

## Antimicrobial Treatment of Different Metal Oxide Nanoparticles: A Critical Review

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Many nanomaterials can be used as metal oxides (Ti, Ag, Zn, Cu, Mg, Ca, Ce, Yt, Al). Metal oxide nanoparticles have strong antimicrobial properties. The oxides that play a large role as antimicrobial agents can be divided into two major groups based on their mechanism of action i.e., those that involve oxidation and those that inhibit the production of Reactive Oxygen Species (ROS). Previous studies have shown that, toxic metals like silver and titanium, and their metals oxides, employ the ROS-mediated mechanism that leads to oxidative stress-related cytotoxicity, cancer, and heart diseases. Oxidative stress further leads to increased ROS production and also delays the cellular processes involved in wound healing. Other metal oxide nanoparticles, like Y<sub>2</sub>O<sub>3</sub>, CeO<sub>2</sub> and Al<sub>2</sub>O<sub>3</sub> act as free radical scavengers. Out of these, aluminium oxide nanoparticles are more effective antimicrobial agents, than the other metal oxide nanoparticles. A combination of Al<sub>2</sub>O<sub>3</sub> and other antimicrobial agents such as TiO<sub>2</sub> may act as ideal antimicrobial agents, along with possessing free radical scavenging activity. This critical review aims to study the antimicrobial properties of different metal oxide nanoparticles and the mechanism of action involved, besides comparing their efficacy to eliminate bacteria.

**Keywords:** Metal oxide; Antimicrobial; Radical scavenger; Reactive oxygen species (ROS).

## INTRODUCTION

Nanotechnology is gaining wide popularity due to its large array of applications, ranging from cosmetics and skin care products to abrasives, car polishes, and drug delivery systems. Man-made nanoparticles, designed in the diameter range of < 100 nm, show exclusive physico-chemical characteristics due to their small size measurement, large surface-to-volume ratio, and also increased reactivity.<sup>1</sup> These modified characteristics of NanoParticles (NPs), could cause the generally inert material to respond differently on the nanoscale.

Moreover, nanoparticles, when scaled down, show different properties as compared to their parent metallic properties. These properties can be manipulated for the required applications.<sup>2</sup> Most of the biochemical reactions, in the body, occur at the atomic level. Therefore, it is safe to assume that there could be a synergy between the fields of nanotechnology and basic life sciences, which could then work together to solve many of the problems faced by biologists. Therefore, nanoparticles are already recognized as the biomaterials that have a great potential for medical and biological applications. They may be utilized as a contrast

agent for medical imaging, or in therapeutic drug delivery, elimination of tumours and labelling of cells. Furthermore, organic and inorganic nanoparticles are widely used in the industry, for the manufacture of biomedical instruments, due to their easy incorporation in biological processes.

Many microbes create problems in the environment, health care industry, food and packaging industry, synthetic textiles and production of biomedical apparatus. To counter this problem, the use of antimicrobial agents is highly relevant in these industries. These agents can be divided into two groups: organic and inorganic.<sup>3</sup> Out of these, inorganic materials have become more popular in the past decade due to their high capacity to resist adverse processes.<sup>3-4</sup> The activity of these materials is directly proportional to the surface area that is in contact with the microbes. To explain, the larger the surface area (as seen in NPs), the greater is the potency of the antimicrobial agent, as it is able to carry out many simultaneous reactions on the microbial cell surface.

There are very few reports that enlist the effects of ecotoxicity of the metal oxide nanoparticles on the microbial species, though their antibacterial properties are well-

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known. Based on this fact, one can state that these metal oxide NPs could be toxic to the bacteria in the environment.<sup>5</sup> The pathogen, *E. coli* can be controlled by disrupting its gram-negative cell membrane by Zinc oxide (ZnO) and cerium oxide NPs. Due to the positive charge on these NPs; they can easily bind to the negative cell membrane of the pathogen by the principle of electrostatic attraction. It thus appears that the physicochemical properties of the bio-material and the biochemistry of the bio-membrane play a major role in determining the toxicity of the NPs against the microbes.<sup>6</sup> There are several metal oxides that act as antibacterial agents, reported in the literature, however they differ in their mechanism of action against the microbes. There are no reports that explain the mechanism of action of metal oxide NPs and their role as antimicrobial agents. In this review, we outline the properties of different metal oxides and their NPs, and explain in brief the different mechanisms employed by them for inhibiting microbes.

