Review Paper

Bio-nanobactericides: an emanating class of nanoparticles towards combating multi-drug resistant pathogens

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Abstract
The recent research on nanomaterials as antibacterials agents have gained significant importance in recent decades. The sustainable development of bio-nanobactericides from biogenic sources have resulted as one of the potent bactericidal agents at nanoscale. Bio-nanobactericides generously offers low toxic profiles in comparison with nanomaterials synthesized from conventional routes. The biological components mediate the synthesis and act as stabilizing agent to participate in the desired activity. These nanobactericides offers efficient alternatives to combat drug resistant pathogens with their unique mode of actions. Owing to their size dependent properties, they can be one of the most attractive tools against both gram +ve and gram −ve pathogens which are resistant to most of the available antibiotics. Based on these keys fundamental facts and considerations, the present mini review is designed to compile the recently published studies on nanomaterials bearing antibacterial activity against clinically important test pathogens.

Keywords Nanotechnology · Nanoparticles · Bactericides · Nanobactericides · Antibiotics · Multi-drug resistance

1 Introduction

Nanotechnology offers synthesis of materials at nanoscale ranging below 100 nm. Nanomaterials are recognized as the most inspiring particles of the century owing to their novel physicochemical properties [1, 2]. Nanomaterials confers prominent surface area compared to volume ratio, quantum effect coupled with lower binding energy results in high chemical reactivity and increased mechanical strength [3–5]. The notable applications of nanomaterials include designing and development of biosensors, tissue engineering, bio-labeling, fuel cell, semi-conductors, bio-engineering and bactericidal agents [5]. Nanobactericides are the emerging class of nanoparticles bearing bactericidal potential against an array of pathogenic bacteria [6, 7].

Different classes of nanobactericides are employed as effective agent to suppress or eradicate the microbial infections [8, 9]. Nanobactericides are reported to interfere with the normal metabolic process of pathogens by destroying or inactivating the vital components required for normal cellular activities [10]. The first usage of antibacterial drug "Penicillin" by Alexander Fleming which was recognized as wonder drug against the treatment of bacterial infection and saved millions of lives and led to the era of antibiotics [11–13]. Over the past decades, different classes of antibiotics have been discovered but as a counterpart, gradual resistance to these antibiotics was reported [12]. These drug resistant pathogens transformed their metabolic processes to develop resistant which has resulted in one of the most serious jeopardies to global health [14, 15]. The deleterious impact of drug-resistant can lead to myriad implications (Fig. 1). The multidrug-resistant pathogens acquire resistance to more than one class of antibiotics and spread widely by targeting different hosts [16–19]. The decline in the innovation gap during the evolution of drug-resistant era has tempered the first line antibiotic treatment [7]. A large number of factors converge to rise

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SN Applied Sciences (2019) 1:699 | https://doi.org/10.1007/s42452-019-0715-x

Received: 20 February 2019 / Accepted: 4 June 2019 / Published online: 10 June 2019

