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Advancements in Zeolitic Imidazolate Frameworks (ZIFs) for Antibacterial Therapy: Recent Innovations and Future Prospects

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Abstract

This review delves into the rapidly evolving field of Zeolitic Imidazolate Frameworks (ZIFs) and their increasing significance in antibacterial therapy. ZIFs have garnered considerable attention due to their distinct structural properties, which enable precise control over key parameters like pore size, surface chemistry, and particle-incorporating capacities. The integration of combination therapy within Ag/ZIF-8, involving the co-administration of multiple antibacterial agents or synergistic combinations of silver (Ag) nanoparticles, emerges as a prominent development. Furthermore, Ag/ZIF-8 inherently possess antibacterial properties rooted in their composition and surface characteristics, offering a multiple-action mechanism of antibacterial therapy. In the near future, ZIFs may revolutionize antibacterial treatment strategies, providing a glimmer of hope for the ongoing battle against bacterial infections due to their tailored properties.

Keywords Zeolitic imidazolate frameworks, silver nanoparticles, antibacterial therapy

1.0 INTRODUCTION

The increasing global prevalence of pathogenic bacterial infections has prompted significant research into antibacterial therapy as a crucial area of study. Bacterial contamination has become a substantial threat over the past few decades, affecting various aspects of life, including food, water, and the environment, resulting in numerous casualties [1-4, 6-7]. Bacteria are naturally present on the skin, in the body, and particularly in the intestines, playing vital roles in human metabolism and overall bodily functions. The consumption of bacterial toxins like endotoxins and exotoxins can lead to bacterial contamination, provoking a range of responses, such as abdominal cramping, vomiting, fever, and diarrhoea, as the immune system combats the threat [2]. Notably, untreated bacterial infections can progress, weakening the immune system over time [3].

By 2050, it is expected that deaths from antibiotic-resistant infections could surpass those from cancer, diabetes, and other diseases [4]. In response, research is now focused on antibacterial agents based on silver (Ag) nanoparticles to combat both Gram-positive and Gram-negative bacteria [5]. Accordingly, the development of thousands of antimicrobial agents has been instrumental in treating infections caused by both Gram-positive and Gram-negative bacteria. Typically, antibiotics, whether bacteriostatic or bactericidal, inhibit bacterial cell multiplication and replication, eventually leading to bacterial cell death [6]. For example, infection by *Staphylococcus aureus* can be treated with ß-lactamase agents targeting the cell wall, while *Bacillus anthracis* can be treated with Rifampicin, which inhibits nucleic acid synthesis [7]. Moreover, different antibacterial agents, like Streptogramins, Rifamycin, and Fluoroquinolones, can be employed against Gram-negative bacteria such as *Neisseria gonorrhoeae*, *Escherichia coli*, and *Neisseria meningitidis* [8]. Unfortunately, antibiotic overuse has led to antibiotic-resistant bacterial strains, posing a significant threat to public health and food security. Interestingly, silver (Ag) has long been recognized for its antimicrobial properties and is extensively used in modern medicine due to its effectiveness in killing microorganisms [8, 9]. Likewise, compounds containing Ag^+ ions are highly toxic to microorganisms, exhibiting strong biocidal effects on bacteria [10]. To enhance the biocompatibility of Ag as an antibacterial agent, researchers have turned to reducing bulk Ag to nanoparticles, which have shown rapid disruption of the proton motive force upon contact with bacteria like *Escherichia coli*, eventually leading to cell destruction [11]. However, Ag nanoparticles (AgNPs) are sensitive to oxygen, leading to the production of unwanted inactive oxides and undesirable agglomeration into larger particles [12]. To overcome this challenge, stabilizing AgNPs by incorporating them into support materials using nanotechnology is crucial for enhancing their stability.

