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The potential of natural antibiotics as a novel antimicrobial strategy: A review of mechanisms and applications

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Abstract. Since the discovery of antibiotics, antibiotics have been developed and used in large quantities, and the misuse of antibiotics has caused the problem of bacterial resistance to become more and more prominent, with an increasing number of drug-resistant bacterial species, a weakening of the unit effect of antibiotics, and a constant increase in the dose of antibiotics, which has greatly endangered human health and production and life. Most of the natural antibiotics come from natural components of plants and animals, which have been vigorously developed and applied in recent years due to their various antibacterial mechanisms, good antibacterial effect, not easy to produce drug resistance, and little harm to human body. In this paper, it will summarize some of the antibacterial mechanisms of natural antibiotics, such as antimicrobial peptides, alkaloids and flavonoids, and the mechanism of the above natural antibiotics to reduce drug resistance. Additionally, based on the research on the application of natural antibiotics in recent years, it will put forward new ideas on the intervention of natural antibiotics in the treatment of common infections.

Keywords: Natural antibiotics, Antibacterial effect, Drug resistance, Infection treatment.

1. Introduction

Antibiotics were discovered by humans in the early 20th century and introduced into the treatment of bacterial infections, achieving good results in the treatment of bacterial infections in the early stages. Based on the excellent antibacterial effect of antibiotics, the types of antibiotics have been expanded, and the use of antibiotics has increased in the following decades. While the misuse of antibiotics has become increasingly severe, the term “bacterial resistance” has gradually entered human health life and posed a significant threat to human health [1]. In order to solve the problem of resistance caused by synthetic antibiotics, research on natural antibiotics is gradually deepening. Natural antibiotics are mainly divided into two categories according to their sources. One is cathelicidin from animal sources, and the other is alkaloids, flavonoids, organic acids and phenols from plant sources. Li’s research shows that they have apparent effects on inhibiting bacterial growth and bacterial infection and have corresponding antiviral and anticancer effects [2]. At the same time, the abundance of plant species and sources provides a vast exploration space for natural antibiotics, and traditional Chinese medicine also provides strong support for the research of natural antibiotics. Therefore, this article will summarize some types of natural antibiotics, their effects and antibacterial mechanisms, propose mechanisms for natural antibiotics to reduce drug resistance, and provide reference and theoretical guidance for applying

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the of natural antibiotic treasure trove. Although there has been progress in research on the inhibitory effects of natural antibiotic synergists and the combination of natural antibiotics and antibiotics on drug-resistant bacteria, Cao et al. have confirmed the synergistic effect and safety of natural antibiotic synergists in inhibiting bacteria [3]. However, the application of natural antibiotic synergists is still in the theoretical stage, and the specific mechanism of action is not clear enough. The application of natural antibiotics is still in traditional Chinese medicine or traditional Chinese patent medicine and simple preparations. Therefore, this paper will propose new ideas for the application of natural antibiotics by analyzing and summarizing the current application of natural antibiotics.

2. Types and effects of natural antibiotics

2.1. Cathelicidin

Cathelicidin is a small-molecule polypeptide. The research of Kang et al. shows that cathelicidin has broad-spectrum antibacterial activity and immunoregulatory function and has certain cytotoxicity to cancer cells, with anticancer effect [4]. As a natural antibiotic, Lei et al. also demonstrated the host defense of cathelicidin; that is, cathelicidin can kill bacteria by damaging the bacterial cell membrane. Therefore, compared with traditional antibiotics, the antibiotic resistance produced by cathelicidin is significantly reduced [5].

2.1.1. Inhibitory mechanism of antimicrobial peptides. The research of Zhang et al. confirm that the antibacterial mechanism of cathelicidin can be divided into two types. Similar to the mechanism of traditional antibiotics, which inhibit bacterial growth or kill bacteria by affecting the normal metabolic activities of bacteria and hydrolyzing bacterial cell walls, cathelicidin also has similar intracellular antibacterial functions; the highlight of cathelicidin bacteriostasis is mainly reflected in its damage to the bacterial cell membrane [6]. The research of Zhang et al. showed that cathelicidin is a positively charged substance, which combines with the bacterial cell membrane with negative charges on the surface through electrostatic adsorption. Since cathelicidin, as a polypeptide, has amphiphilic nature, the hydrophobic end will combine with the phospholipid on the surface of the cell membrane, thus breaking the lipid bilayer structure of the bacterial cell membrane, causing damage to the bacterial cell membrane structure and causing bacterial lysis and death [7].

2.2. Alkaloids

Alkaloids are primarily a class of alkaline organic compounds produced by plants. They have a wide range of types and sources and many different effects. For example, the commonly used analgesic morphine and berberine, summarized by Li et al, which has the effect of treating type 2 diabetes, belong to alkaloids [8]. At the same time, the antibacterial effect of alkaloids, including the effect of inhibiting gram-negative bacteria and gram-positive bacteria, has been demonstrated by a large number of studies. Some studies also show that alkaloids can reverse antibiotic resistance, so alkaloids as a natural antibiotic have been extensively studied and developed in recent years.