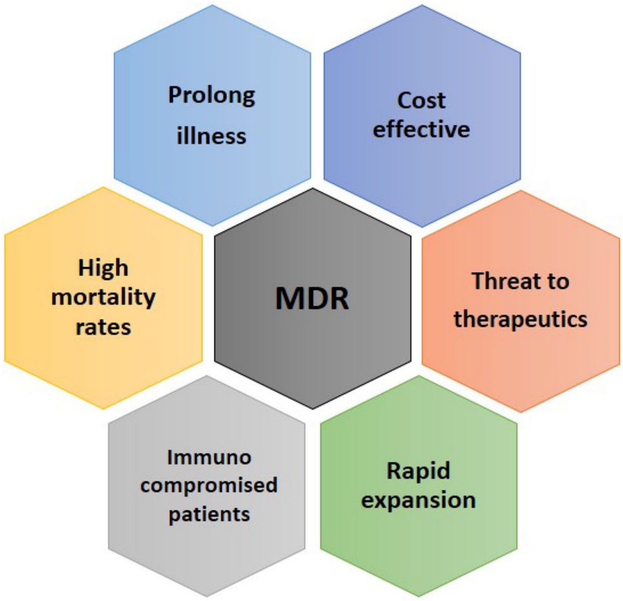

Fig. 1 Implications caused by multi-drug resistant pathogens

in the drug resistance such as genetic modification of drug-resistant pathogen, inappropriate antibiotics usage, poor sanitary conditions, hospital-acquired infections can lead to extending their support for drug resistance [14]. To cope with these microbial infections, higher dosage and combinatorial dosages have been one of the popular choices which in turn results in imparting immune system and damaging the normal physiological and metabolism [20]. The greater the antibiotics volume, higher are the chances of drug resistance [21, 22]. Some of the striking examples of antimicrobial drugs are highlighted in Fig. 2. The pathogens like *E. coli* which inhabits the gut micro flora are reported to cause urinary tract infections when they migrate to urinary tract. These pathogens are often treated with first line of antibiotics but latest reports suggests that most of these disease causing *E. coli* have gained resistance to Cephalosporins and fluoroquinolones [23]. Similarly, the classical example of *Mycobacterium tuberculosis* strains developing resistant to rifampicin, isoniazid and fluoroquinolone are documented this can lead to severe health risk in the management of tuberculosis [24]. Similar situations can be countered with fungal infections, for instance the antifungal drugs like fluconazole and echnocandins used against

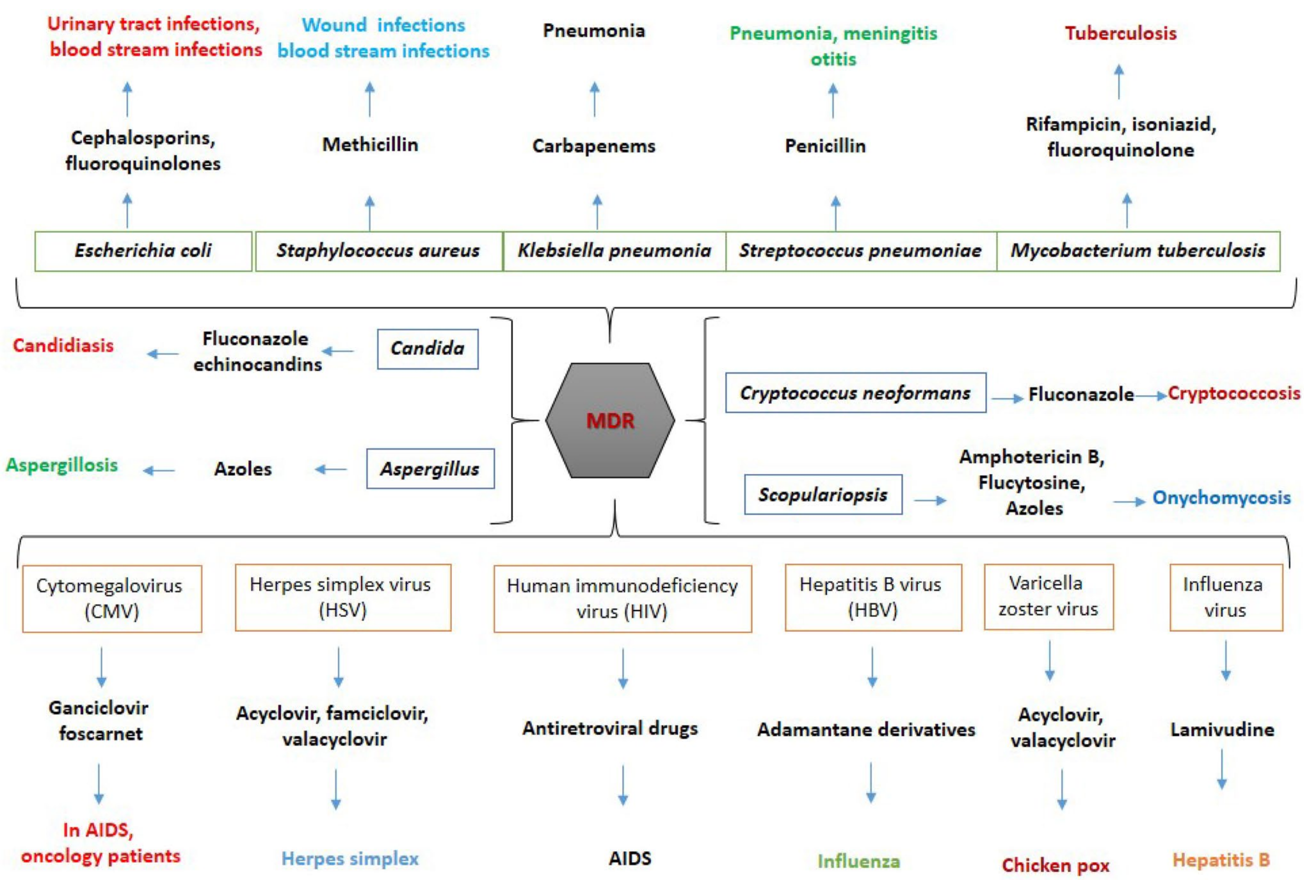

Fig. 2 Some of the microbial pathogens and its resistance to drug leading to severe infections

