Review Article

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Nanozymes – A route to overcome microbial resistance: A viewpoint

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Abstract: The bactericide is one of the major objective consequences related to healthcare in the world. Natural enzymes have been broadly utilized in various applications such as biomedical areas due to their broad catalytic activities and substrate particularity. While anticipating, it has drawbacks like higher cost, low stability, and troubles in reprocessing. Additionally, artificial enzymes (nanozymes) have favors above natural enzymes, for example, the effortless yield on a big scale, low costs, and high stability in coarse surrounds. The amount of antibiotic repellent microorganisms has activated big concern in the growth of stuff with essential bactericide potentials such as metal or metal oxide nanoparticles, cationic polymeric compounds, graphene oxide, and other carbon materials that can be used as antibacterial agents by altering cell morphology. In this report, we have summarized catalytic antibacterial strategies by natural enzymes, artificial enzymes, or photocatalytic activity. Furthermore, the demands and hereafter contents about catalytic antibacterial strategies are supposed in this report.

Keywords: antibacterial activity, strategies, natural enzyme, nanozymes

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1 Introduction

The developing health troubles due to bacteria is one of the major concerns causing infective diseases conducting to millions of illnesses and demises yearly [1–3]. Haunting diseases invariably relate to establishing bacterial colonies [4–6]. The bacteria in the exo-polymeric matrix were highly tolerant to formal antibiotics due to developed resistors, controlled dissemination, and deactivation of antibiotics [7–9]. To overcome this limitation, significant attempts have been devoted to colloidal materials to defend the world *versus* diseases caused by bacteria [10–16]. Due to the lack of bioavailability, they had to be more attentive in their virtual efforts. ROS stands for reactive oxygen species, including chemicals like hydrogen peroxide and superoxide, effective against antibiotic-resistant bacteria [17–20]. ROS and hydrogen peroxide has affected bacterial structure by disturbing biomolecules that lead to the death of a cell [21–23]. Unfortunately, hydrogen peroxide has limitations in applications such as lower efficiency, slow procedure, and eminent concentrations [24]. Particularly, high concentrations of hydrogen peroxide induce immunogenicity and inflammation and have perniciousness extravagantly to healthy tissues and yet delay wound healing [25,26]. Practicality surface modification of nano-stuffs supplies a flexible stage to pattern new disinfectants to fight multidrug-resistant (MDR) pathogens [27]. Similarly, nanomaterials have limitations over antibacterial activity, such as high doses of AgNPs can affect the mammalian cells. Techniques such as core-shell (Au@AgNPs) material production or surface coating of particles on or in electrospun fibers have been introduced to minimize the toxicity of nanomaterials. However, many researchers are still working to develop a superior antimicrobial infection treatment. Recently, catalytic antimicrobial materials are getting more attention; such materials have enzyme-like activities and are safer for cells. Peroxidase and oxidase in lysosomes can catalyze ROS production to fight bacterial encroachment because the living mechanism has a self-defensive arrangement that can work as a biocatalyst to inhibit bacterium or

interrupt biofilm state. Nevertheless, natural enzymes frequently endure underlying defects. Therefore, materials having photocatalytic activity are prominent antibacterial materials due to oxygen reduction and bringing forth ROS as though $^{\cdot}O_2^-$ and hydrogen peroxide [28–30]. Enzyme-mimicking catalytic performances of nanomaterials have been reported by Chen *et al.*, in a recent report [31]. Despite lots of fantabulous exploits that have been described, to our know-how, no comprehensive report has been given on catalytic antibacterial strategies. Despite lots of fantabulous exploits that have been described, to our know-how, no comprehensive report has been given on catalytic antibacterial strategies. In this report, the recent developments in the area of catalytic antibacterial strategies have been presented. Briefly, catalytic antibacterial strategies including natural enzymes, nanozymes, and photocatalytic antibacterial strategies have been discussed.

2 Catalytic antibacterial strategies

Serial publications of examinations have been brought out to figure out the antibacterial mechanisms. The most recent reports on performance of nanozymes have been described by Dong *et al.*, Huang *et al.*, and Sun *et al.* [32–34]. Hence, antibacterial strategies have been well described, but it still needs a flick to make them simpler for the research world.