*2.2.1. Bacteriostatic mechanism of alkaloids.*A large number of studies have shown that the antibacterial mechanisms of alkaloids can be divided into three main types: increasing the permeability of bacterial cell membranes through extracellular action and damaging bacterial cell walls; intracellular interactions affecting the normal metabolic activities of bacteria, such as inhibiting nucleic acid and protein synthesis and other metabolic processes; factors affecting bacterial virulence and reducing infectivity.

Zhao's research observed the cell structure of Escherichia coli and Staphylococcus aureus treated with Gelsemium elegans alkaloids under the electron microscope, and found that the two bacteria treated with the above alkaloids had cell structure damage and changes in cell membrane permeability, and bacterial cells caused bacterial lysis death due to leakage of cell contents [9].

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Other scientists have studied the effect of alkaloids on the bacterial cell wall. After brucine sulfate treatment, the bacterial cell wall is dissolved into blocks. However, bacteria lack the protection of cell walls, and their cell membrane is easily broken by external physical and chemical factors, resulting in exposure to bacterial intracellular protoplasm and rupture death [10].

The growth and reproduction of bacteria are closely related to the metabolism of sugars, lipids, proteins and nucleic acids, while alkaloids can inhibit bacterial growth and reproduction by interfering with the normal metabolic process of bacteria. Dong et al. based on the extraction of Eucommia ulmoides Oliv., a traditional Chinese medicine, found that the extract (Z)-oxodihydroindole-3-subunit ketone as a new alkaloid can inhibit the growth and reproduction of Staphylococcus aureus by inhibiting the activity of DNA gyrase, an enzyme necessary for DNA replication [11]. Matrine, an alkaloid extracted from the traditional Chinese medicine plant Sophora flavescens, has a good inhibitory effect on both gram-negative and gram-positive bacteria. Wang et al. investigated its antibacterial mechanism based on matrine and found that matrine has an inhibitory effect on bacterial growth and synthesis of fission-related proteins. The life cycle of E. coli treated with matrine stagnates before the DNA replication phase, which inhibits the growth and reproduction of E. coli [12]. In addition, a large number of studies have also confirmed the inhibitory effects of various alkaloids on bacterial sugar metabolism, lipid metabolism and protein metabolism, indicating the antibacterial effect of alkaloids.

Numerous studies have shown that alkaloids can target virulence factors, which are important factors in determining the success of bacterial infection, to reduce bacterial pathogenicity. Liu et al. found that although the growth of Staphylococcus aureus treated with piperine was not inhibited, the treated Staphylococcus aureus was inhibited in the expression of a virulence factor - α-hemolysin, resulting in a significant decrease in its pathogenicity after infection [13].

*2.2.2. Mechanisms of resistance to alkaloids.*While alkaloids have sound antibacterial effects, a large number of studies have shown that alkaloids can also reverse antibiotic resistance, filling the gap in traditional antibiotic treatment that produces resistance. The investigation of Chen et al. shows that the biofilm of bacteria is a substance produced by bacteria that contains a large number of extracellular polysaccharides and hydrolase, and it is resistant to foreign antibiotics due to its inactivation effect; at the same time, it can also establish molecular and charge barriers to block the entry of foreign antibiotics, while marine pyridine alkaloids can reduce the biofilm of MRSA by about 25%, effectively inhibiting the development of drug resistance [14]. Zhang et al. measured the changes of drug resistance genes of multidrug-resistant Escherichia coli under berberine treatment by high-throughput real-time fluorescence quantitative PCR method, and found that berberine has the drug resistance genes sul2 and mexE to eliminate multidrug-resistant Escherichia coli, thus reducing the resistance of berberine-treated multidrug-resistant Escherichia coli to levofloxacin and other antibiotics, It has been confirmed that alkaloids can reverse drug resistance by inhibiting the expression of bacterial resistance genes [15].

2.3. Flavonoids

Flavonoids are a class of polyphenols widely found in vegetables, fruits, tea and many kinds of herbs, including flavonoids, flavonols, flavanones, flavanols, isoflavones and anthocyanins, etc., which have a wide variety of types and have a variety of biological activities [16]. In a study of flavonoids by Navrátilová A et al, it was found that they have rich physiological activities in the areas of antibacterial, antiviral, and inhibitory for cancer cells [17]. They are rich in physiological activities [17]. In the current situation of antibiotic abuse and antibiotic resistance, flavonoids, as a kind of natural antibiotics, have been gradually involved in antimicrobial therapy because of their good antibacterial effect and anti-resistance characteristics, so it is valuable to explore the antibacterial and anti-resistance mechanisms of flavonoids to seek an alternative to traditional antibiotics.

