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Countering drug resistance, infectious diseases, and sepsis using metal and metal oxides nanoparticles: Current status

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ABSTRACT

One fourth of the global mortalities is still caused by microbial infections largely due to the development of resistance against conventional antibiotics among pathogens, the resurgence of old infectious diseases and the emergence of hundreds of new infectious diseases. The lack of funds and resources for the discovery of new antibiotics necessitates the search for economic and effective alternative antimicrobial agents. Metal and metal oxide nanoparticles including silver and zinc oxide exhibit remarkable antimicrobial activities against pathogens and hence are one of the most propitious alternative antimicrobial agents. These engineered nanomaterials are approved by regulatory agencies such as USFDA and Korea's FITI, for use as antimicrobial agents, supplementary antimicrobials, food packaging, skin care products, oral hygiene, and for fortifying devices prone to microbial infections. Nevertheless, detailed studies, on molecular and biochemical mechanisms underlying their antimicrobial activity are missing. To take the full advantage of this emerging technology selective antimicrobial activity of these nanoparticles against pathogens should be studied. Optimization of these nanomaterials through functionalization to increase their efficacy and biocompatibility is also required. Urgent *in vivo* studies on the toxicity of nanomaterials at realistic doses are also needed before their clinical translation.

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1. Introduction

Infectious diseases (IDs) remain one of the biggest medical challenges of our time due to the emergence of more than 300 new IDs and the resurgence of some old IDs [1]. Microbial diseases still cause 26% of the total global mortalities and the death toll is particularly higher in sub-Saharan Africa where 50–52% of the people die of IDs [2]. The problem is further complicated by the resurgence of some historically established diseases such as cholera and tuberculosis (TB) [3]. These diseases are still endemic in various regions of the world. Annually 2.86 million cases of cholera are reported in endemic countries, leading to 95,000 deaths per year [4].

The development of resistance to conventional antibiotics in pathogenic bacteria is widely reported adding to the cost of treatment and loss of life. Reports on the resistance against most of the antibiotics commercially used are available from Penicillin (1928) to Ceftaroline (2010) [5]. Even more surprisingly, the reports on the resistance against some antibiotics emerged even before their proper introduction into the market, as exemplified by Ceftaroline Levofloxacin, and Penicillin [5]. Fig. 1 shows the timeline of antibiotic discovery and reports of drug resistance against these antibiotics. Some of these pathogens acquire resistance to multiple drugs and are often referred to as “superbugs”. Drug-resistant *Enterobacteriaceae, Mycobacterium tuberculosis, Klebsiella pneumoniae* and *Neisseria gonorrhoeae* are posing serious threats in the developed world. Biofilm formation by pathogens wherein the bacterial communities behave like a multicellular organism exhibiting greater pathogenicity and resistance to antibiotics is also a grave problem, especially in the developed world [6]. On the contrary financial, regulatory and scientific hurdles have slowed down and discouraged the development and discovery of new antibiotics [5,7,8].

Keeping in view these problems there is a clear and urgent need to discover new economic, biocompatible, competitive and effective alternatives to traditional antibiotics. A number of alternative approaches have been proposed for controlling bacterial infections including the use of antimicrobial peptides, bacteriocins, competitive exclusion, flavonoids, and phage therapy [9–11]. Of these alternatives engineered nanomaterials, metal and metal oxide nanoparticles, in particular, exhibit remarkable antimicrobial activities against a number of bacteria including pathogens [12–14]. Hence, the role of these nanoparticles in a number of biomedical products owing to their remarkable antimicrobial activity is already proposed and is extensively reviewed [15,16]. Nanomaterials containing health care products such as band-aids and skin creams are already being commercially produced and are available in the market. In fact project on emerging nanotechnologies (PEN) lists about 1824 commercial products using nanomaterials [17]. However, to take the full advantage of this emerging technology many other aspects need careful assessment, such as suitability of different nanomaterials for different purposes, their cost effectiveness to compete with other options and their toxicity at realistic doses particularly in long-term clinical studies.

2. Antibiotic resistance in some crucial pathogens

Development of antibiotic resistance in bacteria is a problem of universal proportions. In their wonderful review on antibiotic resistance Beceiro, et al. [18] have summarised the evolution of resistance in bacteria against commonly used antibiotic groups including aminoglycosides, β-lactamase, fluoroquinolones, macrolides, and tetracyclines and their mechanisms. Production of enzymes for the modification or inactivation of the antibiotics like carbapenemases, β-lactamases [19,20], changes in the drug targets and the modification of the antibiotic receptors such as penicillin binding proteins, alterations in porins not allowing the passage of antibiotics into the cells [21], bacterial multidrug efflux pumps [22] are among some important mechanisms bacteria use to counter antibiotics. Genes for antibiotic resistance are widely distributed among bacteria and are often found on mobile genetic elements such as plasmids and transposons. The presence of such genes on mobile elements ensures easy sharing of the genetic information through mechanisms like horizontal gene transfer. Although, the presence of such genes in quite ancient forms of life also was demonstrated through data mining in an interesting report published in Nature [23]. The development of multidrug-resistance in IDs causing pathogens is a matter of great medical importance as such drug-resistant pathogens are often difficult to treat, requiring longer treatments and result in greater loss of lives. As exemplified by the re-emergence of multi-drug resistant TB especially in developing nations. According to world health organization (WHO) in 2013, 480,000 new cases of multidrug-resistant TB were reported (Antimicrobial resistance, Fact sheet N°194) [24]. To further complicate the matter such multidrug-resistant strains also show enhanced virulence and transmissibility [24].

Infections of TB are treated with multiple antibiotics comprising of ethambutol, isoniazid (INH), pyrazinamide, rifampicin and streptomycin (Centre for disease control and prevention; CDC). But multidrug resistant strains show insensitivity to INH, rifampicin, and other TB drugs. In a screening of 1000 isolates from Russian patients 48% exhibit resistance to multiple drugs [25]. Resistance to INH was conferred to *kat*G deletion from the chromosome or mutations in *inh*A gene [26] coding for enzymes (catalase-peroxidase) involved in the activation of INH. Alterations in these enzymes will, therefore, result in insensitivity to INH. While resistance to Rifampicin is mainly due to the point mutation in the *rpo*B gene (RNA polymerase subunit B), consequently resulting in changed *rpo*B locus leading to defective binding of the drug [27]. It was also emphasized that newly discovered mutations help tuberculosisTB to stay infectious while evolving resistance to multiple drugs.

Another deadly ID is cholera especially affecting children aged between 1 and 5 years, claiming 120,000 lives every year (WHO) [28]. The disease spreads through contaminated food and water. *Vibrio cholerae* toxigenic O1 serogroup strains, the causative agent of cholera secretes cholera toxin, colonizes and multiply in the small intestine. The type IV pilus of the bacterium helps in the process of its attachment and colonization [29]. Usually, erythromycin and tetracycline are used as first-line treatment for