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REVIEW PAPER

A comprehensive review of manganese dioxide nanoparticles and strategy to overcome toxicity

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ABSTRACT

Chemical and biological methods are available for synthesizing manganese dioxide nanoparticles, with the characteristic electrochemical features tunable through natural product extract. MnO_2 nanoparticles reduce the prevalence of organism resistance to drugs. Manganese dioxide nanoparticles are effective against various bacteria, including Staphylococcus aureus and E. coli. Manganese dioxide nanoparticles can potentially be used in the treatment of osteoarthritis and the preservation of cartilage. They are also promising ROS scavengers and may be used to fabricate antioxidant polymer microreactors. In cancer treatment, the MnO_2 nanoparticles inhibit ATP production by cancer cells. In magnetic resonance imaging, the nanoparticles improve the signal-to-noise ratio and selectivity. Based on this background information, MnO_2 nanoparticles today find use in photodynamic, chemodynamic, and immune therapy and diagnostics, where the oxygen produced by MnO_2 nanoparticles is said to improve the therapeutic efficiency. Hybrid nanoparticles of gold nanorods and MnO_2 nanoparticles enhance the performance in hormone-, pH-, and NIR- responsiveness. Other applications include glucose oxidase activity, photothermal conversion, and enhanced antitumor immunity. On the other hand, the nanoparticles can cause spermatogenesis failure, oxidative stress, active oxygen, and sperm motility reduction. As surface functionalization can improve the overall functional properties of the nanoparticles, polymer coating on MnO_2 nanoparticles brings about new and improved properties. For instance, the layer of biopolymers such as chitosan enhances the magnetic resonance images' quality and opens up the potential for attaching drugs and targeting moieties.

Keywords: *Biopolymers, Biomedical applications, Metal Nanoparticle, Mutagenicity*

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INTRODUCTION

Nanotechnology is a fascinating new research field with various applications in the medical field [1]. The fields of nanotechnology and nanoparticle (NP) research are seeing rapid expansion. The unique properties of nanoparticles make it possible to create products with new attributes and possibilities for human endeavors, which has significant repercussions on the economy [2]. Manganese dioxide (MnO_2) nanoparticles have caught the attention of material scientists in recent years owing to the extensive number of applications. The band gap of manganese dioxide ranges between 3.3 and 3.8 eV. It is a transition metal oxide that is found in P-type semiconducting semiconductors. Due to the fact that MnO_2 NPs are simple to manufacture and possess a high degree of stability, they have found use in a wide variety of settings [3]. MnO_2 nanoparticles are used for many applications [4] and because of their importance in both technology and electricity, MnO_2 is well recognized as a semiconductor. As a result of the catalysis and ion exchange reaction capabilities that manganese dioxide possesses, these compounds are used as cathode materials in secondary batteries and magnetic resonance imaging. There is a diverse range of oxidation states, structural shapes, and chemical forms that may be found in MnO_2 [5]. These nanoparticles can be manufactured by simple techniques and in addition, it uses cost-effective wet chemical techniques such as hydrothermal sol-gel, emulsion, conventional coprecipitation, and it

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has a broad range of applications in the industrial sector [6]. Because of their chemical and physical interactions, manganese oxide nanoparticles are commonly employed for dye removal. This is a common use for these nanoparticles [7]. Apart from this MnO_2 has a wide range of potential uses in the field of biomedicine. The most common use of manganese dioxide is in theranostics of cancer, namely in photodynamic therapy, chemodynamic therapy, immunotherapy, and other related fields. Manganese dioxide nanoparticles are an excellent option for photo disruption therapy due to their chemical and physical properties. It is interesting to note that MnO_2 NPs are largely used as vehicles for the targeted delivery of drugs to the microenvironment of tumors [8]. It has been shown that MnO_2 may cause the release of Mn^{2+} ions in the microenvironment of a tumor. These free Mn^{2+} ions can potentially be used in magnetic resonance imaging for the early detection of cancer in both *in vitro* and *in vivo* settings. In spite of the fact that they are not oriented in any particular way, MnO_2 nanosheets have the potential to serve as nanocarriers in the diagnostics and therapeutics fields. For this reason, the nanosheets must be able to combine with other chemicals in order to achieve accurate bioimaging [9]. Because of its capacity to catalyze the release of oxygen molecules from hydrogen peroxide, it may also be used as a novel radio sensitizer. This allows it to regulate the hypoxic condition of tumors and enhances the effectiveness of radiation treatment. In the treatment of lung cancer, nanoparticles of manganese dioxide are useful in lowering glutathione levels [10]. The use of albumin-based MnO_2 NPs demonstrated therapeutic importance in xenograft tumor models of murine and human breast cancers by altering tumor hypoxia and promoting radiation efficacy [11]. In addition to this, it plays a significant part in bioanalysis, cell imaging, and the administration of drugs, and it has a variety of distinctive properties that make the distribution of drugs more straightforward [12]. The nanoparticles of manganese dioxide have the ability to shield cartilage from the oxidative damage that is brought on by inflammation. These have the potential to be used in the treatment of osteoarthritis as well as preservation of cartilage. According to recently published research, manganese dioxide nanoparticles have been discovered to have a great deal of potential in the field of gene therapy and nuclear magnetic imaging [13]. Manganese dioxide nanoparticles are attractive for application as reactive oxygen species (ROS) scavengers due to their multienzyme nature, which mimics the activities of catalase and superoxide dismutase concurrently. Therefore, manganese dioxide nanoparticles are considered to be among the most promising groups of ROS scavengers. Manganese dioxide is an alternative inorganic therapeutic option for the treatment of oxidative stress since it degrades these nanoparticles into Mn^{2+} and water rather than letting them accumulate in the body. By using manganese dioxide nanoparticles instead of the conventional encapsulation of antioxidant enzymes, a new approach has been developed for constructing antioxidant polymer microreactors that are both more robust and durable than their organic predecessor [14].

