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Review Article

A Short Review on the Improvement of Antimicrobial Activity by Metal and Nonmetal Doping in Nanoscale Antimicrobial Materials

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ABSTRACT

The largest number of antibiotic and antimicrobial agents are consumed and utilize for various operations throughout the world. Due to the extensive application of these medicinal chemicals number of Antibiotic Resistant Microorganisms (ARM's) are evolved, as a result, it is a major threat that these organisms may spread a lot of new incurable diseases. The traditional antimicrobial agents are not effective because of mutation, change in absorption mechanism and metabolic pathways by microorganisms. High risk diseases like various types of cancers are very common and need to monitor in the early stages to minimize the damage. Prevention or cure both factors are necessary these days to ensure health and safety for various agencies. From the effective use of cisplatin as an anticancer agent, inorganic materials are highly rated as an effective antimicrobial agents. Nanomaterials, nanocomposites and metal organic complexes are the most promising candidates and far more reliable than the conventional and other agents. With the large number of metal oxides, infinite number of metal and nonmetal ratio, the enormous amount of metal-ligands combinations variety of antimicrobial agents can be synthesized and applied for tracing, labeling, inhibiting transcription factor activity and ultimately to the distruction of harmful microbes. In the current short review more emphasize is given to the mechanism, synthesis and application of metal and nonmetal doped antimicrobial agents. Various aspects such as size, morphology, concentration etc. are reviewed to shed the light on the current status of these unique materials. Furthermore, important mechanistic pathways are also discussed which may prove important for further studies. Overallmetal non metal doped antimicrobial agents may open the doors for effective elimination of strong and highly resistant microorganisms.

Keywords: Antibiotic resistant microorganism; Nanomaterial; Doping; Noble metals; Nonmetal doped

INTRODUCTION

With increase in availability of food and habitat there is an increase in the number of various microorganisms is observed through the globe. Many of these microorganisms are beneficial for the development of the ideal environment for living organisms, including human beings [1]. Nitrogen fixers, decomposers, anaerobes and other important microorganisms are the important class of living being that operates at the micro level, but have a serious impact on the ecology of the planet earth [1,2]. But, with beneficial microorganisms there are many dangerous ones, which are causing serious problems by spreading diseases, dominating and eliminating other important species these are known as pathogens [3]. To overcome the influence of these pathogens various inorganic as well as organic agents develop commonly known as antibiotic or antimicrobial agents. Most of the current antibiotics are of organic, synthetic origin since these are biocompatible, highly stable, easier to synthesize with high selectivity [4].

Between 2000 and 2010, consumption of antibiotic drugs increased by 36%. Overall more than 73 620 748 816 standard units of antibiotics are synthesized and used which are very effective against most of the pathogens [5]. But, recent findings suggest that many of these antibiotics are not proving effective against certain strains of microorganisms, these microorganisms which can sustain in the presence of these substances are known as Antibiotic Resistant Microorganisms [6]. With an increase in the use of these antibiotic the resistance of microorganism is also increasing and it is the most lethal thing to happen [6,7]. Various medicinal and household waste contain an enormous amount of these antimicrobial agents and eventually they enter into the nearby water reservoirs in the form of municipal and medical effluent [8]. These effluents when enter into the water bodies temporarily kill the microbial flora, but soon many organisms develop the capacity to resist against these materials and evolve as Antibiotic Resistant Microorganisms by altering their genetic material, mechanism of absorption, by

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transferring their gene into water-indigenous microbes and other methods [9].

Once the microorganism becomes resistant to antimicrobial agents, it starts to reproduce many such organisms and transfers its genetic information and generate large numbers of resistant microorganisms [10]. Here, the conventional antimicrobial agent fails and instead of destroying the microorganism it helps to generate more such a type since, as the concentration of antimicrobial agent increases the resistivity of resistant microbial flora is also increasing [11]. This type of cases is now a days very much common in many water bodies, especially the rivers near cities [10,12]. These situations may cause trouble in the near future if one of the strain becomes a disease causing. This may increase the risk of infectious disease which may prove lethal to the living organisms and eventually humans [13].