In the quest for novel antimicrobial materials to combat bacterial infections, various options have been explored, including metal/metal oxide nanoparticles, nanozymes, cationic polymers, and metal-organic frameworks (MOFs). Among these, Zeolitic Imidazolate Frameworks (ZIFs) have gained attention as a distinct class of hybrid porous polymers with promising applications in biomedicine. ZIFs, comprising both organic and inorganic elements, offer exceptional attributes such as a remarkably high specific surface area, impressive biocompatibility, biodegradability, and outstanding physical and chemical properties. These unique properties enable ZIFs to facilitate antibacterial effects by efficiently allowing small molecules to access their active sites, promoting the transport and diffusion of products, and enhancing material catalytic properties and selectivity. With their versatility and ability to control and release antibacterial agents, ZIFs, particularly when incorporating silver nanoparticles, hold significant promise for bacterial infection therapy. This perspective provides an overview of recent advancements in ZIF-based nanoplatforms for antibacterial applications, addressing the challenges and prospects in this dynamic field.

2.0 ZEOLITIC IMIDAZOLATE FRAMEWORKS (ZIFs)

In recent years, nanomaterials with large surface areas have garnered significant attention due to their ability to facilitate chemical reactions and the stability of other nanoparticles. In this regard, MOFs, with their exceptionally large surface area, have emerged as excellent platforms for supporting metal nanoparticles, making them effective antimicrobial agents [13]. The structural stability and large surface area of MOFs make them ideal candidates for enhancing antibacterial agents, as evidenced by their frequent use in this role [14]. Furthermore, MOFs may inherently possess organic ligands with antibacterial properties. These ligand molecules are incorporated into the spatial structure of MOFs, promoting the mixing of metal ions and thereby creating a synergistic effect that enhances the antimicrobial properties of the organic ligands (Shen *et al*., 2020). Figure 1 illustrates the degradation and synergistic effects of metallic ions and organic ligands contributing to the antibacterial activity of MOFs [13,14].

Within the MOFs, the Zeolitic Imidazole Framework (ZIF) is a widely recognized sub-family known for its crystalline and microporous structure. The interest in ZIFs dates back to the early 1980s when they were introduced as counterparts to aluminosilicates and later to transition-metal-based phosphates and aluminium-phosphates, sparking renewed interest in zeolites in the late 1990s [15]. ZIFs have gained attention due to their ability to combine the advantages of MOFs with the chemical and thermal stability characteristics of zeolites [14, 15]. Moreover, compared to other types of metal-organic framework materials, ZIFs exhibit superior thermal, hydrothermal, and chemical stability, making them increasingly popular for a wide range of applications, including gas storage, separations, catalysis, and chemical sensors.

The unique structural attributes of ZIFs provide them with the adaptability and robust mechanical strength of conventional zeolite structures while preserving the high specific surface area and porous nature of MOFs [16]. As noted by Pan and co-workers [17], ZIFs offer advantages over zeolites, such as enhanced flexibility in surface modification and the potential for improved morphological characteristics, leading to increased efficiency. Figure 1 illustrates the crystal structure of ZIFs, highlighting its distinctive features in this context.