Fabrication of manganese dioxide nanoparticles

The form, size, polydispersity, and surface chemistry of nanoparticles all are important in ruling the property of the particle. For nanoparticles to be functional in chemical sensing, medical diagnostics, catalysis, thermoelectrics, photovoltaics, or pharmaceutics, they must first be manufactured with features that can be carefully controlled. Since nanoparticle synthesis often includes a variety of chemicals and is carried out under various experimental circumstances that are interdependent, this is a procedure that is resource-intensive, labor-intensive, and time-consuming [15]. The synthesis of nanoparticles can be accomplished through a wide variety of techniques [16] and in connection with this, MnO_2 nanostructures may also be synthesized using similar procedures. Compared with other inorganic nanocarriers, MnO_2 nanoparticles can operate as both a carrier and a functional material when it comes to the delivery of medicinal drugs [17]. A typical two-step synthesis was used to create MnO_2 nanostructures on the surface of carbon nanosheets that were cross-linked with biomass [18]. Even it is possible to create 3D hierarchical MnO_2 nanostructures using a chemical technique, and it is not necessary to use surfactants and the shape can be tuned according to temperature [19]. It is also possible to create manganese dioxide (MnO_2) nanosheets using the hydrothermal process over a conductive nickel substrate. Microscopic studies reveal that these thin films exhibit a permeable framework

made of MnO_2 nanosheets that are interlinked. It was reported in the literature that thin-film electrodes based on MnO_2 nanosheets have good capacitance, good rate attributes, and stability. It is possible to generate three-dimensional, highly porous nickel foam with manganese oxide hybrid nanosheet arrays using a hydrothermal co-deposition method that only requires one step. The hydrophobic and ultrathin character of these hybrid nanosheet arrays, together with the synergistic effects of nickel and MnO_2, contribute to the extremely high specific capacitance of 2628 F possessed by the material as a whole. Because of this, manganese oxide nanoparticles are incredibly used in superconductors [20]. In addition to these methods, have also been applied in synthesizing manganese dioxide nanostructures [21]. As mentioned in (Table 1) there are many other precursor components and techniques to fabricate manganese dioxide nanoparticles with different properties based on application.

Electrochemical synthesis

Electrochemical synthesis is a highly effective method for producing nanostructured energy materials [22]. The nanomaterials have all seen significant advancements over the last several decades, which has allowed for a greater understanding of the links between nanostructure, property, and performance [23]. Compounds of α and γ- MnO_2 are excellent possibilities because of their one-dimensional tunnel architectures. According to (reaction), the production of manganese dioxide takes place at the electrode as follows:

$$Mn^{2+} + 2H_2O \rightarrow MnO_2 + 4H^+ + 2e^-$$

Reaction 1: Production of manganese dioxide

It is possible to create manganese oxide nanoparticles with size-adjustable morphologies using a simple electrochemical approach. This may be accomplished by altering the acidity of the potassium permanganate ($KMnO_4$) solution. Electrolysis of $KMnO_4$ in acid results in the production of nanorods of alpha- MnO_2, whereas electrolysis of $KMnO_4$ in base results in the production of nanoflakes of amorphous MnO_2 [24]. A technique that utilizes polymer assistance in chemical reduction can be used to produce electrochemically active MnO_2/graphene oxide composites. On the surface of the graphene oxide nanosheets, MnO_2 nanoparticles were deposited in a manner that ensured their uniform distribution. It has been shown that the synthetic MnO_2 composites may function as a novel kind of alkaline air electrode with remarkable electrocatalytic activity for reducing oxygen [25]. Nanowires of manganese oxide have also been generated electrochemically utilizing nickel as a substrate by a solution of manganese acetate at ambient temperature without needing any template or catalyst. After annealing at 300 degrees Celsius, the produced electrode with high porosity comprises nanowires ranging from 8 to 12 nm in width. These nanowires made of manganese oxide demonstrate a low level of crystallization [26]. Without making use of any kind of template or surfactant, MnO_2 nano worms may be manufactured by a process that is described as being simple, inexpensive, and electrochemical, followed by a heat-treatment step [27].

Green synthesis

In modern times, nanoparticles may be

Table 1. Fabrication of manganese dioxide nanoparticles

Nanoformulation	Precursor	Technique	Observation	Ref.
MnO_2 single-crystal nanowires/nanorods	Manganese (II) sulfate and Ammonium persulfate	The hydrothermal process relies on MnO_4 and Mn^{2+} redox reactions.	This technique demands a low temperature and does not include any catalysts or patterns and does not require precision equipment	[43]
MnO_2 NP	Permanganate aqueous solutions	Sol-gel Method	This process may generate reversible cathodes for use in lithium batteries that do not include an aqueous solution	[44]
Manganese dioxide composite with carbon nanotubes	Poly (sodium 4-styrene sulfonate) and manganese	Polymer-assisted method	This nanocomposite produced using the polymer-assisted technique can potentially be used as a material for air electrodes in batteries to reduce oxygen catalytically	[45]
MnO_2 and graphene oxide composites	Natural graphite powders	Polymer-assisted chemical reduction method	Manganese composites might be manufactured in significant quantities using this approach	[46]
MnO_2 NP	$KMnO_4$	Hydrothermal method	It is possible to synthesize structures with various morphologies, including tube-, wire-, rod-, and flower-shaped systems	[47]
MnO_2 NP	*Gardenia resinifera*	Green synthesis	Spherical in form, range in small size, and exhibit considerable antibacterial activity	[48]
MnO_2 NP	*Syzygium aromaticum* extract	Green synthesis	MnO_2 NP produced using the green chemistry technique is useful for the detection of P-nitrophenol with a detection limit of 15.65 M	[49]
MnO_2 NP	Under alkaline condition	Photo assisted synthesis	Differently synthesized particles	[50]

