Review Article

Greenly Synthesized Manganese Oxide Nanoparticles (MnO NPs) In Tumor Therapy: A Narrative Review

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ABSTRACT

One of the most destructive diseases of the twenty-first century is cancer, which has given rise to significant concerns among medical professionals and academics alike. In order to achieve victory in the fight against cancer, a multitude of therapeutic modalities are currently being investigated. Nanotechnology has emerged as a significant field of scientific inquiry, with potential applications across a range of disciplines. It draws upon insights from a range of disciplines, including chemistry, physics, materials science, engineering, biology, and health sciences. In recent years, there has been a notable surge in the application of nanotechnology in the field of medicine, with the aim of preventing and treating diseases within the human body. Over the past two decades, manganese oxide nanomaterials (MnONs) and their derivatives have garnered increasing interest for applications in bioimaging, biosensing, drug/gene delivery, and tumor therapy. This is due to the tunable structures/morphologies, unique physical/chemical properties, and excellent biosecurity of these materials. The green synthesis of MnNPs using raw materials, vegetables and fruits, plant extracts, microorganisms, and fungi offers several advantages, including non-toxicity, environmental friendliness, cleanliness, and cost-effectiveness. Given the variety of mechanisms through which they act, green-produced MnNPs represent a promising source of new anti-inflammatory and antioxidant compounds. MnNPs have been demonstrated to exert anti-proliferative activity against a range of cancer cells, including those of the colon, liver, cervix, breast, melanoma, and prostate, by activating apoptotic signal transduction pathways or inhibiting angiogenic signaling. In the context of cancer treatment, research is being conducted into the potential of metal nanotherapy, including the use of MnO NPs. The enhanced tissue penetration and retention properties of MnO facilitate its function as a drug carrier. MnONPs have been proposed to exhibit enzyme-like activities, including peroxidase, catalase, oxidase, glutathione peroxidase, and superoxide dismutase. The biocompatibility obtained through green synthesis indicates the potential for its use not only in specific cancer conditions but also in other types of cancer, without the risk of toxicity associated with these compounds. It is conceivable that these therapeutic strategies may prove beneficial not only in the aforementioned cases of cancer but also in other instances of proliferative disorders. The low risk of toxicity associated with these compounds, as evidenced by the biocompatibility obtained through green synthesis, suggests their potential use in a range of biomedical applications.

Keywords: Green Synthesis, Cancer, Manganese oxide nanoparticles, Nanobiotechnology.

1. Context

Cancer is a leading cause of mortality worldwide (1). Carcinogenesis is a multistep process whereby alterations to tissue architecture occur, preceding the formation of preneoplastic nodules and the subsequent appearance of cancerous cells (2). Cancers emerge from the transformation of a single cell, resulting in the disruption of the normal regulatory pathways that govern cellular behavior (3). Over the past two decades, there has been a notable advancement in our understanding of the complex multifactorial mechanisms that ultimately lead to the development of cancer. It is widely accepted that between 80 and 90 percent of human cancers may be attributable to environmental and lifestyle factors, including alcohol consumption, tobacco use, and dietary habits (5). By 2040, the global cancer burden is projected to increase to 28.4 million cancer patients, representing a 47% increase from 2020. Consequently, the current state of cancer control and therapy is highly problematic. A variety of conventional treatment modalities are available for the management and treatment of cancer. Secondary malignancies, as well as hepatotoxicity, nephrotoxicity, cardiotoxicity, neurotoxicity, and ototoxicity, are among the most commonly observed adverse effects of anti-cancer treatments (8). Nanotechnology has the potential to significantly impact the diagnosis and treatment of cancer. Furthermore, the application of nanotechnology in cancer treatment enables the eradication of malignant neoplasms with minimal collateral damage to surrounding healthy tissues and organs (9). Nanotechnology draws upon a diverse range of disciplines, including chemistry, physics, materials science, engineering, biology, and health sciences (10). In recent years, there has been a rapid increase in the number of applications of nanotechnology in the field of medicine, with the aim of both preventing and treating diseases and disorders affecting the human body (11). A chain of nanoparticles (NPs) has been developed and is now entering the clinical application stage. These include MnNPs, which show good biocompatibility and low side effects because Mn is a main constructing of cells and a cofactor for numerous metabolic enzymes (12). Over the past two decades, there has been a growing interest in MnONs and their derivatives for use in biosensing, bioimaging, gene/drug delivery, and tumor therapy. This is due to their tunable morphologies/structures, unique chemical/physical properties, and perfect biosecurity (13).