To avoid such a circumstance, there is a need to find out a stable, cost effective, biocompatible, ecofriendly substitute and one of the promising candidates is nanomaterials [14]. The most important qualities of nanomaterials are it is easy to synthesis, large variety of metal oxides precoursers are available and by doping various metal and nonmetal dopants in variety of concentration, the proficiency of these nanomaterials can be improved. Furthermore, they show various mechanistic pathways to destroy the microorganisams to which development of resistance mechanism is difficult for many microbes [15]. Nano scale materials are highly effective because their multi dimensional properties such as small size, various morbhology and more than one type of mechanism to destroy microorganism [16]. Smaller size is generally the essential factor in the retardation of microbes since, small sized nanomaterials easily penetrate into the cell membrane and alter the transportation, interact with biomolecules of microbial cell, disturb the communication even at genomic level to form courrupt cell constituent that lead to eventual death of microbes [17]. Marphology is importanat for any micro scale material because as morphology changes the properties of nanomaterial also changes especialy in an antimicrobial material size plays an important role to increase the proficiency. For instance Nanofibersaornanorods are more effective than simple spherical nanoparticles and the interesting point is that morphology can be easily controlled by various methods [18].

Nanocscle transition metal complexes are also amongst recent materials which can be applied for the effective destruction of various resistances microbes by virtue of their vast number of properties and modes of applications [19,20]. Metal organic framework especial transition metal centered complexes are amongst most important class these days to either monitoring or inhibiting various diseases very effectively [21]. Luminescent metal complexes interact with macromolescules, functions as a lable and highlight the affected cells [22], metal complexes of Co, Cr, Pt, Ir, Rh etc. are proving their worth as inhibitors of transcription factor activity which directly control the genetic information and regulate the disturb communication and help to form healthy cellular componants instead of corrupt cellular componants [23], Pt since the time of cisplatin and recently Ru metal complexes are gaining attention as modulators of inflammatory and autoimmune responses [24-25]. Non metal based materials, especially from graphene origin is also a major class of material which are easy to synthesize, cheap and effective aginst most of the pathogenic and resisitance organisams specifically bacterium, effectiveness against virus, fungi and algae is yet to establish but have trumendus possibilities [26].

Metal doping is the most promising method for the preparation of effective antimicrobial agent various dopants improve the physical properties, and antimicrobial activity of nanomaterials. Marphology is very important to show the activity for instance nanorods and nanowires are more effective as compared to other morophologies such as hollow or spherical also as the size of nanomaterial decreases antimicrobial activity also increase [27]. Morphology and the size of these nanomaterial, can be easily controlled with the help of many preparation techniques. Furthermore, it is observed that not only non-metal dopant contribute to the size and morphology they also decrease the recombination of photo induced charge carries (electron-hole pair) which is important to generate oxidizing species like •OH, O_2-•, HOO• free radical which may be utilized to break the cell membrane of microbes in aqueous medium [15,27]. All these and many more properties of doping impart effectiveness to the doped nanomaterial to show higher antimicrobial activity [28].

MECHANISMS OF ANTIMICROBIAL ACTIVITY OF NANOMATERIAL

There are many antimicrobial nanomaterials are synthesized and applied for the removal of resistant microorganisms, but the most important aspect to study and understand is the mechanism by which they perform the task. Many scientific community debates on various mechanisms by which a microbe can be killed effectively. Following are the most common mechanisms which are discussed in may research publications.

ROS generation

Reactive Oxygen Species (ROS) are the most common mechanism by which a microbe can be effectively destroyed or at least deactivate by generating the oxidizing species in the form of dioxygen radical ($O_2^{-\bullet}$), these oxidizing radicals are highly reactive and generally react with the macromolecules such as DNA, Enzymes (protein), lipids etc. [29] as shown in Figure 1. When nanomaterials are irradiate with a definite amount of radiation the partial absorbs the radiation and e− is ejected from VB to CB due to this photo induced charge carriers are form (e− and h^+ pair) and e− reduces oxygen to generate the highly oxidizing dioxygen radical ($O_2^{-\bullet}$) [30]. This process is very common and effective against many types of microorganisms in various life stages.