the treatment of candidiasis are reported to be ineffective to control *Candida albicans* [25]. There are also reports of drug resistant strains of *Aspergillus* which causes Aspergillosis [26]. Similarly, a majority of viruses are reported to have developed resistant to antiviral drugs such as acyclovir, famciclovir, lamivudine and valacylovir [27, 28]. These drug resistant pathogens alter their physiological and metabolic activities such as change in the influx systems, destroying the active drug components, causing mutation to inactivate pro-drug, ribosome targets protection, inactivation of acetyltransferases, altering the cell membrane sites [29–31]. Hence, implementing new strategies to combat drug resistance are highly essential and one such alternative are in the form of designing nanobactericides with multiple mode of actions [32]. There are different classes of nanomaterials which can serve as nanobactericides based on the elementary composition and their physicochemical properties [33]. Since not all nanomaterials offers the bactericidal potential but majority of the nanoparticles are reported to possess antibacterial properties. In the present mini review, some of the major variants or classes of nanobactericides are discussed.

1.1 Synthesis of nanoparticles

The process involved in the synthesis of nanoparticles can be grouped into various conventional methods. Based on the type of protocols these conventional methods are assorted into "Top-down process" and "Bottom-up Process as shown in Fig. 3. These approaches are further sub grouped based on their mode of synthesis and their conditions required for the synthesis [3, 33, 34]. In the Top-down approaches, larger components are disintegrated into smaller segments which are then converted into nano scaled particles with different techniques [3]. In contrast, Bottom-up approaches are the building up processes wherein there is formation of simple substance or nuclei which is then attenuate or tend to form nano scaled structures using different protocols as shown in the Fig. 3. Although there have been significant advances in conventional methods employed in the synthesis of nanoparticles but often these methods are bound with limitations such as use of hazardous toxic chemicals, expensive, generation of high heat etc. Hence there is an upsurge towards developing eco-friendly protocols towards the synthesis of nanoparticles [34–36].

1.2 Biosynthesis of nanoparticles

Recently there has been paradigm shift towards employing greener principles to synthesize nanoparticles. This has generated impute interest among the researchers in fabricating nanoparticles bearing nanobactericides by employing various biological entities varying from

