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The Review of Antibacterial Mechanism of Cellulose-based Hydrogel

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Abstract. Wound infection has become an serious challenge in medical field. Cellulose-based gel can be developed for use as biomedical antibacterial materials because of its excellent biocompatibility, biodegradability and abundant sources. However cellulose lacks intrinsic antibacterial properties to resist infections, which severely limits its clinical application. This review systematically elaborates four core mechanisms for imparting antibacterial properties to cellulose-based hydrogels, including physical disruption, electrostatic adsorption, ROS-responsive, and chemical interference or ion release. What's more, this review also analysis the advantages and limitations of every type of antibacterial cellulose-based hydrogels. While the abundant related research has been proposed, how to design cellulose-based hydrogel to achieve a balanced approach to high antibacterial efficacy and biosafety, as well as the advantages and limitations of different antibacterial mechanisms in complex biological settings, remain key issue worthy of attention. The review concludes that the antibacterial efficacy of cellulose-based hydrogels is highly dependent on the employed mechanism.

Keywords: Antibacterial, cellulose, hydrogel, Cellulose-based hydrogel

1. Introduction

Chronic infection and antibiotic resistance have become a significant challenge in global public health, especially in wound care, food packaging, and the medical and health care field. Therefore, the development of safe, efficient, and environmentally friendly new antibacterial materials is an urgent task in the material field. Traditional antibacterial agents face the severe problem of increasing drug resistance and potential ecological toxicity, prompting researchers to turn their attention to natural biopolymers. Cellulose-based hydrogel, derived from the most abundant polymer on earth, have emerged as a prominent alternative because of its excellent biocompatibility, degradability, renewability, and chemically functionalizable structures. Its three-dimensional network structure rich in water provides excellent water retention, breathability, and mechanical support, enabling it to mimic biological tissue [1]. Thus, cellulose-based hydrogel is an ideal biomaterial for medical use. However, cellulose itself lacks antibacterial capabilities against various bacteria, which limits its direct application in anti-infection.

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At present, researchers mainly achieve cellulose-based hydrogel antibacterial effects through physical damage, electrostatic adsorption, reactive oxygen species, and chemical interference or ion release. These materials generally exhibit significant inhibitory effects on various pathogenic microorganisms in vitro, such as Staphylococcus aureus and Escherichia coli. However, the further development of this field still faces several key bottlenecks. Current research only focuses on antibacterial properties, but neglects a core contradiction, which is maintaining a balance among the antibacterial efficiency, mechanical strength, biocompatibility, and degradation. Furthermore, most studies remain at the laboratory performance verification, lacking the research on clinical application, such as the long-term stability of the antibacterial, complex physical environment maintenance and potential cytotoxicity activity.

In view of this, this paper aims to review recent years' various antibacterial mechanisms of antibacterial cellulose-based hydrogel and its advantages and limitations, and to discuss the potential applications and future challenges of the antibacterial cellulose-based hydrogel in wound dressing and food packaging.

2. The main antibacterial principle

2.1. Physical disruption antibacterial cellulose-based hydrogel

2.1.1. The mechanism of physical disruption antibacterial cellulose-based hydrogel

Physical damage type antibacterial cellulose-based hydrogel does not depend on the specific biochemical reactions or ion release, Instead, they incorporate nanomaterials that interact directly with bacteria, using physical and mechanical damage as the primary mechanism to kill bacteria. Their antibacterial activities mainly come from the load of nanomaterials, such as graphene oxide GO.

For the two-dimensional nanomaterials, the primary physical antibacterial mechanism is the direct puncture and destruction of the membrane. When two-dimensional nanomaterials piece layer contact with bacteria, its edge can be a nano knifeto directly puncture and insert a cell's outer membrane or peptidoglycan layer with the role of van der Waals force [2,3]. After the mechanical cutting, the huge specific surface area of the two-dimensional material plays a paramount role in large-scale membrane packages and lecithin extraction. With the strong van der Waals force and hydrophobic interaction, the laminated material tightly wraps the bacteria or covers on the membrane surface in large area [4]. This cover not only sets up a physical barrier between bacteria and the environment to isolate material exchange, but also the strong interaction between the material and the phospholipid bilayer can directly extract phospholipid molecules in the membrane structure, leading to the irreversible dissolution and collapse of the cell membrane. Additionally, many nanomaterials exhibit excellent photothermal conversion capabilities or can be used as photosensitizers. Under near-infrared light or visible light irradiation, they convert light energy into heat energy or generate reactive oxygen species by photothermal effect or photodynamic effect. This localized hyperthermia induces the melting of membrane lipids, irreversible denaturation of proteins and inactivation of enzyme systems in bacteria, rapidly achieving synergistic antibacterial effects with physical mechanisms against various bacteria.