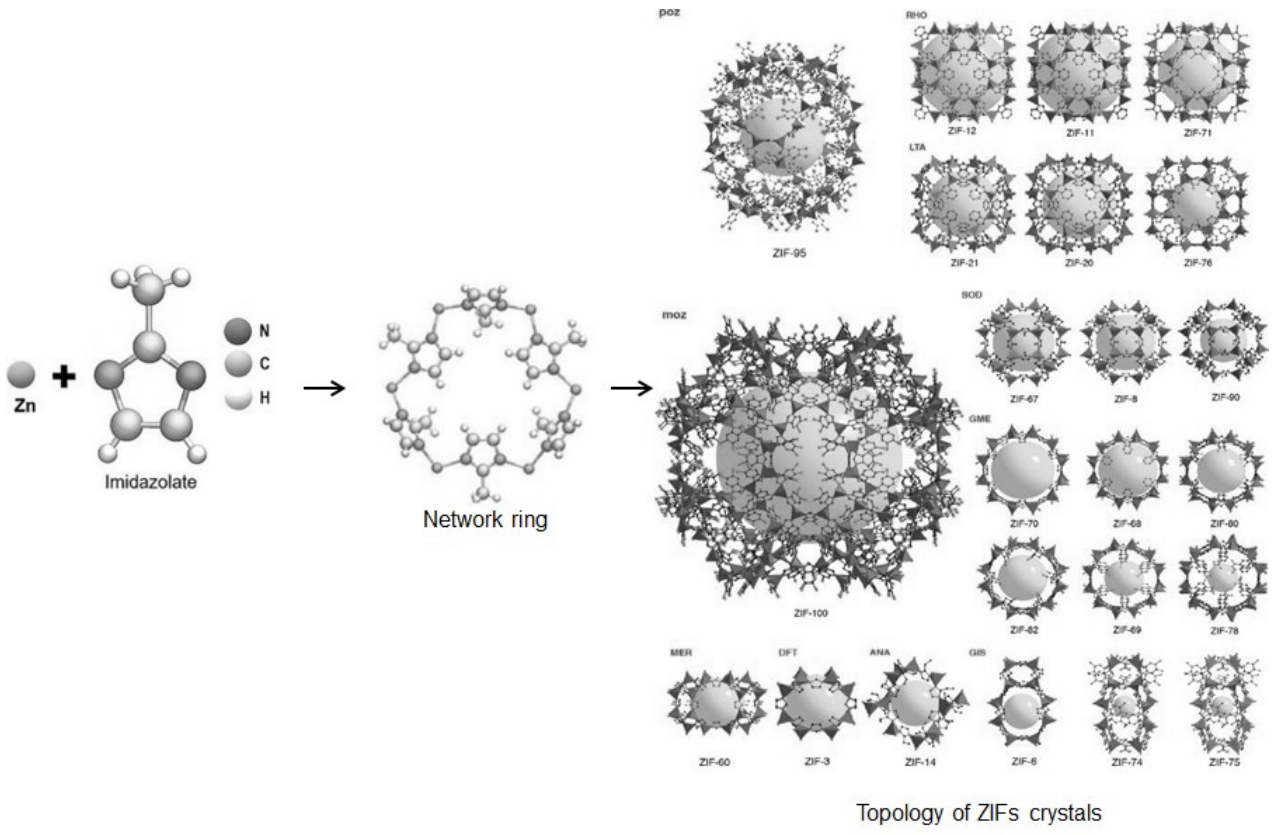

Figure 1 Different topology crystal structures of ZIFs based on imidazolate linkers.

Among the ZIFs crystals, ZIF-8 is intriguing due to its extraordinary stability, high porosity, and versatile characteristics. Its strong structure, made up of metal centre (Zn) and organic linkers (imidazolate), can survive extreme environments. Because of its porous nature, it is useful for stabilizing smaller particles, especially Ag nanoparticles. Furthermore, the flexibility to alter its pore size and shape increases its applicability for a variety of applications. It is interesting to note that the ZIF-8 crystals are smaller due to an excess of ligand molecules that sterically limit their growth.

3.0 THE UNIQUE STABILIZATION PROPERTIES OF ZIF-8

As mentioned, Ag is well-accepted in medical research as an effective treatment for antibacterial therapy [18]. Their low processing temperature and simplicity make them widely applicable [18,19]. However, despite their promising results, Ag faces limitations due to their tendency to easily aggregate and precipitate, causing a rapid decline in their antibacterial effectiveness. This issue arises from the inherent nature of nanoparticles, which promotes the rapid agglomeration of silver particles, leading to larger, less stable aggregates [19,20]. Also, it was found that Ag nanoparticles are highly sensitive to oxygen, leading to the formation of partially oxidized Ag_2O with chemisorbed Ag^+ [18-20].

