TOPICAL REVIEW

Current trends in the green syntheses of tin oxide nanoparticles and their biomedical applications

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Abstract

Metal oxide nanoparticles had found a variety of applications in numerous fields of industrial, medical, and environmental technologies, attributable to recent advances nanotechnology field. Tin oxide nanoparticles (SnO₂ NPs) have gained importance as metal oxide nanoparticles due to their potential in various fields, particularly nanomedicine and other biomedicine fields. Tin oxide nanoparticles can be made using a variety of biological, chemical, and physical methods. Physicochemical methods are costly, emit high levels of toxic chemicals into the atmosphere, and consume a lot of energy. On the other hand, the biological approach is an environmentally safe, cost-effective, dependable, convenient, and easy way to synthesize tin oxide nanoparticles. In this review, the bio-mediated synthesis, as well as various biomedical applications of tin oxide nanoparticles, were discussed.

1. Introduction

Nanotechnology, which involves technologies from interdisciplinary fields such as physics, chemistry, biology, material science, and medicine, has recently emerged as one of the most significant research fields [1]. There was a considerable need to remove harmful reagents, and the green synthesis of nanoparticles was mainly cob [2]. The bio-mediated formation of nanoparticles has attracted the interest of researchers, including biologists, chemists, and materials scientists, as well as those looking forward to inorganic material synthesis utilizing environmentally friendly technologies [3, 4]. Because of their phyto-synthesizing potential, the application of transition metal nanoparticles has gained further prominence due to their properties of being biocompatible, low-toxicity, and enable environmentally friendly synthesis and usage [5]. Various chemical and physical methods to synthesize SnO₂ nanoparticles have been developed over the last few decades. The commonly used methods are chemical and physical methods such as hydrothermal, electrochemical, sputtering, microwave irradiation, photochemical synthesis, laser ablation, and chemical, physical and solid vapor deposition [6–10]. However, these processes involve the use of various dangerous and toxic chemicals, high amounts of electricity, and incur high expenditure. Thus, techniques with green chemistry methods that are pure, non-toxic, and environmentally sustainable are sought [11, 12]. The environmentally friendly and sustainable green technology approach of utilizing living organism such as plants and microbes in the synthesis of metallic oxide nanoparticles have captured attention and interest of many scientists [13, 14]. The biosynthesis of metallic oxide nanoparticles is a novel production method in a non-toxic, clean, and environmentally friendly manner [15, 16]. Bacteria were
found to act as cost-effective nano-factories that can convert metal ions into metallic nanoparticles [17]. Furthermore, the bacterial detoxification process that converts toxic metal ions into non-toxic metal NPs has been studied [18, 19]. This process has an intriguing reduction efficiency due to the chemical detoxification mechanism and energy-dependent ion efflux from the bacterial cell by membrane protein [17, 20, 21]. As a result of these fascinating features, bacteria are a top alternative for the green synthesis of nanoparticles. Biomolecules in bacteria can regulate the growth of inorganic crystals during biomineralization processes [14]. Various bacterial species, including *Pseudomonas aeruginosa*, *Pseudomonas stutzeri*, *Bacillus subtilis*, *Bacillus licheniformis*, *Lactobacillus casei*, *Rhizopus oryzae*, *Zooglea ramigera*, and others, have been investigated in recent years for the fabrication of metallic nanoparticles [17, 22–24]. Previous studies had examined multiple bacterial species, but only *Erwinia herbicola* was found to be capable of synthesizing SnO2 nanoparticles. SnO2 is an important material for various advanced engineering and medical applications, and studies on its mechanical, antibacterial properties, antioxidant properties [25–27], and cytotoxicity (Hepatocellular Carcinoma Cell Line) properties [28] have been undertaken.

Referring to the recent trend in bio-mediated production of metal oxide, the bio-mediated production of tin oxide nanoparticles from a variety of living organisms (plants, microbes, and other biological molecules), as well as various applications of tin oxide was reviewed here. The review covers the general perspective of the synthesis of metal oxide nanoparticles, the synthesis in green chemistry perspective, and the overview on the use of, particularly SnO2 nanoparticles in biomedical applications.

