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Plant-Based Nanoantibiotics: An Effective Strategy to Overcoming Antibiotic Resistance †

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Abstract: Commonly used antibiotics use multiple administrations for providing a continuous bactericidal effect but can increase systemic toxicity, as well as lead to bacterial drug resistance. The use of plant-based antibacterial compounds in combination with conventional antibiotics to treat drug-resistant infections could be an alternative to overcoming the problem of bacterial resistance. The combination of antibiotics with plant-based antibacterial compounds has shown synergistic advantages due to the inhibition of drug efflux and the presence of alternative mechanisms of action. Moreover, the nanoencapsulation of antibiotics is another effective technique to overcome antibiotic resistance. Nano-encapsulated antimicrobials have a better performance in comparison with traditional antibiotics due to their small size which leads to better interaction with bacterial cells. The different nanocarriers are effective in efficiently administering antibiotics by improving pharmacokinetics and accumulation while reducing the adverse effects. Additionally, the surface engineering of nanocarriers provides benefits such as targeting and modulating various resistance mechanisms. Furthermore, most nanocarriers are suitable platforms for co-loading of plant-based antibacterial compounds and traditional antibiotics to provide synergistic effects. This study outlines recent attempts to combat infectious diseases, with a focus on the use of plant-based nanoantibiotics as novel tools to address today's issues in infectious disease treatment.

Keywords: nanocarriers; antibacterial compounds; plants extracts; synergistic activity

1. Introduction

Infectious diseases were the greatest cause of death worldwide at the turn of the 20th century. The introduction of antimicrobial drugs was largely responsible for the decline in morbidity and mortality from these diseases throughout the last century. Antibiotics are frequently used to prevent and cure bacterial infections in medical care. However, free antibiotics have a low in vivo ingestion rate and are unable to effectively accumulate at the infection site [1]. As a result, a sizeable antibiotic dosage is necessary to obtain an effective bactericidal concentration and results in systemic drug distribution. Antibiotic misuse and overuse, together with the fast mutation and evolution of bacteria, have resulted in a growing number of side effects that influence human health and result in the rise of drug-resistant microorganisms capable of surviving traditional antibiotic therapies. Long-term or high-dose antibiotic therapy may produce toxicity in human tissues and organs to variable degrees [2]. Widespread antibiotic use contributes to the expansion of drug-resistant bacteria, which pose a severe threat to human health. Thus, the long-term treatment of bacterial illnesses requires the discovery of novel and effective antibacterial medicines [3]. To avoid these undesirable effects associated with antibiotics, current research is focusing on the use of plant-derived extracts as antibiotic substitutes [4]. In plant-based edible materials, a large range of natural compounds with antimicrobial activity has been found, although the efficacy of natural antimicrobials can be influenced by a variety of factors [5]. The bioavailability of these plant-based compounds is limited by their hydrophobicity, volatility, and instability, which dramatically reduces their biological and antibacterial action. A variety of techniques for encapsulating these plant-derived antibacterial substances have been reported to meet these issues. By altering antibiotic delivery systems on the nanoscale, nanotechnology is increasingly being used to build effective antimicrobial delivery systems [6]. In the context of research on this novel technique, this study proposes using nanotechnology as a new paradigm in controlling infectious diseases, particularly in overcoming antimicrobial medication resistance, with an emphasis on plant-based nanoantibiotics.

2. Plant-Based Antimicrobials

Numerous plants produce secondary metabolites and other compounds to ward off pathogens such as microorganisms (bacteria, fungi, and viruses), insects, and herbivores. These plant-derived chemicals are classified according to their botanical source, chemical structure, and mode of action [7]. Recently, there has been renewed interest in isolating natural antimicrobials from waste materials recovered from the food and agricultural industries, including such waste products of fruits and vegetables. Among them, some of the most significant plant-based antimicrobial compounds are highlighted below.

2.1. Phenols and Polyphenols

Phenols and polyphenols are secondary metabolites produced by plants to protect them from bacteria, insects, and herbivores. Simple phenols, phenolic acids, flavonoids, quinines, tannins, and coumarins are some of the main antimicrobial classes of polyphenols [8]. The toxicity of simple phenols and phenolic acids to microorganisms is dependent on the hydroxylation site(s) and degree of hydroxylation, with a more oxidized structure exhibiting more inhibitory activity [9]. Other studies believe that the antibacterial effect of phenolic acids is due to membrane disruption, which causes leaking of critical intracellular components, direct changes in microbial metabolism, and inactivation of essential substrates for microbial development. Figure 1 schematically depicts the capacity of phenolics to inhibit bacteria by modifying their surface characteristics [10].

2.2. Essential Oils

Essential oils (EOs) are complex extracts from aromatic plants that contain a variety of aldehydes, terpenes, and phenols. They are widely known for their biological and antibacterial activities. EOs and their components have demonstrated remarkable antimicrobial activity against multidrug-resistant (MDR) pathogens such as methicillin-resistant *Staphylococcus aureus* [11]. Because of its impact on one or more cell components, EOs can affect bacterial cell integrity, resulting in growth inhibition or, at high enough concentrations, cell death. Thus, using EOs to fight or inhibit MDR bacteria development shows promise [12].