### INORGANIC ANTIMICROBIAL AGENTS

Inorganic antimicrobial agents that include metal oxides play a big role as antimicrobial agents. These oxides are divided into two different groups based on the mechanisms involved in the inhibition of bacteria. Figure 1 represents the classification of the inorganic nanomaterials as antimicrobial agents based on their different toxicities. Figure 2 demonstrated the mechanisms of different metal oxide nanoparticle-induced antimicrobial activity.

1. The first mechanism employed by the metal oxides involves the direct contact of the metal oxide with the bacterial cell wall, and its destruction by the oxidation reaction. However, this mechanism by the metal oxides can prove to be harmful to human health. The free oxygen

radical generated after the oxidation reaction, remains in the human cell. This reactive oxygen species (ROS) can prove to be detrimental to human health and give rise to a number of health issues like lung cancer, cardiovascular disorders and oxidative stress-related inflammatory diseases.<sup>7</sup> A brief list of important inorganic nano-materials is shown in Table 1.

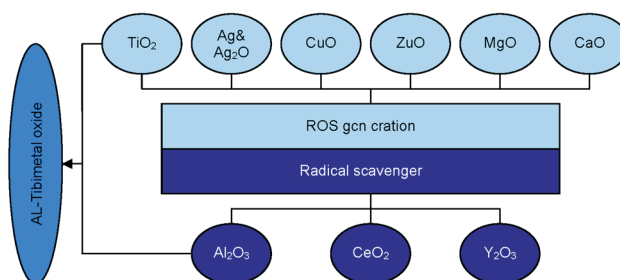


Fig. 1. Classification of nano-inorganic antimicrobial agents based on toxicity.

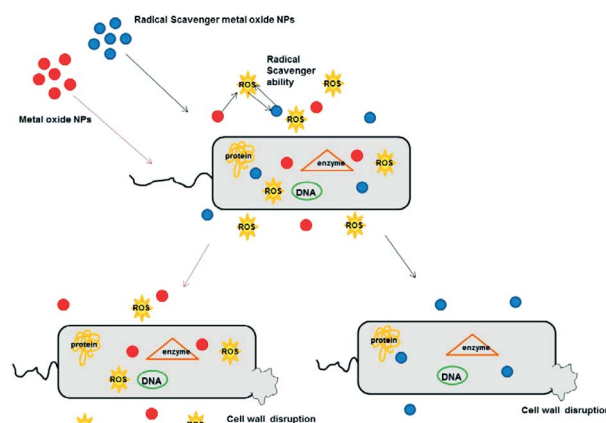


Fig. 2. The mechanisms of different metal oxide nanoparticle-induced antimicrobial activity.

Table 1. A brief list of toxic and nontoxic inorganic antimicrobial agent nanoparticles

Materials	Applications
TiO <sub>2</sub> nanoparticles <sup>134</sup>	Antimicrobial, photo-catalyst, self-cleaning, UV protecting, water and air purifier, dye degradation, gas sensor, solar cell, hydrophilic, super hydrophobic, co-catalyst for cotton cross-linking, photo stabilizing wool
Silver nanoparticles <sup>135</sup>	Antimicrobial, disinfectant, electrical conductive, UV protection, antifungal
ZnO nanoparticles <sup>136</sup>	Antimicrobial, UV blocking, photo catalyst
CuO nanoparticles <sup>114</sup>	Antimicrobial, UV protection, electrical conductive
MgO nanoparticles <sup>119</sup>	Antimicrobial, flame re-tardant, UV absorber
CaO nanoparticles <sup>120</sup>	Antimicrobial, catalyst, effective chemisorbents
CeO <sub>2</sub> nanoparticles <sup>125</sup>	Antimicrobial, catalyst support, radical scavenger
Y <sub>2</sub> O <sub>3</sub> nanoparticles <sup>125</sup>	Antimicrobial, UV protection, radical scavenger
Al <sub>2</sub> O <sub>3</sub> nanoparticles <sup>131</sup>	Antimicrobial, catalyst support, radical scavenger, abrasive material, absorbent, reinforcements
Al-Ti bimetal oxide nanoparticles	Antimicrobial, radical scavenger, wound healing