Metal cation release

Most of the metal generates cationic species in water and the sources of metals are metal oxide nanoparticles. These cations are positively charged and have an affinity towards the cell membrane and doe to smaller size and high permeability they enter into cell via cell membrane and interfere various metabolic processes by targeting protease enzymes and functionalities such as sulfhydryl, amino and hydroxyl groups, to change the structure and performance of overall molecule. This leads to toxic products or process which eventually proves fatal for the microbe [31].

Membrane dysfunction

Membrane dysfunction is a very active method since most of the metallic materials are of positive charge and the have electrostatic attraction towards the cell wall. The attachment of small size metal particles blocks the essential pores and cavities of cell membranes, which is semi permeable and fragile, due to the blockage the transportation and absorption process is interrupted and various deformations of cells are carried out which are known as bacteriolysis. This leads to rapid killing of various microorganisms 32].

Nanoparticle internalization

Nanoparticles, especially smaller nanomaterials are highly active because there large surface area and high permeability generally how severe effect on the cell wall of microbes. High surface are elps for high adsorption of parcels on cell membrane and affect ransportation and causes malfunctioning of delicate membrane, hey also enter into the metabolism through penetration and show oxic effects by acting negatively on exchange of matter and energy 33] as shown in Figure 2.

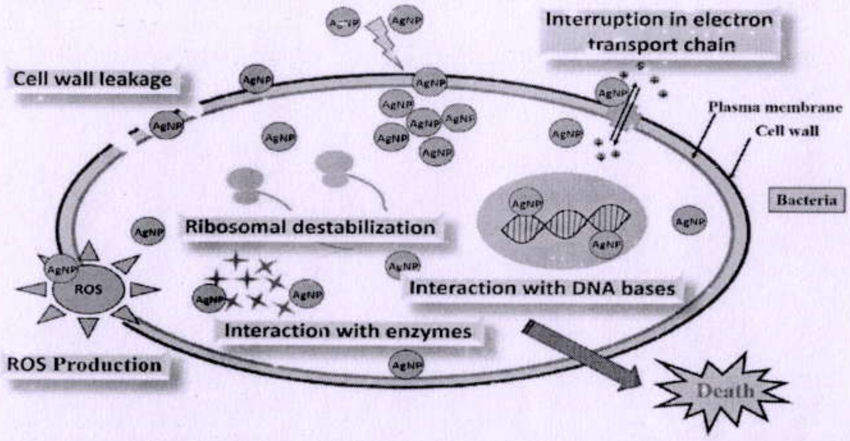
METHODS TO ENHANCE ANTIMICROBIAL ACTIVITY

t can be concluded from the mechanism discussion that the ssential criteria for the highly active antimicrobial nanomaterial re the generation of photo induced charge carriers that is an lectron-hole pair (e nd h and secondly the size of nanomaterial. oth these properties affect the destruction of pathogen physically s well as chemically and both and other important properties of anomaterials can be controlled by various synthesis processes.

Doping metals

Doping transition metals: Transition metals are the most mportant and active dopants in many metal oxides for their trength, variable valencies, availability and other properties [34]. ne of the key advantages of doping these metal dopants is, they ecrease the band gap between VB and CB and covert low efficient ight absorber into highly efficient UV- visible light absorbing ateria! [35] they also affect the morphology and surface area of verall inactive metal oxide [36]. The decrease in the band gap enerates photo induced charge carriers effectively and eventually elp to generate highly oxidized species such as H, O OO which are directly attacking on cell membrane and kill the icroorganism by plasmolysis [37]. Yadav et al. Introduced Fe in o TiO and it was evident from the study that the antimicrobial haracteristics of TiO ncreased in fluorescent light much more fficiently than undoped TiO 15], Nair et al. doped Co in ZnO by co-precipitation method and it was highly effective against . *oli lebsiella pneumoniae, Shigella dysenteriae, S. typhi, P. aeruginosa, . subtilis* nd *S. aureus* bacterial strains [38], Karunakaran et al. also sed TiO nd doped Cu for the disinfection of microbes under visible light irradiation and was more impressive than bare TiO 39] these and other transition metals like Ni, Mn, Zn and many ore can be employed for the same and can prove effective against any strains of microbes.