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2.1.2. Advantages and limitations of physical damage type antibacterial cellulose-based hydrogel

Antibacterial by physical mechanism is broad-spectrum which means physical disruption is effective against various bacteria and even some fungi. Furthermore, the physical mechanism makes it difficult for bacteria to develop resistance through genetic mutations. This process can also respond rapidly and controllably make a response within minutes while reducing the exposure to the normal tissue simultaneously. In addition, nanomaterials often bring additional properties to the hydrogels. For example, GO enhances the mechanical strength of hydrogels and provides photothermal therapy function.

However, this antibacterial method still has several limitations. Potential biotoxicity arising from the incorporation of nanomaterials presents a major obstacle to the clinical translation of the hydrogel system [5]. Existing research indicates that the sharp edges of GO may cause physical damage to mammalian cells [6]. Furthermore, many performances depend on external stimulation, such as an external near-infrared light source. Moreover, the release and stability of nanoparticles remain challenging, which is critical for ensuring safety and long-term effectiveness.

2.2. Electrostatic adsorption antibacterial cellulose-based hydrogel

2.2.1. The mechanism of electrostatic adsorption antibacterial cellulose-based hydrogel

This type of hydrogel primarily relies on the electrostatic interaction between the positive charges carried by the antibacterial components and the negatively charged bacterial cell membranes, leading to bacterial death by disrupting membrane functions [7]. Chitosan and its derivatives are representative examples of such antibacterial hydrogels.

This antibacterial process begins with electrostatic attraction. In the weakly acidic wound microenvironment or neutral environment, the functional groups on the antibacterial component chain undergo protonation, forming positively charged ions, resulting in the entire molecular chain exhibiting strong positive polarity. For instance, the free amino groups on the chitosan chain are protonated to generate positively charged ammonium ions [8]. Most bacteria bear a negative charge on their cell membranes due to teichoic acids or lipopolysaccharides on their surfaces. Positively charged antibacterial components are strongly attracted and tightly adsorbed onto bacterial cell surfaces via strong Coulombic forces, forming a polymeric film. This high-density positive charge coverage neutralizes the negative charges on the membrane surface, thereby disrupting the electrostatic repulsion that maintains the normal structure and stability of the membrane [9]. Charge shielding interferes with the structure and function of proteins on the membrane that depend on the charge environment. It also impairs the continuity and integrity of the phospholipid bilayer. The formation of pores compromises the selective barrier function of the membrane, affecting energy synthesis and active transport. Antimicrobial components with high molecular weight or at high concentrations can even form a polymeric film, completely obstructing the exchange of substances between the cell and its external environment. As membrane permeability increases, crucial metabolites and proteins within the cytoplasm begin to leak out. The disorderly influx of external substances completely disrupts the intracellular ion balance and osmotic pressure, ultimately leading to cytoplasmic condensation, metabolic arrest, and bacterial death. Furthermore, the antimicrobial agents that enter the cell may bind to DNA, interfering with RNA transcription and protein synthesis, or bind to negatively charged intracellular enzymes [10]. By inhibiting their activity, these agents undermine the metabolic activities of bacteria both intracellularly and extracellularly.

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2.2.2. Advantages and limitations of electrostatic adsorption antibacterial cellulose-based hydrogel

The chitosan nanocellulose composite hydrogel primarily utilizes electrostatic adsorption for antibacterial activity. As chitosan is a natural polysaccharide, its degradation products are low-toxic and can promote wound healing and cell growth [11]. Such hydrogel exhibits excellent biocompatibility and degradability, along with high biosafety. Additionally, the cationic charge of chitosan can attract red blood cells to aggregate, endowing it with natural hemostatic ability [12]. Moreover, chitosan can stimulate macrophage activation and collagen deposition, thereby promoting tissue regeneration. Thus, this hydrogel also possesses hemostatic and wound-healing properties. At the same time, similar to physically disruptive antibacterial hydrogels, due to its antibacterial mechanism relying on physical interactions, it exhibits broad-spectrum antibacterial activity. From an industrialization perspective, the raw materials for this type of hydrogel are widely available, relatively low-cost, and facilitate large-scale production.