In light of this, ZIF-8 has garnered significant attention due to its unique properties within the family of ZIFs. ZIF-8, also known as $Zn(mIM)_2$ (where mIM = 2-methylimidazolate), stands out as the most extensively studied ZIF material. It features a sodalite structure comprising 1.16 nm cages connected by six-membered windows measuring 0.34 nm micropores, 1.1 nm cavities, exceptional heat stability (up to 400°C), and hydrophobic characteristics [21, 22] Consequently, it has become a favoured choice for encapsulation and stabilization of Ag [22]. Additionally, owing to their similar tetrahedral connectivity, ZIF structures closely resemble certain zeolitic silica morphologies, making them excellent candidates for amorphization. Table 1 shows examples of existing research on the incorporation of Ag nanoparticles into ZIF-8 crystals for various applications.

Table 1 Various works on Ag nanoparticles incorporated into ZIF-8

Research Highlight	Advantages	Disadvantages	Method	Remarks	Ref.
Synthesis of Ag/ZIF-8 photocatalyst with excellent performance for dye degradation and antibacterial properties	Ag-X@ZIF-8 catalysts can maintain is activity between four cycles	ZIF-8 has a high band gap therefore decreasing the performance	A mixture of $AgNO_3$ with ethanol and DI water. Stirred for 15 minutes, ZIF-8 powder was added. Synthesis of Ag/ZIF-8 separated by centrifuge, washed with ethanol and dried	Good photocatalytic performance under UV-Vis	[23]
Ag/H-ZIF-8 nanocomposite as an effective antibacterial agent against pathogenic bacteria	The synergistic effect of Ag/ZIF-8 shows a good antimicrobe agent	Ag nanoparticles are easily agglomerate without further stabilization	Ratio mass of ZIF-8 against $AgNO_3$ (1:25). Shake for 2 hours, add 2.4mL of $NaBH_4$ dropwise in an ice bath and shake. Washed with CH_3OH and centrifuge to obtain yellow powder	Low cytotoxicity and good biocompatibility	[24]
Controlled synthesis of AgNPs/ZIF-8 composite: Efficient heterogeneous photocatalyst for degradation of methylene blue and congo red	Insitu AgNPs and ZIF-8 provide well-distributed components and enhanced interfacial interaction in resulting complex wastewater treatment	In-situ growth of ZIF-8 is not suitable since it can aggregate silver nanoparticles	Two methods: 1. In-situ synthesis of AgNPs. ZIF-8 was added in $AgNO_3$ with DI H_2O solution and purged N_2 gas. Precipitate collected by centrifugation 2. In-situ synthesis of ZIF-8. ZIF-8 formed through $ZnCl_2$ and 2-methylimidazole, methanol , and Ag was added	Fast migration to the interfaces of photo-induced/generated electrons and holes to react with pollutants	[25]
Rapid synthesis of Ag/AgCl/ZIF-8 as a highly efficient photocatalyst for degradation of acetaminophen under visible light	Degrade the characterization of ACT	Ag compounds have low adsorption ability and a fast recombination of photo-generated charges with high electron-hole.	ZIF-8 was dispersed in $AgNO_3$ water-ethanol (v/v = 1: 6). Solution was added dropwise into NaCl water-ethanol (v/v = 1: 6). Products obtained by centrifugation, washed with deionized water and dried	Colour change from white to light blue during the experiment	[26]
Facile synthesis of Ag/ZIF-8 core-shell heterostructure nanowires for improved antibacterial properties	Decelerate the growth of both types of bacteria	Loss of ZIF-8 nanoparticles by adding too much amount of Ag	The prepared Ag nanowire was dispersed in ethanol by ultrasonication and placed in an ice bath. 2-methylimidazole and zinc acetate hexahydrate were added. The samples were isolated by	High selectivity	[27]