### 2. Synthesis of metal oxide nanoparticles

Nanostructures can be obtained in one of two ways: top-down or bottom-up. Grinding, milling, sputtering, and thermal ablation are examples of top-down methods that require breaking down bulk material into small particles by size reduction. Bottom-up methods concentrate on making nanoparticles (NPs) from smaller entities, such as atoms, molecules, and smaller particles [29]. Chemical and biological techniques are mainly used in bottom-up approaches. This has the benefit of increasing the probability of producing NPs with more uniform chemistry and fewer metallic NPs with fewer deficiencies.

#### 2.1. Green synthesis

Green synthesis of NPs enables effective, sustainable, and environmentally friendly production while avoiding the creation of undesired by-products. To achieve this aim, ideal solvent systems and natural resources (such as organic systems) are needed. Green syntheses of metallic NPs have utilized a range of biological materials (e.g., plant and microbial extracts). Plant extracts enable a relatively simpler process to generate nanoparticles at a bigger amount as compared to microbes mediated synthesis, considering the available metal oxide NPs green synthesis methods. Biogenic nanoparticles are the common name for these materials (figure 1). The solvent, temperature, pressure, and pH conditions all play a role in green synthesis methodologies. Diverse plant extracts have been extensively studied to be used in the green synthesis of metal/metal oxide NPs as various useful phytochemicals are available from various extracts of the plant especially from leaves, such as terpenoids, flavones, ketones, amides, phenols, aldehydes, ascorbic acids, and carboxylic acids. Metal salts can be reduced into metal nanoparticles by these components [30] and these NPs have been studied for applications in diagnostic systems, anti-microbial applications, and a variety of other biotechnological applications [31].

#### 2.2. Biosynthesis of tin oxide (SnO2) nanoparticles

In the last decade, there has been a significant increase in interest in biologically synthesizing SnO2 NPs because the process is more reliable, eco-friendly, cost-effective, low input-high yield, and simple procedures that do not harm the environment. For the green synthesis of SnO2 NPs, a variety of biological substrates such as plant extracts, bacteria, and natural biomolecules have been successfully used. Green synthesis is primarily driven by phytochemicals from various plants and enzymes from bacteria. During the synthesis, the active compounds found in green sources act as a reducing, capping, and stabilizing agent. SnO2 NPs can be synthesized by various methods, including physical, chemical, photochemical, biological, and hybrid approaches [32, 33] (figure 2). Physical synthesis approach includes spray pyrolysis [34], ultrasonication [35] sputtering [36] thermal decomposition [37] laser irradiation and ablation [38, 39] electrolysis [40] and chemical vaporization [41]. Nevertheless, there are pros and cons to the chemical synthesis of NPs. The chemical synthesis process is normally straightforward, can be conducted in ambient conditions and the resulting nanoparticles are homogeneous and have a narrow range of size [41]. Nanoparticles can be made chemically by reduction reactions, or by electrolysis of aqueous solutions that precipice metal ions from the aqueous solution. Chemical processes, on the other hand, have one of the most serious drawbacks: the generation of toxic by-products during the process. Such waste materials would inevitably accumulate during large-scale industrial activity,
resulting in bioaccumulation. This is dangerous to people’s health and the environment [42]. Thus, environmentally safe and non-hazardous synthesis approaches are favoured and used in the production of NPs. Biological synthesis methods that fulfill the above-mentioned condition have been studied extensively in metal oxide NPs production [34, 37]. Bioleaching and bioaccumulation fields have been studying the interaction and build-up of metal ions in micro- or micro-organisms in natural settings or due to industrialization; however, the approach of using living organisms for the biosynthesis of metallic NPs is a relatively new advance [43]. Nanoparticles have been synthesized using a range of micro-and macro-organisms, including bacteria, algae, fungi, algae, and plant biomass/derivatives (figure 3) [44]. Living organisms are increasingly being used in this area because they are less expensive and environmentally friendly compared to physicochemical methods, and also due to more successful application of synthesized NPs.
2.3. Plant-mediated synthesis of tin oxide (SnO₂) nanoparticles.

