

Chapter 8

Light-Activated Nanoparticles for Antibacterial Studies



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Abstract Photolysis or light activation of electrons to an energy excited state to aid a release of energy could be utilized in many applications like industries and semiconductors as well as for antimicrobial action. This electron transfer mechanism is widely being incorporated to metals and metal oxides or sometimes with nanoparticles (NPs) to increase its reactivity. However, three forms of NP formulations are used for antibacterial action like nanocomposites, doped NPs, and metal oxide NPs. The preparation, synthesis, and antimicrobial application of the metal oxide NPs are explained coherently in this chapter. Moreover, the future prospects of these NP-assisted light-activated antimicrobial actions are also dealt in detail.

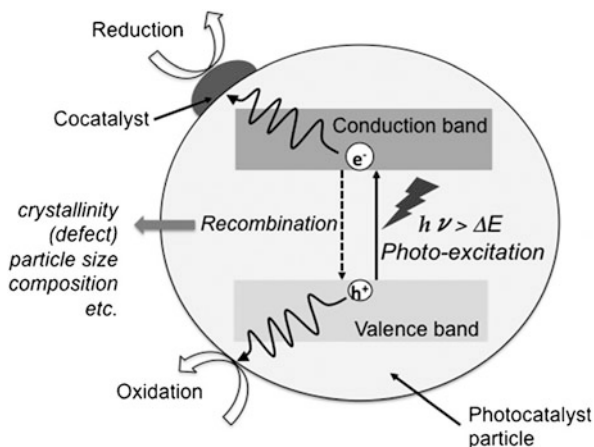
Keywords Photolysis · Nanocomposites · Doped nanoparticles · Metal oxides · Metal oxides NP synthesis · Antimicrobial action

8.1 Introduction

The photocatalysis process gained attention in the scientific world, since Fujishima and Honda (1972) initially stated the use of TiO₂ as a catalyst for water splitting through solar energy conversion. Ever since, these suspended semiconductors have been used widely as an agent of pollutant degradation, water purification, indoor self-cleaning surfaces, as well as antimicrobials (Kumar et al. 2018). In a natural purification system, photocatalysis is initiated by sunlight (the ultraviolet [UV] rays) by the breakdown of organic molecules. However, the antimicrobial effect of this system is restricted. Thus, to promote specific redox reactions on semiconductor surfaces through the employment of semiconductors and the incorporation of catalysts was introduced (Miller 1971). Since then, an enhancement in the purification process and antibacterial action could be achieved to the expected levels.

The photocatalytic reaction proceeds over a semiconductor powder through several steps (Fig. 8.1) in accordance with band theory (electron transfer theory) escorted by the interaction of photo-generated electrons and holes with the reactants which potentially occurs at low temperatures. The bandwidth of the reaction categorizes the desirable light energy, reducing ability and oxidizability of the products.

Fig. 8.1 Model of reaction, charge separation, and recombination over photocatalyst. (Tetsuya et al. 2011; open access)



This even contributes to the lifetime of the generated catalyst (Tetsuya et al. 2011; Saravanan et al. 2018a). Thus the activated electrons are highly reactive and could produce reactive oxygen species, causing oxidative stress to the cell membranes and thus the killing of bacteria. This may even happen through the interaction of such electrons to the functional enzymes or proteins of the bacterial cells and hence pose a threat to the progression of the microbes in their habitat (Tetsuya et al. 2011; Thakur et al. 2017). This can even be achieved by altering the hydrogen adsorption properties of metals. A recent study has demonstrated that silver (Ag)-decorated TiO₂ nanomaterials altered the hydrogen absorption and thereby the photocatalytic ability (Saravanan et al. 2018b). Moreover, the metal nanoparticle (NP)-assisted photocatalysts can be found in various industrial, medical, personal, and military applications (Jiang et al. 2009). However, this chapter deals with the antimicrobial action of the light-activated metal particles.

8.2 Nanoformulations for Antibacterial Action

It should be noted at this juncture that the properties of the NPs like composition, size, properties, and doping effect add on to the applications of the NP-assisted photocatalysis and its related antibacterial effect. The major three forms of NPs used for antibacterial action are nanocomposites, doped NPs, and metal oxides. The publications for various nanoformulation over past five years are depicted in Fig. 8.2.

8.2.1 Nanocomposites

Nanocomposites are amalgams possessing dimensions in the nanometer range (1 nm = 10⁻⁹ m) and have emerged as suitable alternatives to incredulous

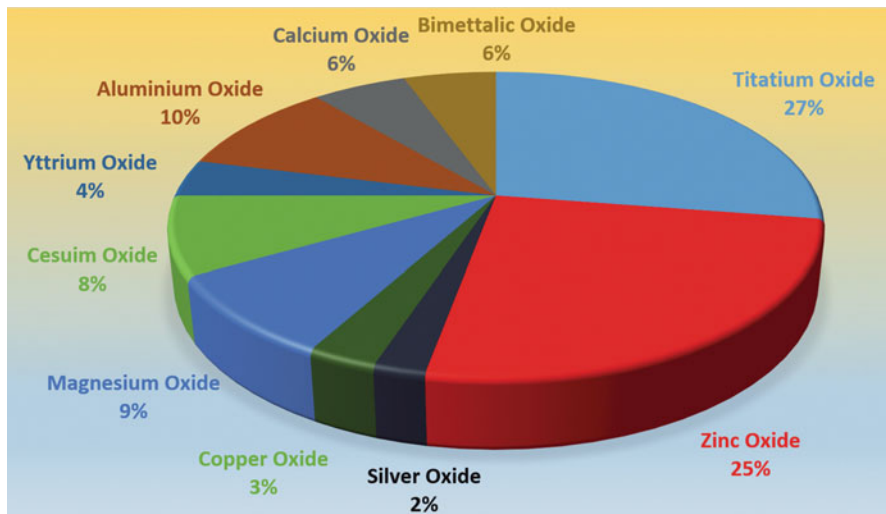


Fig. 8.2 Number of publications on Google Scholar on light-activated nanoparticles for antibacterial studies over the period 2013–2018 recovered from sources as a part of literature survey

Table 8.1 Different types of nanocomposites (Pedro et al. 2009; open access)

Class	Examples
Ceramic	$\text{Al}_2\text{O}_3/\text{SiO}_2$, SiO_2/Ni , $\text{Al}_2\text{O}_3/\text{TiO}_2$, $\text{Al}_2\text{O}_3/\text{SiC}$, $\text{Al}_2\text{O}_3/\text{CNT}$
Metal	$\text{Fe-Cr}/\text{Al}_2\text{O}_3$, $\text{Ni}/\text{Al}_2\text{O}_3$, Co/Cr , Fe/MgO , Al/CNT , Mg/CNT
Polymer	Thermoplastic/thermoset polymer/layered silicates, polyester/ TiO_2 , polymer/ CNT , polymer/layered double hydroxides

restrictions of microcomposites and monolithic, due to their fundamental stoichiometry composition at microphase (Roy et al. 2010; Rajendran et al. 2018), looking to enter to the cell membranes of microorganisms and causing the desired effect. Since the twenty-first century, researchers have reported that design distinctiveness and proper combinations than conventional composites offer better applications in industrial and health-care clinics (Schmidt et al. 2002). Even though the first extrapolation of them was testified as early as 1992 (Gleiter), nowadays, nanocomposites deal innovative technology (Choa et al. 2003). As in the case of microcomposites, according to their matrix materials, nanocomposite materials can be categorized in three dissimilar classes as shown in Table 8.1, namely, ceramic matrix nanocomposites (CMNC), metal matrix nanocomposites (MMNC), and polymer matrix nanocomposites (PMNC) with examples. The report of Saravanan et al. (2016) has emphasized that an enhanced photocatalytic degradation and electrochemical detection competence were observed in a ZnO/CeO_2 (90:10) nanoformulation.