produced using various physicochemical processes. On the other hand, the bio-mediated reduction of metal precursors to form the required particles is eco-friendly, low cost, and chemical free. This makes it ideal for use in medical and biological applications, which put a high priority on NP purity. A bottom-up technique that is analogous to chemical reduction is implemented by using natural extracts. In addition, the concentration and type of biological entities, as well as reducing chemical agents, may influence the size and structure of NPs [28]. Synthetic mixes and physical procedures were extensively employed for several years. Still, the damaging consequences that they had on human health and well-being significantly impacted the researchers' perspectives of the world. Nanoparticles from plants and their metabolites are now referred to with the term green synthesis. This innovation significantly compensates for previous shortcomings in lessening the potentially harmful effects brought about by naturally occurring NPs [29]. Utilizing plant extracts is the most straightforward approach, the least expensive, and the most environmentally friendly way to reduce manganese metal into manganese nanoparticles [30]. In the larger process of using plants to generate metallic nanoparticles, the dried biomass of plants is put to use as a bio-reducing agent. In contrast, metallic salt is used as a precursor. It is feasible to synthesize nanoparticles by biological means using a bottom-up technique, which requires reducing and stabilizing agents. When utilizing a biological system, three primary procedures need to be carried out to successfully produce nanoparticles:

a. The selection of a solvent medium

b. The selection of an ecologically friendly material

c. Environmentally benign reducing agent, and the selection of a substance that is not toxic to use as a capping agent [31].

The MnO_2 NPs may be made by stirring an aqueous solution of manganese acetate at different pH levels (four, six, or eight) together with the leaf extract of *Y. gloriosa* for forty to one hundred and twenty minutes while the temperature is kept at room temperature [32]. This research has shown that manganese nanoparticles may be manufactured by continuously swirling *C. pepo* extract and $KMnO_4$ (7.90 mg) salt for around four hours. According to the findings, the customary location of MnO_2 NPs absorption peak is at 404 nm [33]. In addition, the juice or peel of a lemon might be used in the green synthesis of MnO_2. This compound's crystallization and electrochemical characteristics of MnO_2 obtained from the lemon peel are superior to those obtained from lemon juice. Lemon juice only includes two of these reducing (antioxidative) reagents–citric and ascorbic acids–but the peel of the fruit contains all three of them (as well as volatile oils). Even while employing the peel produces better results than simply using one of these two acids, the yield is still lower than if all three of the peel's active components were used instead. The electrochemical features of MnO_2 formed from the peel are equal to those achieved with usual chemical reducing agents, which are both expensive and polluting [34]. Recent studies have shown that freeze-drying may be utilized to produce nanoparticles of MgO and MnO_2 from chamomile flower extract. First, the nanopowder and its yellow and brownish-black end products served as a preliminary indicator that the nanopowder had been effectively formed [35]. Reducing agents made from *Datura stramonium* leaf extract were used to produce manganese dioxide nanoparticles. Synthetic biology has several advantages, including being very cost-effective, efficient, and safe for the surrounding ecosystem. For the purpose of identifying manganese dioxide nanoparticles, UV-visible spectroscopy and visually observable color changes in solutions were noted [36]. In addition, manganese dioxide nanoparticles might be generated by utilizing *A. vera.* Cooking the plant paste in water that had been distilled for up to half an hour was done before filtering it. For the plant extracts, the temperature of the filtrate was kept at a level lower than four degrees Celsius. After being exposed to a solution of 0.1 M $KMnO_4$, the color of the solution underwent a discernible change. Before subjecting this solution to sonication for an hour and a half, it was stirred with a magnetic stirrer for three hours while it was at room temperature. After that, the suspension went through a few minutes of centrifugation at a speed of 10,000 rpm. After the MnO_2 nanoparticles had settled, the collected particles were cleaned using ethanol and water that had been thrice distilled [37].

Coprecipitation method

During the coprecipitation process, metal hydroxide is formed from a salt precursor with the assistance of an acid in a solvent. This process takes

place in a solution. By managing the nucleation and growth kinetics of particles, manufacturing of monodispersed nanoparticles may be sped up by the controlled release of regulated anions and cations. This, in turn, helps to achieve the desired result. Mixed oxide precipitation, on the other hand, makes it difficult to exert control over the chemical homogeneity and particle size of the resulting material. Coprecipitation assists in the precipitation of metal hydroxide from a salt precursor. Regulating anions and cations may speed up monodispersed nanoparticle production, and proper control of experimental parameters affects precipitation [38]. The most important advantage of the coprecipitation technique is that it can readily manufacture vast numbers of water-soluble nanoparticles in a short amount of time [39]. The following is a list of standard synthetic techniques for producing coprecipitation:

a. Production of nanomaterials involves the use of aqueous solutions and electrochemical reduction.

b. Breakdown of metal-organic precursors with templates.

c. Microwave and sonication help in the process of coprecipitation at the nanoscale.