However, this antibacterial hydrogel also faces several developmental barriers. Firstly, its antibacterial activity heavily depends on the environmental pH. Under alkaline or physiological pH conditions, the degree of amino protonation is significantly reduced, leading to reduced positive charge and a significant decline in antibacterial performance. This is the primary limitation hindering the application of such hydrogels in the medical field. Additionally, chitosan-containing hydrogels are typically only soluble in acidic solutions, which restricts their processability due to solubility constraints. Secondly, pure chitosan hydrogels often exhibit low strength and high brittleness, so they are usually compounded with other materials to improve their mechanical properties. In terms of antibacterial effectiveness, chitosan is less effective against the cell walls of certain fungi compared to bacteria, resulting in limited antifungal efficacy of such hydrogels.

2.3. ROS-responsive antibacterial cellulose-based hydrogel

2.3.1. The mechanism of ROS-responsive antibacterial cellulose-based hydrogel

The antibacterial mechanism of the reactive oxygen species (ROS)-attack hydrogel involves activating sensitive components within the hydrogel via external stimuli, which enables the in situ generation of reactive oxygen species. These ROS launch a destructive oxidative assault on bacteria from the outside in, disrupting their respiratory and metabolic systems, ultimately leading to bacterial death and lysis.

At the beginning, under specific stimuli such as light exposure, the photosensitizer within the hydrogel is activated, generating a high concentration of reactive oxygen species (ROS) in the microenvironment surrounding the bacteria through electron transfer or energy transfer pathways. Follow then, the bacterial cell membrane becomes the primary target of attack. ROS attack the unsaturated fatty acid double bonds in the phospholipid bilayer of the cell membrane, [13] This alters the fluidity of the membrane, increases its permeability, and leads to the formation of lipid peroxidation end products, which are toxic. When ROS penetrate the damaged cell membrane, they react with nearly all key biological macromolecules within the cell. Thus, proteins undergo oxidative inactivation. and nucleic acids suffer damage. Furthermore, ROS disrupts metabolites, thereby completely dismantling the cell's metabolic network and antioxidant defense system. Under the combined effects of these multiple factors, damage accumulates rapidly until it exceeds the repair capacity of the bacterial antioxidant system. This induces the cessation of ATP synthesis, which subsequently disrupts the respiratory chain and inactivates core enzymes. These dual perturbations

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collectively arrest both biosynthesis and catabolism, ultimately culminating in bacterial death and lysis.

2.3.2. Advantages and limitations of ROS-responsive antibacterial cellulose-based hydrogel

ROS-attacking antibacterial strategies offer numerous advantages. The multi-target attack of reactive oxygen species makes it difficult for bacteria to develop resistance through single mutations, resulting in more thorough antimicrobial efficacy [14]. Additionally, the small molecular nature of ROS allows it to penetrate into structurally dense biofilms, killing protected bacteria, which is crucial for treating chronic infections. This antibacterial mechanism is also easily regulated, as the antimicrobial effect occurs and persists only when external stimuli are applied, enabling on-demand treatment and minimizing damage to normal tissues.

However, the issues associated with reactive oxygen species should not be overlooked. The generation mechanism of some reactive oxygen species is highly oxygen-consuming, making it less effective in hypoxic wound or biofilm areas. Furthermore, the production of reactive oxygen species relies on external stimuli, but the limited penetration depth of effective stimuli in tissues severely restricts the application of such hydrogels in treating deep tissue infections.

2.4. The chemical interference or ion-releasing antibacterial cellulose-based hydrogel

2.4.1. The mechanism of the chemical interference or ion-releasing antibacterial cellulose-based hydrogel

Current research largely supports that chemical interference or ion-releasing antibacterial hydrogel is a type of hydrogel that works by continuously releasing biochemically active ions or molecules from the material, interfering with vital life processes inside bacteria, and is effective against a broad range of bacteria.

