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Review Article

Green Approach to the Synthesis of Metal Oxide Nanoparticles Used As Alternative Remedy to Multidrug Resistance

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Abstract

The introduction of nanotechnology into our world has ushered in a slew of changes and provided a wealth of knowledge that has fuelled progress in many sectors of existence. Recent advances in nanotechnology have shown the importance of metal oxide nanoparticles due to their potentials in different sectors, particularly in nanomedicine and related biomedical fields. Metal oxide nanoparticles (MOx-NPs) such as titanium dioxide nanoparticles (TiO_2-NPs), copper oxide, silicon dioxide, zinc oxide and Iron oxide have gained a lot of prominence as a result of their unique properties. Metal and MOx-NPs based nanoparticles are being employed to create a novel antibacterial drug formulation, which is a revolutionary and ground breaking method to drug discovery and development. Different methods are employed for the synthesis of these nanoparticles of which green synthesis is found to be a better option. It involves the use of plant extracts which is a non-toxic solvent. Green materials offer a variety of advantages, such as low energy consumption and the capacity to operate under moderate operating conditions (such as pressure and high temperature) without the use of harmful chemicals or catalysts. Therefore, more research efforts should be geared toward the advancement of this important technology.

Keywords: Metal oxide nanoparticles, Antimicrobial activity, Green synthesis, plant extract.

INTRODUCTION

The use of nanoparticles as an alternative means of solving the problems and the challenges of multidrug resistance has been the focus of researchers in recent times. Nanotechnology has immensely contributed to the growth and development in all facets of life and found its applications in various fields such such as chemistry, medicine, biotechnology, pharmacology, engineering, microbiology, inexpensive catalyst, cytotoxicity research owing to their distinct chemical, electrical, physical and mechanical properties [1, 2]. One of the most important applications of nanoparticles in biomedicine and pharmacology is their use in enhancing effective antimicrobial activity.

In recent times, researchers are majorly focusing on the development of microbial pathogen resistance to currently used synthetic antibiotics. Several species, including *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus vulgaris,* and *Staphylococcus epidermidis* are the major organisms that are responsible for human disease. In order to eradicate infections caused by these microorganisms, appropriate antibiotic treatment is required. The antibiotic administered may not always be effective in killing or suppressing the growth of dangerous bacterial strains. Antibiotics developed by pharmaceutical corporations were shown to be ineffective against multidrug-resistant microorganisms. As a result of these overwhelming problems, it's critical to find and develop nano-based drugs or agents to combat bacterial infections [3, 4].

Antimicrobial action of some nanoparticles has been studied extensively. We recently reported the use of alginate stabilized iron oxide nanoparticles against *Bacillus subtilis, S. aureus, Candida albicans, Vibrio cholerae, P. vulgaris,* and *Micrococcus luteus* in our prior study [5]. Also, we investigated, the antibacterial activity of silver conjugated magnetic iron oxide nanoparticles against *Serratia marcescens* and *S. aureus* [6]. Green synthesis of nanoparticles has received a lot of interest, with plant extracts and other natural resources (e.g., microbes and enzymes) proven to be suitable for the control of microbial pathogens [7, 8]. The use of green materials provides a wide range of benefits, including low energy consumption and the ability to operate under moderate operating conditions (e.g., pressure and high temperature) without the need of hazardous chemicals or catalysts. As a result, the synthesis of nanoparticles utilizing plant extracts appears to be promising due to its simplicity, cost-effectiveness, and environmental benefits [9, 10]. Green synthesis of metal oxide nanoparticles could arise from different sources which include plant extracts, microbes and biomolecules (Figure 1).

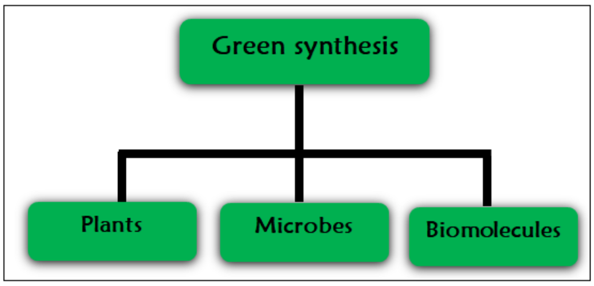

Figure 1: Approaches for the synthesis of metal oxide nanoparticles

Green synthesis has gotten a lot of interest as a way to make a range of nanomaterials that is both sustainable and environmentally benign. It is described as a marvel of medicine that leads to the industrial revolution in the twenty-first century [11]. Silicon dioxide (SiO_2), ferric oxide (Fe_2O_3), zinc oxide (ZnO), titanium dioxide (TiO_2), and magnesium oxide (MgO) are among most important examples of the single metal oxide group. This review centred on the green synthesis of some selected metal oxide nanoparticles and their antimicrobial activities.