2.1 Enzymes effective antibacterials and antibiofilms

Enzymes are effective biocatalysts and are primarily made up of proteins, although some are catalytic RNA molecules [35,36]. Where distinctive catalysts are frequently employed in coarse considerations like level of temperature and pressure [37,38], they are principally applied to catalyze the salvation of biological specks, and these reactions are generally brought out beneath comparatively modest circumstances [39,40]. Enzymes have been broadly employed in the area of industry, medicine, and biology [41–44]. The classification of bactericide enzymes is shown in Figure 1. However, it has been depicted that natural enzymes have intrinsic shortcomings or disadvantages. Extremely developed enzymes – lysins have a bacterial effect (Figure 2). Phage lytic enzymes are extremely effective specks that have been purified over decades of evolution. This lysin directs the incorruptibility of the cell wall and is intended to affect one of the five important bonds in the peptidoglycan. However, lysins only exploit gram-positive bacterium because they can interact with the cell wall and are intended to affect one of the five important bonds in the peptidoglycan. However, lysins only exploit gram-positive bacteria because they can interact with the cell wall carbohydrates and peptidoglycan since the gram-negative bacterium defends this contact due to the outer membrane. Furthermore, T4 lysozyme is acknowledged as a bactericide protein having antibacterial activity *versus* both types of bacteria. The bacterial property of T4 lysozyme is supposed to occupy in its muramidase action that extends to change in the state of the murein layer and reduction of the mechanical intensity of the microbial cell wall and finally leading to death by lysis. It has been detailed on construction and role states the value of amino acid components for the muramidase action of T4 lysozyme. The performance of T4 lysozyme for bacterial membrane degradation or lysis is as detected for respective antimicrobic peptides [45].

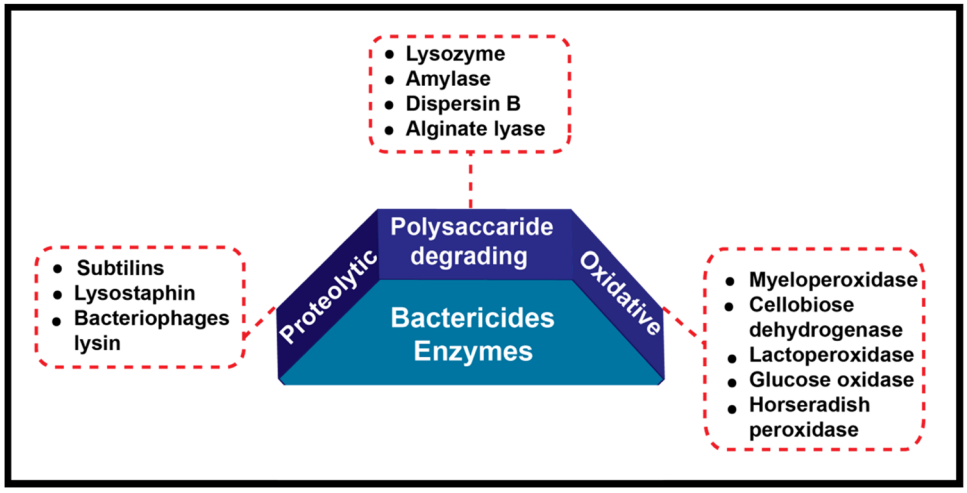

Figure 1: Antimicrobial enzymes.

Figure 2: Lysine-affected bacillus displaying attribution of the cytoplasmic membrane [49].