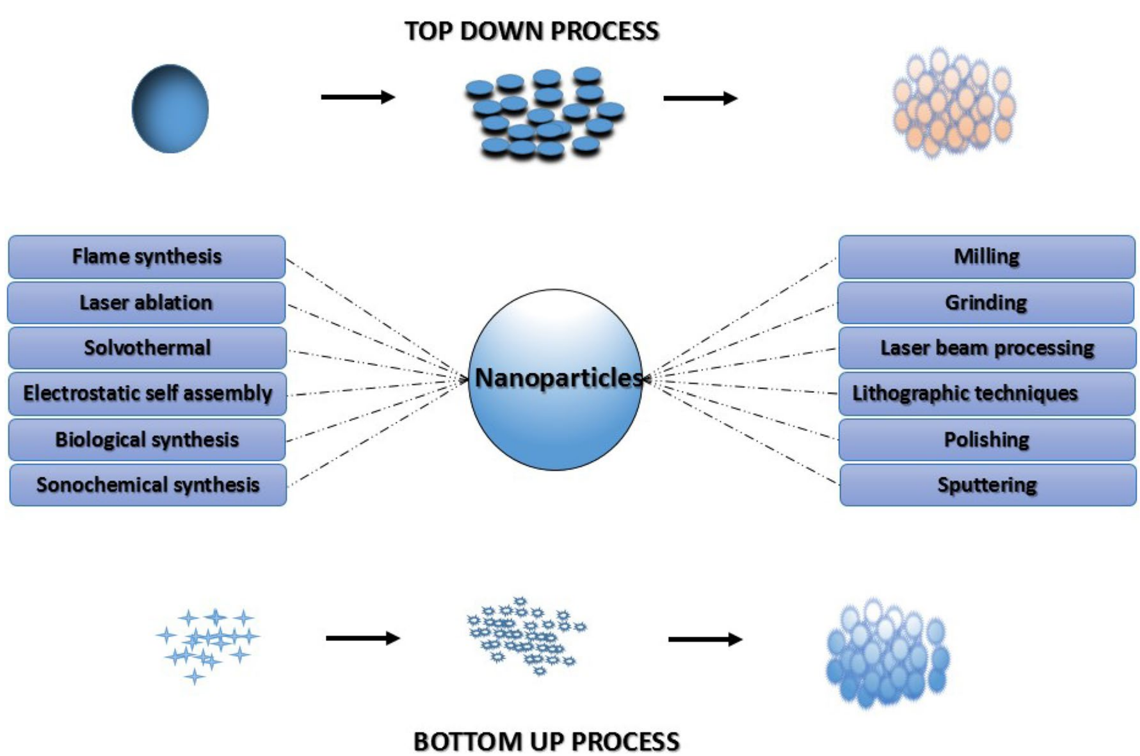

Fig. 3 Different modes of nanoparticles synthesis

simple prokaryotic bacteria to multi-cellular eukaryotic organisms such as fungi and higher plants. The biological molecules secreted by these living organisms are reported to have potential to reduce the metal salts to synthesize nanoparticles [5, 37]. The biological components might be macromolecules such as polysaccharides, proteins, lipids and phyto-components secreted from plants. Microbial metabolites are also responsible for synthesizing nanoparticles of desired properties and forms one of the most eco-friendly approaches to nanoparticles production [7]. In biologically mediated nanoparticles synthesis, the biological components not only reduce the metal salts, but also act as capping agent across the synthesized nanoparticles [34]. These capped layer across the nanoparticles are often considered to be important factor to obtain desired biological activity [6]. The functional groups associated with capping agents helps in tailoring or engineering the functional properties to the nanoparticles [7, 9, 37]. These biomimetic approach has driven great potential towards mastering technical advances in nanobactericides production by meeting the substantial challenges [38].

Different classes of nanoparticles bearing antibacterial potentials are discussed in the following sections with the compilation of latest reports with the given emphasis towards their applications as targeted antibacterial agents against wide range of pathogens with clinical significance.

2 Different classes of nanoparticles as nanobactericides

2.1 Silver nanoparticles as nanobactericides

Silver is considered as one of the valuable metals with a broad range of applications [8]. The usage of silver and its components can be traced down to millennia in curing diseases like ulcers and healing of wounds [39]. The bactericidal potential of silver was in practice prior to the invention of first antibiotic [40]. Till date, silver-based products are used in topical creams, disinfectants, polymer composite, dental amalgam and most of the Ayurvedic formulations consists of trace silver amount [41, 42]. In recent years, with the inventions of nano-silver, their applications have gained more attention [43, 44]. In the study conducted by Syed et al. [6], silver nanobactericides were synthesized by employing novel endophyte *Aneurinibacillus migulanus* and assessed in vitro bactericidal activity against the significant human and phytopathogens. The activity was measured via disc diffusion, well diffusion, MIC, broth dilution and CFU. The obtained results expressed profound activity of silver nanobactericides against *P. aeruginosa* (MTCC 7903) followed by *E. coli* (MTCC 7410), *S. aureus* (MTCC 7443), *B. subtilis* (MTCC 121) and *K. pneumoniae* (MTCC 7407). The possible mode of action of silver nanobactericides was studied with DNA damage activity compared to control DNA. The study forms first report on *Aneurinibacillus migulanus* as an endophyte and its ability to reduce silver nitrate to synthesize silver nanobactericides [6].

Similarly, Study conducted by Baker et al. [7], reported the extracellular synthesis of silver nanoparticles bearing bactericidal potential against a panel of human and environmental pathogens. The activity was measured as a zone of inhibition with the highest activity against *Pseudomonas aeruginosa* [7]. The mycosynthesis of silver nanoparticles was obtained with endophytic fungi *Colletotrichum* sp. ALF2-6. The synthesized nanoparticles were well characterized and evaluated for bactericidal property activity against targeted test pathogens *Escherichia coli* (MTCC 7410), *Salmonella typhi* (MTCC 733), *Bacillus subtilis* (MTCC 121) and *Staphylococcus aureus* (MTCC 7443) which resulted in significant activity against *Staphylococcus aureus* (MTCC 7443) compared to other test pathogens. The activity was further confirmed with MIC and study also predicted the mode of action of nanoparticles on DNA which resulted in shearing of DNA treated with silver nanoparticles compared to the control DNA [45].