The most significant benefits are the low creation of radioactive dust as well as the simple accessibility of low-cost reactants. Concerns have been raised over the reduced availability of pure plutonium and fissionable actinides and the reduced rate of proliferation [40].

The coprecipitation method was used to bring about the formation of these manganese dioxide nanoparticles. The technique is simple, inexpensive, and produces a significant volume of results. During the coprecipitation process, manganese sulfate, which acts as a precursor agent, and sodium hydroxide as a reducing agent, may be combined to produce manganese dioxide nanoparticles [6]. Sodium hydroxide is used as a reducing agent, while manganese dichloride tetrahydrate is used as a precursor agent in the manufacturing process. After 7 hr of drying in the open air at a temperature of 100 degrees Celsius, nanoparticles of MnO_2 were produced [41]. The production of manganese ferrite powder has been accomplished by the use of the ultrasonically assisted coprecipitation method. The first generation of manganese ferrite nanoparticles powder was produced by washing and drying the residue at a temperature of 80 °C for two hr [42].

Biomedical applications of manganese oxide nanoparticles

Manganese-based nanoparticles have recently been employed extensively in theranostics applications. Their unique physical and chemical features, notably their high surface-to-volume ratio, make them effective drug delivery platforms. Manganese nanoparticles are unique in that they may be employed as chemotherapeutic drug delivery systems. Tumor microenvironments are well-known for their high acidity and glutathione content. As a result, manganese nanoparticle drug delivery systems can be modified based on the notion of pH and glutathione responses to overcome toxicity [51]. The applications of manganese dioxide nanoparticles are represented in (Fig. 1).

Antimicrobial applications

Antimicrobial resistance is a significant issue that must be addressed in modern therapeutic practice. Altering standard antimicrobial procedures and using innovative strategies may help reduce the prevalence of organisms resistant to several drugs in the future [52]. Treatment of bacterial infections is made more difficult when germs develop resistance to antimicrobial drugs. Antimicrobial medications are typically classified into several groups based on the primary mechanism of action. Bacteria can gain resistance to a single class of antimicrobial medications either via spontaneous mutation or by the transfer of genes responsible for resistance to other species [53]. A resurgence of interest in nanoparticles has been triggered due to the rise of drug-resistant bacteria and the increased frequency of infection outbreaks in hospitals. The antimicrobial properties of nanoparticles have led to their widespread use across various business sectors because each kind of nanoparticle has its own set of advantages and applications. Antibacterial activity may be affected by several factors, including mean particle size and shape, specific surface area, and surface curvature. The use of NPs in the fight against bacteria has led to a reduction in the frequency of bacterial infections [54]. It was discovered that the inhibitory zone of manganese dioxide nanoparticles against Gram-positive bacteria, such as *S. aureus, E. coli, Klebsiella pneumonia*, and *Bacillus*, was much larger than it was against Gram-negative bacteria. When tested against Gram-negative bacteria, manganese dioxide

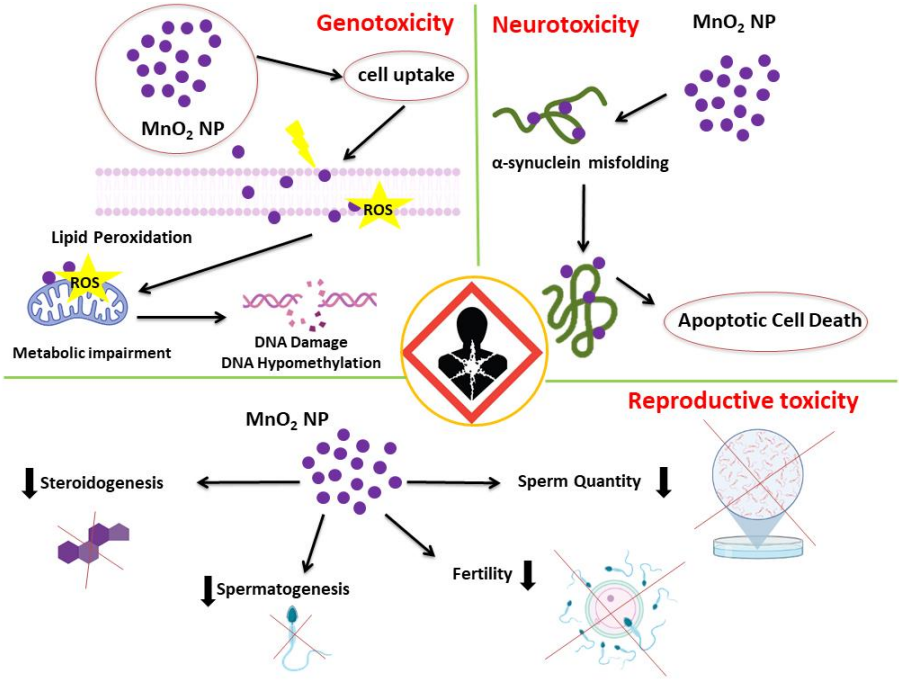

Fig. 1. Application of manganese dioxide nanoparticles

nanoparticles were more effective at inhibiting *K. pneumonia* than at inhibiting *Escherichia coli* or *Pseudomonas aeruginosa* [6]. Through the disc diffusion method, it was established that some strains of *S. aureus* and *P. aeruginosa* are susceptible to silver-doped MnO_2 nanoparticles when they are present in low quantities. MnO_2 nanoparticles have been found to have a potential application in the battle against multidrug-resistant bacteria and other pathogens [55]. It has been shown that the antibacterial activity of curcumin-stabilized manganese nanoparticles is more remarkable than that of curcumin alone against every bacterium. In the battle against *S. aureus* and *E. coli*, manganese nanoparticles proved more effective than chloramphenicol, remaining virtually on the scale [56]. It is advocated that indigenous medicinal plants be utilized to synthesize nanoparticles and employed as active photocatalysts and antibacterial agents in nanotechnology. This is because biogenic synthesis is both simple and environmentally friendly. Such nanoparticles have shown positive antibacterial activity against *S. aureus* and *E. coli* bacterial strains. In addition to its use as an antibacterial agent, MnO_2 has potential applications in sensing, photocatalysis, and medicines [57].

