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Cinnamaldehyde as a Potential Antibiotic Substitute against Antibiotic-Resistant Bacteria during Antimicrobial Resistant Challenges

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ABSTRACT

Cinnamaldehyde, found in cinnamon essential oils, has been found to obstruct harmful bacteria both in laboratory experiments and in human food. Conformist antibiotics and antibacterial drugs have been effective in obstructing bacterial infections, but their excessive use has directed the development of resistant bacterial strains.

Keywords: Cinnamaldehyde, Antimicrobial Resistant [AMR], Gram-Positive Bacteria, Gram-Negative Bacteria, Inhibition of ATPase, Biofilm Formation

Introduction

Cinnamaldehyde is a natural compound in cinnamon bark that is commonly known as "dar cheeni دار چینی", an aromatic aldehyde, reported to have antibacterial activity against a variety of foodborne pathogens [1]. Scientists are studying cinnamaldehyde because it might be able to inhibit bacteria that are becoming resistant to antibiotics [2]. Multidrug-resistant bacterial infections are increasing day by day due to the irrational use of conformist antibiotics. The rising global issue of antibiotic resistance is demanding suitable alternatives or substitutes to the currently available antibiotics [3]. An emerging strategy to cope with this issue is the use of antibacterial substances acquired or developed from natural resources. Cinnamaldehyde is a phytochemical that has been shown to inhibit the growth of antibiotic-resistant bacteria like *E. coli*, which can be resistant to treatment with regular antibiotics [4]. Cinnamaldehyde has been utilized in many studies and has shown significant antimicrobial properties. The antimicrobial activity of cinnamaldehyde was found to be more efficient when compared with commonly used antibiotics [5]. Cinnamaldehyde and its derivatives have displayed antibacterial properties against various gram-positive bacteria and gram-negative bacteria [6]. Cinnamaldehyde is "Generally Recognized as Safe" [GRAS] by the United States Food and Drug Administration [FDA] and the Council of Europe has given "A" status to cinnamaldehyde which means it may be utilized as phytomedicine and also in foodstuffs [1]. This review discussed the antimicrobial properties of cinnamaldehyde and its various derivatives which can be used as natural antimicrobial substitute against a variety of microorganisms in a cost-efficient manner.

Methodology:

This study analyzes the complex relations between cinnamaldehyde and antibiotic-resistant bacteria during antimicrobial resistant challenges and highlighting the demand for individualized treatment strategies. The factors examined were cinnamaldehyde as a natural antibiotic substitute, antibacterial susceptibility of cinnamaldehyde, and antibacterial mechanism of action of cinnamaldehyde. The review was conducted through a detailed study of the previous literature of the last 15 years.

Cinnamaldehyde as Natural Product:

Cinnamaldehyde abstained from the bark of certain trees in the *cinnamomum* genus, which has around 250 different types of plants [7, 8]. The main types are *C. cassia* [known as Cassia] and *C. verum* [also called true cinnamon]. These species have different amounts of cinnamaldehyde, up to 85.3% and 90.5% respectively [7]. Cinnamaldehyde is the part that gives cinnamon its antimicrobial abilities [6, 8]. It can inhibit the growth of many types of bacteria, molds, and yeasts, and can also inhibit these microorganisms from making toxins [9]. Cinnamaldehyde, found in the essential oils of *cinnamomum* trees, is effective against various microorganisms, and used in clinical practices [10].

Antibacterial susceptibility of Cinnamaldehyde:

Cinnamaldehyde antibacterial susceptibility refers to its antibacterial ability to inhibit the growth of many harmful bacteria that show resistance to commonly used antibiotics [2]. Several researchers described that cinnamaldehyde exhibits significant antibacterial activity against both gram-negative and gram-positive bacteria [6, 11, 12]. Goni *et al*. [2009] described that the combined therapy of cinnamaldehyde and clove oils has been shown to have antibacterial properties against Gram-negative and Gram-positive bacteria [13]. Some of the gram-positive and gram-negative bacteria that are susceptible to cinnamaldehyde are shown in Table 1.

Gram-positive bacteria:

Cinnamaldehyde essential oil has displayed antibacterial properties against various gram-positive bacteria [6]. The relatively thick cell wall of gram-positive bacteria makes them susceptible to various phytomedicine [1, 14]. Several researches declared that cinnamaldehyde is strongly effective against *Bacillus cereus* [15], *Enterococcus faecalis* [16], *Leuconostoc species, Micrococcus luteus [6], Staphylococcus aureus, Streptococcus species* [17], *Listeria monocytogenes, and Listeria grayi* [18].

Gram-negative bacteria:

Cinnamaldehyde is effective against various gram-negative bacteria including *Escherichia coli* [19], *Pseudomonas aeruginosa* [20], *Pseudomonas fluorescens* [20], *Shigella dysenteriae* [21], *Salmonella Typhimurium* [22].

Compound	Bacteria		Reference
Cinnamaldehyde	Gram Positive	*Streptococcus pyogenes*	[8, 9, 23, 24]
		Bacillus subtilis	[8, 23-25]
		Staphylococcus aureus [*S. aureus*]	[8, 9, 26, 27]
		Lactobacillus sakei	[24]
	Gram Negative	*Listeria* spp. and	[8, 9, 23, 24]
		Campylobacter jejuni	[25, 28]
		Pseudomonas spp.	[8, 23, 26, 29]
		Escherichia coli	[30] [8, 23-26]
		Vibrio spp.	[8, 23, 29]
		Porphyromonas gingivalis	[8]
		Cronobacter sakazakii	[8, 9]
		Salmonella sp Salmonella enterica	[8, 23-25]

Table 1: Antimicrobial Effect of Cinnamaldehyde against Various Gram Positive and Gram Negative Bacteria

Antibacterial mechanism of action of Cinnamaldehyde:

Recent research highlighted the antibacterial mechanism of action of cinnamaldehyde and its components. They emphasized several effects observed when cinnamaldehyde or its constituents interact with bacteria, including changes in the cell membrane and its lipid composition, suppression of ATPase, cell division, membrane protein, motility, and the formation of biofilms as shown in Figure 1 [8]. Therefore, understanding the antibacterial mechanism of these derived compounds will aid in the development of new antibacterial substances.