2.2 Gold nanoparticles as nanobactericides

In ancient times, gold was used to treat fever and syphilis and it was in the early nineteenth century, Robert Koch developed gold cyanide against *Bacillus* species which led to progress in treating tuberculosis in the twentieth century [46]. In recent decades, gold nanoparticles owing to their unique properties have traded their applications in diverse fields [47]. Some of the prime properties of gold nanoparticles include high electric conductivity, improved surface catalytic activity, high heat conductivity and enhanced photoemission properties [48]. Interestingly, gold nanoparticles are regarded as one of the stable metallic nanoparticles and their easy surface functionalization has led to their potential applications in the biomedical sector for instance in diagnosis, drug delivery and potent antimicrobial agents [47].

In addition, scientific studies highlight potent bactericidal activity of gold nanoparticles in combating bacterial infections at a reduced dosage of standard antibiotics with minimal adverse effects [37]. The study conducted by Abdel-Raouf et al. [49], reported the synthesis of gold nanoparticles using *Galaxaura elongata* which displayed antimicrobial activity. Similarly, gold nanoparticles were synthesized using marine brown algae *Turbinaria conoides* average size of 60 nm which displayed bactericidal properties against *Streptococcus* sp, *Bacillus subtilis* and *Klebsiella pneumoniae* [50]. According to Patra and Baek [51], gold nanoparticles bearing bactericidal properties was synthesized using the aqueous extract of water melon rind. The synthesized nanoparticles displayed antimicrobial activity against food borne pathogens and also showed DPPH radical scavenging activity, ABTS scavenging, nitric oxide scavenging and reducing power [51].

2.3 Zinc oxide nanoparticles as nanobactericides

Zinc oxide nanoparticles are considered as one of the most versatile nanomaterials owing to their diverse physic-chemical properties. The large surface area, low toxicity and the direct band gap of 3.37 eV at room temperature with large quantum efficiency have traded their applications in surface coating, optical communications, sensor, semiconductors, used in fabricating rubber, lubricant, ceramics, cement and potent antimicrobial properties [52]. Interestingly, zinc oxide nanoparticles possess photo-oxidation and catalysis which generates an impact on pathogenic microorganisms. Most importantly use of zinc oxide nanoparticles are generally recognized as safe (GRAS) for commercial exploitation [53]. Hence, they have been employed in various sectors like food and medical sector especially in developing packaging materials for preserving foods. The potent activity of zinc oxide nanoparticles is based on the generation of reactive oxygen species leading to cell wall damage and membrane permeability resulting in loss of proton motive force. The uptake of zinc ions weakens the mitochondria, causes oxidative stress which in turn inhibits the cell growth [54]. According to Sirelkhatim et al. [55], zinc oxide nanoparticles are considered to represent a biologically safe particles which exhibits photocatalysis and photo-oxidizing impacts on biological species.

2.4 Iron oxide nanoparticles as nanobactericides

The applications of iron oxides are widespread and have served mankind for centuries especially in diagnostic practices [56]. The recent implementation of iron oxide nanoparticles has led to innumerable applications owing to the unique properties. The advances in iron oxide nanoparticles based research are constantly explored and transforming the fundamental knowledge to technological application oriented for instances in targeted drug delivery, biosensors, magnetic resonance imaging, bioengineering, electrochromic devices, batteries, solar cells and potent antimicrobial activity against microbial pathogens [57]. The primary mode of action of iron oxide nanoparticles includes the production of ROS and releases toxic ions leading to oxidative damage and disruption of membrane transport activity [58].