Doping noble metals: Noble matals (Au, Ag and Pt) are the mportant class of metals used enormously as an antimicrobial agent 40]. By using these expensive metals as a dopant the overall cost s reduced and effectiveness can be achieved [41]. Wong et al. used Ag as a dopant and impregnated to prepare TiO coating and study evealed the destruction of the cell membrane of . *coli* bacteria [42]. erni et al. reported light-activated antimicrobial polymers doped with Au by simple swell-encapsulation-shrink method and its was



igure 1: A mechanism for the Antimicrobial activity Reprinted from (Ref. 52) copyright 2017 applied microbiology and biotechnology.

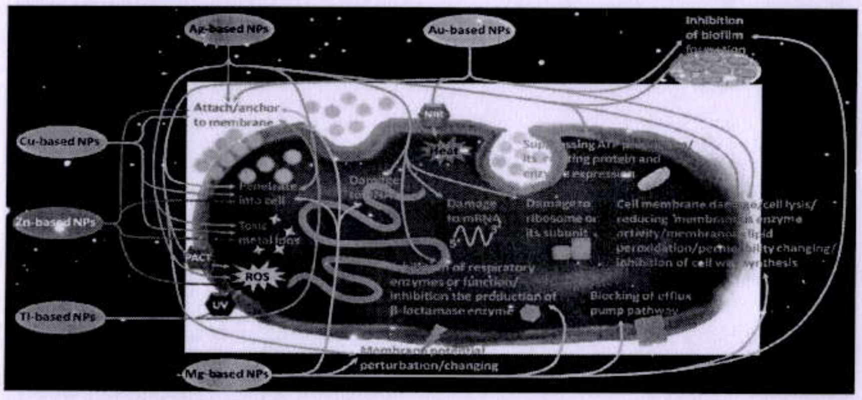


Figure 2: Mechanism of metallic nanoparticles against the drug resistant bacteria reprinted from (Ref. 12). Copyright 2014 Advanced drug delivery reviews.

bserved that the coating was effective to produce large amount f ROS through which high antimicrobial activity was observed nd gold played an important role to generate ROS [43]. Tseng et l. developed a visible-light responsive platinum-containing titania TiO Pt) exerted high performance antibacterial property against oilborne pathogens even in soil highly contaminated water and he most essential aspect was its effectiveness in visible range of adiation [44]. It is evident from the discussion that these noble etals can play an important role in further development of highly ffective antimicrobial doped materials. Furthermore, they are ffective in very small amount with effective destroying capacity, which is applicable for antimicrobial coating and thin films.

Doping non-metals: Nonmetal doping is the current aspect use or the development of nanomaterials because of their various ualities. Loading of non-metals like B, C, N, S, halogen, etc. are mongst many nonmetal used as dopant from simple precursors ike urea, thiourea, amino acids and other organic materials [45]. The introduce into the crystal lattice because they minimize the lectron-hole recombination and shift the absorption in UV-visible ange by decreasing the band gap. Furthermore, they have effective ontrol of the size as well as the morphology of Nanomaterials.

inimization of electron-hole recombination and particle size is he most essential requirement for an inorganic material to show ts antimicrobial activity physically and chemically. Many workers ntroduced various non-metal dopant and proved its effectiveness, specially in TiO 46]. El-Ghenymy et al. reported a boron-doped iamond (BDD) anode and a stainless steel cathode for the effective ntimicrobial assembly which was highly effective in generation of OH radical which eventually destroyed the microorganisms [47]. him et al. synthesized C doped TiO by simple sol-gel method nd employed for the accelerate inactivation of bacterium L. onocytogenes in visible light [48]. These and many examples re available which show the importance of these cost effective on-metal dopant. The future possibility is that the combination f these metal and non-metal multidoped antimicrobial agent ay provide an essential breakthrough for the removal of highly esistance microorganisms. The various applications of different ypes of nanomaterials are shown by the flow chart in Figure 3.