Cancer therapy

Although cancer is the main cause of mortality, very few effective treatments are available. As a direct consequence of the rapid advancements in nanotechnology and materials science, several novel diagnostic and therapeutic approaches for cancer are now being developed. The development of nanostructured MnO_2 biomaterials has progressed into a new phase in recent years. In addition to its use in drug delivery systems, nanostructured manganese dioxide has applications in photodynamic treatment, bioimaging, and cancer diagnosis. The tumor microenvironment may affect several cancer treatments now in use [58]. Studies in ontogenetic have shown evidence that reversing the immunosuppressive effects of the tumor can activate antitumor immunity and reduce cancer progression. This is accomplished by utilizing oxygen produced by MnO_2 nanoparticles to improve photodynamic, radio dynamic, and sonodynamic treatment. A relatively new approach to the treatment of cancer is called starvation therapy. This therapeutic strategy interferes with cancer cells' capacity to get the nutrients and energy they need to grow and increase, leading to metabolic irregularities. It is effective since cancer cells need many resources and energy to grow and multiply. In treatment, MnO_2 nanoparticles with enzymes are often used. In this context, the nanoparticles primarily affect glucose metabolism

through a cascade reaction, ultimately inhibiting ATP production [59]. To measure alpha-fetoprotein, an immunoassay based on the detection of manganese dioxide nanoparticles was developed. This immunoassay can give increased stability at room temperature and more tyramine signal amplification [60]. In addition, manganese dioxide nanosheets may disintegrate in the tumor microenvironment, resulting in an activatable magnetic resonance imaging signal. This would increase the signal-to-noise ratio and selectivity of the magnetic resonance imaging pictures produced as a consequence of the magnetic resonance imaging scans. MnO_2 nanosheets are good materials for creating magnetic resonance imaging-based theranostic platforms and multimodal imaging nanoprobes because of their high surface area, fluorescence quenching, and chemo-dynamic therapy capabilities. Nanosheets of manganese dioxide have shown significant potential in various *in vitro* and *in vivo* applications, including the detection and treatment of cancer, as well as theranostic [61]. Using hydrogen peroxide-responsive oxygen generator manganese oxide nanoparticles covered in erythrocyte membranes to enable cancer chemotherapy and photothermal therapy red blood cell membranes can function as oxygen precursors or catalyzers for the generation of hydrogen peroxide. This allows the loading capacity of doxorubicin to be increased and the duration of *in vivo* circulation to be extended. Cancerous cells and tissues produce an abnormally high quantity of hydrogen peroxide. When hydrogen peroxide is present, the hypoxia that is caused by the tumor is alleviated with the injection followed by releasing doxorubicin is released more rapidly as a direct consequence of this oxygen production, breaking the red blood cells coating on the surface of the photobiomodulation therapy. Combining photothermal therapy with chemotherapy can significantly enhance the antitumor effects of doxorubicin-loaded manganese oxide by inhibiting the development of tumors and the conditions for reducing hypoxia in tumors and improving chemotherapy and progression-free survival in cancer patients [62]. To make use of both the photothermal effect of gold nanorods and the glutathione-sensitive and pH-responsive features of MnO_2, hybrid nanoparticles were developed. Mesoporous manganese dioxide was destroyed due to an acidic microenvironment and high glutathione concentrations in the medium. Hybrid nanoparticles showed excellent performance in hormone-responsiveness, pH-responsiveness, and near-infrared responsiveness. They could release around 47 percent of the loaded drug in 12 hr. It is anticipated that this nanoplatform will be used for photothermal therapy, pharmaceutical delivery, and the change of the microenvironment around the tumor in the treatment of cancer [63]. In a one-pot technique, manganese dioxide, doxorubicin, and IR780 are combined to form a hybrid nanostructure, which is then stabilized with bovine serum albumin to alleviate tumor hypoxia and improve tumor growth suppression. In addition to producing oxygen, manganese dioxide may also react with glutathione to inhibit the release of medications that target tumors. In addition, the Mn ions increased the magnetic resonance signal, making it a candidate for use as a contrast agent in magnetic resonance imaging scans. MnO_2 was added to doxorubicin to improve its anticancer activity further. This resulted in efficient inhibition of tumor formation both *in vitro* and *in vivo*, as well as a reduction in tumor size. The use of photothermal therapy was almost successful in stopping the tumor progression. These hybrid nanostructures as potential therapeutic carriers to reduce tumor development show substantial promise [64].