2. Some of the metal oxide nanoparticles, like aluminium oxide ( $\text{Al}_2\text{O}_3$ ), cerium oxide ( $\text{CeO}_2$ , Ceria) and yttrium oxide ( $\text{Y}_2\text{O}_3$ , Ytria), act as free radical scavengers.

**TiO<sub>2</sub> nanoparticles:** Currently, reports indicate that TiO<sub>2</sub> NPs can be used for many industrial applications and can act as a multi-functional material. These nanoparticles are very durable and work on a wide spectrum of bacteria as anti-microbial agents.<sup>8</sup> The photocatalytic properties of TiO<sub>2</sub> are especially useful in the eradication of bacteria.<sup>8</sup> This property, along with its size and surface characteristics determine the industrial applications of TiO<sub>2</sub> NPs. These NPs are used in paints, cosmetics, antibacterial agents, sunscreens, treatment of waste water, water treatment for drinking purposes, self-cleaning applications, antifogging agents, gasoline detectors, as well as for a large number of biomedical applications.<sup>9</sup> The photocatalytic property of TiO<sub>2</sub> depends on its nanostructure, size, along with the purity of the metal oxide used.<sup>10-11</sup> There are several well-known poly-morphs of TiO<sub>2</sub>, out of which the most popular ones are anatase, rutile and brookite poly-morphs. Even the antimicrobial property of the metal oxide depends on its shape, size and crystal structure.<sup>10,12-13</sup> It has been reported previously that oxidative stress after the formation of reactive oxygen species (ROS) could play a very important role in the antimicrobial mechanism of TiO<sub>2</sub> nanoparticles. The generated ROS, causes damage to the molecular structure of the cell, including DNA, lipid and protein damage.<sup>14-18</sup>

Titanium dioxide irradiation by lighting or UV produces band gaps or electron–holes and free electrons that allow redox reactions to take place on the surface of the TiO<sub>2</sub> semiconductor. Thus, when the TiO<sub>2</sub> absorbs a high-energy photon, electrons in TiO<sub>2</sub> are excited, which then bounce from the valence band to the conduction band, creating an energy hole ( $\text{h}^+$ ) and a free electron ( $\text{e}^-$ ) which, along with an oxidant reduce the product. In the case of reductive reactions, these electrons combine with an oxygen molecule to form  $\text{O}^{2-}$ , which along with water generate hydroxyl radicals. The photo-catalytic activity of titanium dioxide is very useful in the degradation of hydrocarbons and organic contaminants in the soil and water. Moreover, this activity also enables the metal oxide to degrade noxious chemicals along with inhibiting biofilms and resisting bacterial growth.<sup>19-24</sup>

Among the polymorphs of TiO<sub>2</sub>, rutile is the more stable one thermodynamically than the other two polymorphs, i.e., anatase and brookite. In high temperatures, the anatase

and brookite forms are converted to the rutile form. Also, the rutile form possesses an immediate group distance, whereas the anatase form provides a more indirect group distance that is based on the group structure. Rutile has a bright white colour and is very popular in the dye industry. Anatase has greater band-gap strength than rutile. On the other hand, some researcher reported a wide range in the band-gap energies for the crystalline structure of both, anatase as well as rutile.<sup>25</sup> When  $\text{Zr}^{4+}$  and  $\text{Si}^{4+}$  are added to the titanium structure, it increases the anatase stability along with helping in rutile alteration (ART).<sup>26-27</sup> There are numerous approaches that bring about the formation of TiO<sub>2</sub> NPs. The most popular technique is the sol–gel process.<sup>27-29</sup>