2. Evidence Acquisition

An understanding of the applications of nanotechnology in the treatment of disease and the mechanisms of action of active nanoparticles is essential for the completion of this review, which aims to highlight the significance of MnO NPs as a cancer treatment and for other disorders.

3. Methods

The data were collected through a comprehensive search of the following databases: Science Direct, Google Scholar, PubMed, Scopus, Springer, and the National Center for Biotechnology Information (NCBI). The following keywords were used as search terms: "tumors," "manganese oxide nanoparticles," "green synthesis of nanoparticles," "anti-inflammatory power of nanoparticles," "cancer and oxidative stress," and "antibacterial activity of nanoparticles."

4. General Method of Synthesis for Metal Nanoparticles

Nanoparticle formation can be achieved through a variety of physical, chemical, and biological techniques (14). The physical method has numerous disadvantages, including high cost, low productivity, high energy consumption, exposure to radiation, generation of large amounts of waste, temperature and pressure, reduced stability, difficulty in controlling the size and shape of the nanoparticles, alteration of the surface chemistry and physicochemical properties of the nanoparticles (15). Moreover, nanoscale metals are predominantly synthesized via chemical procedures that have unintended consequences, including significant energy consumption, environmental contamination, and potential health concerns (16). The green synthesis of nanoparticles, which employs plant extracts as an alternative to industrial chemical factors for the reduction of metal ions, has been developed with the objective of enhancing environmental safety and human health, reducing costs, and minimizing pollution (17). The phytochemicals present in medicinal plants have been proposed as a cost-effective, biocompatible, and renewable source of materials that can be employed in the green synthesis of nanoparticles (18).

5. Green Synthesis of MnO NPs

Nature functions as a vast "bio-laboratory," comprising a multitude of organisms, including algae, plants, yeast, and fungi, which are composed of biomolecules. These naturally occurring biomolecules have been identified as playing an active role in the generation of NPs with distinct sizes and shapes, thereby acting as a driving force for the design of greener, safer, and more environmentally benign protocols for the synthesis of NPs (19). It is proposed that phytochemicals found in medicinal plants can be used as cost-effective, biocompatible, and renewable sources for the synthesis of nanoparticles (NPs) in a green manner (18). The green synthesis of NPs based on plants is now regarded as the gold standard among these green biological approaches due to its ease of use and the diversity of plants (20). The green synthesis of Mn-NPs can be conducted at room temperature and normal pressure, offering several advantages. These include the absence of toxicity, environmental friendliness, cleanliness, and cost-effectiveness when utilizing raw materials, fruits and vegetables, plant extracts, microorganisms, and fungi (12). The mechanism of green synthesis of MnO NPs is illustrated in Figure 1.

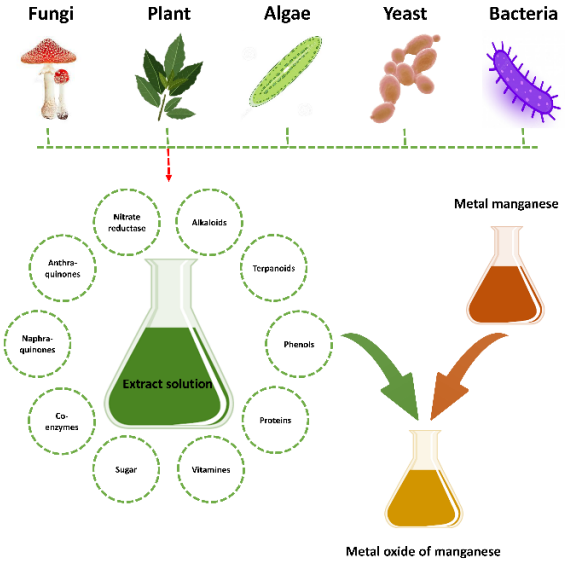

Figure 1. Schematic demonstration of green synthesis mechanism of MnO NPs.