Titanium dioxide (TiO_2) nanoparticles

Titanium dioxide (TiO_2) is an inert, nontoxic, and low-cost substance with a high refractive index and UV absorption capacity, making it an interesting white pigment and ecologically friendly catalyst [12]. TiO_2 nanoparticle is frequently employed in sunscreen lotions, paints, plastics, papers, inks, food colorants, and toothpastes to provide whiteness and opacity [13] due to its good physical stability and lack of toxicity. It is well-known among metal oxides as a versatile material that plays an important role in a wide range of applications [14]. The unique antimicrobial capabilities and chemical stability make TiO_2-NPs more valuable in the fields of chemistry and nanomedicine. TiO_2-NPs are used in cosmetics, and lotions and ointments with these nanoparticles are used to prevent skin aging and sunburn [15]. The efficacy of TiO_2 nanoparticles is attributed to the increased surface area, which adds to an increase in surface energy, which improves their microbial suppression ability. TiO_2 NPs have been found to be effective in the treatment of bacterial infections, which have become a threat due to their resistance to currently available antibiotics [16, 17].

The application of TiO_2-NPs as an antimicrobial agent was reported by Ansari *et al.*, [18]. The disc diffusion technique was used to assess the antimicrobial activity of the synthesized nanoparticles. The authors reported that the biosynthesized nanoparticles showed a greater zone of inhibitory activity against Gram-positive (*B. subtilis*, *S. aureus*) pathogenic bacteria than Gram-negative (*P. aeruginosa*, *E. coli).* TiO_2 nanoparticles were also found to have a stronger antimicrobial effect against both (Gram-negative and Gram-positive) human pathogenic bacteria. Furthermore, based on in vitro antibacterial activity against human pathogenic bacteria, the authors concluded that these biosynthesized nanoparticles can be used in medicine as therapeutic agents.

Further investigation on the antimicrobial property of TiO_2-NPs was carried out by Shimi *et al.*, [19]. The authors investigated the photocatalytic and the antibacterial activity of an eco-friendly synthesized TiO_2-NPs. The antibacterial activity was carried out against both Gram positive and Gram-negative bacteria (*S. aureus* and *E. coli*). Higher performance of the antibacterial activity was recorded for the Gram-positive bacteria than *E. coli*. In related study by Aravind *et al.*, [20], green synthesis and the hydrothermal approach (chemical method) were employed for the successfully synthesis of TiO_2 NPs. Agar diffusion method was used to observe antibacterial activity of titanium oxide nanoparticles. TiO_2 NPs were investigated for antibacterial action against *S. aureus* (Gram-positive bacterium), *E. coli* and *K. pneumoniae* (Gram-negative bacteria). The authors reported that the biologically synthesized nanoparticles gave a better antibacterial activity. According to their findings, TiO_2 nanoparticles offer properties that are suitable for biomedical and wastewater treatment.

Moreover, Rajakumar *et al.*, [21] reported the synthesis of TiO_2 NPs using *Aspergillus flavus* as the reducing agent and its antimicrobial efficacy was evaluated against the following organisms; *S. aureus, E. coli, P. aeruginosa, K. pneumoniae* and *B. subtilis.* The author reported higher antimicrobial potency against all tested organisms. Subhapriya *et al.*, [22] investigated the antimicrobial activity of TiO_2 nanoparticles using *Trigonella foenum-graecum* extract. The bio-mediated synthesized nanoparticles were characterized using HR-TEM, HR-SEM, FT-IR, UV spectroscopy, and XRD to confirm the synthesis of the nanoparticles. The antimicrobial activity of the nanoparticles was further evaluated using standard disc diffusion method. The nanoparticles was tested against some selected organisms which include *S. aureus, Enterococcus faecalis, K. pneumoniae, Pseudomonas aeruginosa, E. coli, P. vulgaris, B. subtilis, Yersinia enterocolitica* and *a fungus*, *C. albicans*. It was reported from their result that the plant extract mediated nanoparticles showed considerable antimicrobial activity against *Y. enterocolitica, E. coli, S. aureus* and *E. faecalis.*