Researchers suppose that chemical interference or ion-releasing hydrogels initiate bacterial destruction through targeted binding and membrane interactions [15]. Similar to the principle of electrostatic adsorption hydrogels, these positively charged hydrogels create strong electrostatic adsorption with the negatively charged bacterial cell membrane, enabling antimicrobial agents to efficiently accumulate on the bacterial surface or enter through membrane channels [16]. Subsequently, ions, like reactive oxygen species (ROS), begin indiscriminately attacking critical biomolecules. Metal ions readily bind to sulfhydryl groups on proteins, causing structural deformation and loss of function, thereby impairing bacterial metabolism and respiration. Metal ions can also bind to DNA bases, interfering with the normal replication and transcription of genetic material and inhibiting bacterial reproduction [2]. Additionally, excessive metal ions disrupt the ion balance within bacteria, affecting osmotic pressure and signal transduction. It is noteworthy that some ions can catalyze the production of small amounts of ROS within cells, further exacerbating internal oxidative damage. Through the aforementioned synergistic effects, bacterial energy metabolism is paralyzed, biosynthesis is halted, ultimately leading to bacterial death.

2.4.2. Advantages and limitations of chemical interference or ion-releasing antibacterial cellulose-based hydrogel

Unlike antibacterial hydrogels—such as those that operate via ROS-mediated attack—this hydrogel's antibacterial mechanism does not depend on external conditions like light exposure. Additionally, by leveraging controlled deployment of nanoparticles or carriers, it enables sustained

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long-term antibacterial effects. Additionally, it is effective against a variety of bacteria, fungi, and even viruses, and its multi-target attacks make it difficult for bacteria to develop resistance through single mutations.

However, its effective antibacterial concentration is close to the toxic concentration for human cells, requiring strict control over dosage. Prolonged or high-dose use may lead to related diseases or cumulative toxicity. At the same time, proteins and other components in wound exudate can bind to metal ions, reducing their antibacterial efficacy.

3. Conclusion

While substantial advancements have been made in current research, challenges persist in terms of underlying mechanisms, collaborative applications, and clinical translation. Although various mechanisms have been proposed, the dynamic processes of different antibacterial substances in the wound microenvironment remain insufficiently understood. Most studies have only established correlations between phenomena and effects, lacking research and evidence at the molecular and cellular levels. Additionally, single antibacterial mechanisms have limitations, making the construction of synergistic systems an emerging trend. The most classic example of antibacterial cellulose-based hydrogels is the photothermal-photodynamic synergistic system. However, many current studies merely involve the physical blending of different functional materials without deeper synergistic design, making it difficult to achieve a synergistic effect where the whole is greater than the sum of its parts. Finally, and most importantly, a large portion of current research is conducted under idealized laboratory conditions. While demonstrating excellent antibacterial performance, these studies often overlook the complex challenges that may arise in practical applications. This remains a challenge that will take time to overcome for the broader adoption of antibacterial cellulose-based hydrogels in the medical field.

Future research on antibacterial cellulose-based hydrogels will focus on three key directions: intelligence, synergy, and clinical translation, aiming to achieve more precise, safer, and more effective antibacterial therapies. Presently, most hydrogels passively release drugs, making the development of intelligent systems that can sense and respond to infection signals a major research priority. Promising approaches include environmentally triggered release mechanisms, time-controlled and feedback-regulated systems, and biomimetic designs. Secondly, single antibacterial mechanisms often have limitations, while current synergistic methods are oversimplified and fail to deliver efficient antibacterial effects. Therefore, another future direction involves constructing highly efficient synergistic antibacterial systems based on existing mechanisms. Finally, clinical translation and application expansion of these hydrogels are crucial. This includes designing hydrogels with tailored properties for specific scenarios to address refractory infections, developing next-generation hydrogels that combine antibacterial, anti-inflammatory, and tissue-regenerative functions, and utilizing advanced technologies to precisely control the internal structure of hydrogels for gradient drug release.

Research and development of antibacterial cellulose-based hydrogels hold significant importance for both public health and environmental sustainability. The development of cellulose-based hydrogels with multiple antibacterial mechanisms, which are less likely to induce drug resistance, plays a paramount role in treating chronic wounds, preventing implant-related infections, and addressing multidrug resistance. At the same time, cellulose-based hydrogels contribute to replacing petroleum-derived products and reducing medical waste. Their low environmental impact throughout the entire life cycle aligns with the principles of the circular economy and sustainable development.

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