6. Phytosynthesis of MnO NPs Using Plant Extract

The green synthesis of NPs based on plants is currently regarded as the gold standard among green biological approaches due to its ease of use and the diversity of plants that can be employed (20). Furthermore, a variety of plant components, including leaves, fruits, and stems, as well as their extracts, have been employed in the synthesis of metal nanoparticles (21). It has been demonstrated that phytochemical components found in plants, such as terpenoids, alkaloids, polyphenols, and flavonoids, cause reduction of metal ions and eventually form metal NPs (22). The synthesis of MnO_2 NPs was visually observed by demonstrating a color shift produced by the addition of a precursor to the extraction of leaf matter (23). The quality, stability, quantity, and yield rate of the NPs are influenced by a variety of parameters, including pH, temperature, contact time, metal salt concentration, and the phytochemical profile of the plant leaf particles (24). The pathway for the biosynthesis of MnO NPs using plant extract has been illustrated in Figure 2, and the biosynthesis of MnO NPs by various plants has been presented in Table 1.

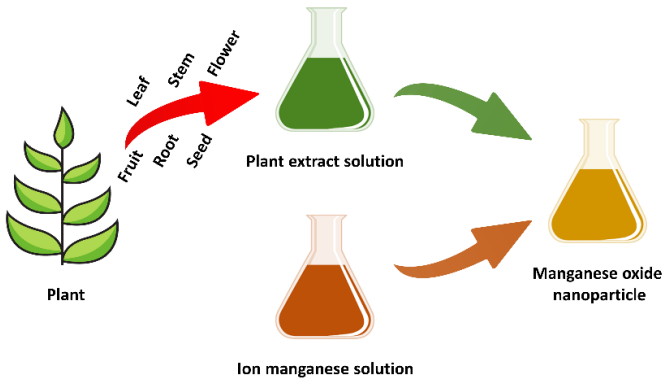

Figure 2. Schematic representation of biosynthesis of MnO NPs using plant extract.

7. Analytical Characterization Methods of MnO NP

To guarantee the reproducibility of their production, biological activity, and safety, it is imperative that these NPs undergo comprehensive and precise characterization. A variety of physicochemical techniques are employed for this purpose, including ultraviolet-visible spectroscopy (UV-Vis), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and X-ray diffraction (XRD). These techniques are used to accurately characterize the synthesized NPs (Figure 3) (20). Ultraviolet-visible spectroscopy (UV-Vis) is a widely utilized approach for characterizing nanoparticles (NPs) due to its capacity to provide precise analysis of characteristics such as the maximum absorption wavelength (λmax) and the maximum absorption intensity (Absmax). It is postulated that MnO NPs exhibit an absorption peak within the range of 350–410 nm (26). As reported by Saod et al., the MnO NPs solution displays a peak at 410 nm in the visible region of the UV-Vis spectrum (26). Fourier transform infrared spectroscopy (FT-IR) represents a significant analytical technique employed to ascertain the presence and characteristics of various functional groups in metal oxide nanoparticles. A strong absorption band at 538 cm-1 was identified by Mylarappa et al. in their experiment, which may be associated with the Mn-O stretching mode in the infrared domain (27). The morphology of the MnO NPs, including their size and shape, was characterized using scanning electron microscopy (26). In regard to the findings of Anar et al., scanning electron microscopy (SEM) corroborated the nanoscale dimensions of MnO NPs and revealed their near-spherical morphology (28). X-ray diffraction (XRD) is a valuable technique for determining the average crystallite size, phase composition, and crystal structure of nanomaterials (29). In the investigation conducted by Anar et al., X-ray diffraction analysis revealed the dimensions (39 nm) and crystalline nature of the synthesized manganese dioxide nanoparticles (MnO NPs).