Green synthesis of TiO_2 was achieved and reported by Santhoshkumar *et al.,* [23], disc diffusion method were used to evaluate the antibacterial activity of the synthesized nanoparticles. The antibacterial efficiency was tested against *S. aureus* with zone of inhibition of (25 mm) and *E. coli* (23 mm). Result obtained showed that the synthesized nanoparticles had a great antibacterial potency against the tested organisms. Sundrarajan *et al*., [24] reported the synthesis of TiO_2 nanoparticles using leaf extract of *Morinda citrifolia.* TiO_2 nanoparticles were tested against human pathogens like *S. aureus, E. coli, B. subtilis, P. aeruginosa*, *C. albicans,* and *A. niger* using agar well-diffusion method. TiO_2 nanoparticles exhibited superior antimicrobial activity against Gram-positive bacteria.

Durairaj *et al*., [25] evaluated the antimicrobial activity of the biosynthesized TiO_2 NPs from *A. niger.* UV visible spectrophotometer was used to characterize the synthesized titanium dioxide. XRD and SEM were also employed to confirm successful synthesis of the nanoparticles. The antimicrobial activity of the synthesized nanoparticles was tested against the following organisms which include *Bacillus, Klebsiella, Pseudomonas*, and *Streptococcus* sp. Different concentrations of the TiO_2 NPs were used to assess the antimicrobial activity of the nanoparticles. The authors reported that *Pseudomonas* gave the highest antimicrobial performance at a concentration of 30 µg of the synthesized nanoparticles. It was further concluded that the synthesized nanoparticles was active against the tested organisms.

In a study reported by Jayaseelan and co-workers in 2013 [26] TiO_2 nanoparticles antibacterial efficacy using well diffusion method was tested against *Aeromonas hydrophila, E. coli, P. aeruginosa, S. aureus, Streptococcus pyogenes* and *E. faecalis.* The synthesized nanoparticles showed a high antibacterial activity against *S. aureus* and *S. pyogenes* with the diameter of zone of inhibition of 33 mm and 31 mm respectively. Thandapani and co-worker in 2017 [27] reported the synthesis of TiO_2 NPs using leaf extract of *P. hysterophorus* the synthesized nanoparticles was further assessed for its antimicrobial activity. The tested organisms were *E. coli, S. aureus*, *P. aeruginosa, K. pneumoniae*, *P. vulgaris,* and *S. epidermidis*. The authors reported high antimicrobial activity of the synthesized nanoparticles against some of the tested organisms. Singh [28] investigated the biosynthesis of TiO_2 from *B. subtilis*. The author reported an effective antibacterial property of the synthesized nanoparticles when tested against *E. coli.* The author was able to confirm a good inhibitory effect of the synthesized nanoparticles on the organisms.

Magnesium oxide nanoparticles (MgO-NPs)

Magnesium is a crucial element for plant growth. In the photosynthetic process, it acts as a driving force. It also demonstrates a strong interaction with phytoconstituents in plants to produce nanoparticles. According to FDA [29] magnesium oxide nanoparticles (MgO-NPs) are very safe and suitable alternative with exceptionally excellent antibacterial properties. MgO is a hygroscopic white solid mineral with a lattice of Mg^{2+} ions and O_2 ions. MgO is a significant inorganic oxide that is considered to be beneficial to human health. It is used in medicine to treat a variety of diseases, including heartburn and indigestion [30]. Due to its low volatility and excellent temperature tolerance, magnesium nanoparticles may have a long-lasting antibacterial effect. George and colleagues in 2016 [31] reported the synthesis of MgO nanoparticles using the plant extract of *Lepidium Sativum*. The authors reported successful synthesis of nanoparticles. The nanoparticles were further investigated for its antibacterial activity against four organisms using well-diffusion method. The result showed a considerable activity against the tested organisms which were *S. aureus, E. coli, B. subtilis* and *P. aeruginosa.*

Fatiqin *et al*., [32] investigated the green synthesis of MgO using *Moringa oleifera* leaf aqueous extracts. Different characterization techniques such as UV-visible spectroscopy, FTIR, XRD and SEM were used to confirm the successful synthesis of the nanoparticles. The nanoparticles antibacterial efficiency was tested against two organisms. The results obtained from the antibacterial assessments on Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria revealed that MgO nanoparticles have the ability to inhibit both *S. aureus* and *E. coli*. In a study reported by Younis and co-workers in 2021 [33]. The authors investigated the biological synthesis of MgO from *Rosa floribunda* charisma extract. The synthesized nanoparticles were tested for its antioxidant, antiaging and antibiofilm properties. The nanoparticles antibacterial activity was tested against *S. epidermidis, S. pyogenes* and *P. aeruginosa,* which constitute a substantial hazard to human health. It was concluded from the results of their investigations that the synthesized nanoparticles could be useful in the cosmetic industries.