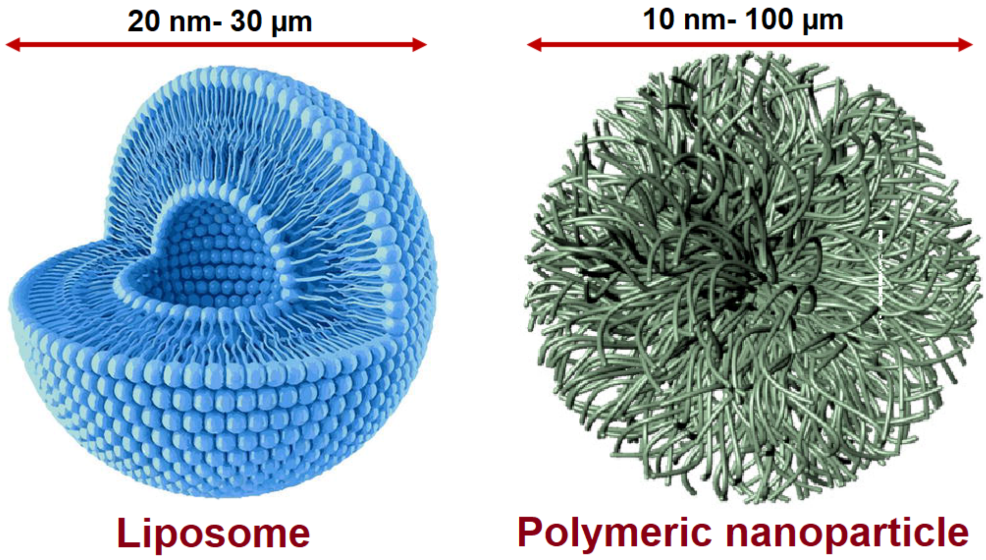

Figure 1. The schematic of the used liposomes and polymer-based NPs for encapsulation of natural antimicrobials.

3. Nanoencapsulation of Plant-Based Antimicrobials

An efficient antimicrobial agent should interact with the desired target while interacting with nonspecific targets as little as possible to improve potency and avoid adverse effects. Plant-derived antimicrobials like EOs have some limitations in this aspect since they are highly influenced by environmental conditions. In particular, poor water solubility decreases bioavailability and significantly reduces antibacterial activity, whereas volatility makes prolonged release and regulated delivery difficult [13]. To address these problems, a range of techniques for encapsulating plant-derived antibacterial compounds as colloidal systems have been reported, including nanoemulsions, lipid-based nanocarriers (e.g., liposomes, and solid lipid nanocapsules), and polymer-based carriers [14]. Moreover, the majority of nanocarriers are suitable platforms for the co-loading of plant-based antibacterial agents and conventional antibiotics to generate synergistic effects [1].

3.1. Antimicrobial Nanoemulsions

Oil-in-water nanoemulsions, including lipid nanoparticles (NPs) disseminated in water, are the most often employed nano-enabled delivery method for natural based antimicrobials. Antimicrobial nanoemulsions can be classified according to the characteristics and location of the antimicrobials they carry. Nanoemulsions are colloidal dispersions composed of two incompatible fluids, one distributed in the other as small particles (d < 200 nm). Although these systems are thermodynamically unstable, they can be made to be metastable for long enough durations to be useful in a variety of commercial applications [6,15].

3.2. Liposome-Based Nanoantibiotics

Liposomes are nano- to micro- sized vesicles made up of a bilayer of phospholipids and an aqueous core. Liposomes have been extensively studied as potentially useful carriers of enzymes, proteins, and drugs for the treatment of a variety of diseases [16]. Liposomes are also the most extensively utilized antimicrobial drug delivery vehicle due to their bilayer lipid structure, which mimics the cell membrane and readily fuses with infectious bacteria. Additionally, both hydrophilic and hydrophobic antimicrobial agents can be encapsulated and maintained in the aqueous core and the phospholipids bilayer, respectively, without requiring chemical modification [17].

3.3. Polymer-Based Nanoantibiotics

Antibiotics encapsulated in polymeric NPs have various advantages: (1) structural stability in biological fluids and under harsh and varied situations for preparation (e.g., spray drying and ultrafine milling) and storage, (2) precisely tunable characteristics (e.g., size, zeta-potentials, and drug release profiles) by attempting to manipulate polymer lengths, surfactants, and organic solvents used throughout NPs preparation, and (3) simple and versatile surface functionalization for conjugating drugs and targeting ligands. Polymeric NPs have been investigated for their ability to administer a variety of antimicrobial agents, with significantly increased therapeutic efficacy in the treatment of a variety of infectious diseases [6]. Figure 1 illustrates liposomes and polymer-based NPs used to encapsulate natural antimicrobials.

4. Concluding Remarks

Antibiotics have saved a huge number of lives from a variety of infectious diseases for more than half a century. However, the emergence of antibiotic resistance gained by microbial variations poses a significant challenge to the fight against infectious diseases. The use of antimicrobial compounds derived from plants instead of conventional antibiotics has become a significant topic of research. A number of these chemicals are incompatible with utilization in their pure form due to solubility, stability, and activity concerns. As a result, nanoemulsion-based delivery systems are being developed to address these constraints. Nanomaterials are prospective antibacterial agents of a new class due to their high surface area to volume ratio and unique physicochemical characteristics.

Taken together, the utilization of plant-derived NPs has demonstrated benefits and applications in medicine and the pharmaceutical sector. More precisely, investigations demonstrate that NPs possess antibacterial characteristics on their own or in conjunction with antibiotics, alleviating the current problem of acquired resistance caused by antibiotic overuse or misuse. With this application in mind, future research should focus on two areas: determining the safety of plant-based NPs (toxicity to humans and the environment) and mitigating the environmental impact of their synthesis. Not only is it necessary to refine the synthesis procedures, but also to investigate the mechanisms by which NPs exert their antibacterial effect, to transform plant-based NPs into a viable strategy capable of meeting society's demand for an effective solution to antibiotic resistance.

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