2.5 Titanium oxide nanoparticles as nanobactericides

Titanium oxide is one of the extensively studied transition metal oxides with innumerable applications which includes the development of biosensor, electronic devices, batteries and also evaluated in biomedical applications as a potent antimicrobial agent, toothpaste and ointments [59]. These applications are attributed to its unique chemical and physical properties for instances high surface area, refractive index, chemical, and thermal stability, low absorption and dispersion in spectral regions [60]. The profound bactericidal activity of titanium dioxide nanoparticles is based on its photocatalytic property which triggers and releases hydroxyl radicals and superoxide ions and significantly decreases the expression of vital genes and proteins which are responsible for regulatory signaling and growth functions. These modes of actions indirectly affect ion homeostasis and coenzyme-independent respiration [61].

2.6 Platinum nanoparticles as nanobactericides

The platinum nanoparticles are majorly explored in developing electronic devices and capacitors owing to their optical and catalytic properties [62]. In recent years, scrawling progress with platinum nanoparticles has resulted in its usage as potent antimicrobial agents against an array of pathogenic microorganisms [63]. Platinum nanoparticles are reported to inactivate the pathogen by interacting with vital enzymes and proteins which in turn restrain cell proliferation [64]. Reports also suggest that platinum nanoparticles bind to negatively charged components of the bacterial cell wall which in turn disturbs the integrity and rigidity of the cell which results in loss of cellular content [65]. Platinum nanoparticles were synthesized using leaves extract of *Cerbera manghas*. The synthesized platinum nanoparticles were subjected to antimicrobial potential against selected bacterial pathogens.

The results exhibited significant activity against *V. cholera* with 20 mm zone of inhibition in comparison with the control streptomycin followed by *S. aureus* with 19 mm, *S. pyogens* 12.8 mm and least activity was observed against *E. coli* and *S. typhi* with 11 mm. The study concluded with green processed platinum nanoparticles with the potential of antibacterial properties [66]. Platinum nanoparticles were synthesized with carbohydrates like fructose and sucrose as stabilizing agents. The synthesized nanoparticles at concentration 100 µg/ml exhibited bactericidal activity against *P. Stutzeri* and *Lactobacillus* species [67]. The potential of platinum nanoparticles as antimicrobial agents are less explored compared to other nanoparticles with scanty reports are majorly available hence future studies will be interesting to reveal the mode of action of these nanoparticles.

2.7 Copper nanoparticles as nanobactericides

The applications of copper-based products are overwhelming with significant properties like magnetic, optical, catalytic and electric properties. In recent years, copper nanoparticles have influenced the biomedical sector with its potential roles [68]. Studies confer that biosynthesized copper nanoparticles represents profound antimicrobial activity. In the study conducted by Abboud et al. [69], brown alga (*Bifurcaria bifurcata*) was evaluated for biosynthesis of copper nanoparticles and assessed for antimicrobial activity against *Enterobacter aerogenes* and *Staphylococcus aureus.* Similarly, Caroling et al.[70] reported the production of copper nanoparticles with aqueous extract of Goose Berry (*Phyllanthus Embilica*) under optimum conditions and examined for anti-microbial activity against human pathogens viz. *S aureus* and *E. coli*. Copper nanoparticles were synthesized from a plant leaf extract of *Vitis vinifera* and assessed bactericidal activity against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhi*, and *Klebsiella pneumonia*. Among the test pathogens, *Staphylococcus aureus* exhibited the maximum inhibition with copper nanoparticles followed by *Escherichia coli*, *Klebsiella pneumonae*, *Bacillus subtilis* and *Salmonella typhi* [71].

2.8 Magnesium oxide nanoparticles as nanobactericides

Magnesium oxide nanoparticles are extensively studied for antimicrobial activity in order to develop best suited alternatives for drug-resistant pathogens. In a study conducted by Tony and He [72], antibacterial activities of magnesium oxide (MgO) nanoparticles were tested in combination with like nisin and zinc oxide nanoparticles against *Escherichia coli* O157: H7 and *Salmonella* species. The study showed that magnesium oxide nanoparticles were effective and were capable of reducing 7 log in bacterial count. The activity of magnesium oxide increased with the increased in the concentration and synergistic activity was more in combination with nisin as compared to zinc oxide nanoparticles [72]. Based on the literature available, scanty reports are available for the usage of magnesium oxide nanoparticles as nanobactericidal agent and hence it will be interesting to investigate on these nanomaterials which may open new avenues.