Ammulu and co-workers in 2021 [34] reported green synthesis of MgO using heartwood aqueous extract of *Pterocarpus marsupium. P. marsupium* heartwood extract is high in polyphenolic compounds and flavonoids and can be used as a green source for large-scale, easy, and environmentally friendly synthesis of MgO-NP. The synthesized nanoparticles had antibacterial activity against *S. aureus* and *E. coli*. Similarly, Abdallah and colleagues in 2019 [35] investigated the biological synthesis of MgO nanoparticles from *Rosmarinus officinalis* L. (Rosemary). DLS, SEM, EDS, XRD, FTIR were some of the characterization techniques that was employed to confirm the successful synthesis of the nanoparticles. The nanoparticles inhibited *Xanthomonas oryzae* pv. *oryzae* (Xoo).

Copper Oxide nanoparticles (CuO-NPs)

Copper oxide (CuO), also known as copper (II) oxide or cupric oxide, is a monoclinic semiconducting chemical. Much attention has been on the use of CuO because it's the simplest copper compound and has a lot of interesting physical features like high temperature, superconductivity, electron correlation effects, and spin dynamics. CuO-NPs are useful as antimicrobials and in gas sensors, batteries, high-temperature superconductors, solar energy and conversion devices [36-39]. Cu and Cu complexes have been used by humans for ages as water purifiers, algaecides, fungicides, antibacterial and anti-fouling agents, among other things [40].

The plant-mediated synthetic route entails the use of metal salts which is mixed with plant extracts for a reaction period of about 1-3 h at room temperature. The plant extracts comprise of various bio-active components which include phenols, flavonoids, proteins, tannins and terpenoids. These components act as reducing and stabilizing agents thereby transforming metallic ions into nanoparticles. The bio-mediated synthesis of copper oxide nanoparticles is represented in Figure 2.