Titanium dioxide nanoparticles can be used in a wide multitude of application. Some of these include the use of these NP as antibacterial agents,<sup>30</sup> self-cleaning, UV-protection, super-hydrophilic as well as ultra-hydrophobic coats on houses, dye degradation in effluent water along with forming a nano-catalyst when the metal oxide is coupled to cellulose and poly carboxylic acids.<sup>31-38</sup> As mentioned above, the photocatalytic properties of TiO<sub>2</sub> NPs play a major role in the eradication of microbes. The NPs produce reactive oxygen molecules in the presence of UV light.<sup>39-40</sup> This photocatalytic activity resulted in lipid peroxidation that caused an increase in the membrane fluidity and disrupted the cell structure.<sup>41-42</sup> However, TiO<sub>2</sub> NPs could cause considerable damage to the DNA, and other bio-molecules in human cells and tissues.<sup>43-45</sup> TiO<sub>2</sub> thus possesses strong antimicrobial properties due to its mechanism of ROS generation; however, it can prove to be very toxic to human health.

#### **Silver and silver oxide (Ag<sub>2</sub>O) nanoparticles:**

Many reports in the literature state that Ag NPs are one of the most popular inorganic NPs to be used for inhibition of microbes.<sup>46-48</sup> These NPs find wide applications in the production of injection mould plastics materials, in the form of coatings and in textiles.<sup>49-50</sup> In addition, they are also widely used in the manufacture of biomedical instrumentation.<sup>51</sup> Its ionic form is more active against the microbes.<sup>46,52-53</sup> Since ancient times, silver has been used in homes and industries as a preferred antimicrobial agent to deal with the microbial attack and avoid spoilage. Currently, scientists are exploring various other applications of Ag NPs along with its bactericidal properties.<sup>54-57</sup> Ag NPs can be produced on a preparatory scale by various techniques,<sup>58-60</sup> like - photocatalysis, matrix biochemistry, photochemical or radiochemical, photoreduction, sonolysis,

wire explosion, polyols, micelle-based and biological synthesis.<sup>61-67</sup> As mentioned above, though silver has strong anti-microbial properties,<sup>68-69</sup> it can have an adverse effect on the human body.<sup>70-71</sup> Silver has an 'oligo-dynamic' effect, i.e., it is able to exert a bactericidal effect on the containers that are coated with it, e.g., silver pots that store water. This is on account of the inherent antimicrobial property by the silver metal.<sup>72</sup> The efficacy of silver NPs has been tested against a wide range of bacteria. Silver NPs, even in low concentrations, have shown a positive effect on more than 650 disease-causing microbes, including bacteria, algae and fungi, present in the human body. The mechanism of action of Ag NPs is similar to that employed by its ionic form.<sup>73</sup>

Silver nanoparticles are not toxic along with being a non-tolerant disinfectant. Silver NPs can be produced in different size ranges, depending on the method used for their production, thus indirectly maximizing the efficacy of their use as antimicrobial agents.<sup>46,74</sup> The basic bactericidal mechanism of Ag NPs can be explained in brief: generally, inorganic ions destroy the cell structure by disrupting the membrane and the disulphide linkages present on the various protein in the transmembrane layer.<sup>75</sup> The destruction of this membrane eventually leads to a slowdown in the metabolic processes, leading to cell death. The metal ions further catalyze the formation of free radicals, which oxidize various macro-molecules in the cell. There is no contact between the metal ion and the microbes in the body, as the free radicals can travel through the bloodstream and diffuse in the body. This inhibits the microbial cell population. As the microbes are not exposed to the radicals for long durations, they are not capable of developing resistance to it. However, in spite of the many advantages, silver ions can affect the biomolecules and lead to cell disruption. They have an affinity for the nucleophile amino acid residues on the proteins and can even react with the sulfhydryl, imidazole, amino, carboxy and the phosphate residues in the proteins and the various cellular components.<sup>69,76-77</sup> Silver also combines with an oxygen molecule and reacts with the sulfhydryl groups, to form R-S-S-R bonds, thus hindering respiratory activities and resulting in cell death.<sup>78-79</sup>

Silver NPs inhibit many oxidative enzymes, including alcohol dehydrogenase, and inhibit the uptake of succinate by the membrane vesicles. They cause oxidative DNA damage and interfere with DNA replication processes,<sup>81-82</sup> mitochondrial functioning and destroy the cellular membrane structure.<sup>69,83-86</sup> Ionic forms of silver or Ag