Aforementioned, one enzyme catalytically should be enough to properly break bonds to inhibit bacteria. Regarding the efficacy of lysin, it only kills the organisms that produced it. Particularly, it is C *streptococcal* phage that destroys C, A, and E *streptococci* set, also *Streptococcus uberis* and the horse-infective bacteria *S. equi* can be resisted by a bovine infectious agent. Moreover, *streptococci* did not found effective in the oral cavity. Recently, lysin CF-301 phage has been introduced for the disruption of *Staphylococcus aureus* biofilm [46]. Figure 3 shows the morphology of control and lysin CF-301 phage biofilm using scanning electron microscopic images. Before and after treatment of lysin CF-301 phage has different morphologies, which means it has an effect on lysin. Bacteriophage as a bicomponent molecule, such as holin and endolysin, allow novel produced phage offspring to depart dead bacterium and occupy early sensitive host bacterium. In the inner membrane of the bacterium kiln, a molecule of permeable enzyme can create pores, thereby inhibiting bacterial growth. Another component of phage disturbs the exo-membrane of cells that demolish the peptidoglycan layer [47]. The clinical testing CF-301 against methicillin-resistant *Staphylococcus aureus* (MRSA) is currently complete. Human trials are currently underway to cure patients in hospitals with MRSA germs or inflammation of the endocardium and heart valves [48].

2.2 Nanozymes – effective antibacterials

The name "artificial enzyme" was created verbally by scientists to explain mimic enzyme models [50]. It is a material with sizes of 1–100 nm [51,52]. Artificial enzymes are productively employed as chemical catalysts. Newly published literature is significantly lined up on consideration of nano-size materials that possess the biocatalytic ability. Artificial enzymes have benefits over natural

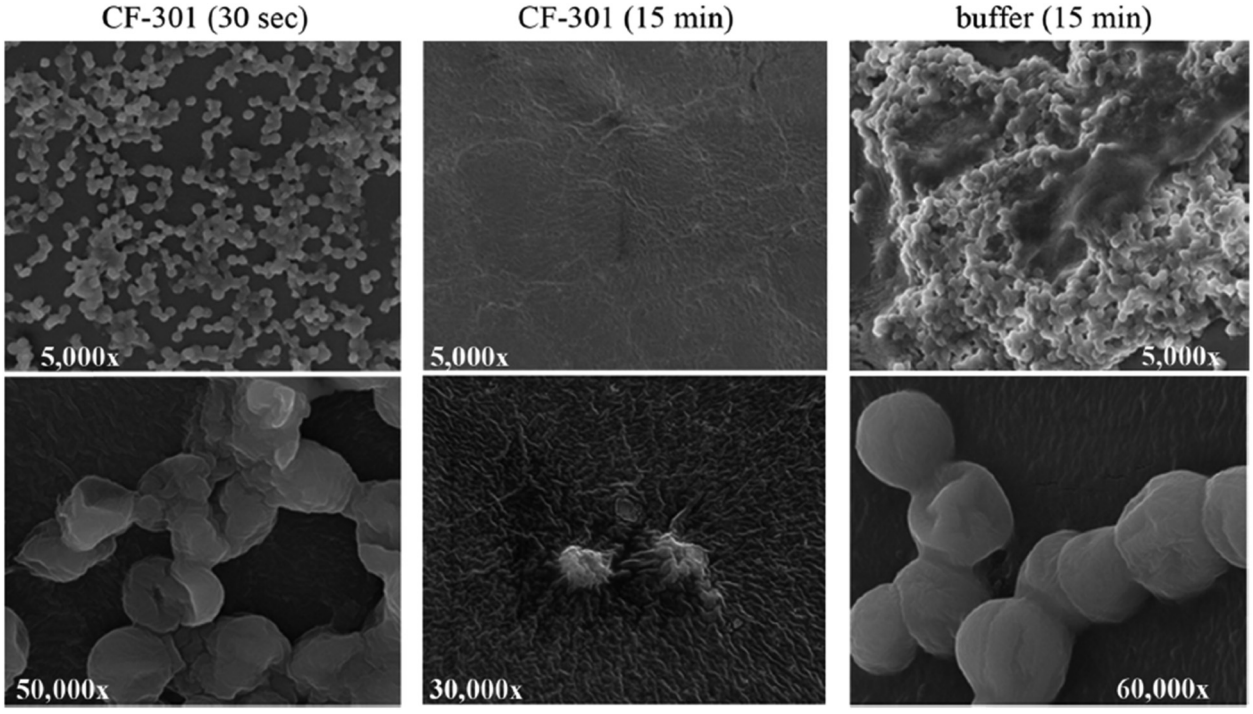

Figure 3: MRSA strain ATCC BAA-42 biofilms developed for 3 days in the catheter lumen against CF-301 [46].