8. Antioxidant Activity of MnO NPs

Oxidative stress is defined as "an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage" (30). Oxidative stress is a primary contributor to physiological and metabolic alterations, as well as the development of various pathological conditions within the body (31). MnO2 NPs have the capacity to consume surplus H2O2 in situ and convert it to O2, which is the inverse of the aberrant ROS generation process (32). The experiment conducted by Kuthati et al. demonstrated that the synthesized MONPs exhibited biocompatibility and effective antioxidant activity against DPPH free radical scavenging (33). The antioxidant potential of MnO_2 NPs was evaluated by Faisal et al. by exposing DPPH-free radicals to test samples at varying doses (23). The antioxidant properties of a given substance can be rapidly and efficiently evaluated through the use of the DPPH assay. Antioxidants transfer a hydrogen atom to the

Table 1. Biosynthesis of MnO NPs by different plants

Sl. No.	Plants/ plant extract	Part used	Precursor salt	Size of NPs (in nm)	Shape/structure/morphology	Characterization techniques used	Reference
01	Green tea (*Camellia sinensis*)	Leaves	Manganese sulfate **($MnSO_4$)**	Around 18	-	UV-Vis, XRD, FTIR and SEM	**(1)**
02	*Fagonia cretica*	Leaves	Manganese acetate	15.5 ± 0.85	Spherical with homogenous dispersity	UV-Vis, XRD, SEM, EDX, and FTIR	**(2)**
03	Banana Peel *(Musa paradiasca)*	Peel	Potassium permanganate **($KMnO_4$)**	~ 1	Crystalline	UV-vis, EDX, XRD and FTIR	**(3)**
04	Cabbage (*Brassica oleraceae*)	Leaves	Potassium permanganate **($KMnO_4$)**	10.70	Spherical and ellipsoidal	Visual observation, UV-vis, XRD, FT-IR, SEM and EDX	**(4)**
05	*Viola betonicifolia*	Leaves	Manganese acetate	10.5 ± 0.85	Spherical with homogeneous dispersity	XRD, EDX, TEM and Zetasizer Dynamic Light Scattering	**(5)**
06	*Aloe vera*	Aerial parts	Potassium permanganate **($KMnO_4$)**	-	Agglomerated sphere-shaped	FTIR, XRD and FESEM	**(6)**
07	*Matricaria chamomilla* L.	Flower	-	16.5	Irregularly spherical shaped	UV-Vis, FTIR, XRD, TEM and SEM	**(7)**
08	*Gardenia resinifera*	Leaves	Manganese acetate	20 - 30	Spherical in shape	UV–Vis, PSA, FTIR, XRD, SEM-EDAX, and HR-TEM	**(8)**