NPs can interact with the bacterial cell wall by electrostatic interactions and form small pits on the cell wall.<sup>87</sup> Generally, low concentrations of Ag<sup>+</sup> can lead to loss of protons from the cell membrane, resulting in the destruction of cellular structure.<sup>88-89</sup> Besides, silver NPs are more effective in their nanomolar concentrations, whereas the ionic forms are required in micromolar concentration to be efficient.<sup>90-92</sup> The antimicrobial action of Ag NPs was due to the formation of free radicals, which disrupted cell membranes. Furthermore, these free radicals on the membrane surface result in Electron Spin Resonance (ESR), which is another bactericidal effect.<sup>77</sup> Some researchers compared the antimicrobial effect of Ag, Au and ZnO NPs on *Streptococcus mutans* (*S. mutans*).<sup>93</sup> Out of the three metals, Ag NPs was very effective in inhibiting the growth of the microbe. The authors further suggested that, since *S. mutans* affects teeth and causes dental caries, the Ag NPs could be used to prevent its growth.<sup>93</sup> To conclude, the Ag NPs have good bactericidal properties and use the mechanism involving enzymatic inhibition which results in the disruption of metabolic activities, leading to inhibition of cell growth and death. But due to the production of free radical species by Ag NPs, it could also affect the human cells and cause oxidation of metabolic biomolecules before the microbe is eliminated.<sup>71,76</sup>

The Ag<sub>2</sub>O nanoparticle is another metal oxide nanoparticle with great antimicrobial activity. The previous study reported the antimicrobial activity of these nanoparticles against gram-negative bacteria (*E. coli*). The Ag<sub>2</sub>O nanoparticles might be demonstrated as a novel antibiotic. These nanoparticles can be damaged the DNA of *E. coli* and it can terminate the cell cycle at the G<sub>2</sub>/M phase due to the DNA damage. The mechanism of this action is through oxidative stress. Therefore, these nanoparticles demonstrated strong antimicrobial activity with high toxicity.<sup>76,94</sup>

**ZnO nanoparticles:** ZnO NPs are very effective antimicrobial agents and are efficient against both, gram-positive and gram-negative bacteria, in addition to the thermophilic and barophilic spores.<sup>95-96</sup> The metal oxide, ZnO, has many applications involving their use as solar cells, detectors, displays, gasoline detectors, piezoelectric units, varistors, electro-acoustic transducers, sun-screens, anti-reflection films, photo-diodes accompanied by UV light emitters, UV absorbers, and photocatalysts.<sup>97-99</sup> The structural formations of ZnO are as nanowires, nanotubes, nanobelts and nanocages.<sup>100</sup> The ZnO NPs are effective



antimicrobial agents as they reduce the microbial viability. The exact mechanism of this activity is not understood yet. However, one theory proposes the formation of a strong oxidant, hydrogen peroxide ( $\text{H}_2\text{O}_2$ ).<sup>101</sup> Another hypothesis for antibacterial activity of ZnO NPs, involves their accumulation on the bacterial cell membrane, with the help of electrostatic attractive forces.<sup>95</sup> Some other possible mechanisms that involve cell membrane disruption include, generation of ROS on the NP surface, the release of zinc ion in the cell, membrane dysfunction, or internalization of NPs, which could aid in its antimicrobial activity.<sup>102</sup> Besides, ZnO NPs also possess very high photocatalytic properties, which help its role as an antibacterial and antifungal agent. ZnO NPs are capable of forming ROS even under the presence of UV light.<sup>103-107</sup>

**CuO nanoparticles:** Due to unique physicochemical and biological properties along with their wide antibacterial properties, Cu nanoparticles have become very popular amongst the scientific community.<sup>102,108-110</sup> Copper nanoparticles set directly into submicron contaminants connected with Sepiolite particles, and compared the bactericidal efficacy of this mixture with the known antibacterial agent, triclosan.<sup>111-113</sup> Cu NPs were also deposited on polypropylene by magnetron sputter, to improve its resistance to UV radiation. The improvement in the electromechanical conductivity of the material after deposition of Cu NPs in the form of a thin film was also investigated.<sup>114-115</sup> Cu NPs can easily penetrate across the cell membrane and bring considerable damage to the enzymatic processes of the cell. This property makes them very effective antimicrobial agents.<sup>116</sup>