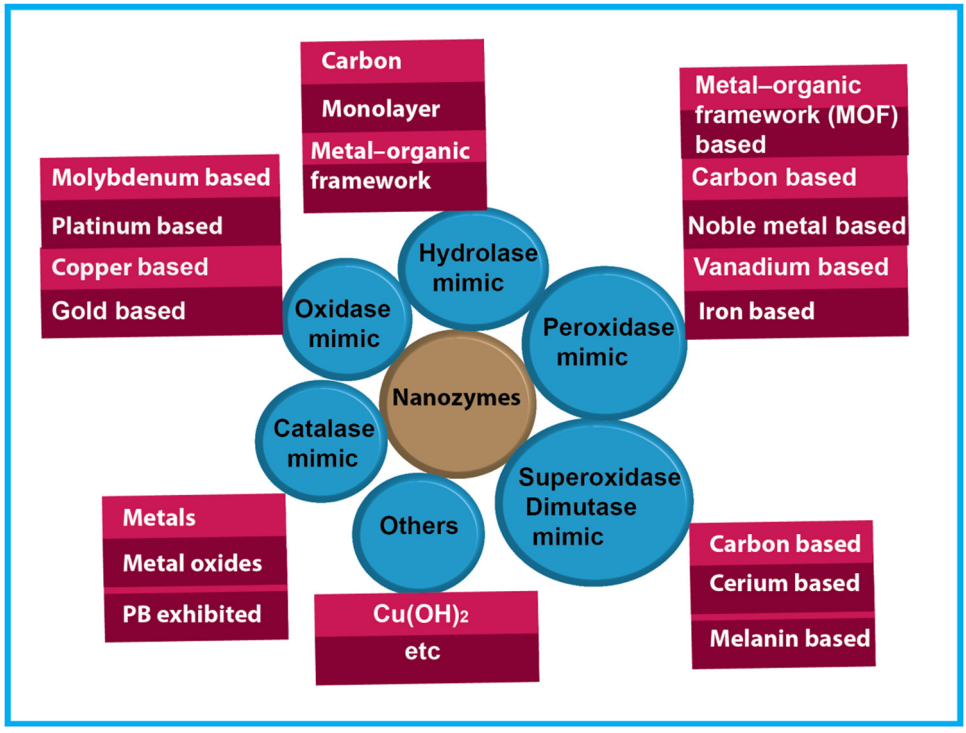

Figure 4: Types of nanozymes.

enzymes like low cost, high stability, and so on [29,53–55]. Artificial enzymes have contributed to the area of medical science. Subsequently, a number of nanozymes have been found, and from those, some are shown in Figure 4 with types of nanozymes. New scientific findings for artificial enzymes are as follows:

1) Sensing, ion determination, molecule determination, nucleic acid determination, protein determination, and cancer cell determination.
2) Environmental intervention and degradation of contamination in the environment.
3) Nanozymes for cancer treatment and the most important for this report, antibacterial, and antibiofilm. The basic of nanozymes antimicrobial properties was necessary before the antibacterial flick performance of nanozymes.

2.2.1 Antibacterial performance of nanozymes

A series of nanozymes have been discovered for antibacterial activities and biofilms such as single atom nanozyme [56], *o*-carbon nanotubes [13], copper oxide nanorods [57], GQDs [58], gold nanoclusters [59], platinum hollow nanodendrites [58], hybrid GQD AgNPs [60], mesoporous silica/AuNPs or porous Pt/AuNPs [31], PEG-MoS_2 nanoflowers [61], CaO_2/H-G@alginate [62], IOPs [63], DMAE [64], V_2O_5 nanowires [31], CeO_{2-x} nanorod [65], PAN/FeNPs nanofibers [108], *etc*. In brief, the antibacterial mechanism of nanozymes is based on the release of $^{\cdot}OH$ and $^{\cdot}O_2^-$. Figure 5