8.2.2 *Doped Metal Oxide NPs*

Various attempts were done to shift metal oxide NP absorption into a visible light region, which chiefly focus on the doping with transition metal ions (Choi et al. 1994; Nalage et al. 2015). Nonetheless, the limitations of doped metal oxide NPs, such as the inclination to form charged carrier recombination centers, thermal instability (Choi et al. 1994), and the exclusive accommodations for ion implantation, make metal-doped metal oxides unrealistic for its applications (Wang et al. 1999). During the last decade, anion doping of metal oxides was positively achieved using anions of nitrogen (Asahi et al. 2001), carbon (Sakthivel and Kisch 2003), sulfur (Umebayashi et al. 2002), phosphorus (Lin et al. 2005), and fluoride (Ho et al. 2006). Among these anion dopants, nitrogen appears to be the most operational because of its metastable AX center formation, similarity in size to oxygen, and lesser ionization energy (Park et al. 2002). The major long wavelength region (>700 nm) in N-doped TiO₂ and ZrO₂ of absorption spectra is the significantly improved absorption at which it offers better photocatalytic light activities at visible range (Qiu et al. 2007). The active, visible wavelength of TiO₂ and ZrO₂-doped complexes promises a varied array of antibacterial applications under visible lightening (Asahi et al. 2001).

8.2.3 *Metal Oxide NPs*

Due to the amplified reactivity and comfort of handling into useful electrode formats, NP metal oxide photocatalysts are striking. However, their preparation is quite tedious. The prompt bulk synthesis of photocatalytic NPs with consistent shape and size via the cathodic corrosion method is used for the nifty research through several composite metal oxides (Matthew et al. 2017).

Synthesis of Metal Oxide NPs

The method by which the metal oxide particles were synthesized is précised in Fig. 8.3. For the synthesis of H₂WO₄ particles, a tungsten wire is flooded with a KHSO₄ solution (1 M). A voltage of 0 V to -10 V in the range square wave was applied between a W wire (working electrode) and a tall surface area Pt foil (counter electrode) occasioning in the instant materialization of the NPs. While submerged in a 10 M NaOH solution, TiO₂ nanowires were arranged with a titanium wire that was exposed to an AC square wave in the range of 0 V to -10 V with a frequency of 100 Hz. Similarly, the BiVO₄ NPs were produced by means of a vanadium wire occupied in 10 mL of a mixture (1:1 by volume) of the saturated CaCl₂ solution and MilliQ water, to which saturated Bi₂O₃ solution was supplemented successively, by

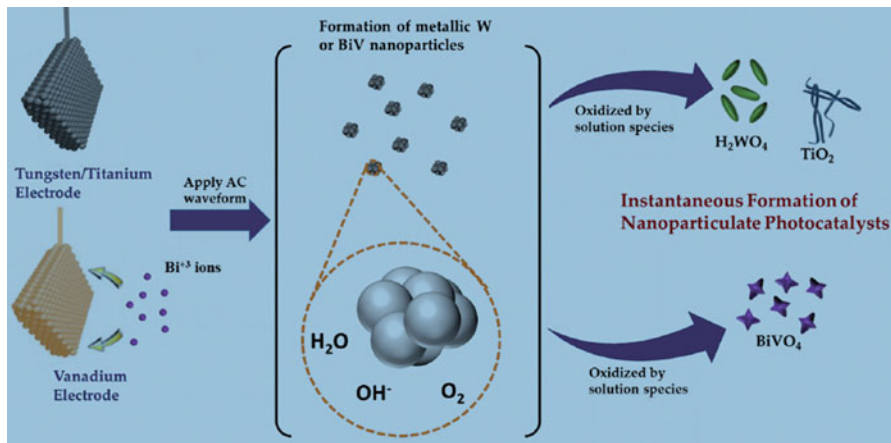


Fig. 8.3 Schematic depicting how cathodic corrosion was used to prepare H₂WO₄, TiO₂, and BiVO₄ photocatalysts. (Matthew et al. 2017; copyright received)

applying a -8 V to 2 V. Once synthesized, the resulting suspensions of NPs were centrifuged at and elucidated in a UV-Vis spectrophotometer (Matthew et al. 2017).

8.3 Factors Affecting the Antimicrobial Action of NP Metal Oxides

Many factors affect the antimicrobial action of the synthesized metal oxide NPs which are light activated. The photocatalytic efficiency also varies according to the temperatures used for synthesis of nanocomposites, the nature of the doping materials, as well as methods used for synthesis of nanocomposites (Saravanan et al. 2013a, b, c). Some of the aspects are listed below.

8.3.1 Size

The smaller size of NPs synthesized in a photocatalytic manner encountered antimicrobial operations through fighting intracellular bacteria (Ranghar 2012). The drugs of ordinary size pose limited impact on intracellular microbes (Andrade et al. 2013). Because of antibiotics' condensed membrane transport, an improved treatment method using metal oxide NPs is developed to combat microorganisms, which could excite its electrons upon photoactivation posing an ROS threat to the microbes (Qi et al. 2013).

8.3.2 Protection

NP carriers like metal oxides (ZnO, CuO, etc.) could prevent the drug being resistant to targeted bacteria. The presence of metal oxides very often shelters the NPs from serious chemical reactions which are harmful for the potency of the assisted NPs for its action against microbial population. Moreover, healthier efflux and condensed endorsement of antibiotics in the bacterial cells (such as in *E. coli*, *P. aeruginosa*, etc.) are the normal and significant explanations for bacterial resistance than traditional antibiotics. Nevertheless, investigators have demonstrated that abundant NPs can incredulous this type of mechanisms (Muhling et al. 2009), preventing drug resistance. For example, Roy et al. (2010) estimated the influence of TiO₂ nanoparticles with different antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA). However, TiO₂ nanoparticles enhanced the antimicrobial effect of cephalosporins, beta-lactams, glycopeptides, aminoglycosides, macrolides, tetracycline, and lincosamides against MRSA.

8.3.3 Precision and Security

NP metal oxides can curtail side effects and precede antibiotics to the infection site. When we use a beneficial carrier, we can moderate the side effects (including drug toxicity) and can boost absorption at an anticipated site. The focused NP-based drug delivery demands either active targeting or passive targeting (Xiong et al. 2012).

8.3.4 Controllability

Well-regulated constant discharge of drugs can be achieved passively. With the appropriate NP drug release method, like metal oxide photocatalysts (Liu et al. 2016), they are operative even by dissimilar kinds of stimulatory factors (such as a light, heat, and pH) (Lim et al. 2018).

8.3.5 Shape

The shape of NPs accounts for antimicrobial activity by interacting with periplasmic enzymes causing gradations of bacterial cell damage, according to the shape of NPs (Cha et al. 2015). A comparison of pyramid-, plate-, and sphere-shaped ZnO NPs which exposed the β -galactosidase (GAL) rearrangement produced differential photocatalytic activity (Prasannakumar et al. 2015). *Pseudomonas desmolyticum* and *Staphylococcus aureus* were greatly affected with Y2O₃ NP prismatic-shaped

owing to the straight interaction among the NPs and the bacterial cell membrane surface (Hong et al. 2016). Moreover, cube-shaped Ag NPs display tougher antibacterial activity than the sphere-shaped and wire-shaped Ag NPs with similar diameters, due to the specific facet reactivity and surface area (Actis et al. 2015) consuming a smaller effect on microbiota susceptibility (Talebian et al. 2014). In several studies, experimenters concluded that the nanostructures and its morphological variations primarily account for its photocatalytic properties (Thangaraj et al. 2017; Qin et al. 2017).

8.3.6 Roughness

Roughness is another key factor acting in NP-assisted antibacterial action. As the roughness of NPs rises, the size and the surface area-to-mass ratio upholding the adsorption of bacterial proteins, followed by a reduction in bacterial adhesion, occur (Sukhorukova et al. 2015).