**MgO nanoparticles:** Magnesium oxide NPs are very stable, biocompatible and are very efficient antibacterial agents. Microbes are capable of developing resistance to any chemical that is added to their natural environment. MgO NPs, being a relatively new ceramic antimicrobial agent, have very effective bactericidal properties. The high alkalinity and presence of oxygen gaps on the MgO NPs, also add to their antibacterial property. When used in combination with the other antibacterial agents, they can bring about complete eradication of the pathogenic microbes.<sup>117-119</sup> According to published reports, MgO NPs damage the cell membrane and cause lipid peroxidation, leading to the leakage of intracellular contents, which results in cell death.<sup>118</sup>

**CaO nanoparticles:** The CaO NPs demonstrated the strong antimicrobial activity due to alkalinity and reactive

oxygen species (ROS). The antimicrobial mechanism of these nanoparticles is related to the generation of ROS and increase of pH due to the hydration of this nanoparticle in water. The CaO NPs showed antimicrobial activity against both Gram-negative and Gram-positive bacteria such as *E. coli* and *S. aureus*. The antimicrobial mechanism of CaO NPs was due to the ROS generation. Therefore, it can damage the cell membrane and then leading to the leakage of intracellular contents which can cause cell death. Therefore, CaO nanoparticles indicated excellent antimicrobial activity but it shows toxicity due to the generation of ROS free radicals.<sup>117,120</sup>

**CeO<sub>2</sub> nanoparticles:** Cerium oxide ( $\text{CeO}_2$ ) is a non-stoichiometric compound. The cerium (Ce) atom is characterized by three and four oxidation states ( $\text{Ce}^{4+}$ ,  $\text{Ce}^{3+}$ ). Many reports in the literature state that the concentration of  $\text{Ce}^{3+}$  increases as compared to  $\text{Ce}^{4+}$  as the size of the particles decreases, with  $[\text{Ce}^{3+}]$  is less than 1% in 10 nm particles, while it increases to 6% when the size decreases to 6 nm. There are oxygen gaps present in the oxidation states of these two  $\text{CeO}_2$  NPs. The creation of an oxygen vacancy is accompanied by the reduction of the  $\text{Ce}^{4+}$  form to the  $\text{Ce}^{3+}$ , resulting in the loss of an oxygen molecule. This unique radical scavenging property of ceria makes them an attractive option in wound healing.  $\text{CeO}_2$  nanoparticles have a good antimicrobial activity, as they can act as radical scavengers and block the ROS production to eliminate bacteria.<sup>121-125</sup>

**Y<sub>2</sub>O<sub>3</sub> nanoparticles:** Yttrium oxide ( $\text{Y}_2\text{O}_3$ ) has a cubic structural composition. The metal oxide, Yttrium oxide, is important due to its highest value for free energy released from the formation of its oxide form, from its elemental form.<sup>126</sup> Yttrium oxide ( $\text{Y}_2\text{O}_3$ ) does not deviate from its stoichiometry under the normal temperature and pressure conditions or by the effect of atmospheric  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . Yttrium oxide has two polymorphs, A and B form. Both the forms have a similar structure of a hexagonal close-packing (hcp). However, Form A has a seven-fold coordinate structure, whereas Form B has a six-fold. This makes Form B less dense with the cations present in the non-equivalent sites of the yttrium crystal. Moreover, the antioxidant properties of these NPs also prevent the cell death due to excessive oxidative stress.<sup>127</sup> The properties of NPs are dependent on its structure but not on its size, with similar activity seen in the size range of 6-1000 nm. These nanoparticles are able to rescue cells from oxidation cell death induced by stress in a way that seems to be dependent

on the structure of the particle but independent to its size in the range of 6-1000 nm. The yttria NPs are relatively non-toxic to macrophages and neutrophils. This is a very useful wound healing property.<sup>125</sup>