Methods for the synthesis of metal, non metal doped anomaterials

ollowing table depict out of many methods few commonly known nd less common methods for the preparation of metal, nonmetal nd multidoped nanomaterials. Since, size is one of the most mportant factors in deciding the outcome of antimicrobial activity s considered by avoiding other aspects. Furthermore, metal and onmetal dopant precursors are also discussed with a few not so opular materials in the later section of the Table 1.

FFECT OF MORPHOLOGY, SIZE AND ONCENTRATION

Morphology

Morphology such asnanorods, nanosheets, microspheres, uantum Dots and many more are an effective parameter for he enhancement of antimicrobial activity of nanomaterials and re manageable by proper synthesis and growth techniques. For nstance, normal ZnO NP's are less effective than the nanoroads nd nanofibers and ZnO nanoflowers are highly effective ntimicrobial agents thanthe nanoroads and nanofibers [49] so, as he morphology change activity also changes.

Particle size

article size can be controlled and as discussed in mechanism ection, can play a crucial role to increase efficiency of any ntimicrobial agents because size determines the penetration and urface area of any nanomaterial, as the particle size decreases the roficiency of the nanoparticle also increases and it's not necessary o have very small size the size in micrometers μ is enough to ompare the activity [50,51].

oncentration

oncentration of NP's to kill various microbes varies from aterial and to microorganisms, generally as the concentration f NP's in solution increases the proficiency also increases [27]. NP concentration in the range of 10^{-3} M is sufficient to kill many est microbes and as the concentration decreases the efficiency a ercentage of total removal also decreases [52]. The approach to enerate an effective process which work on less concentration is he prime challenge since, low concentration disinfection will be co-friendly and cost effective process. Various combinations of ulti doped catalysts have the potential to solve this problem.

APPLICATION OF DIFFERENT TYPES OF DOPED MATERIALS AS AN ANTIMICROBIAL AGENTS

ollowing is one of the few of many antimicrobial agents reported

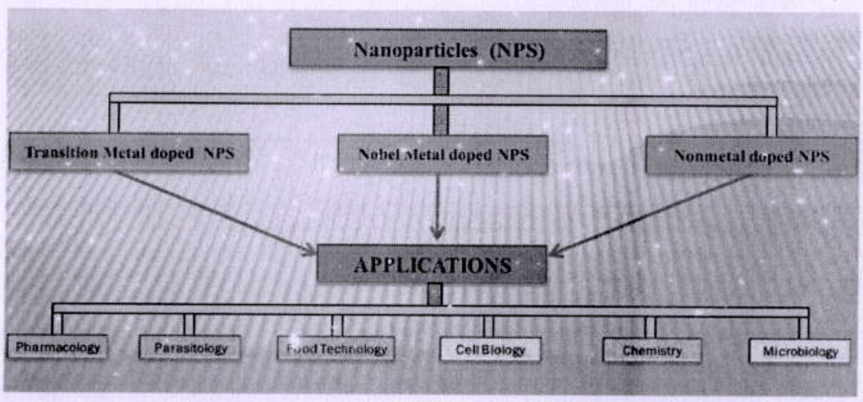


Figure 3: A flow chart of different types nanomaterials and its applications in different fields.

Table 1: Methods for the synthesis of various metal, non-metal doped nanoparticles.