Plant-mediated synthesis has surpassed traditional physicochemical methods as the best synthesis platform because it is free of toxic chemicals and provides natural capping and reducing agents. Furthermore, it is simple and environmentally friendly, producing a quantity-enriched product free of impurities. This method eliminates the need for high-temperature, high-pressure, and expensive equipment. Extracts from plant leaves, bulbs, roots, stems, petals, or fruits have been used to prepare metal oxide NPs, which is considered a more effective and environmentally friendly process. Various plant derivatives have been used in the synthesis of NPs such as proteins, polysaccharides, and organic compounds such as citrates, flavonoids, carbonyls, amine, and amide [45]. The advantages of using plant-extract-mediated synthesis include [46, 47] a plentiful supply of resources; a non-hazardous, cost-effective, quicker, environmentally friendly, and direct process; stable NPs; and tunability of shape and size of NPs and production of NP with stable and uniform properties.

In addition, secondary metabolites also can be utilized for the bio-reduction of tin salt precursors. Various phytochemical compounds, reduce metal ions (Sn²⁺) to be Sn⁰. Further oxidation process converts Sn⁰ into SnO₂ NPs. Figure 4 depicts an example of the bioreduction mechanism of Sn²⁺ by gallic acid from bioreactor plants [48].

Numerous studies had examined the capacity of extracts of various plant species to synthesize SnO₂ NPs due to the benefits of this method and also the NPs biosynthesis process is simple (figure 5).

The abundance of plant extracts leads to low-cost chemicals, moreover, by using H₂O as a solvent in the extract preparation, the process is safer [49]. Thus, the interest in the green synthesis of various types of metal oxide NPs and semiconductors in bulk has grown tremendously. Plant extracts are being used as capping and reducing agents in the green synthesis of metal NPs. Plant extracts can be used as bio-templates to monitor the NPs’ morphology [50]. Variety of plant materials have been studied for green synthesis of SnO₂ NPs, such as Ficus Carica leaf [49], Persia Americana seed [51], fruit [52], Saraca indica flower [53], Psidium guajava leaf [54], Litsea cubeba fruit Cymophomandra betacea [55], Piper nigrum seed [56], Aspalathus linearis leaf [57], Clerodendrum inerme leaf [58], Piper beetle leaf [59], Parkia speciosa Hassk pods [60], Trigonella foenum-graecum seeds [61], Aspalathus linearis leaf, Camellia sinensis leaf, Punica granatum fruit, Saraca indica flower, etc.

2.4. Fungal mediated synthesis of tin oxide (SnO₂) nanoparticles

Fungi are eukaryotic non-phototrophic organisms that possess a cell wall. This includes yeast, molds, and mushrooms. While some fungi live off on decaying matters such as a dead tree, others parasitize on living matter. The cell wall of fungi is mainly made of glycoproteins, glucan, and chitin. Intracellular and extracellular reactions of fungi with aqueous metal ions can produce NPs [62]. Extracellular synthesis of nanoparticles by fungi is known to be quicker and also yields NPs bigger in size compared to the intracellular synthesis [63]. The nucleation of particles that happens inside the fungus could be the reason for the difference in NPs’ size [64]. Studies have reported syntheses of NPs from various genus fungi’s such as Aspergillus spp., Alternaria alternata,
2.5. Bacterial synthesis of tin oxide (SnO$_2$) nanoparticles