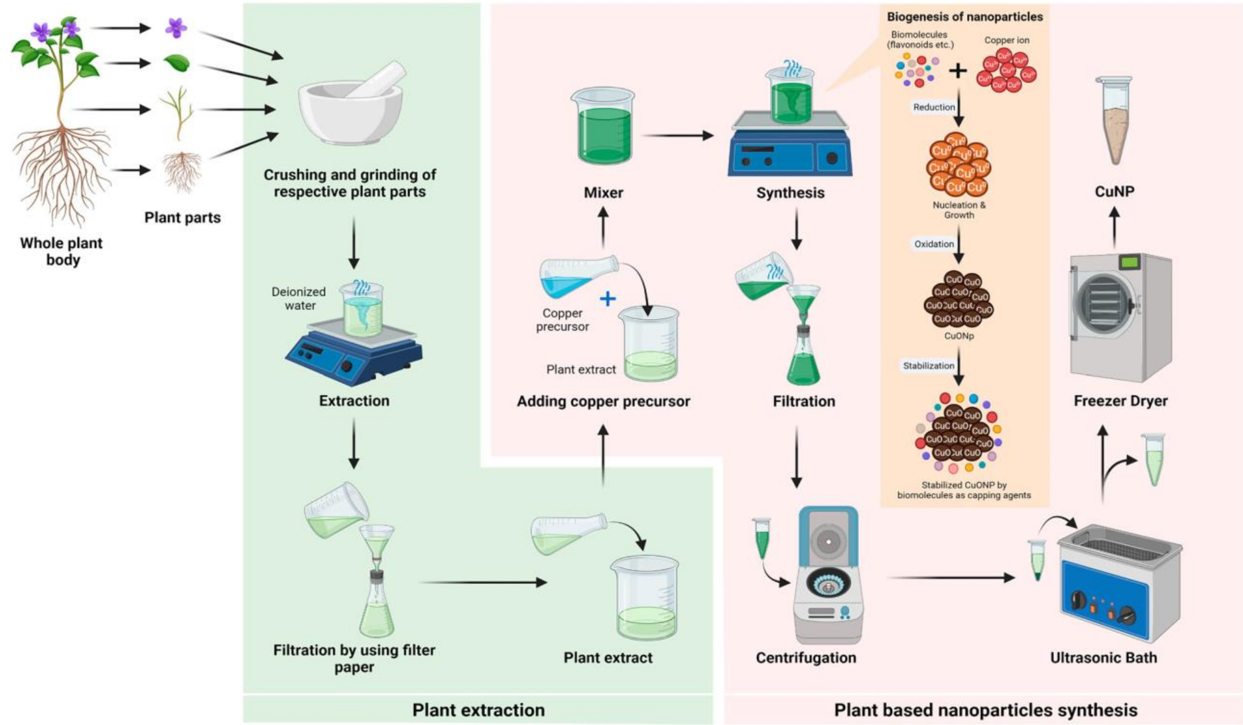

Figure 2: Graphical representation of biomediated synthesis of copper oxide nanoparticles using plant extract. Adapted from Chakraborty *et al.*, [41]

Green synthesis of CuO nanoparticles using *Ocimum basilicum* plant extract was investigated by Altikatoglu and co-workers in 2017 [42]. Successful synthesis of the nanoparticles was confirmed using SEM, FT-IR and UV spectroscopy and the synthesized nanomaterial inhibited *E. coli* and *S. aureus.* In related study by Naika *et al.* in 2015 [43], green synthesis of CuO-NPs was achieved using *Gloriosa superba* L. extract. The authors reported a considerable activity against *K. aerogenes, E. coli, P. desmolyticum* and *S. aureus* using agar well diffusion method.

The use of gum karaya for the green synthesis of copper oxide nanoparticles was employed by Černík in 2013 [44]. CuO-NPs had a stronger antibacterial effect against Gram-negative bacteria compared to that of Gram-positive bacteria. The authors attributed the difference in the activity to the structural and compositional changes in the cell membrane of the bacteria. The structural and compositional changes in the cell membrane could explain the differential in action against these two types of bacteria. Also, Amin *et al.*, [45]. The synthesis was carried out using *Aerva javanica* leaf extract. The antibacterial and the antifungal activities was tested against some selected organisms which include bacteria; *P. aeruginosa, E. coli, S. aureus*, fungi; *C. albicans, C. krusei*, and *C. tropicalis.* The report from the authors' investigation revealed that the synthesized nanoparticles had a considerable inhibitory effect on the selected organisms.

Qamar *et al*., [46] investigated an eco-friendly synthesis of CuO nanoparticles using the fruit extract of *Momordica charantia*. The analytical techniques that were employed to characterized the successful synthesis of the nanoparticles were TEM, SEM, FT-IR, XRD and EDS. *In vitro*, the biomedical applications as a therapeutic potential was assessed against eleven multidrug-resistant clinical bacterial strains, as well as a fungus, *Trichophyton rubrum*, using the well diffusion method. Report of their investigation revealed a strong antimicrobial effect against eleven tested organisms. The tested organisms were seven Gram-positive (*S. aureus, Streptococcus mutans, S. pyogenes, S. viridans, S epidermidis, Corynebacterium xerosis,* and *B. cereus)* and four *Gram-negative (E. coli, K. pneumonia, P. aeruginosa* and *P. vulgaris*) multidrug-resistant bacterial strains. Results obtained showed that the tested organisms had a reasonable zone of inhibition which ranges between 23 mm – 31.66 mm.

Further investigation was reported by Taran *et al.*, in 2017 [47] about the green synthesis of copper oxide nanoparticles using *Bacillus* sp (FU4). Antibacterial activity of the biologically synthesized nanoparticles was evaluated against *E. coli* and *S. aureus*. The effect of different concentrations (0.1, 0.01 and 0.001 M) of the $CuSO_4$ salt used was evaluated. The effect of incubation and culturing time (48,72, and 96 hours) was also evaluated (Figure 3). The authors reported a high level of antibacterial activity was obtained with the 0.1 M concentration with the diameter of zone of inhibition (33±0.57 mm) with the *E. coli*. The authors further reported that the major factor in the biosynthesis of copper oxide nanoparticles has to do with the concentration of $CuSO_4$ and those other factors like incubation and culturing time had no significant effect on the antibacterial activity of the synthesized CuO nanoparticles.