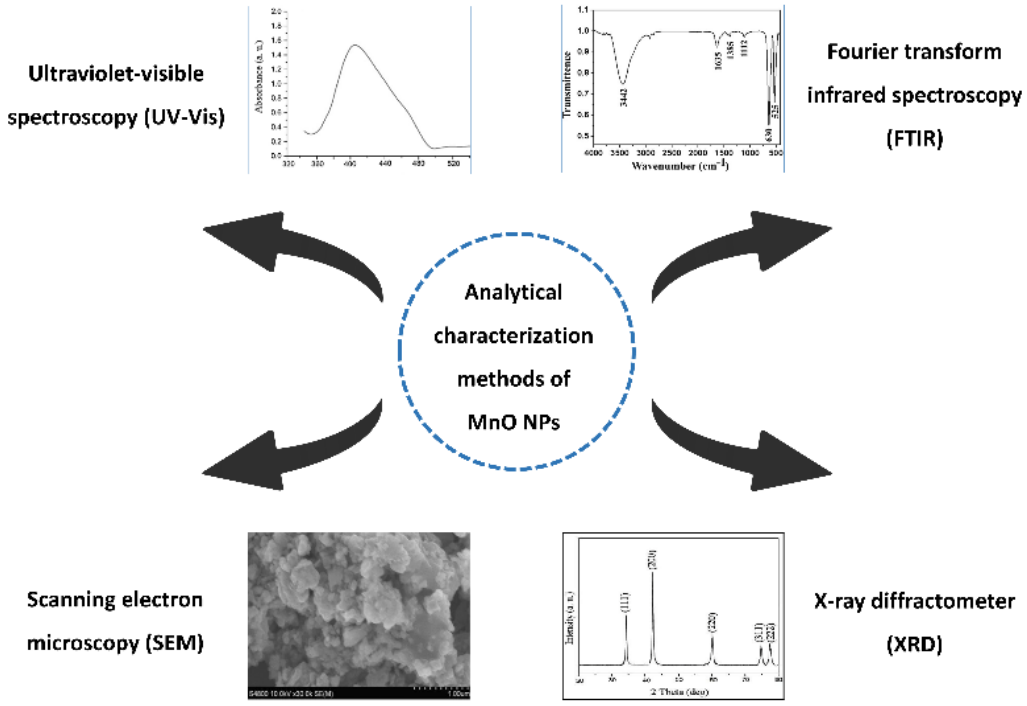

Figure 3. Analytical characterization methods of MnO NPs.

equivalent hydrazine, thereby reducing the odd electron of the nitrogen atom in DPPH (34).

9. Anti-Inflammatory Activity of MnO NPs

It is a fundamental tenet of the disease process that inflammation plays an indispensable role. Some varieties of NPs have been demonstrated to possess anti-inflammatory properties (35). Furthermore, MnO_2 particles have the capacity to regulate the level of inflammation by influencing the expression of genes that are responsible for the production of cytokines. During this process, MnO2 undergoes a gradual breakdown, resulting in the production of Mn2+, which is excreted with bodily fluids and facilitates the restoration of the body's internal environment to its optimal state (36). Moreover, immune cells may play a role in the delivery of NPs to inflammatory sites (37). In a study conducted by Kumar et al., it was observed that MnO2 NPs exhibited a protective effect on cartilage against inflammation-induced oxidative stress (38). Additionally, Li et al. demonstrated that the combination of MnO2 and FTY could have a synergistic neuroprotective effect on ischemic stroke patients by reducing oxidative stress and regulating the inflammatory response (32).

10. Anti-Bacterial Activity of MnO NPs

Due to their diminutive size, MnO_2 NPs exhibit antibacterial activity, as they are capable of rapidly penetrating bacterial cells and causing their cell membranes to rupture (39). The study conducted by Wahran and colleagues demonstrated that the extensive surface area and nanoscale dimensions of MnO NPs confer a synergistic effect when combined with antibiotics. Consequently, the antibiotic materials are more readily incorporated and delivered within cells, distributed into transfer channels and cell walls, and released metabolites with greater ease (26). The secondary metabolites in Mn NPs, which were synthesized via a green method, have anti-diabetic, anti-cancer, anti-inflammatory, anti-plasmodium, anti-fungal, and anti-bacterial properties. They can also combat a species of bacterial strains (40). MnO2 NPs demonstrated a markedly elevated antibacterial capacity against both gram-negative and gram-positive bacteria (41). A previous study demonstrated that MnO2 NPs have been shown to exert antibacterial effects against a range of bacterial species, including S. aureus, E. coli, K. pneumonia, B. subtilis, and P. aeruginosa, with varying inhibition zone diameters (42). Additionally, Lu et al. demonstrated that the antibacterial activity of MnO2 NPs synthesized using the leaf extract of Viola betonicifolia exhibited a killing efficiency exceeding 80% against both K. pneumoniae and S. aureus (22). The different zones of inhibition (ZOI) for various bacterial strains are presented in Table 2.