			centrifugation and rinsed.		
The synergistic effect of Ag/AgCl/ZIF-8 modified g-C_3N_4 composite and peroxymonosulfate for the enhanced visible-light photocatalytic degradation of levofloxacin	Ag/AgCl@ZIF-8 shows a gradually increase amount in composite	During the grinding process, destruction occurs in the ZIF-8 structure	Zinc nitrate and dimethylimidazole with a molar ratio of 1:8 dissolved in methanol. Solutions were mixed and stirred. White precipitated was centrifuged, washed with ethanol, and then dried.	Formation of SO_4^- and ▪OH increase the reaction rate to degrade the levofloxacin	[28]
Corncob-supported Ag/ZIF-8 nanohybrids as multifunction biosorbents for wastewater remediation: Robust adsorption, catalysis and antibacterial activity	Has good repeatability and reusability	-	Dry ZIF-8s/P-OCBs, placed in the small “tea bag” with water/ethanol mixture of 1:4 (Solution A). $NaBH_4$ was added into Solution A. $AgNO_3$ dissolved in water/ethanol mixture solution (Solution B). Add B to A and stir. A solid sample obtained was rinsed with ethanol and dried	Good adsorptive and catalytic capacity	[29]
Antibacterial applications of metal-organic frameworks and their composites	MOFs can be used as a good support towards a variety of compound	Silver nanoparticles and ZIF cannot stand alone as good antimicrobial agents	-	Antibacterial occurs through organic ligand	[30]

It is learned that the incorporation of Ag into a ZIF framework enables the development of composite materials that possess unique properties and functions. These materials have potential applications in catalysis, sensing, antimicrobial technology, and various other fields that benefit from harnessing the synergistic qualities of Ag and the porous and adaptable nature of ZIFs. Nevertheless, the exact compatibility and performance of Ag within a ZIF structure rely on the specific synthesis methods and conditions used, necessitating meticulous planning and thorough characterization during the research and development process.

4.0 SILVER INCORPORATED ZIF-8

Among the listed composites in Table 1, Ag/ZIF-8 nanocomposites stand out as particularly impressive antimicrobial agents. Moreover, Ag-ZIF has demonstrated significant potential as an antibacterial agent due to the presence of potent antimicrobial Ag^+ ions [30,31] While Ag nanoparticles are known for their effectiveness as antibacterial agents, their utility in biomedical applications is hampered by stability issues and rapid agglomeration [31]. The synthesis of Ag-ZIFs can likely help stabilize the incorporated nanoparticles. Table 2 represents various methods for synthesizing Ag nanoparticles with different MOFs as composites.

According to Table 2, Guo and co-workers [27] successfully synthesized a specific nanocomposite comprising Ag/ZIF-8, in which ZIF-8 nanoparticles were applied to the external layer of Ag nanowires. They then conducted experiments to assess the antibacterial effectiveness of Ag/ZIF-8 nanoparticles against *B. subtilis* and *E. coli*. The results demonstrated that Ag/ZIF-8 nanowires were highly effective in eradicating bacteria. Specifically, Ag/ZIF-8 achieved a 100% inhibition of *B. subtilis* bacteria at a concentration of 200 µg/mL, while individual silver and ZIF-8 nanoparticles exhibited significantly lower antibacterial effects, at 49.3% and 85.2%, respectively. This enhanced antimicrobial activity of Ag/ZIF-8, when compared to Ag alone, can be attributed to the unique metal cluster properties of MOFs [33]. Notably, prior to this study, there had been no examination of the synthesis of silver nanoparticles with ZIF-8 as an antimicrobial agent.

The antibacterial action of Ag/ZIF-8 possesses complexity from the intricate interactions between the Ag nanoparticles and the ZIF-8 framework, which forms a porous structure with a high surface area. The mechanisms responsible for its antibacterial effects involve disrupting bacterial cell membranes and interfering with intracellular processes, though the precise mechanisms and their combined impact remain subjects of ongoing research. Additionally, the effectiveness of Ag/ZIF-8 can vary depending on the specific bacterial species it targets, introducing variability in its performance. Also, environmental factors,

such as pH, temperature, and the presence of organic matter, can influence its efficacy. More importantly, balancing antibacterial effectiveness with biocompatibility and safety considerations adds another layer of complexity, as does the potential for bacteria to develop resistance over time. Nowadays, rigorous testing, both in vitro and in vivo, is essential for evaluation, and navigating the regulatory approval process for medical or consumer applications presents a formidable challenge. Nonetheless, understanding and effectively utilizing the antibacterial properties of Ag/ZIF-8 requires a comprehensive grasp of numerous factors and careful consideration to ensure its safe and effective use against bacterial infections.