8.3.7 Zeta Potential

Several researchers have authenticated the zeta potential of NPs has long-term influence on bacterial adhesion. For example, the electrostatic magnetism between the negatively charged cell membrane of bacteria and positively charged NPs has a positive charge on its surface which are disposed to get adsorbed to microbial surface (Pan et al. 2013) and enhances vascular permeability (Maeda 2010), through ion exchange by limiting attachment of the bacteria (Fang et al. 2015). When the negatively charged and neutral NPs are compared to its positively charged equivalents, it is proved that the positively charged metal oxide NPs enhance the ROS production, which primes to influential relations among the metal oxide NPs and the bacterial surfaces (Arakha et al. 2015)

8.3.8 Doping Modification

Doping modification is another effective strategy to regularize the interaction of bacteria with the desired type of NPs. The NPs used in clinics are now altered to disperse in hydrophilic or aqueous environment aggregations using doping modification techniques. For instance, the ZnO NPs doped with Au (Gold) to form ZnO/Au co-doped nanocomposites were directed to progress photocatalytic activity by

increasing ROS production. These effects are due to an altered metal oxide bandwidth, improved light absorption for gold's surface plasmon resonance wavelength, and photoinduced charge carrier reactivity causing amplified electron-carrying efficiency and its charge separation (He et al. 2014). The ZnO NPs have "O" content at the surface that regulates antimicrobial activity against both Gram-positive and Gram-negative bacteria (Mehmood et al. 2015).

8.3.9 Environmental Conditions

The environmental conditions in which the NPs should exhibit its action also affect its antimicrobial function. One such condition is the temperature, which could potentially alter the activity with respect to its effect on potential ROS production. When ZnO NPs are stimulated by temperature variations, electrons are captivated at its active site, which interact with oxygen molecules (O₂), thereby advancing the antimicrobial efficacy of the metal oxide NPs. Another factor is the decrease in the pH, which potentates the rate of dissolute ZnO NPs production by elevating the antimicrobial properties (Saliani et al. 2015). Certain results projected the protonation of the imidazole molecules under acidic conditions which at times leads to surface charge switching. At lower pH, the surfaces of the NPs were positively charged being beneficial to the contact with the bacterial cell barrier stimulating strong electrostatic multivalent regulation. Moreover, Li and his coworkers (2012) proved that antibacterial tests in five types of media due to free Zn ions and zinc complexes are mainly through ZnO NPs (Khan et al. 2016).

8.4 Mechanisms Through Which Metal NP Oxides Express Antimicrobial Action

NPs attain its contact with the bacterial cells, the foremost step to achieve antibacterial action through van der Waals forces (Armentano et al. 2014), electrostatic attractions, 86 and receptor-ligand hydrogen bond formations (Gao et al. 2014), and hydrophobic interactions (Luan et al. 2016), ensuring its entry to the metabolic pathway and impelling the function and shape of its cell membranes. In tail with it, NPs communicate with the bacterial cell's basic components, such as enzymes, lysosomal organelles, as well as DNA, causing oxidative insults, cell membrane permeability alternations, heterogeneous changes, electrolyte balance loss, protein deactivation, enzyme inhibition, and even alterations in gene expression (Xu et al. 2016). However, the most frequently proposed mechanisms in the current NP research focus on oxidative stress (Gurunathan et al. 2012), metal ion release

(Zakharova et al. 2015), and non-oxidative mechanisms (Leung et al. 2014) about which is explained in detail in the following sections.

8.4.1 Oxidative Stress and ROS Generation

Oxidative stress, generated by ROS (reactive oxygen species), is an efficient reason for the antiseptic action of the synthesized metal oxide NPs. There are mainly four types of ROS produced like the superoxide radical (O_2^-), hydrogen peroxide (H_2O_2), the hydroxyl radical ($\cdot OH$), and singlet oxygen (O_2) which reveal different levels of activity and crescendos. For example, CaO and MgO NPs can generate O_2^- , whereas ZnO NPs can generate H_2O_2 and OH but not O_2^- . In the meantime, CuO NPs can yield the four mentioned types of reactive oxygen species. Studies have indicated that O_2^- and H_2O_2 reason minute stress reactions which are acute and could be counteracted by the endogenous antioxidants, like superoxide and catalase enzymes, although ROS could aggravate the microbial death. The principal cause of ROS attacks is restructuring of cell membranes, defective sites, and oxygen vacancies in their crystal forms, owing to sites of electron replacements (Malka et al. 2013). In a normal cell, the assembly and disassembly of ROS are poised. In dissimilarity, with excessive ROS assembly, the situation gets unbalanced and cell ultimately favors oxidation, which damages the organelles of microbes (Li et al. 2012; Peng et al. 2013).

8.4.2 Dissolved Metal Ions

Metal ions of the metal oxide NPs were gradually loosened over time after adhering to the cell wall, monitored by uninterrupted interface with the functional groups of biomolecules, such as amino ($-NH$), mercapto ($-SH$), and carboxyl ($-COOH$) groups, enzyme inactivation, cell structure demolition, and altering normal physiological processes, eventually constraining the microbial progression. However, the influence of metal ions on the pH of lipid vesicles is insignificant as far as the antibacterial course of metal oxide suspension is concerned. Thus, dissolved metal ions are not the foremost reason for the antimicrobial machinery of metal oxide NPs (Yu et al. 2014). By the same token, a study revealed that superparamagnetic iron oxide counteracts with microbial cells by unswervingly penetrating the membrane of the cell by interfering with the transmembrane electron transfer. Furthermore, heavy metal ions could incidentally perform as transporters of many antimicrobial substances (Hussein et al. 2014).

8.4.3 Non-oxidative Mechanisms

The pioneer study of Leung et al. (2014) revealed that antibacterial machineries of NPs are unconnected to the membrane lipid peroxidation followed by oxidative stress, based on the many observations, chiefly:

1. In the absence of intact cell membrane of microbes and surface pores are distinctly visible, metal oxide (MgO) NPs that are not detected in the cell. Moreover, the lack of presence of unwarranted Mg ions was invisible in energy-dependent X-ray spectroscopy studies, thus proving the inhibitory effect of metal oxides to disrupt the cell membrane.
2. The phosphatidylethanolamine (PE) and lipopolysaccharide (LPS) of the cell wall were unchanged due to MgO NP treatment, indicating that MgO failed to stimulate lipid peroxidation. Furthermore, the quantity of ROS-aggravated proteins in the cell remained constant.

However, many perilous cellular metabolic developments related to proteins, including amino acid metabolism, energy metabolism, carbohydrate metabolism, as well as nucleotide metabolism, are significantly abridged (Leung et al. 2014). This paved a way for biologists to think about alternative non-oxidative mechanisms causing microbial cell death by the NPs treatment. Some of such proposed mechanisms are described below.

The Interaction of the Cell Barriers

Cell walls and membranes are the physical and biological barriers to self-defense from the external environment, particularly providing a natural shape to organisms. The components of the cell membrane (for Gram-positive and Gram-negative bacteria are different) result in dissimilar adsorption pathways for NPs (Lesniak et al. 2013). LPS categorizes the structural uniqueness of the cell walls of Gram-negative bacteria which have a negatively charged constituency that appeals to NPs. In disparity, expression of teichoic acid in the Gram-positive bacteria's cell wall assists the NPs distribution beside the molecular phosphate chain opposing its aggregation (Sarwar et al. 2015). In one study, a nanocomposite of hydroxyapatite whisker and nano-zinc oxide (HAPw/n-ZnO) exhibited a durable antimicrobial effect on *Staphylococcus mutans*, *S. aureus*, and *Candida albicans* than to that on *E. coli* which is causing bacterial death as a dependent factor of components and structure, cell membrane, and NP interaction. Moreover, some elements specific to Gram-negative species, like LPS, can inhibit the linkage of ZnO NPs to the cell and may even normalize the stream of ions in and out of the membrane. However, the depth of the microbial cell wall in Gram-negative bacteria often hinders the antibacterial function of NPs (Yu et al. 2014). In another study, Wehling et al. (2014) considered the antibacterial activity of nano-diamonds in countless bacterial

surface structures with varied reactive groups by establishing covalent bonds with adjacent proteins and molecules on cell walls.