Diagnostics and imaging

Researchers can locate and diagnose tumors with the use of bioimaging. Nanostructured manganese dioxide has recently been employed effectively in imaging and diagnostic procedures for tumors. Magnified resonance imaging produces high-quality 3D pictures with great contrast between hard and soft tissue and high spatial resolution. Contrast agents are an essential component of magnetic resonance imaging which offers a high level of diagnostic accuracy. Mn-based contrast agents are suitable for use in magnified resonance imaging due to their biocompatibility as well as their clear images. Magnified resonance imaging contrast agents made from nanoparticles of manganese dioxide allow for the detection and diagnosis of tumors [65]. In order to diagnose and tackle a broad variety of diseases, such as cancer, heart disease, musculoskeletal issues, and neurological problems, several studies have also looked at manganese-enhanced magnetic resonance imaging. This is due to the fact that

manganese ions slow T1 relaxation, which leads to better T1-weighted scans and, as a consequence, higher signal intensity in T1-weighted pictures [66]. Due to Mn^{2+} ability to produce paramagnetic relaxation, it is suitable for use as a magnetic resonance imaging contrast agent. There are several advantages to using contrast agents that include Mn^{2+} due to its strong paramagnetism, even a little amount of Mn^{2+} may have a noticeable impact. Furthermore, Mn^{2+} contrast agents have low toxicity, which enables them to be used in neuroimaging [67]. In recent years, applications such as biosensors, bioimaging, the transport of drugs and genes, and the treatment of tumors have all profited from the use of MnO_2 nanomaterials. Because of their easy manufacturing process, high specific surface area, adjustable size and morphologies, facile surface modification, thermal responsiveness, and oxygen generation, among other benefits, all-in-one thermal responsive MnO_2-based nanoagents have become a focal point of research. Chemotherapy, photodynamic therapy, and radiation are all potential treatments that might benefit from MnO_2 nanoparticles because of their increased radical generation and decreased glutathione levels and can be used for imaging using photoacoustic and ultrasonic modalities. Meanwhile, the manufactured Mn^{2+} ions have the potential to be used in magnetic resonance imaging. Recently, new properties of MnO_2 nanomaterials have been discovered. These properties include the Mn^{2+} mediated Fenton reaction, glucose oxidase-like activity, photothermal conversion capability, and enhanced antitumor immunity. These properties expand the applications of MnO_2 nanomaterials in chemodynamic therapy, starvation therapy, and immunotherapy. Recent developments made feasible by MnO_2-based nanomaterials of various morphologies have been of significant use to biomedical applications, which have profited immensely from these advancements [68].

Applications in electrocatalysis and biosensors based on manganese oxide nanocomposites with enhanced surface areas, synthesized through a one-pot surfactant method showed promising development in the medical field [69].

Challenges

Although research on nanoparticles has been going on for more than 30 years, the development of methodologies and standard procedures necessary for verifying their safety and effectiveness for human use is still being developed [70]. Nanoscale medicine delivery technologies are meant to minimize toxicity, yet nanoparticles have harmful qualities that are intrinsic to them [71]. The current efforts to evaluate the toxicity of produced nanoparticles are primarily centered on the environmental repercussions, including the toxicity to organisms from a range of ecological food webs [72]. Several essential issues must be considered when switching from an animal inhalation toxicity setting to *in vitro* aerosol pulmonary toxicity studies. The following procedures are included in this analysis. However, this is not a complete list. To effectively mimic the lung microenvironment in a lab, it is crucial to choose which cell types will be used in a co-culture or tri-culture system. Calculating the number of lung epithelial cells or their ratio to the number of alveolar macrophages present in a co-culture plate represents a progression from primary cell types collected from animals to immortalized cell types produced from cell lines and assessed for biological viability. Evaluation of particle inhalation deposition is necessary to identify the aerosol-generating technology for particles and nanoparticles and appropriate, repeatable, and quantifiable dosage metrics [73]. For future research and activities to be relevant and responsive to engineered nanomaterial dangers, what causes a novel material to display new, unanticipated, or ill-defined human health issues must be carefully considered. The toxicity associated with manganese dioxide nanoparticles is mentioned in Table 2.

The difficulty is to discern between materials with traditionally recognized concerns that can be addressed and materials with unique risks that need new knowledge and ways to assure safe product use [74]. Despite a large number of researches that have been conducted on the subject of nanoparticle toxicity, there is still a considerable deal of obstacles to overcome to determine the effect that exposure to these substances has on one's health. The literature contains attributes that are contradictory and often contradict one another concerning the safety of nanoparticles. As a result, not a lot of information is known regarding their impact on human health [75]. The toxicity associated with overproduction of manganese ions can lead to genotoxicity, neurotoxicity, and reproductive toxicity as represented in (Fig. 2).

Table 2. Toxic effects of manganese dioxide nanoparticles

Nanoformulation	Study	Observation	Ref.
Manganese dioxide (MnO_2) nanoparticles	Oxidative Stress resulting in damage to DNA	In human neuronal cells, NPs can cause the death process known as apoptosis and fragmentation of the DNA	[82]
2D MnO_2 nanosheets	Fish gill epithelial cells – Mitochondrial toxicity	An investigation of the toxicity to cells to 2D nanosheets of chemically produced manganese dioxide. The hypothesis is that mitochondrial toxicity is caused by the cellular import of manganese oxide nanoparticles or nanosheets into lysosomes	[85]
Manganese oxide NPs	Nanoparticles and neurotoxicity	Dopamine and its metabolites, dihydroxyphenylacetic acid and homovanillic acid, were reduced dose-dependent in catecholamine cells after exposure to 40-nm manganese oxide nanoparticles and this depletion was coupled with a considerably enhanced generation of ROS	[86]
MnO_2 nanoparticles	Reproductive toxicity in male rats	As hazardous compounds, nanoparticles and microparticles of manganese dioxide induce disruptions to the process of spermatogenesis	[76]
Manganese nanoparticles and radiofrequency	In male Wistar rats	Drop in sperm count, which dropped even more when both treatments were applied together. According to the findings, an additive toxic response may be triggered in the male reproductive system when these stressors are combined	[87]