**Al<sub>2</sub>O<sub>3</sub> nanoparticles:** Alumina forms stable NPs, which are resistant to temperature changes and have a hexagonal close packing structure, comprising of the oxygen and the Al<sup>3+</sup> ions that fill 65% of all the octahedral sites present in the structural network.<sup>128-130</sup> Alumina NPs act as anti-oxidants and block the production of reactive oxygen species, indirectly blocking apoptosis, which initiates the ROS defense system, before completing the cell death program.<sup>131</sup>

Moreover, in a report published in 2009, the authors reported the inhibition of the pathogen, *E. coli*, to alumina NPs in the concentration range of 10-1000 µg/ml. Most of the metal oxides act as antimicrobials by employing the strategy of generation of ROS, which disrupts the bacterial cell wall; however alumina can also act as a radical scavenging agent. Moreover, these NPs are non-toxic to the human cell.<sup>131</sup>

**The mode of action of Alumina NPs is explained as follows:** The initial step involves the attachment of positively charged alumina NPs to the negatively charged bacterial cell surface. When a bacterial cell affects a human cell, it leads to the production of ROS, which can be very harmful to human health, as it can cause DNA damage, which could be a probable cause of cancer.<sup>131</sup> Since, Al<sub>2</sub>O<sub>3</sub> NPs have a radical scavenging property, they block the generation of ROS, and lead to bacterial cell death, before the mammalian cell is damaged.<sup>131</sup>

**Bimetallic oxide NPs:** Bimetallic oxides are new materials containing dual active metal oxide NPs (Fe, Ni, Mg, Zn and Ag) that has been considered to have special properties such as high antimicrobial activity. The previous published study reported antimicrobial activity of different bimetallic oxide against gram-negative and germ-positive bacteria. ZnMgO NPs is one of the bimetallic oxide NPs that showed antimicrobial activity against Gram-negative (*E. coli*) and Gram-positive (*B. subtilis*). The ZnMgO NPs also showed high antibacterial activity against *B. subtilis* bacteria. The Fe-Ag NPs is showe high antimicrobial activity against gram-negative bacteria (*E. coli*). The antimicrobial mechanism of both might the ROS generation and cell wall damaged. Therefore, the combination of this metal oxide can be improved only antimicrobial activity.<sup>132,133</sup>

## CONCLUSIONS

Metals, such as Ti, Ag, Zn, Cu, Ca and Mg and their metal oxides, can eliminate bacteria through an oxidation reaction. Therefore, these metal oxides are classified in group one. Though they are strong antimicrobial agents, they are toxic, as they lead to the generation of reactive oxygen species. On the other hand, Y, Ce and Al oxide (Y<sub>2</sub>O<sub>3</sub>, CeO<sub>2</sub>, and Al<sub>2</sub>O<sub>3</sub>) NPs, act as free radical scavengers. Therefore, these metal oxides are classified in group two. Y<sub>2</sub>O<sub>3</sub>, CeO<sub>2</sub> are able to rescue cells from oxidative stress-induced cell death, in a manner that is dependent on the structure but independent of the size of the particle, in the range of 6-1000 nm. This helps to heal all kinds of wounds. In addition, three alternative explanations have shown that Y<sub>2</sub>O<sub>3</sub> and CeO<sub>2</sub> protect against oxidative stress. They carry out the process by acting as direct antioxidants, blocking the generation of ROS, thus inhibiting the programmed cell death pathway. Due to low ROS production, the defense mechanism is activated before the apoptosis pathway is induced by glutamate. Aluminium oxide (Al<sub>2</sub>O<sub>3</sub>), cerium oxide, and yttrium oxide are useful for healing all types of wound due to their ROS scavenging potential. However, aluminium oxide (Al<sub>2</sub>O<sub>3</sub>) shows an average antimicrobial potential but is cheaper than cerium and yttrium oxide. Therefore, the combination of this nanoparticle with other oxides like TiO<sub>2</sub>, is ideal as they can act as an antimicrobial agent and also possess radical scavenger activity. Hence, this review suggests the use of Al-Ti bimetal oxide nanoparticles, due to their dual activity.

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