Inhibition of Bacterial Proteins as well as DNA Synthesis

The intervention of NPs with bacterial protein synthesis machinery progressively fascinated the microbiologists in the near future. The effect of CuO NPs on denitrification of bacterial enzymes was analyzed by Su et al. (2015) which could modify the manifestation of key proteins. When these NPs enter the cell, it resulted in the regulation of proteins tangled in electron transfer, nitrogen metabolism, or substance transport. Similarly, TiO₂ NPs enhance bacterial DNA degeneration, compression, and fragmentation resulting in the reduced physiological activities of the microbial genes (Zhukova 2015). Moreover the molecular docking studies between TiO₂ NPs have predicted the potential NPs to inhibit GC-rich regions of bacterial DNA (Iram et al. 2015). In addition, it may even lead to bacterial cell apoptosis, which is proved in *E. coli* model (Su et al. 2015). The study even revealed that around ten mutant genes are responsible for the gene expression and the molecular structure and functions, leading to ribosomal composition and RNA modification and protein expression. Furthermore, the gold-superparamagnetic iron oxide NPs inhibit some proteins in bacteria over a solid affinity formed by disulfide bonds affecting the metabolism and redox systems of the cells (Niemirowicz et al. 2014).

NPs Regulate the Expression of Metabolic Genes

Bacterial metabolic pathways are not secluded but reasonably are joined with the complex activity of living cells. For illustration, the metabolism of glucose in *S. mutans* is a significant mechanism that bases, various metabolic genes. Moreover, *Fusobacterium nucleatum* could use the amino acid metabolites, like butyric acid, which could enhance the advancement of periodontal disease. Thus, decisive variations in the metabolic rate of bacteria are used to control bacterial cell pathology by diverse mechanisms (Padmavathy and Vijayaraghavan 2011; Yu et al. 2014). Liquid hue spectrum of magnesium oxide nanoparticles (MgO NPs) altered the metabolic protein expressions, by upregulating action of weak thiamine ester-binding proteins as well as riboflavin metabolic protein. The downregulation of the protein charted to a critical signaling of cell metabolism also added its mechanism resulting in a decrease in metabolic cellular activity, suggesting NP's regulation in the processes of bacteria on target proteins (Leung et al. 2014). However, copper oxide NPs (CuO NPs) downregulated the protein expression of nitrate and nitrite reductases causing bacterial death (Su et al. 2015). Moreover, considerable evidences are there which proves the adhesive efficiency of titanium dioxide to the bacterial biofilms (Rogusha 2015) and disrupt its metabolite levels (Pan et al. 2015). For instance, d-alanine metabolism is indispensable for the formation and growth of *S. mutans* biofilm.

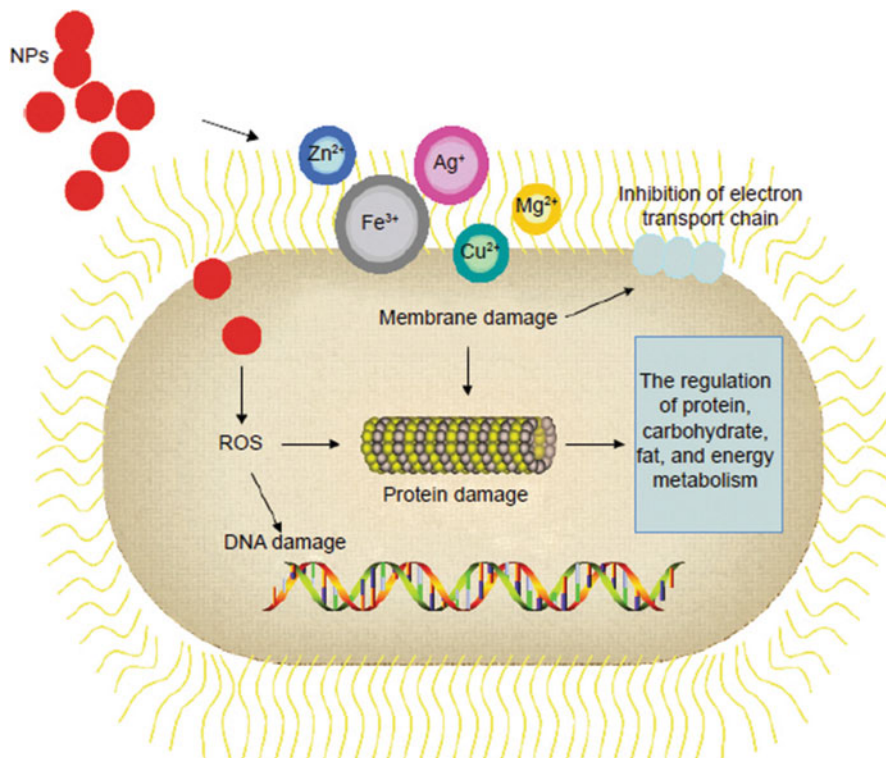


Fig. 8.4 Mechanisms of NP action in bacteria cells. **Notes:** NPs can attack bacteria cell through multiple mechanisms: the formation of ROS leading to membrane, protein, and DNA damage; direct interaction occurs with cell membrane because some metal-based NPs can generate metal ion via dissolving, for example, inhibition of electron transport chain; and the regulation of bacterial metabolic processes. **Abbreviations:** NPs, nanoparticles; ROS, reactive oxygen species. (Wang et al. 2017; open access)

Thus, NPs can attack through multiple mechanisms on bacteria cells, a diagrammatic representation of which is provided in Fig. 8.4.

8.5 Different Metal Oxides Exhibiting Antimicrobial Action

8.5.1 *TiO₂ Metal Oxides*

The photocatalytic disinfection has gained great research attraction in the last century. It was first reported with the NPs of TiO₂ by UV procedure which successfully inactivated many microorganisms, like bacteria and fungi such as *Micrococcus luteus*, *Escherichia coli*, *Bacillus subtilis* (cells and spores),

Streptococcus faecalis (Melian et al. 2000), *Staphylococcus aureus* (Kuhn et al. 2003), *Candida albicans* (Kuhn et al. 2003), *Lactobacillus acidophilus* (Saito et al. 1992), and others. Moreover, the activation of TiO₂ with UV was found to be effective against parasites such as *Giardia intestinalis* and *Acanthamoeba castellanii* cysts (Sokemen et al. 2008).

The crystal structure, shape, and size of TiO₂ are connected with the antimicrobial activity (Haghighi et al. 2013). Sometimes, this may be due to the oxidative stress exerted by TiO₂ nanoparticles (anatase forms), causing specific DNA damage (Cioffi and Rai 2012; Roy et al. (2010) with dissimilar antibiotics assessed the antimicrobial effect of TiO₂ nanoparticles against methicillin-resistant *Staphylococcus aureus* (MRSA). They reported that TiO₂ NPs improved the antimicrobial effect of aminoglycosides, beta-lactams, glycopeptides, cephalosporins, lincosamides, macrolides, and tetracycline against MRSA.

TiO₂ nanoparticles possess photocatalytic properties which enhance the efficiency of them to eradicate the bacteria. Carré et al. (2014) measured the photocatalytic antibacterial activity that was accompanied by lipid peroxidation that grounds for membrane fluidity and cell integrity (Carre et al. 2014). However, doping them with metal oxide ions improves the antibacterial and photocatalytic properties of TiO₂ nanoparticles (Allahverdiyev et al. 2011; Zaleska 2008) by shifting TiO₂ NPs' light absorption to visible range so that UV light irradiation can be avoided. Conjugation of nontoxic polymers with TiO₂ nanoparticles is an alternative method to tackle toxicity issues. For instance, *Aeromonas hydrophila*-mediated TiO₂ were synthesized by Jayaseelan et al. (2013) which showed better zone of inhibition when compared to that of tetracycline treatment (Fig. 8.5 and Table 8.2).