Reproductive toxicity

MnO_2 nanoparticles and microparticles reduce sperm motility, as well as cause several effects. Due to this, MnO_2 nano- and microparticles appear hazardous to spermatogenesis because of their toxic qualities. Because it may negatively impact fertility, the level of toxicity of MnO_2, which can be found in many different medical supplies and devices, must be carefully monitored and controlled [76]. At 400 parts per million, manganese dioxide nanoparticles are likely to be seen in male testicular tumors, spermatogonial cells, primary spermatocytes, spermatids, and Leydig cells, and to lower the sex hormones. Because of oxidative stress, the ROS generated by manganese dioxide nanoparticles is hazardous. The production of ROS is the primary factor responsible for the toxicity of manganese dioxide nanoparticles. It has been shown that exposure to manganese dioxide nanoparticles may disrupt the mitochondrial activity of cells, which can result in harm to the tissues [77]. According to the findings of a recent study, rats exposed to Mn^{2+} had a failure in testicular spermatogenesis as well as exfoliation of their germ cells [78]. Mn should be avoided since it has the potential to change the testicular histomorphology and slow down the progression of the cell cycle through the G2/M phase. Therefore, as a direct result, spermatogenesis will deteriorate [79]. Recent investigations found that myometrium proliferative activity and levels of follicle-stimulating hormone and luteinizing

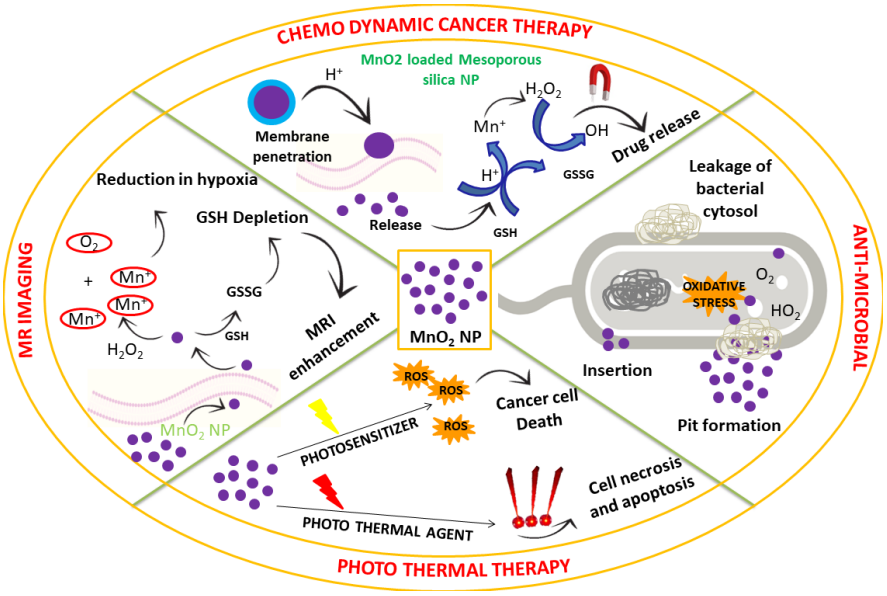

Fig. 2. Toxicity associated with manganese dioxide nanoparticles.

hormone were considerably impacted by Mn^{2+} [80].

Cytotoxicity

In addition to being hazardous to reproduction, it is expected that manganese dioxide nanoparticles would also have cytotoxic effects. Nanoparticles of MnO_2 have the potential to induce genetic damage, metabolic abnormalities, and histological modifications if they are exposed to living organisms for an extended length of time [81]. According to research that measured the amount of DNA fragmentation for 48 hr, there is a possibility that the cells would undergo apoptosis as well as DNA fragmentation [82]. In a recent investigation on the cytotoxic effects of MnO_2 NPs researchers found that the viability of cell lines was significantly reduced. The experiment was carried out using a range of different MnO_2 NPs concentrations. Inductively coupled plasma mass spectrometry evaluated the cellular uptake of NPs, and the findings indicated that fibrosarcoma took up a greater quantity of NPs than other cell lines did. Although the mechanisms of cytotoxicity for both cell lines are the same, the cell lines behave quite differently [83]. While investigating the cytotoxicity of MnO_2NPs in the neuroblastoma cell line, it was discovered that the caspase-3/9 pathway was activated, which caused a significant increase in the rate of apoptosis. The findings revealed an increase in the expression of genes, which lends credence to the hypothesis that MnO_2 NPs induced apoptosis in the neuroblastoma cell line by way of the mitochondrial pathway. It was discovered that a change in the proportion of Bax to Bcl_2 was responsible for the activation of caspases 9 and 3, which, in turn, initiated the process of apoptosis in the cells [84].

Strategies to overcome toxicity associated with manganese dioxide nanoparticles

The researchers proposed several preventative measures to mitigate these potentially detrimental effects.