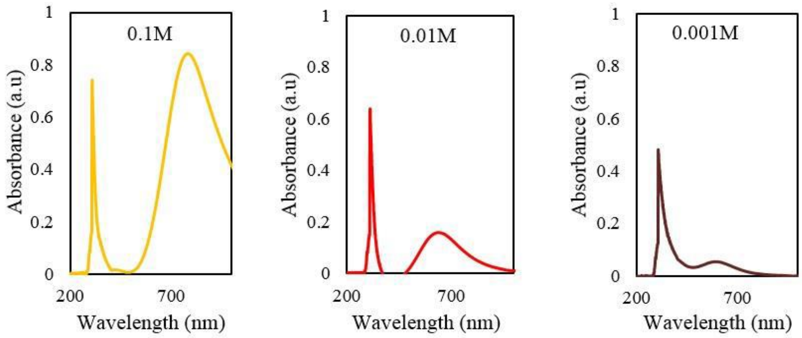

Figure 3: UV-Vis spectrum of CuO NPs produced by *Bacillus* sp. (FU4) at different concentration 0.1, 0.01 and 0.001 M. Adapted from Taran *et al.*, [47]

Silica nanoparticles (SiO_2 NPs)

The efficacy of a wide range of nanomaterials for efficient antibiotic medication delivery has been proven [48]. The interest in silica nanoparticles as a mechanism to transport pharmaceuticals such as antibiotics is growing [49, 50] due to their high thermal and chemical stability, high surface area, and strong biocompatibility. Silica nanoparticles are a special type of inorganic nanoparticle with a variety of functional properties that make them useful in the fight against bacterial infections [51-53]. Sometimes silica nanoparticles are employed as a mediator to improve antimicrobial delivery dosages at target areas, such as copper, zinc, and silver NPs, and therefore lower antibiotic doses [54]. Due to their unique features, which have various applications in different fields, silica nanoparticles have been recognized as crucial in the fields of chemistry, physics [55] and in biomedical applications.

Babu *et al*., [55] reported the green synthesis of silica nanoparticles from *Cynodon dactylon*. Different analytical methods like DLS, UV vis spectrophotometer, XRD, SEM and TEM were used to characterized the synthesized nanoparticles. The inhibitory effects of synthesized nanoparticles were tested against some selected organisms. The bio-mediated synthesized silica nanoparticles showed antibacterial efficacy against a variety of microbiological infections in antimicrobial investigations. The tested organisms were *E. coli P. aeruginosa*, *B. subtilis* and *S. aureus.* The authors compared the bio-mediated synthesized silica nanoparticles with chemically synthesized nanoparticles it was reported than the green synthesized nanoparticles gave a better inhibitory effect than the chemically synthesized nanoparticles.

A further investigation on the green synthesis of silica nanoparticles was equally reported by Periakaruppan *et al.*, [56]. The biosynthesis of silica nanoparticles was carried out using *Punica granatum.* The plant mediated synthesized nanoparticles were evaluated for its antibacterial activity against two organisms namely *E. coli* and *Salmonella sp.* which are Gram negative organisms. Antibacterial investigations show that silica nanoparticles aided *by P. granatum* have good antibacterial capabilities. The authors suggested that their investigations will aid in the development of a new nano medication or therapy for bacteria that are multidrug resistant.

Plant mediated synthesis of silica nanoparticles was reported by AL-Azawi *et al.*, [57]. The green synthesis was achieved using hot aqueous leaves extract of *Thuja orientalis* for the synthesis of silica nanoparticles. The antibacterial efficiency of the synthesized nanoparticles was tested against *S. aureus* and *E. coli*. The report of their investigations revealed a strong antibacterial efficacy of the bio-mediated synthesized silica nanoparticles to be highly effective against the tested organisms.

CONCLUSION

A growing interest in developing nanotechnology-based treatment strategies for infectious diseases has been sparked by rising antimicrobial resistance and a lack of treatment options. Metal oxide nanoparticles, in particular, have a lot of potentials for treating infectious diseases because of their diverse and controllable properties. Different approaches which include physical, chemical, and biological methods can be employed in the synthesis metal oxide nanoparticles. Biological method is the most promising due to its environmental friendliness, low cost, and ease of experimentation. As a result of these, more emphasis should be placed on green synthesis method of metal oxide nanoparticles, which would help to decrease toxicity to the environment to some extent. Also, there is much room for new ideas and concepts to be learned and implemented in order to improve efficacy without jeopardizing safety or biocompatibility. Therefore, considerable effort should be implemented towards the incorporation of nanoparticles as a means of overcoming the scourge of multidrug resistance arising from the uncontrolled usage of antibiotics.

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