*2.3.1. Inhibitory mechanism of flavonoids.*A large number of studies have shown that the bacteriostatic mechanism of flavonoids can be divided into two aspects. One of them is to act directly on the bacteria itself, by increasing the permeability of the bacterial cell membrane, causing damage to the bacterial

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cell wall and inhibiting the normal metabolic activities of the bacteria, such as nucleic acid, protein synthesis and energy metabolism so as to achieve the effect of bacterial inhibition; in addition, flavonoids can also regulate the host cells infected by bacteria, promote the immune response, and achieve the effect of bacterial inhibition indirectly.

The majority of natural antibiotics work by increasing the permeability of bacterial cell membranes and causing damage to the bacterial cell wall. Wu studied the bacteriostatic effect of flavonoids by affecting the permeability of E. coli cell membranes based on membrane interaction, and confirmed that flavonoids could kill bacteria by increasing the permeability of cell membranes and decreasing the fluidity of the membranes, resulting in the loss of cytoplasm and even cell rupture [18]. At the same time, Wen et al. treated Staphylococcus aureus with naringenin, and the treated Staphylococcus aureus also showed the phenomena of increased cell membrane permeability, decreased membrane fluidity, and loss of cellular contents, which also confirmed the above-mentioned inhibitory mechanism of flavonoids [19].

Inhibition of bacterial nucleic acid synthesis is another inhibitory mechanism of flavonoids. Plaper et al. showed that isoflavones and flavanols in flavonoids could inhibit the activity of DNA topoisomerase affecting the bacterial DNA synthesis pathway, and the quercetin-treated bacterial DNA rotamase activity was reduced, which ultimately resulted in the cleavage of the DNA because of the structural damage [20].

Inhibition of bacterial energy metabolism is a characteristic inhibitory mechanism of flavonoids. ATP synthase is an important enzyme in biological energy metabolism, and studies have shown that there is a polyphenol binding site at the junction of α, β, and γ subunits in the F1 segment of ATP synthase, so as one of the polyphenols, flavonoids can be bound to this site, and play a hindering role in the normal rotational movement of the γ subunit, thus inhibiting ATP synthase synthesizing the energy flux ATP [21]. Thus, it inhibits ATP synthase from synthesizing energy flux ATP and inhibits bacterial energy metabolism [21].

Flavonoids can not only play an antibacterial effect by directly acting on the bacteria themselves, but also act on the host cells, and indirectly achieve the antibacterial effect by affecting the immune response of the host cells. The study of Wang et al. summarized that flavonoids intervene in the gastric mucosal lesions caused by Helicobacter pylori infections, colitis caused by Escherichia coli, pneumonia caused by Mycoplasma mycoides, the influenza virus complications caused by Streptococcus pneumoniae, and the treatment of Klebsiella pneumoniae infections. The mechanism of host immune response induced by the treatment of Klebsiella pneumoniae infection reflects the positive effect of flavonoids on the modulation of cytokines and the corresponding effect on the downstream immune response for bacterial suppression [22].

2.3.2. Antidrug resistance mechanisms of flavonoids. Flavonoids have a good antibacterial effect at the same time, and their inhibition of drug resistance is also multi-faceted; in addition to the above effects on the bacterial cell membrane and cell wall, flavonoids can also be inhibited through the inhibition of β-lactamase activity, the elimination of plasmids containing drug-resistant genes and inhibit the bacterial efflux pumps from achieving the effect of inhibition of bacterial resistance, antibacterial and anti-drug-resistant dual role of flavonoids as a natural antibiotic is very valuable for development. β-lactamase is a natural antibiotic for Gram-positive bacteria.

β-lactamases are enzymes produced by Gram-negative enterobacteria that induce drug resistance in bacteria [23]. Liu et al. treated drug-resistant Staphylococcus aureus with three kinds of flavonoids, namely rutin, curcumin, and quercetin, respectively, with obvious inhibitory effects, and measured the β-lactamase activity of bacteria during the treatment process by using enzyme labeling instrument, and hypothesized that flavonoids could reduce bacterial drug resistance by decreasing β-lactamase activity [24]. It has also been shown that the possible mechanism by which astragaloside inhibits antibiotic resistance in multidrug-resistant Acinetobacter baumannii is also the inhibition of β-lactamase activity [25].

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Studies have shown that multiple resistance genes contained in drug-resistant plasmids are passed between bacterial strains through transformation, transduction, and conjugation, and therefore, drug-resistant gene-mediated generation of resistance is a common way for bacteria to acquire drug resistance [26]. Wang et al. treated multidrug-resistant Acinetobacter baumannii with astragaloside and found that the plasmid content of treated multidrug-resistant Acinetobacter baumannii was reduced, while the MIC for some antibiotics was restored to the sensitivity level, indicating that flavonoids such as astragaloside can sensitize drug-resistant bacteria to antibiotics by eliminating the drug-resistant plasmids [27].

