bark in managing tinea infections[26,27].

5.2 *In-vivo* Studies and Efficacy [28-30]

Although in vitro findings confirm the direct fungicidal properties, the true pharmacological potential of cinnamon extracts is substantiated through in vivo research using animal models, typically mice or rats that simulate human infections. These models yield essential information on efficacy, safety, pharmacokinetics, and the host's immune response.

Reduction of Fungal Burden: Models of systemic candidiasis treated with cinnamon extracts (or primary components like cinnamaldehyde) consistently show a notable decrease in fungal presence within key organs, such as the kidney, spleen, and liver. This decrease is directly linked to the extracts' capacity to disrupt fungal spread and colonization in the host[28].

Improvement in Survival Rates: In models of lethal systemic infections, administering cinnamon bioactives significantly enhances the survival rates of infected animals compared to untreated control groups[29]. This result strongly supports its therapeutic potential, comparable to some standard antifungal medications.

Immunomodulatory Effects: Beyond direct fungicidal action, cinnamon extracts also display valuable immunomodulatory effects study indicates that treatment can boost the host's immune response, particularly by increasing the activity of innate immune cells like macrophages. This dual action of directly killing pathogens while supporting the host's immune system is highly desirable in therapeutic agents[30].

6. Research Gaps

Although in vitro and in vivo studies have convincingly demonstrated the antifungal properties of bioactive compounds from *cinnamomum* bark, there are several crucial gaps that need to be addressed to enable their effective incorporation into standard clinical treatments[31]. These gaps highlight the areas that future research should prioritize.

6.1 Lack of Large-Scale Clinical Trials

The primary obstacle is the absence of comprehensive, large-scale randomized controlled trials (RCTs). Current evidence from human studies is mostly confined to small pilot projects or observational data, with a focus on superficial fungal infections such as oral candidiasis. To gain clinical acceptance and regulatory approval, extensive trials are necessary to:

Efficacy: Thoroughly assess the clinical outcomes of cinnamon-based treatments compared to conventional antifungal medications (e.g., fluconazole) in human subjects[32].

Safety: Provide conclusive information on long-term safety, particularly regarding the potential hepatotoxicity risks associated with systemic administration of coumarin[33].

6.2 Necessity for Consistent Extract Preparations

The variability in antifungal activity documented in the literature is primarily due to the absence of standardized extraction techniques. Future advancements in pharmaceuticals demand consistency.

Chemical Profiling: It is essential to develop methods that ensure extracts are consistently defined by their Minimum Inhibitory Concentration (MIC) and standardized according to the amount of key active components, such as cinnamaldehyde for effectiveness and the maximum permissible level of coumarin for safety.

Species Differentiation: There is a need for clear guidelines to promote the use of low-coumarin species (*C. verum*) in internal formulations, ensuring that the therapeutic index remains advantageous.

7. Conclusion

The preclinical studies reviewed highlight cinnamon bark (Cinnamomum spp.) and its primary components, particularly cinnamaldehyde, as powerful natural antifungal agents. The evidence demonstrates its extensive activity against significant fungal pathogens, such as Candida, Aspergillus, and dermatophyte species. Importantly, its effectiveness is backed by a pharmacological profile that targets multiple areas, including the disruption of ergosterol synthesis and cell membrane integrity, the prevention

of pathogenic biofilm formation, and synergistic effects with traditional antifungal medications.

In the face of rapidly increasing global antifungal drug resistance, cinnamon presents a promising option for complementary or alternative therapeutic approaches. However, moving from laboratory research to clinical application necessitates thorough translational efforts. Future research should focus on

1. Clinical Validation: Conducting large-scale controlled human trials to verify efficacy and establish optimal dosing regimens for both topical and systemic fungal infections.

2. Safety and Standardization: Enforcing strict controls for extract preparation, prioritizing low-coumarin species (*C. verum*), and developing comprehensive pharmacokinetic/ pharmacodynamic profiles.

Informed Consent

Not Applicable.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare no conflict of interest among themselves. The authors alone are responsible for the content and writing of this article.

Financial Interests

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Human and Animal Rights

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