8.5.2 ZnO Metal Oxides

ZnO nanoparticles projected many bactericidal effects on Gram-positive and Gram-negative bacterial strains which are at times even resistant to high temperature and pressure (Azam et al. 2012). The improved antibacterial activity of ZnO nanoparticles was attained due to the improved surface area (Xie et al. 2011), varying particle sizes (Padmavathy and Vijayaraghavan 2011), as well as interruption of transmembrane electron transportation. Moreover, studies have suggested that the antibacterial mechanism of ZnO nanoparticles in *C. jejuni* might be a result of the cell membrane disruption and ROS stress (Xie et al. 2011). The outcomes indicated that ZnO nanoparticles triggered considerable membrane leakage, morphological alterations, and upregulation (up to 52-fold) in oxidative stress-related gene expression in *C. jejuni*. In addition, the antimicrobial activity of the ZnO nanoglobules prepared using 0.05 M TWEEN80 was demonstrated by Rajendar et al. in 2017 (Fig. 8.6) which showed considerable antibacterial effects on four major microorganisms.

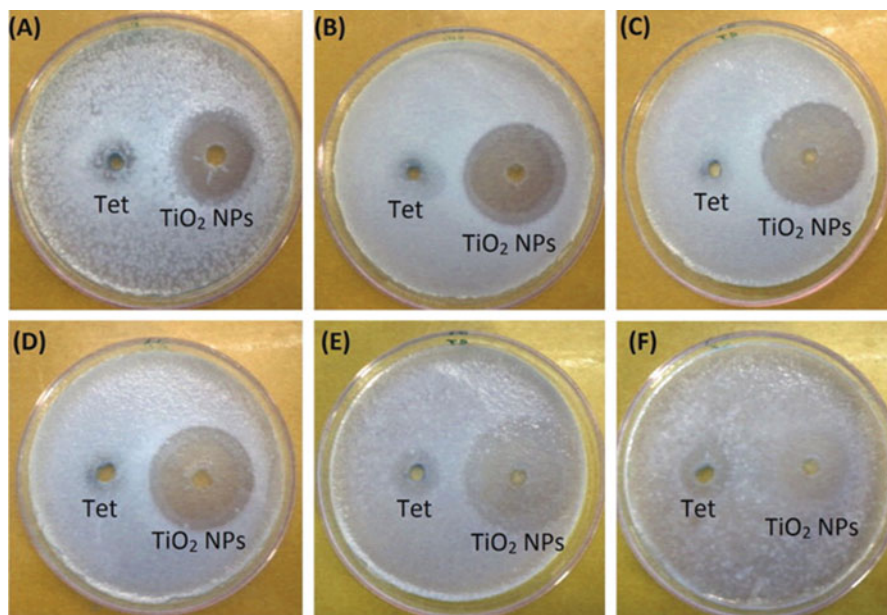


Fig. 8.5 Well diffusion assay for TiO₂ nanoparticles against *A. hydrophila* (a), *E. coli* (b), *P. aeruginosa* (c), *S. aureus* (d), *S. pyogenes* (e), and *E. faecalis* (f). (Jayaseelan et al. 2013; copyright received)

Table 8.2 Zone of inhibition (mm) and MIC (lg ml⁻¹) of *A. hydrophila*-synthesized TiO₂ nanoparticles against various microorganisms (Jayaseelan et al. 2013; copyright received)

Microorganisms	<i>A. hydrophila</i> -synthesized TiO ₂ nanoparticles		Tetracycline	
	Zone of inhibition (mm)	MIC (lg ml ⁻¹)	Zone of inhibition (mm)	MIC (lg ml ⁻¹)
<i>A. hydrophila</i>	23	25	14	20
<i>E. coli</i>	26	20	14	20
<i>P. aeruginosa</i>	25	30	12	25
<i>S. pyogenes</i>	31	10	15	15
<i>S. aureus</i>	33	10	15	10
<i>E. faecalis</i>	29	15	16	15

Even though ZnO moderates the viability of many human pathogenic bacteria, the precise machinery is not established till date. One such possibility was the cohort of hydrogen peroxide which act for ROS insult and thus antibacterial activity. The electrostatic force attraction between the metal oxides and the cell membrane could also be a reason (Zhang et al. 2008). Besides these two, other factors like membrane dysfunction due to nanoparticles internalization through zinc ion release also add to

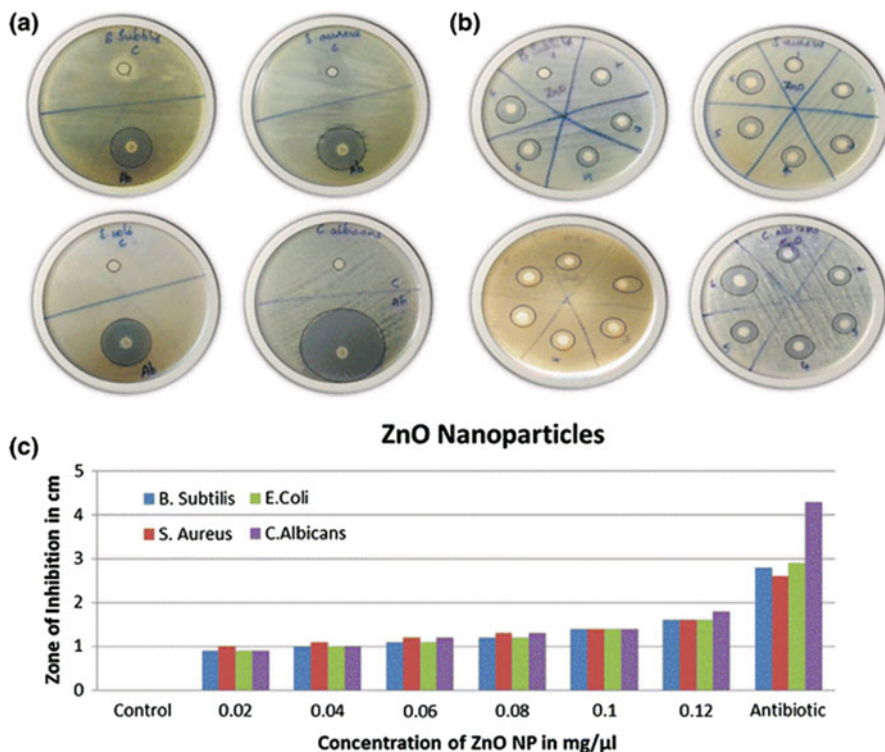


Fig. 8.6 Antimicrobial activity of the ZnO nanoglobules prepared using 0.05 M TWEEN80. (a) Positive and negative control for measuring the zone of inhibition, (b) antimicrobial activity of ZnO nanoglobules at various concentrations, (c) diameter of the zone of inhibition for different concentrations of ZnO nanoglobules. (Rajendar et al. 2017; copyright received)

a probable explanation of the cell damage (Rao et al. 2013). Moreover, the antibacterial activity of ZnO nanoparticles is contingent on the concentration and surface area. The metal oxide NPs in its higher concentrations and larger surface area demonstrated superior antibacterial action (Buzea et al. 2007). According to Hosseinkhani et al., as a result of particle size reduction, a considerable decrease in the bacteria number was observed against *Shigella dysenteriae* (Hosseinkhani et al. 2011). Emami-Karvani and Chehrazi (2011) evaluated that higher concentration and lesser particle size enhanced the antibacterial activity of ZnO nanoparticles.

8.5.3 Ag_2O Metal Oxides

Nowadays, Ag_2O nanoparticles have been considered as an innovative substitute to the marketed antibiotics (Sathyanarayanan et al. 2013). Sondi and Salopek-Sondi

(2004) demonstrated that when *E. coli* was exposed to Ag₂O NPs, genetic replication ability was lost and the cell cycle stopped at the G₂/M phase. Further ROS insult occurred, followed by apoptosis. Furthermore, Ag had reported to be less toxic than many other disinfectants. In 2016, Qin et al. proved that the photocatalytic activity and stability gets enhanced when the rich Ag⁺⁺ ion of Ag₃PO₄ formulates the surface plasmon resonance (SPR) of Ag NPs. Marambio-Jones and Hoek (2010) had reviewed the antibacterial machineries of the Ag NPs and its potential insinuations for the environment. Similarly, the antimicrobial activity of Ag NPs synthesized from *Linum usitatissimum* L. whole plant extract (WPE) and thidiazuron-induced callus extract (CE) is tested against many pathogenic microorganisms, which is depicted in Fig. 8.7 (Anjum and Abbasi 2016). Moreover, the supplementary investigation could be achieved to develop Ag-related compounds, composites, and metal co-dopants with maximum antimicrobial effect and minimum toxicity.