Alterations in the cell membrane and its lipid profile:

Gram-negative bacteria show resistance against plant extracts due to their complex cell walls, while Gram-positive bacteria are more susceptible [31]. Cinnamaldehyde found in plants, can penetrate bacterial cell walls, disrupting their functions and leading to cell damage [23]. Cinnamaldehyde can affect membrane integrity differently in various bacteria, either by making it more rigid or changing its lipid content [32] [33]. These changes can allow other substances, like antibiotics, to enter the cell, causing cell death [34]. Studies have shown cinnamaldehyde impact on various bacteria such as

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porphyromonas gingivalis causing damage to their membranes and leaking essential components [35]. This shows that cinnamaldehyde primarily targets the membrane, affecting the cell in multiple ways.

Inhibition of ATPase:

In the process of cell energy production, cinnamaldehyde affects a vital enzyme called F1F0-ATPase, essential for making ATP. By changing the shape of certain proteins, cinnamaldehyde hinders the activity of this enzyme, leading to a decrease in ATP synthesis and overall bacterial growth. This effect has been seen in various bacteria, where cinnamaldehyde disturbs the balance of protons and ATP, resulting in decreased energy production. Similar impacts have been observed in mitochondria, where cinnamaldehyde alters the proton gradient, leading to reduced ATP levels and disrupted mitochondrial function [8]. Cinnamaldehyde achieves this by interacting with specific parts of protein molecules, affecting their ability to produce energy. Further studies on purified enzymes are necessary to better understand these interactions
[8, 9]

Inhibition of cell division:

Bacteria multiply through a process called cell division, which is regulated by a protein called FtsZ. Cinnamaldehyde disrupts this process by stopping FtsZ from working properly. It prevents the formation of the Z-ring, which is crucial for cell separation [1]. In both *E. coli and Bacillus cereus*, cinnamaldehyde affects the arrangement of this Z-ring, leading to incomplete cell separation and the formation of long, connected cells [1]. Through computer models, it's suggested that cinnamaldehyde binds to a specific part of FtsZ, hindering its ability to form the Z-ring and ultimately stopping the bacteria from dividing.

Inhibition of membrane porins:

For any substance to kill bacteria, it must first enter the cell. Gram-positive bacteria allow easy penetration for hydrophobic substances, while Gram-negative bacteria are more resistant due to their complex outer structure [23]. Cinnamaldehyde can lower the expression of certain genes responsible for the transportation of amino acids, which disrupts the movement of substances through the bacterial membrane. Some specific proteins, called porins, help molecules move through the membrane. Cinnamaldehyde affects these porins, decreasing their effectiveness in helping the cell manage osmotic stress and desiccation. This disruption can make the bacteria more vulnerable to cinnamaldehyde's antibacterial effects [8]. Further research on bacteria lacking these porins could provide more insight into how cinnamaldehyde affects them.

Inhibition of motility and biofilm formation:

Movement is crucial for bacteria to interact with their environment and cause infections. They form complex communities called biofilms, which protect them from threats and allow them to communicate. Cinnamaldehyde was found to decrease the ability of bacteria to move and form biofilms. It does this by affecting genes related to both movement and biofilm formation. Cinnamaldehyde has been effective in stopping biofilm formation in various harmful bacteria, including those causing urinary tract and skin infections [1]. It works by interfering with the bacteria's communication system, making it hard for them to coordinate their actions. Proteins crucial for biofilm formation were also found to be affected by cinnamaldehyde, making the bacteria more vulnerable to stress. This makes cinnamaldehyde a promising candidate for combating difficult-to-treat infections and biofilm-related issues in both medical and industrial procedures [1].

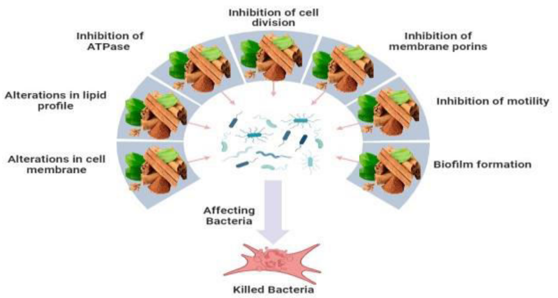

Figure 1: Antibacterial mechanism of action of Cinnamaldehyde

Conclusion:

In this review, we discussed how a natural compound called cinnamaldehyde and its variations can inhibit bacterial pathogens. This is important because we need alternatives to inhibit bacteria that are becoming resistant to antibiotics. Cinnamaldehyde seems auspicious because it can inhibit many types of bacteria without any side effects in consumers. Some altered forms of cinnamaldehyde work even better against both gram-positive and gram-negative bacteria. More research is needed to figure that out. This summary will help scientists develop new antibacterial treatments based on cinnamaldehyde. It might also help in other fields where cinnamaldehyde is used. Further studies in this area could lead to the discovery of even more effective treatments for infections, benefiting both healthcare and agriculture.

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