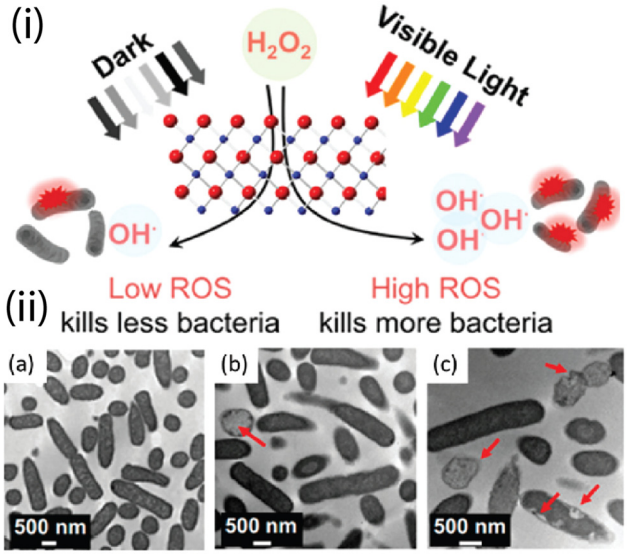

Figure 5: (i) Illustration of antibacterial mechanism of nanozyme; (ii) transmission electron microscopic images of copper oxide nanorods against *E. coli* at various treatments: (a) control; (b) copper oxide nanorods with hydrogen peroxide in the absence of light; and (c) copper oxide nanorods with hydrogen peroxide in the presence of light [57].

demonstrates oxidase- and peroxidase-like activity and death of bacteria due to $^{\cdot}OH$ release; however, in the absence of light, the dark copper oxide nanorods release lower ROS than visible light and also affect the death rate of bacteria. The bactericide effect of artificial enzymes initiates from their capability to regulate the phase of ROS like –OH and $^{\cdot}O_2^-$ [66]. Due to higher oxidation potentiality, ROS may affect bacteria and biofilms; undiscriminating disturbs the function of biomolecules inside or in the cell resulting in damaging of the cytoplasmic membrane and the death of bacteria. Enhancing the ROS and the death of bacteria faster destroys bacterial cell membrane and makes bacterial resistance rate lower toward nanozyme [30,61,67]. Moreover, it is well known that only hydrogen peroxide can work as an antimicrobial agent, but it may have an effect on tissues as well; therefore, the presence of nanozymes having an activity like peroxidase has fortune in the biomedical era [61,67–69].

The catalytic activity of nanozymes can be tuned by altering pH, temperature, ionic changes, light and morphology [70–80]. It is well described in a previous report by Huang *et al.* [33]. Many factors have been described well but still, nanozyme is a hot research topic and it is gaining importance day by day. Considering these challenges, Gao and co-workers have introduced the impact of metal states and their antimicrobial effects that are predominately little known [81]. Further investigation has shown that copper/carbon is a mimic enzyme material and is described as copper/carbon state-dependent nanozymes; Cu^0 has shown better enzyme-like activity than Cu^{2+}. Bactericide performances of copper/carbon hybrid nanozyme showed that ROS and transfer of ions from Cu^{2+} are responsible for the inhibition of bacteria. However, Cu^{2+} release can inhibit only gram-negative bacteria, and ROS generation can kill both gram-positive and gram-negative bacteria; therefore, controlling the state of metal can be beneficial for selective bacteria destruction. In addition, injury of the intestine caused by *S. typhimurium* can be treated by copper/carbon artificial enzyme [81]. Furthermore, iron oxide has been used against the influenza virus, which had a great breakthrough in the nanozyme area [82]. An excellent impact on the viral lipid envelope was demonstrated to deactivate it and give shelter from the contagion of the virus. The mechanism of antiviral nanozymes can be understood through the oxidative breakdown of lipids presented in Figure 6. Ag@Fe_3O_4 core@shell has been developed for antibiofilm activity [83], due to the well-known magnetic property of Fe_3O_4 antimicrobial activity, which can be enhanced by external magnetic force. Hence,