8.5.4 CuO Metal Oxides

The CuO nanoparticles were tested against various microbes like *Klebsiella pneumoniae*, *Salmonella paratyphi*, *P. aeruginosa*, and *Shigella* strains for its antibacterial activity (Mahapatra et al. 2008). As per their investigations, these nanoparticles specified appropriate antibacterial activity against all the selected microbes which were achieved through the microbial cell membrane passage by decomposing the vital bacterial enzymes which were crucial for triggering cell death. Moreover, a recent study by Pulicherla et al. (2017) reported that the bioinspired green synthesis of CuO NPs from the stem bark extract of *S. alternifolium* has potent antimicrobial effects (Figs. 8.8 and 8.9).

The size-dependent antibacterial activity of CuO nanoparticles was done by Azam et al. (2012). Their study with *S. aureus* and *B. subtilis*, *Pseudomonas aeruginosa*, and *E. coli* projected the bactericidal activity of CuO NPs influenced by their stability, size, as well as the concentration of the metal nanoparticles, which restricted the growth via transistors over nanometric pores on the bacterial cellular membranes. However, Ahamed et al.'s (2014) studies revealed that CuO nanoparticles (23 nm) had substantial antimicrobial activity in bacterial strains like *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Shigella flexneri*, *Enterococcus faecalis*, *S. typhimurium*, *S. aureus*, and *Proteus vulgaris*. But the nanoformulations were much more resistant to *K. pneumoniae*, while *E. coli* and *E. faecalis* disclosed the maximum sensitivity (Ahamed et al. 2014).

8.5.5 MgO Metal Oxides

Several scientists have proved the strong antimicrobial action of MgO nanoparticles through either cell membrane damage or oxidative stress (Jin and He 2011). Hewitt

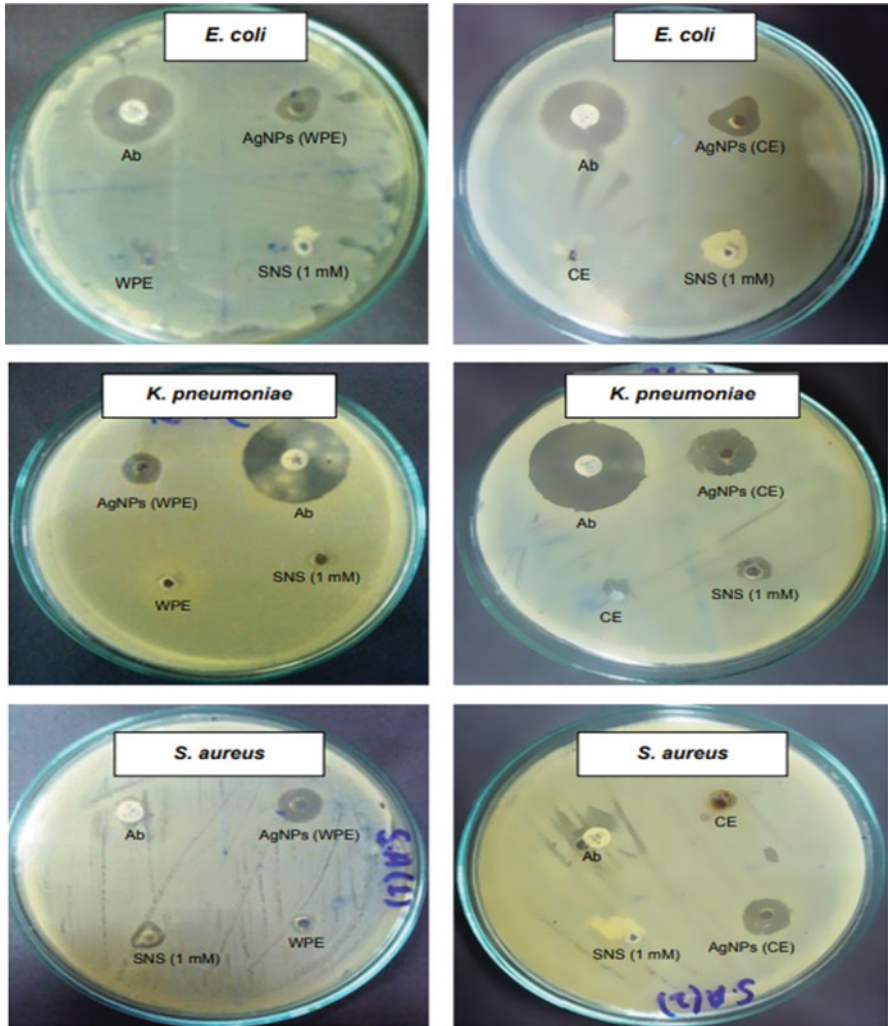


Fig. 8.7 Antibacterial assay of Ag NPs. Notes: zone of inhibition of WPE (10 mg mL⁻¹), CE (10 mg mL⁻¹), Ab (10 mg disk-1), WPE-mediated Ag NPs (10 mg mL⁻¹), and CE-mediated Ag NPs (10 mg mL⁻¹) against multiple drug-resistant bacterial strains was measured in mm. Abbreviations: Ag NPs, silver nanoparticles; WPE, whole plant extract; CE, callus extract; Ab, antibiotic; *E. coli*, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*; *S. aureus*, *Staphylococcus aureus*; SNS, silver nitrate solution. (Anjum and Abbasi 2016; open access)

et al. (2001) stated that MgO introduced the changes in sensitivity against *E. coli* encouraged by active oxygen. However, Leung et al. declared the mechanism of MgO antimicrobial activity due to the damage of cell membranes (Leung et al. 2014). In recent studies, the MgO nanoparticles presented the bactericidal activity in contradicting both Gram-positive and Gram-negative bacteria (Vidic et al. 2013).

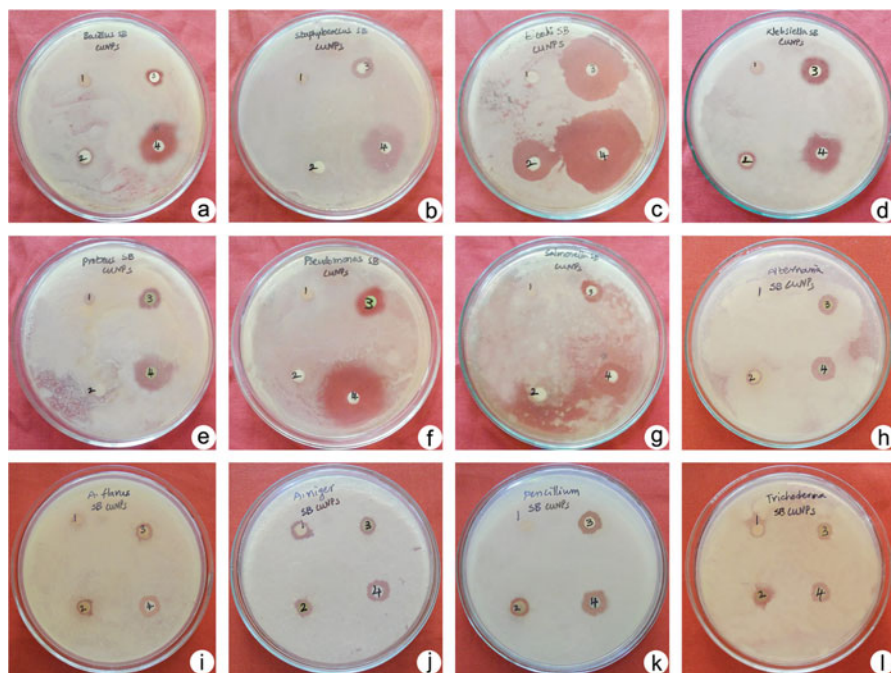


Fig. 8.8 Antimicrobial activity of synthesized CuO NPs. (a) *B. subtilis*, (b) *S. aureus*, (c) *E. coli*, (d) *K. pneumoniae*, (e) *P. vulgaris*, (f) *P. aeruginosa*, (g) *S. typhimurium*, (h) *A. solani*, (i) *A. flavus*, (j) *A. niger*, (k) *P. chrysogenum*, (l) *T. harzianum*; (1) plant extract, (2) $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, (3) CuO NPs, (4) streptomycin/fluconazole. (Pulicherla et al. 2017; Open access)