2.9 Bi-metallic nanoparticles as nanobactericides

The bimetallic nanoparticles are one of the most fascinating nanomaterials as they are capable to perform multiple functions with the composition of two or more different nanomaterials. Hence in recent times, bimetallic nanoparticles are extensively studied as antimicrobial agents against an array of pathogenic microorganisms. According to a study conducted by Malapermal et al. [73], silver–gold bimetallic nanoparticles were synthesized using aqueous leaf and flower extracts of *Ocimum basilicum* as a natural reducing agent. The synthesized bimetallic nanoparticles remained stable and showed significant activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and *Pseudomonas aeruginosa* [73]. Similarly, a study conducted by Sawle et al. [74], fungal mediated bimetallic nanomaterials of silver–gold nanoparticles were synthesized possesses catalytic and antimicrobial which have a broad range of applications in health care sector.

3 Nanobactericides mode of action

Nanobactericides are reported to effective against wide range of pathogens. The exact mechanism is yet to be elucidated, whereas scientific studies demonstrate they possess multiple modes of action. The mode of action may include, paralyzing the physiological process of the bacterium by inactivating the vital components or protein responsible for DNA replication. Further studies also demonstrate that these nanobactericides are capable of disturbing the cell membrane by binding to the negatively charged components. They are also reported to interact with cytoplasmic components and nucleic acids, to inhibit respiratory chain enzymes, and to interfere with the membrane permeability Dehydrogenase of complex I [75]. Nanobactericides are equally capable of producing reactive oxygen species (ROS), inhibition of respiratory enzymes, ATP production, creating pits resulting in disruption of membrane integrity and rupture the cell membrane causing death of the pathogen [76]. Whereas in some cases for instance dendrimers lead to sponge effect and induce cytotoxicity. Furthermore, to attenuate a potent activity, various characteristics and parameters are of prime importance such as size, surface charge, functional sites, solubility and type of target site [77].

4 Future perspective

The increased in the drug-resistant pathogens have influenced deep crisis in the health care sector and it is expected to grow in future decades. As the population is expanding, preventive measures to combat drug resistance forms one of the top priority research across the globe. According to WHO, drug resistance is growing at an alarming rate which can travel across the borders with human beings forming one of the leading carriers. The situation is undesirable especially in the developing countries where comprises the poor sanitary conditions. Hence to combat these conditions, different strategies are being investigated and designed. One such strategy includes the use of nanobactericides as one of the potent bactericidal agents. Whereas the mode of synthesizing to produce these agents must form critically important as they must not carry any adverse effects and health implications. In recent studies, it has been demonstrated that, developing novel strategies of nanotechnological principles coupled with the green route to produce nanobactericides forms ideal and best-suited alternative. Use of biological resources can provide a safe mode of synthesis and most importantly, the biological agents acting as reductant can equally contribute to display activity. Studies have also demonstrated that biologically mediated production of nanobactericides can provide multiple modes of action in comparison to a sole agent. Hence, it will be interesting to evaluate and design novel strategies to produce bio-nanobactericides by exploiting an untapped reservoir such as endangered plant species or from microbial flora from extreme climatic conditions. These resources are largely explored and can provide a structurally diverse class of biological agents which can offer promising avenues especially in combating drug-resistant. Based on these facts and considerations, different expertise is expected to play a vital role by collaborating and designing novel nano bactericidal agents for instance in developing nanohybrid conjugates. These nano-hybrid conjugates can be synthesized by tailoring one or more biological entities to nanoparticles. These tailored components are expected to deliver desire multiple activities. Further use of nanoparticles as an adjuvant for development of a vaccine remain an area of thrust which can open new avenues.

5 Conclusion

Antibiotic resistance is a continually evolving and dangerous problem that requires immediate attention as well as future planning to impede a global health crisis. Increase in infectious diseases attributed to one of the leading causes of mortality across the globe in the twentieth century. As multi-drug resistant microorganisms have governed their way towards resistant against the available antibiotics, the researchers across the globe need to synchronize various strategies to combat these pathogenic microorganisms. Screening of new antimicrobial substance and chemical modification of the existing drugs with respect to the pathogens has developed simultaneously but unfortunately, with the rate of emergence of antibiotics resistant strain some novel strategies must be adopted, one such strategy is with the intervention of nanotechnology as summarized in the present review.

Acknowledgements Authors also thank Krasnoyasrk State Medical University named after Prof. VF. Voino-Yasenetskiy, for providing infrastructure.

Funding All authors are thankful for Directorate of Minorities, Government of Karnataka, India for providing Financial support for the present study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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