When bacteria are treated with drugs, they can actively excrete the drugs through the exocytosis pump on their cell membrane. Active excretion of antibiotics by bacteria leads to resistance to this class of antibiotics. Lechner et al.'s study treated Mycobacterium species with lignocellulosides, and found that lignocellulosides are a kind of Mycobacterium species exocytosis pump inhibitor, which inhibits the exocytosis of drugs in Mycobacterium species, and inhibit the growth of Mycobacterium species [27]. And inhibit the growth of mycobacteria [28]. ABC membrane protein family is an important class of bacterial efflux pump system component proteins. Zou et al.'s study found that chickpea budgerigar A-treated Staphylococcus aureus ABC efflux protein synthesis is inhibited, and efflux genes NorA transcription is inhibited, thus inhibiting the efflux pump function of Staphylococcus aureus to achieve elimination of the effect of drug resistance [29]. In summary, flavonoids can eliminate the effect of bacterial drug resistance by inhibiting the role of the bacterial efflux pump.

3. Research progress in the application of natural antibiotics

In recent years, with the increasing bacterial resistance brought about by the misuse of traditional antibiotics, multi-drug resistance and extensive drug resistance of bacteria has been increasing globally, posing great challenges to human health. Natural antibiotics have been extensively studied for their low toxicity, excellent antibacterial properties and good resistance. Currently, there are two main aspects of the application of natural antibiotics, one of which is to apply them to the food and aquaculture industry with their low toxicity characteristics, using natural antibiotics instead of traditional antibiotics added to the feed in order to enhance the safety of artificially cultivated food; the other is to intervene in the treatment of common infections with their excellent antibacterial and anti-drug resistance effects, mainly using natural antibiotics as synergistic agents of traditional antibiotics to enhance the antibacterial effect of traditional antibiotics, and to improve the antibacterial effect of traditional antibiotics. The second is to intervene in the treatment of common infections with its excellent antimicrobial and anti-resistance effects. The study by Cao et al. summarized the anti-resistance effects and some mechanisms of natural antibiotics as synergists in combination with traditional antibiotics on a variety of common drug-resistant bacteria, including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and ultra broad-spectrum β-lactamase-producing (ESBLs) bacteria in recent years, and confirmed that the combination of natural antibiotics and traditional antibiotics can be used to intervene in the treatment of drug-resistant bacterial infections. The use of interventional treatment of drug-resistant bacterial infections can enhance the antimicrobial effect and reduce the resistance of drug-resistant bacteria [3]. A large number of studies have shown that natural antibiotics are safer than traditional antibiotics because of their lower toxicity, and Cao et al.'s study also showed that not only are natural antibiotics safer, but their synergistic combination with traditional antibiotics to reduce the dose of traditional antibiotics also reflects their safety [3]. However, the current research on natural antibiotics is still insufficient, and the specific anti-resistance mechanism of some natural antibiotics is still not clear enough, in addition to this, the pharmacological study of natural product extracts is still rarely entered into clinical trials, and its suitability as a drug to intervene in the clinical treatment of infections or synergistic agent still requires a large number of more in-depth studies.

4. Conclusion

The emergence of drug-resistant bacteria, increasing bacterial resistance, increasing antibiotic dosage, increasing cases of superbugs, etc. have shown that the problem has been a serious threat to human health and productive life, and the efficacy of traditional antibiotics has been increasingly challenged.

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Natural antibiotics, including antimicrobial peptides, alkaloids, flavonoids, organic acids, phenols, and other substances with a wide range of sources, low toxicity, and high bacteriostatic and anti-drug resistance characteristics cater to the current infection treatment continue to solve the problem. Therefore, the research on natural antibiotics should pay more attention to their specific anti-drug resistance and bacterial inhibition mechanisms, expand the research on the broad-spectrum inhibition of natural antibiotics for different kinds of pathogenic bacteria, explore the effect of compound natural antibiotics, and enhance the broad-spectrum of antibacterial inhibition of natural antibiotics. In the upstream research field, we should increase the research on the extraction and synthesis process to make them more suitable for large-scale use. In the downstream application stage, the research on natural antibiotics should be focused on advancing to the clinical research stage, and enhancing the appropriate ratio of natural antibiotics to traditional antibiotics to enhance the antibacterial and anti-drug resistance effects, and reduce the toxicity and side effects of drugs. At present, the research on natural antibiotics is still in the primary stage, and their antibacterial and anti-drug resistance mechanisms are still in the in vitro stage; however, with the deepening of the research on the mechanism of action and application of natural antibiotics, the intervention of natural antibiotics in the clinical anti-infective treatment will be endowed with more favorable conditions.

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