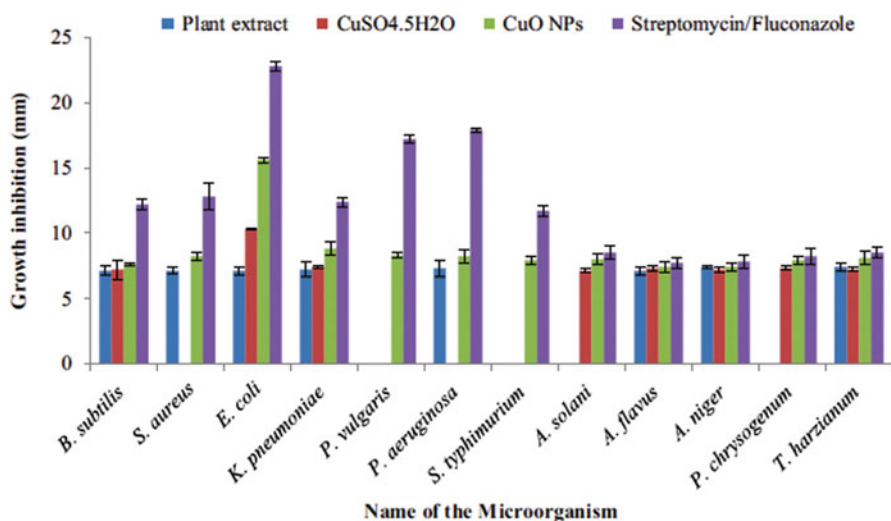
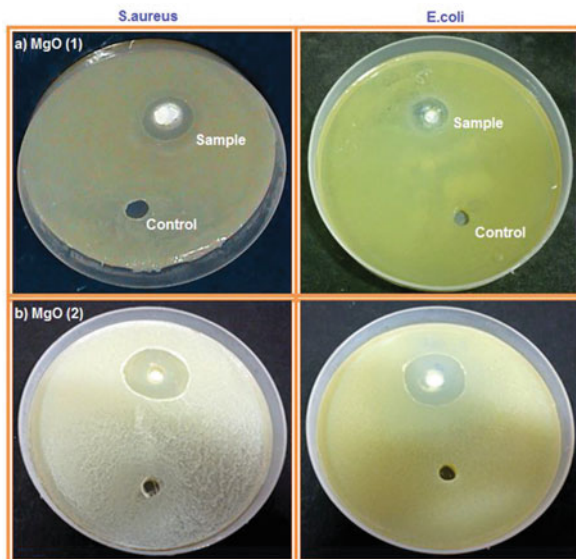


Fig. 8.9 Antimicrobial activity of bioinspired green synthesis of CuO NPs from stem bark extract of *Syzygium alternifolium* (Wt.) against various pathogens. (Pulicherla et al. 2017; Open access)

Fig. 8.10 Antibacterial studies of MgO (1) and MgO (2) nanoparticles. (From http://shodhganga.inflibnet.ac.in/bitstream/10603/56541/15/15_chapter%209.pdf; open access)



Sawai et al. (2000) examined the antibacterial activity of MgO against *E. coli* or *S. aureus*. They recommended that the manifestation of active oxygen, like superoxides, on the MgO NPs' surface as the primary aspect that marks the antibacterial activity (Fig. 8.10).

8.5.6 Cerium Oxide Nanoparticles (CeO_2 NPs)

The cerium oxide (CeO_2) is a nonstoichiometric compound having three and four oxidation states (Ce^{4+} , Ce^{3+}). Many reports in the literature state that the concentration of Ce^{3+} proliferations is more as compared to Ce^{4+} as the size of the particles decreases, the bioactivity also increases up to 6 nm of zone of inhibition. The oxidation states of these two CeO_2 NPs develop many oxygen vacancies which accompanies the Ce^{4+} form to Ce^{3+} reduction resulting in the oxygen molecule loss. These CeO_2 nanoparticles have a moral antimicrobial activity, as they can act as scavenger radicals and ROS production to eliminate bacteria (Dos Santos et al. 2014).

8.5.7 Yttrium Oxide Nanoparticles (Y_2O_3 NPs)

Yttrium oxide (Y_2O_3) has a cubic structural composition having the highest free energy value which is unconstrained from the oxide form, from the elemental form

(Kosfstad 1972) due to excessive oxidative stress (Atou et al. 1990) and its structure, size variations are able to cause death induced by stress in a way that seems to be dependent. The antibacterial behavior of synthesized Y_2O_3 NPs using *Acalypha indica* leaves extract was also demonstrated (Becker et al. 2002).

8.5.8 Aluminum Oxide (Al_2O_3)

Alumina forms temperature-resistant, stable NPs, having a hexagonal structure, containing oxygen and Al^{3+} ions filling around 60% of total octahedral sites of the structural network (Ganguly and Poole 2003). Alumina NPs possess an antioxidant activity and wedge the release of ROS, ramblingly by stalling apoptosis, before finalizing cellular death (Sadiq et al. 2009). The antibacterial activities of Al_2O_3 NPs against *E. coli*, *Proteus vulgaris*, *Staphylococcus aureus*, and *Streptococcus mutans* are demonstrated in Fig. 8.11 and Table 8.3.

Moreover, in a report of 2009, the authors stated that the pathogen inhibition of *E. coli* by alumina NPs in 10–1000 g/ml range acts as antimicrobials by paying the ROS generation, by disrupting bacterial cell wall. Moreover, Al_2O_3 NPs' radical scavenging possessions block ROS generation leading to bacterial death (Sadiq et al. 2009).

Fig. 8.11 Antibacterial activities of aluminum oxide nanoparticles against bacteria using the agar well diffusion method; the fig. showed (1) *E. coli*, (2) *Proteus vulgaris*, (3) *Staphylococcus aureus*, (4) *Streptococcus mutans*. (Manyasree et al. 2018; open access)

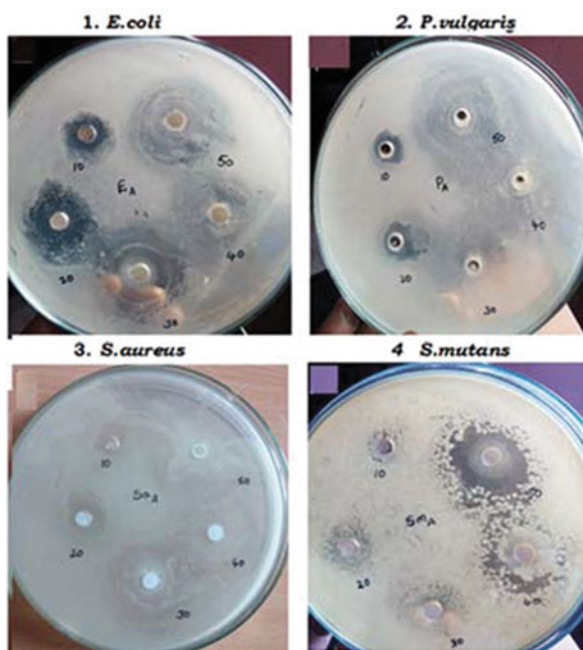


Table 8.3 Inhibition zones at different concentrations against two Gram-positive and two Gram-negative organisms (Manyasree et al. 2018; open access)