Table 2 Antibacterial application of MOF composites with Ag nanoparticles.

Composites	Nano-particles	Combination type	Bacteria type	Antibacterial activity	Ref.
Ag/Zn MOFs	AgNPs.	Ag^+ ions were encapsulated in the Zn-MOF framework.	*E. coli, S. aureus, B. subtilis*	Exhibit good results since all bacteria are sensitive to Ag/Zn-MOFs nanocomposite.	[32]
Ag-NPs @ Ni-MOF	AgNPs	Ag-NPs and Ni-MOF were mixed	*B. subtilis, E. coli* *P. aeruginosa, and C. albicans.*	All bacteria except *C. albicans* are degraded with a concentration of Ni-MOF (27 µg/mL). *C. albicans* need a higher concentration of (136 µg/mL).	[33]
Ag/CD MOFs	AgNPs.	Facile reaction-diffusion between Ag and CD-MOFs	*S. areus* and *E. coli*.	Bacteria can degrade but take a longer time.	[34]
Ag@CU/GMP	AgNPs.	Coating of Ag with Cu and GMP (Cu/GMP).	*E. coli* and *S. aureus.*	Inhibition zone for bacteria: *S. aureus* = 21(± 0.3) mm *E. coli* = 12(± 0.4) mm. Abled to kill the cells of bacteria.	[31]
Ag/ZIF-8	Ag nanowires	ZIF-8 were located on Ag nanowires.	*B. subtilis .and E. coli.*	100% inhibit the growth of the bacteria.	[27]

5.0 ANTIBACTERIAL ACTION THERAPY

As previously stated, ZIFs are frequently used to support antibacterial therapies due to their reliable frameworks and large surface areas. Furthermore, the organic ligands within ZIFs themselves may possess antibacterial properties. These ligand molecules are enclosed within the spatial structure of ZIFs, facilitating the mixing of metal ions and thus creating a synergistic effect with the antimicrobial properties of the organic ligand [30]. As indicated in Figure 2, the antibacterial activity of ZIFs is due to the synergistic effects of metallic ions and organic ligands. Specifically, ZIF-8, with a crystal structure reminiscent of zeolites, has been favoured for this purpose because ZIFs can stabilize AgNPs, enhancing their antibacterial properties [27, 35].

In detail, ZIF-8, boasts impressive antibacterial properties attributed to the potent antibacterial action of its zinc ions. These zinc ions play a pivotal role by inducing various antimicrobial effects, including cell deformation, cell wall rupture, and creating an alkaline environment within bacterial cells. Previously, these adverse conditions not only inhibited bacterial growth but also had the potential to result in bacterial cell death [27]. According to Figure 2 (A), the positively charged Zn^{2+} ions effectively engage with the negatively charged biomolecules present within bacterial cells, thereby facilitating their antimicrobial action in alignment with the findings by others [27, 36]. One of the standout merits of ZIF-8 lies in its heightened antibacterial efficacy, even under conditions devoid of light. It necessitates lower dosage levels and demonstrates a swifter bactericidal rate than alternative antibacterial agents. Furthermore, as elucidated by Liu and co-workers, ZIF-8 assumes a dual role as an exceptional carrier and supporter for silver nanoparticles, adeptly averting their aggregation and oxidation [37]. This attribute holds significant value as it ensures the stability and prolonged antibacterial potency of Ag nanoparticles, thus amplifying the overall effectiveness of ZIF-8 as a formidable antimicrobial agent.