11. Discussion

By leveraging the intrinsic characteristics of MnO NPs, which are enveloped by a layer of active molecules derived from a biological compound extract of plant origin, including alkaloids, polyphenols, flavonoids, and terpenoids. In addition to the aforementioned biological activities, including antioxidant, anti-inflammatory, and anti-bacterial activity, there are numerous proposals for therapeutic strategies involving MnO NPs in the treatment of cancer. These strategies may be based on either the treatment of the underlying causes of cancer or the direct elimination of the disease. It is estimated that approximately 20% of all cancers in humans are caused by infectious agents (43). In the twenty-first century, researchers began to postulate that: It has been postulated that bacterial infections that generate chronic inflammation may be a causal factor in carcinogenesis. Similarly, it has been suggested that bacterial toxins and secondary metabolites produced by chronic bacterial infection may also play a role in carcinogenesis (44). Some varieties of NPs have been demonstrated to possess anti-inflammatory properties (35). Both intrinsic and extrinsic pathways are associated with the relationship between inflammation and cancer. These pathways activate transcription factors, including HIF-1, STAT-3, and NF-κB, which in turn cause oncogenic factors to accumulate in the tumor and surrounding tissue (45). Additionally, Li et al. demonstrated that the combination of MnO2 + FTY exerts a synergistic neuroprotective effect in ischemic stroke patients by reducing oxidative stress and regulating the inflammatory response (32). Antioxidants facilitate the transfer of a hydrogen atom to the equivalent hydrazine, which subsequently reduces the anomalous electron of the nitrogen atom in DPPH (34). In particular, oxidative stress is well documented to cause damage to DNA molecules, alter signaling pathways, and regulate the development of a number of malignancies, including brain, ovarian, lung, liver, colon, breast, and prostate cancers (46). The development of cancer is the result of a series of genetic alterations that impair the normal control of cell growth and survival. Moreover, immune cells may play a role in the delivery of NPs to inflammatory sites (37). Oxidative stress is a primary contributor to physiological and metabolic alterations, as well as the development of various pathological conditions within the body (31). Firstly, as transition metal oxides, all MONs demonstrate acid-responsive behaviours. Secondly, a range of Mn oxides have been observed to exhibit catalase (CAT) activity, which is the process of catalyzing the conversion of H+/H2O2 into oxygen (O2) and Mn2+ (13). The hypothesis proposed by Ding et al. that MnO_2 catalyzes the decomposition of H_2O_2 into oxygen and water was confirmed by Zhang et al. This process can relieve oxidative stress reactions and provide an oxygen equivalent for cells. Moreover, nanoparticles have emerged as a potential anti-inflammatory agent in recent decades (47). Moreover, MnO_2 particles have the capacity to regulate the level of inflammation by influencing the expression of genes that are responsible for the production of cytokines. During this process, MnO_2 undergoes a gradual breakdown, resulting in the excretion of Mn^{2+} with bodily fluids and the restoration of the body's internal environment

Table 2. Different zones of inhibition (ZOI) for various bacterial strains.

Sl. No.	Bacterial strain	Gram nature	Zone of inhibition (ZOI) (in mm)	Route of synthesis	Size of NPs (in nm)	Reference
01	*Escherichia coli*	Gram (-)	12	Green synthesis using plant	20 - 30	**(1)**
	Klebsiella pneumoniae	Gram (-)	14			
	Pseudomonas aeruginosa	Gram (-)	18			
02	*Pseudomonas aeruginosa*	Gram (-)	18 ± 1.71	Green synthesis using algae	115.8	**(9)**
	Micrococcus luteus	Gram (+)	25 ± 1.53			
	Staphylococcus aureus	Gram (+)	18 ± 1.42			
	Escherichia coli	Gram (-)	18 ± 1.16			
03	*Staphylococcus aureus*	Gram (+)	*10 (1% Mn NPs) *13 (10% Mn NPs)	Green synthesis using plant	10.70	**(4)**
	Escherichia coli	Gram (-)	*12 (1% Mn NPs) *12 (10% Mn NPs)			
	Salmonella typhi	Gram (-)	*10 (1% Mn NPs) *10 (10% Mn NPs)			
04	*Escherichia coli*	Gram (-)	22	Green synthesis using plant	-	**(6)**
	Streptococcus mutans	Gram (+)	18			
	Staphylococcus aureus	Gram (+)	16			
05	*Escherichia coli*	Gram (-)	10	Precipitation method	35 - 40	**(10)**
	Staphylococcus aureus	Gram (+)	19			
	Bacillus subtilis	Gram (+)	18			
	Pseudomonas aeruginosa	Gram (-)	12			
06	*Acidovorax oryzae*	Gram (-)	23 (16 mg/ml)	Green synthesis using plant	16.5	**(7)**
07	*Staphylococcus aureus*	Gram (+)	*15.00 ± 1.15 (10 ug/ml) *19.67 ± 2.08 (20 ug/ml) *24.00 ± 1.00 (30 ug/ml)	Green synthesis using plant	20 - 30	**(8)**
	Pseudomonas aeruginosa	Gram (-)	*10.33 ± 0.58 (10 ug/ml) *15.33 ± 1.15 (20 ug/ml) *28.00 ± 1.00 (30 ug/ml)			
	Serratia marcescens	Gram (-)	*15.67 ± 1.00 (10 ug/ml) *25.00 ± 1.15 (20 ug/ml) *29.33 ± 0.58 (30 ug/ml)			
08	*Klebsiella pneumonia*	Gram (-)	*23 (250 ug/ml) *27 (500 ug/ml) *28 (750 ug/ml) *30 (1000 ug/ml)	Co-precipitation method	40.5 - 70	**(11)**
	Pseudomonas aeruginosa	Gram (-)	*20 (250 ug/ml) *23 (500 ug/ml) *25 (750 ug/ml) *27 (1000 ug/ml)			
	Escherichia coli	Gram (-)	*16 (250 ug/ml) *18 (500 ug/ml) *19 (750 ug/ml) *21 (1000 ug/ml)			
	Staphylococcus aureus	Gram (+)	*23 (250 ug/ml) *25 (500 ug/ml) *28 (750 ug/ml) *30 (1000 ug/ml)			
	Bacillus subtilis	Gram (+)	*22 (250 ug/ml) *23 (500 ug/ml) *26 (750 ug/ml) *30 (1000 ug/ml)			