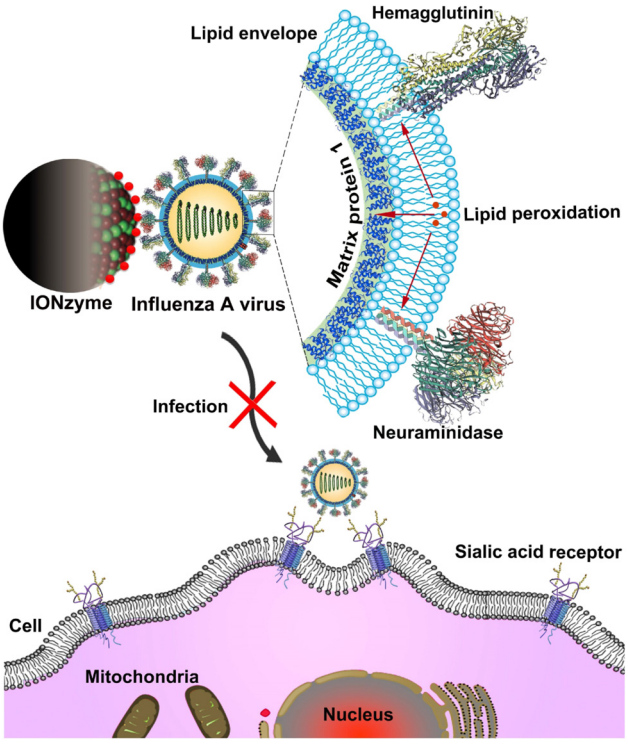

Figure 6: Illustration of viral oxidative breakdown of lipids by iron oxide nanozyme [82].

the magnetic property of Fe_3O_4 and silver ions released from silver are responsible for the killing of microbes [84].

2.3 Photocatalysis as an antibacterial agent

Photocatalysis plays an important role in microbial degradation, but it is well known for the degradation of pollutants [85,86]. Herein, we have briefly described the best photocatalytic antimicrobial agent. Ferrite nanoparticles (NPs) have been examined as antibacterial and antibiofilm [87] agent that is an excellent catalyst for many reactions [88]. The CeO_2–TiO_2 has shown excellent antibacterial effect against gram-positive and gram-negative bacteria in the presence of light [89]. However, ferrite NPs and CeO_2–TiO_2 mechanism has not been described. The possibility of bacterial disruption is due to photocatalytic activity of relevant stuff such as TiO_2. TiO_2 possesses low antibacterial activity due to a band gap [90], but it can be improved by the addition of substitutes or increasing visible light [91]. Wang *et al.* have designed photocatalytic CT/poly(vinyl alcoho) (PVA) hydrogel as an antimicrobic agent and wound dressing material [92]. The antibacterial effect of CT/PVA hydrogel

is due to the generation of –OH and ROS. Zinc oxide is widely utilized as a photocatalytic and antimicrobial agent due to its unique properties such as being cheaper, atoxic, *etc*. [93–101]. The toxic effect of ZnO is restricted, and bacterial death is usually due to the generation of ROS and disrupting bacteria. Moreover, nano-ZnO is atoxic to mammalian cells and more effective toward bacteria [102–104]. Commonly employed organic compounds such as pigments, dyes, and catalysts in organic synthesis are known as Schiff bases. It has been demonstrated with a wide range of antimicrobial activities [105,106]. Recently, it has been studied against MDR bacteria (MDRB), while the mechanism is not well defined [107]. Furthermore, the attachment of groups, such as aldehyde or amino with cell wall of bacteria, could be the reason for bacterial inhibition.

3 Conclusion

In this report, recent development in the area of catalytic antibacterial strategies has been presented. Briefly, catalytic antibacterial strategies including natural enzymes, nanozymes, and photocatalytic antibacterial strategies have been discussed. As a result, ROS, –OH, aldehyde or amino can inhibit microbes and Cu^{2+} can only inhibit gram-negative bacteria. Iron oxide possesses antiviral activity, and carbon-based material has been reported as a great enzyme mimic material. Yet researchers have many challenges to produce novel antibiotics such as for nCovid-2019.

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