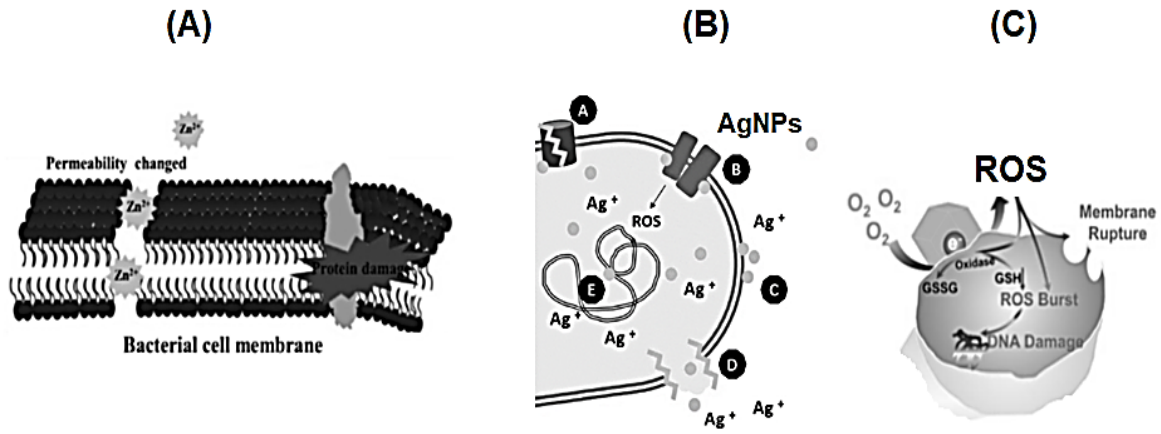

Figure 2 Antibacterial mechanism of action for Ag/ZIF-8 via (A) Zn^{2+} penetration (B) AgNPs activity and (C) ROS generation.

For the overall antibacterial action, the enhanced antibacterial efficacy of Ag-loaded ZIF-8 can be attributed to several mechanisms. Significantly, the positively charged Zn ions within ZIF-8 electrostatically adsorb onto the negatively charged components of bacterial phospholipid membranes, creating a barrier. Subsequently, adding Ag ions further enhances this effect, limiting the penetration of antibiotics into the bacterial cells, as shown in Figure 2 (B). Additionally, Ag nanoparticles have a strong affinity for sulfur-containing proteins, causing them to adhere to the bacterial cell membrane. This interaction can disrupt or alter the structure of the bacterial strain [38]. Moreover, Ag nanoparticles can be complex with DNA and RNA, potentially impeding DNA replication. Furthermore, they can attach to thiol groups in proteins, deactivating respiratory enzymes [39].

Furthermore, Ag nanoparticles are pivotal in generating reactive oxygen species (ROS), highly reactive molecules with unpaired electrons. ROS, such as superoxide ions and hydrogen peroxide, can inflict oxidative stress on bacterial cells by damaging cellular components like proteins, lipids, and DNA [38, 40], as shown in Figure 2 (C). This oxidative stress disrupts cellular functions, compromises cell membranes, and ultimately contributes to bacterial cell damage and death [41, 42]. As shown in Figure 2, by combining these mechanisms, Ag/ZIF-8 provide a powerful and multifaceted approach to combating bacterial infections, as corroborated by studies conducted earlier [27, 41-43]. Likewise, the antibacterial action of Ag/ZIF-8 results from a multi-pronged approach involving electrostatic interactions with bacterial membranes, interference with genetic material, and disruption of essential cellular functions, collectively contributing to its potent antibacterial effects [44, 45]. Amidst these promising advancements, it is imperative to underscore the necessity of rigorous biocompatibility and toxicity assessments to translate Ag/ZIF-based antibacterial platforms into clinical applications successfully.

6.0 CONCLUSION

The antibacterial properties of Ag are widely recognized in healthcare worldwide. Incorporating the ZIF-8 framework enhances the stability of Ag, preventing its rapid agglomeration. The incorporation of ZIF-8 and Ag is particularly significant for stable Ag/ZIF-8 and reproducible antibacterial action therapy. The release of silver and zinc ions into the environment targets bacterial ribosomes, disrupting protein synthesis machinery and eventually leading to bacterial inhibition or death. This review has advanced our understanding of Ag/ZIF-8 as potential antibacterial agents and their controlled release into the environment, offering possible solutions to address antibacterial resistance and bacterial contamination. In the future, accelerating the development of effective antibacterial agents can help mitigate these challenges.

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