Microorganisms are capable of producing a wide range of distinct nanostructures. This has piqued the interest of scientists in using these microbes to synthesize nanostructures for a variety of applications. Bacteria and fungi can produce inorganic molecules through biologically mediated and induced synthesis. Nanostructures of desired geometries and compositions can be formed by controlling biological synthesis. Despite the precision of nanoparticle physicochemical synthesis, biological nanoparticle synthesis is still limited in terms of particle geometry controllability and process scalability. Additionally, biologically induced synthesis has enabled scientists to create inorganic nanoparticles from common metal precursors, while also providing a wide range of
NPs were found to significantly inhibit Candida albicans activity compared to that of Escherichia coli. This difference can be associated with the structural and compositional differences in the cell wall of the different classes of organisms. The main difference is that the cell wall made up of a peptidoglycan layer protects bacteria while the cell wall made up of chitin protects yeast [86]. As with many other nanoparticles, the behavior is linked to the ability of the nanoparticles to block cell growth through cell wall cleavage via the mechanism depicted in figure 7. Many factors influence the antibacterial activity of SnO₂ NPs, including particle size, the capping agent used during synthesis, and nanoparticle morphology. For example, 16 mg ml⁻¹ of SnO₂ NPs were found to significantly inhibit E. coli and C. albicans growth, with 22 mm and 14 mm zone of inhibition, respectively (figure 7). The minimum inhibitory concentration (MIC), and minimum bactericidal/fungicidal concentration (MBC/MFC) was of 0.5 mg ml⁻¹ and >1 mg ml⁻¹ respectively for E. coli, while the MIC and MFC were of 8 mg ml⁻¹ and >16 mg ml⁻¹ respectively for C. albicans [86]. The increase in the concentration of NPs increased the antimicrobial activity of the prepared NPs. The lower concentration of NPs needed to reach MIC and MBC for bacteria compared to that of fungi can be explained by enhanced binding of positively charged metal NPs to the negatively charged surface of the bacteria, conferring a higher bactericidal effect compared to fungicidal effect at the same concentration of NPs. In addition, Cobalt-doped SnO₂ (Co-doped SnO₂) NPs also showed broad-spectrum antibacterial properties, whereby it was effective against both Gram-negative and Gram-positive bacteria [87].

The potential mechanism of SnO₂ NPs’ antibacterial activity is shown in figure 8. Metal oxide NPs are able to break into the outer membrane and cell wall of bacteria, and then inactivate the cells. These properties enable...
SnO₂ nanoparticles to penetrate the cell membrane to elicit antibacterial activity\cite{88}. As the bactericidal activity increase in a nanoparticles dose-dependent manner, a higher concentration of SnO₂ nanoparticles can significantly increase its bactericidal effect. Metal oxide nanoparticles have been reported to act thru few mechanisms such as nanoparticle decomposition that cause reactive oxygen species production, and electrostatic interaction of NPs with the cell wall\cite{89}. Bactericidal activity of SnO₂ NPs through these mechanism causes a zone of inhibition (ZOI) around the area containing NPs and the size of ZOI is determined by the bactericidal potency of the SnO₂ NPs.

### 3.2. In vitro antioxidant activity

Estimation of free radical scavenging activity using 1, 1-diphenyl-2-picryl hydrazyl (DPPH) is commonly used to evaluate the antioxidant potential of NPs. DPPH, a deep purple colour stable free radical turns into yellow colour when scavenged or reduced. When the SnO₂ NPs are mixed into DPPH solution, the solution will slowly change from deep purple to yellow, demonstrating the scavenging potential or antioxidant activity of SnO₂. The odd electron or the free radical of the DPPH pair with a cation from an antioxidant compound thus reducing or scavenging the DPPH to form DPPH-H. The amount decolourisation is relative to the number of scavenged electrons. Figure 9\cite{90} shows an example of the scavenging capacity of SnO₂ nanoparticles. The antioxidant activity was directly proportional to the concentration of SnO₂ nanoparticles. The free radical scavenging activity is a surface reaction as the free radical’s reaction occurs on the surface of the antioxidant compound. Particle size, morphology, defects, and other variables influence the radical scavenging potential. More extensive studies on the influence of the aforementioned factors on the antioxidant potential of SnO₂ are necessary to better understand the antioxidant potential and mechanism of SnO₂ nanoparticles.

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Figure 7. Agar well diffusion assay showing the zone of inhibition at 16, 8, 4, 2, 1, 0.5 mg ml⁻¹ of SnO₂ NPs. Control: Sterile water. (A) E. coli; (B) C. albicans. Reprinted with permission from\cite{86}).