S. No	Method for synthesis	Material	Starting material	Metal dopant	Non metal dopant	Size	Ref.
1.	Hydrothermal method	C, N, S doped TiO_2	$TiCl_4$	-	l-cysteine	40-50 nm	[40]
2.	Sol-Gel Method	Fe, C, S, N doped TiO_2	Titanium isopropoxide	$FeCl_3$	Thiourea	9-10 nm (for 0.3 w% of Fe)	[41]
3.	Co-precipitation Method	La doped ZnO	Zinc acetate	$La(NO_3)_3$	-	10.18 (for 0.07 mole% La)	[42]
4.	Green Synthetic Approach	C-doped TiO_2	$Ti\ (SO_4)_2$		$C_{12}H_{22}O_{11}$	20	[43]
5.	Microemulsion Method	CuOx-TiO_2composite	Titanium Tetra isopropoxide solution	$Cu\ (NO_3)_2$	-	6.09 nm (FOR 1.4 W% cu)	[44]
6.	Photoimpregnation Method	Ag doped TiO_2	Evonik TiO_2 P25	$AgNO_3$	-	4-5 (for 1w% Ag)	[45]
7.	One-pot microwave-assisted hydrothermal synthesis	Cr/Ni/Cu/Nb, N doped TiO_2	$Ti\ (SO_4)_2$	$NbCl_5$, $CrCl_3$, $CuCl_2$, $NiCl_2$	Urea	7.6 nm (for Ni/Ti=0.06) 10.6 (for Cr/Ti= 0.06)	[46]
8.	Oxalate assisted sonochemical method	Cu doped ZnO	$Zn\ (NO_3)_2$	$Cu\ (NO_3)_2$	-	2-4 µm (microballs)	[47]
9.	Metallic and Bimetallic Cross-Linked Poly(vinyl alcohol) Nanocomposites under Microwave Irradiation	Pt-In/ Ag-Pt/ Pt-Fe/ Cu-Pd/ Pt-Pd/ Pd-Fe cross-linked PVA nanocomposites	Polyvinyl alcohol	Na_2PtCl_6, $InCl_3$, $AgNO_3$, $Fe(NO_3)_3$, $CuCl_2$, $PdCl_2$	-	nm to µm acoording to morphology	[48]
10.	Thermal-driven self-assembly process	RGO/AgNP hybrid	Natural graphite flakes	Ag NPs (Synthesized with the help of Sodium Citrate)	-	16-18 nm	[49]

Table 2: Different types doped nanomaterials as an antimicrobial agent.

S. No	Material	Target Microorganism	Ref
1.	Co doped ZnO	*S. dysenteriae, S. typhi, V. cholera* and *E. coli*	[53]
2.	Cu-Doped TiO_2	*E. coli* colonies and (b) *S. aureus*	[54]
3.	Ta-doped ZnO	*P. aeruginosa, B. subtilis, S. aureus, E. coli*	[55]
4.	N doped ZnO	*E. coli, S. aureus.*	[56]
5.	Ag embedded graphitic carbon nitride	*E. coli, S. aureus.*	[57]
6.	PEI-ce6 and BB6 etc. by PDI(Photo Dynamic Inactivation)	*S. aureus*, Gram-negative *Escherichia coli* and fungal yeast Candida albicans	[58]
7.	$g\text{-}C_3N_4/TiO_2$/kaolinite	ciprofloxacin and S. aureus	[59]
8.	ZnO/Au Hybrid Nanostructures	gram positive *S. aureus* and gram negative *E. coli*	[60]
9.	ZnO/graphite composites	*S. aureus, E. coli, P. aeruginosa*	[61]
10.	Pd doped SnO_2 and TiO_2 thin films	*E. coli, S. aereus, S. cerevisiae, A. niger* spores	[62]

by various workers. The mentioned materials have a variety in which some are common and extensively found out in the literature, few are unique and seldomly found. The table itself is the evidence of the variety in inorganic antimicrobial agents. Current focus as evident from Table 2 is on some common gram positive and negative microorganisms, but many workers are shifting their attention on high resistance microbes [53-62].

CONCLUSION

Multidrug resistance microbes can emerge as a potential threat in future. The conventional antimicrobial agents released by anthropogenic activities, making these microbes stronger and stronger as the time is progressing therefore, are proving less useful and there is a need to find out the solution which can tackle the problem. Doped nanomaterial synthesized by conventional method can provide an effective solution by virtue of their variety and infinite compositions. The important aspects like morphology, particle size and concentration must be considered. Furthermore, the mechanism by which they incorporate and perform their function has to be kept in mind to design ideal material. The toxicity mechanism of nanomaterials remains poorly understood, therefore, new methods and approach to study the effects on microbes is required. The nanostructure development by following discussed aspect in this review will be helpful to develop long live antimicrobial agents which may be eco-friendly, effective, low concentration and cost-effective. Revived points are just an attempt to scratch the surface of this enormous field and many possibilities can be explored to increase the sustainable existence of all of us on this planet.

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