Surface functionalization

When using NPs in biomedical research and development, toxicity and cellular absorption should be taken into consideration. There are several methods for enhancing nanoparticles' medicinal potential. One of these techniques is surface functionalization [88]. For nanoparticles to be functional in biomedical applications, they must be able to manage their interactions with biological systems. Research into nanoparticle imaging, sensing, and delivery has used a range of surface configurations [89]. NPs have been extensively studied for their biological compatibility and utility to gain an edge in biomedical applications, including bioimaging, biosensing, and medicine administration. Therefore, incorporating synthetic ligands or natural biomolecules onto the NP system's surface has emerged as an important factor in the system's efficacy. Using phospholipid-based artificial cell membranes has proven useful. It is now a viable option for more common changes such as direct polymer conjugation to increase biocompatibility [90]. The properties are determined by the surface of nanoparticles [91]. As a novel class of fluorescent nanoprobes, semiconducting polymer dots have recently emerged, demonstrating incredible fluorescence brightness, remarkable photostability, a rapid radiative rate, nonblinking behavior, and limited cytotoxic potential. Polymer dots have proven very useful for a wide range of applications due to recent surface functionalization and enhanced energy transfer inside conjugated polymers [92]. Bovine serum albumin reduced and stabilized MnO_2 nanoparticles were shown to have excellent water dispersibility and excellent biocompatibility. MnO_2 can be produced by the one-pot method, which is highly biocompatible. A study by Wang Y *et al*. revealed that bovine serum albumin reduced and stabilized MnO_2 nanoparticles, improved near-infrared photothermal efficiency, and photostability, making them a novel class of anticancer agents [93].

Polymer-coated MnO_2 nanoparticles

Many components are intertwined in a complicated relationship, and the polymer coating can give new properties to MnO_2 NP. Polymer surfaces, which are sensitive to temperature and the surrounding environment, possess significant changes in the characteristics of the polymer, and its lifetime may occur. It is possible to categorize components as either internal or external, depending on where they originate. Internal components originate inside the polymer itself, whereas external components originate from their surrounding environment [94]. Polymers may come from natural or artificial sources, depending on where and how they are synthesized. Because of their ability to degrade naturally, these natural polymers have been used

for decades in various technological and biological applications. Polyethylene, polyurethane, silanes, and styrene are some of the synthetic polymers that have significantly contributed to the creation of long-lasting and wear-resistant polymer systems. Microfluidics, textiles, pharmaceutical applications, electronics, water treatment, and the energy sector all employ surface-treated polymers in their respective processes [95]. Polymer coatings are fragile polymer films applied to various surfaces, whether flat or heterogeneous. Coatings are made of polymers. It is possible to purchase polymeric coatings in the form of paint, which may then be used to alter the appearance of surfaces via the application of, for instance, paper coatings or hydrophobic coatings [96]. The production of polymeric nanoparticles that are highly selective to tissues, biocompatible, and efficient in administering targeted medications in medicine, in addition to their potential for commercial use, has been the primary focus of research [97]. According to several specialists' opinions, combining natural and synthetic polymers in one product is possible. Natural polymers provide cytocompatibility, whereas synthetic polymers provide structural support and resist mechanical forces. Both types of polymers may be biodegradable with few applications of polymer-coated manganese oxide composites [98]. Polymeric materials are susceptible to altering their chemical or physical characteristics when subjected to an external stimulus and find applications in the administration of medicines [99]. As a fundamental component of their construction, nanoparticles and microparticles were first produced using poly-alkyl-cyanoacrylate. Because of their diminutive proportions, microparticles were first met with great excitement when they were proposed for application in medical practice. If the medication particles are smaller than a specific size, they will be able to pass through the mucosal barrier like those present in the gastrointestinal system. Macroparticles often prevent them from passing through the mucosal barrier, which leads to ineffective administration of the drug. Nanoparticles, on the other hand, have a size advantage over microparticles. Because of their greater size, they work better when administered through an intravenous route. Within a short amount of time, the intravenous nanoparticles were eliminated from the body by the phagocytic cells of the body. As a consequence of this, the therapeutic efficacy of medications that were given via nanoparticles declined, and finally, it was eliminated altogether [100]. Chitosan is an essential biomedical polymer because it increases molecular cell membrane contacts at physiological pH. Its low toxicity, exceptional biocompatibility, and polycationic nature make it one of the most biocompatible substances known to humans. Chitosan coatings can open tight junctions between epithelial cells and have antibacterial effects [101]. Medical professionals have used manganese compounds to enhance MR pictures' quality [102]. For instance, covering MnO_2 with a biopolymer to increase their biocompatibility and provide a place at which targeting moieties may be attached to the drug molecules contained inside the NPs is an example of this. Experiments on rats proved it to be safe when given up to 10% of their food. It was demonstrated to be biocompatible with live tissue since it does not induce allergic responses or rejection since it does not cause a denial or allergic reactions [103]. Hence based on several studies it is understood that coating polymers on nanoparticles improves biocompatibility [104].

CONCLUSION

A literature survey indicates an equal benefit between chemical and biological methods in synthesizing MnO_2 nanoparticles. Even among the synthesis methods, the electrochemical characteristics did vary based on the natural product employed. The synthesized nanoparticles had a range of biomedical applications ranging from microbial resistance to cancer therapy and magnetic resonance imaging. Like other nanoparticles, polymer surface coating of oxide nanoparticles reduced the toxicity and improved the properties of the nanoparticles. In this, the potential of biopolymers, such as chitosan as coatings on the nanoparticle surface, improved the image quality and enabled attachment of targeting moieties and other drugs, thus improving the therapeutic and diagnostic features. In essence, chitosan-coated MnO_2 nanoparticles are ideal for further investigation, including clinical trials, to obtain further proof of their advantages.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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