to its optimal state (36). Moreover, immune cells may play a role in the delivery of NPs to inflammatory sites (37). The development of antimicrobial agents using metallic nanoparticles has been demonstrated to offer an alternative to traditional antibiotics, with encouraging results that have significant clinical implications (48). A substantial body of research has highlighted the antibacterial potential of metal oxide NPs, which is attributed to their nanoscale dimensions, enabling penetration into bacterial cells and subsequent disruption or poisoning of their internal structures (26). The observed increase in antibacterial activity may be attributed to the robust interaction between bacteria and NPs, which induces toxicity in bacteria and kills sick cells (40). The literature indicates that metal or its oxide particles of 100 nm in size can readily enter bacterial cell membranes with larger pore sizes and interact with bacterial cells, resulting in significant alterations to physiological processes and damage to bacterial cells. Furthermore, the death of bacterial cells is attributed to an electrostatic interaction between the electropositive nature of MnNPs and the electronegative character of the cell membrane surface (49). The antimicrobial activity of MnO2 NPs is primarily attributable to the generation of highly reactive species, including membrane-associated OH-, H2O2, and O22+. H_2O_2 is capable of penetrating the cell. The generation of OH- and O22+ species results in damage to the cell membrane and cell wall from the exterior (50). Hano and Abbasi (20) report that MnO NPs made from an extract of the leaves of Abutilon indicum exhibited robust antibacterial activity against both Gram-positive and Gram-negative bacteria.

Conclusion

MnO NPs produced using environmentally friendly substances, including plant, microbial, fungal, and algal extracts, have a variety of applications as antioxidant and anti-inflammatory agents. Furthermore, this work provides new insights into the cytotoxic effects of MnO NPs on cancer cells. Research is being conducted on the potential of metal nano-therapies, such as MnO NPs, for the treatment of various cancers, including breast and prostate cancer. It is therefore possible that these therapeutic strategies may prove beneficial not only in the treatment of these specific cancers but also in the management of other proliferative disorders. Given the low risk of toxicity associated with these compounds, the biocompatibility achieved through green synthesis indicates the potential for their use in a range of biomedical applications.

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Authors' Contribution

Conceptualization and supervision: S.D.
Writing original draft: I.B.
Preparing analysis of the laboratory parameters: SD., I.B.
Writing review and editing I.B., S.D., J.N.
Conceptualization and supervision: S.D. and J.N.
All authors have read and agreed to publish version of the manuscript.

Ethics

We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors declare no competing interests.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

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