Name of the organism	Mean zones of inhibition [mm] \pm SD [$n = 2$]				
	10 mg/ml	20 mg/ml	30 mg/ml	40 mg/ml	50 mg/ml
<i>Escherichia coli</i>	9 \pm 0.20	18 \pm 0.25	27 \pm 0.25	31 \pm 0.10	39 \pm 0.35
<i>Proteus vulgaris</i>	5 \pm 0.30	10 \pm 0.40	15 \pm 0.45	20 \pm 0.20	26 \pm 0.45
<i>Staphylococcus aureus</i>	6 \pm 0.15	12 \pm 0.10	18 \pm 0.35	23 \pm 0.25	29 \pm 0.40
<i>Streptococcus mutans</i>	8 \pm 0.35	14 \pm 0.35	19 \pm 0.30	25 \pm 0.10	30 \pm 0.30

8.5.9 CaO and CaCO₃ Nanoparticles

Under alkaline conditions, the CaO NPs confirmed a sturdy antimicrobial activity due to ROS by the NPs' hydration with water. The CaO NPs presented antimicrobial activity against both Gram-negative and Gram-positive bacteria like *E. coli* and *S. aureus* causing damage to cell membrane and leading to intracellular content leakage and cell death (Sawai 2003). Moreover, Jeong et al. (2007) inspected the antimicrobial efficacy of CaCO₃ NPs. As per their results, CaCO₃ often gets converted to CaO owing to temperature rise. The produced CaO nanoparticles designated a durable bactericidal activity against *E. coli*, *S. aureus*, *S. typhimurium*, and *B. subtilis* (Zhou et al. 2015).

8.5.10 Bimetallic Oxide Nanoparticles

Bimetallic oxides containing twofold active metal oxide NPs (Fe, Mg, Ni, Ag and Zn) have gathered special attention in the modern era owing to its extraordinary activity against Gram-negative and Gram-positive bacteria. For instance, Zn-MgO NPs are a unique bimetallic oxide NPs that displayed antimicrobial activity in *E. coli* and *B. subtilis* microbes. Moreover, Fe-Ag NPs had high antimicrobial activity against *E. coli*. The mechanics behind for both were explained as the ROS insult and cell wall damage. Thus, the combination therapy has enhanced the antimicrobial activity (Niemirowicz et al. 2014).

The formulation of metal ion-doped NPs could improve antimicrobial properties of metal NPs synthesized by the Ti-doped ZnO powders which resulted in an enhanced antibacterial accomplishment against *S. aureus* as well as *E. coli*. related to the particle size decrease and crystallinity. The antibacterial activity of CaCO₃/MgO nanocomposites allowed superior antibacterial action against *S. aureus* than *E. coli* (Yamamoto et al. 2010). In addition, V₂O₅ when coupled with ZnO, these nanocomposites enhanced its photocatalytic activity (Saravanan et al. 2014). Moreover, Vidic et al. (2013) reported antimicrobial activity of co-doped nanostructure of ZnO-MgO against the same microbes suggesting a safe novel therapeutics for bacterial infections. Many results designated that MgO and CaO NPs blended with

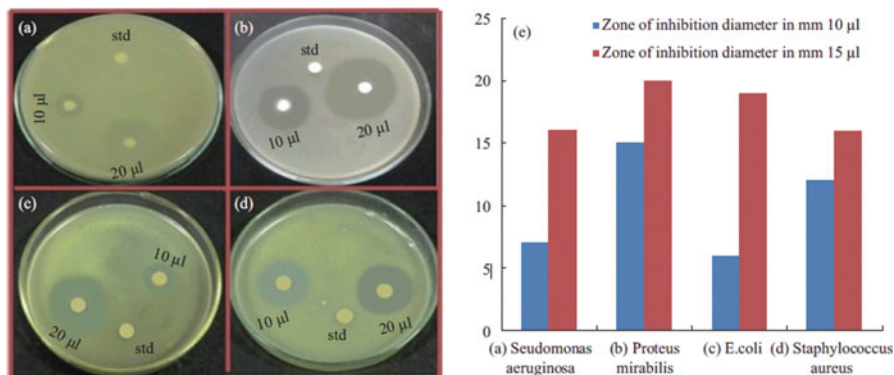


Fig. 8.12 (Color online) The photographic image of an inhibition zone produced by ZnO-CuO nanocomposite (3: 1 M) for (a) *Pseudomonas aeruginosa*, (b) *Proteus mirabilis*, (c) *E.coli*, and (d) *Staphylococcus aureus*. (e) Bar graph representing the size of the zone of inhibition formed around each disc, loaded with test samples, indicating the antibacterial activity toward the same for ZnO-CuO nanocomposite 3:1 M. (Saravanakkumar et al. 2018; open access)

supplementary disinfectants illustrated exceptional antibacterial effect (Leung et al. 2014). In addition, the ZnO-CuO nanocomposite (3: 1 M) formed zone of inhibition around each disc with loads test samples (Fig. 8.12). However, the presence of a third metal in bimetallic nanocomposite can also enhance the catalytic action. For instance, Mn^{2+} ion was able to increase photocatalysis of Mn-ZnS composite (Joicy et al. 2014).

8.6 Limitations and Future Prospects

The recombination between photo-generated electrons and holes in a photocatalyst is crucial for a successful reaction, as the lifetime of the charge separation decides the photocatalytic action. Consequently, a huge quantity of revisions is linked to the regulation of band structure and the charge separation. On the other hand, diminutive evidence regarding the adsorbed species and the intermediates in photocatalytic reactions is obtainable. Photocatalytic reactions may occur on the photocatalyst's surface or in the ordinary catalysts. The difference between the both is the driving force to stimulate the adsorbed reactants being photo-energy and thermal energy, respectively. Therefore, the kinetic clarification of surface structure, surface species, and surface property during the photoreaction is obligatory to comprehend the photocatalysis. Commonly a catalytic reaction contains many elementary steps like absorption of light in a photocatalytic reaction. Hence, there is identification of thermodynamic constraint in the photocatalysis than with the ordinary process. However, further clarification of the reaction mechanism is needed to get beneficial information on the additional development of the photocatalysis and novel insight on photocatalytic chemistry.

Many of the factors add to the future prospects of the photocatalysts. Countless NPs stabilize at least any one of the common resistance mechanisms. These possessions are due to specific physicochemical properties and bactericidal means of NPs (Chen et al. 2014). The uniquely small size helps NPs to interact with cells due to a larger surface area-to-mass ratio with the handy and manageable application, in disparity to traditional antibiotics. Besides the interruption of bacterial membranes, difficulty of biofilm formation is another significant mechanism, as they portray a major measure in the progress of bacterial resistance (Peulen and Wilkinson 2011). The distinctive structure and arrangement of bacterial biofilms deliver protection to the implanted microorganisms, assisting them to escape from most antibiotics. Moreover, bacterial biofilms act for regular resistance mutations and the interchange or variation of mutations among diverse bacterial cells (Khameneh et al. 2016). Studies have discovered that countless NPs can overcome biofilm formation, comprising Au-based NPs (Yu et al. 2016), NPs, CuO NPs (Miao et al. 2016), Ag-based NPs (Markowska et al. 2013), Mg-based NPs (Lellouche et al. 2012), NO NPs (Hetrick et al. 2009; Slomberg et al. 2013), and YF NPs (Lellouche et al. 2012). The best prevention of biofilms is attained by a lesser size and larger surface area-to-mass ratio, as well as the shape of NPs with an extraordinary outcome on biofilm obliteration (e.g., NPs with rodlike shape are more operative than NPs with spherical shape).

8.7 Conclusion

The usage of metal oxide NPs pooled with visible light irradiation unlocks innovative opportunities for surface decontamination. As described, it is promising to encompass the absorption constituency of the NPs to the red/NIR by doping with the transition metal ions or organic molecules. In cases where NPs might be toxic, it is promising to coat them with a massive selection of surfaces. This property is thus exploited as a solicitation by encountering many pathogenic microbes.

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