Figure 8. Schematic diagram showing the possible mechanism of antibacterial activity.
3.3. Anticancer activity
The previous study has explored the SnO₂ NPs’ size-dependent cytotoxic impact on HCT116 and A549 cancer cell lines. SnO₂ NPs in 3 different sizes were tested to check their effect on cancer cell line viability. The SnO₂ NPs samples of S1, S2, and S3 were in diameter of 8.85 ± 3.5 nm, 12.76 ± 3.9 nm, and 25.99 ± 8.2 nm respectively. The findings showed that NP size is an important factor in determining its cytotoxic effect where the smallest NPs sample had the highest cytotoxic effect on A549 and HCT116 cancer cell lines. Besides that, the cytotoxicity increased in a dose-dependent manner too where a higher concentration of SnO₂ NPs caused higher cell death. Thus, the cytotoxic activity of NPs can be increased by reducing particle size and increasing the concentration of SnO₂ NPs. The effect of the capping agent on the cytotoxicity of the cell lines was also investigated in this study. Under similar conditions, MTT assay was performed with *Piper nigrum* seeds extract, which mediated the green synthesis of SnO₂ NPs in this study, and it was found that the capping agent was not cytotoxic on carcinoma cell lines. The S1, S2, and S3 samples of SnO₂ NPs showed IC₅₀ (half maximal inhibitory concentration) values of 165, 174, and 208 μg l⁻¹ respectively against HCT116; 135, 157, and 187 μg l⁻¹ respectively against A549 carcinoma cell lines as shown in figure 10 [91].

Another study reported, the synthesis of SnO₂ NPs using sugar apple (*Annona squamosa*) peel extract mediated process, and the cytotoxicity of SnO₂ NPs against the hepatocellular carcinoma cell line (HepG2) [28]. These SnO₂ NPs were found to have an IC₅₀ value of 148 μg ml⁻¹. Besides that, a previous study also found that 24 h of exposure of HCT116 human cells with 1 μg ml⁻¹ super-paramagnetic iron oxide nanoparticles (SPIONPs) did not affect the viability of the cells [92]. These findings show that the SnO₂ NPs may have a different cytotoxic effect on different cell types and the cytotoxicity activity is NPs’ size-dose-dependent. It is inferred that the metal oxide NPs interact with cell-membrane proteins, penetrate cells, produce reactive oxygen species (ROS), and finally cause oxidative stress and cell damage due to ROS imbalance and the redox state of the cell [93–97]. The presence of pro-oxidant functional groups on the surface of NPs or NP-cell interactions determines the cytotoxicity of NPs [98–100] as it affects cellular signalling and the immune system. Mechanism of cytotoxic effect on cancer cells by SnO₂ NPs as shown in figure 11.

4. Conclusion
Tin oxide nanoparticles have gotten a lot of attention because of their numerous applications. It has antibacterial, antifungal, antiviral, anticancer, antioxidant, drug delivery, and several other biomedical applications. Tin oxide nanoparticles have been created using a variety of methods, including chemical, physical, and biological methods. Physical and chemical methods are also costly and include the use of a dangerous chemical that may have a harmful impact. The biological approach, on the other hand, is an environmentally sustainable, cost-effective, efficient, safe, low-energy-consuming, and simple method. This review summarized the synthesis of tin oxide NPs using various biological methods, as well as their properties, mechanism of action, and various biomedical applications. More research should be done on potential methods of reducing SnO₂ NPs’ toxicity while preserving and enhancing their biological activities to improve the biomedical applications of SnO₂ NPs.
Figure 10. Cytotoxic effect of S1, S2, and S3 samples on (a) HCT116 (b) A549 cancer cell lines. NPs sizes of samples S1, S2, and S3 are 8.85 ± 3.5 nm, 12.76 ± 3.9 nm, and 25.99 ± 8.2 nm respectively. CDDP: Cis-diamminedichloridoplatinum (II). A negative control is cell culture without any NPs or additional compounds. Reprinted with permission from [91].

Figure 11. Mechanism of cytotoxic effect on SnO\textsubscript{2} NPs.
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Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

Conflict of interest

The authors declare no conflict of interest with this work.

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