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Biogenic Fabrication And Multidimensional Characterization Of Manganese Dioxide Nanostructures In Biomedical Systems

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Nanotechnology encompasses the creation and manipulation of materials in sizes ranging from 1-100 nm. The properties of materials at nanoscale are quite different from other scale materials both physically and chemically. These include higher surface area to volume ratio, better catalytic performance and quantum effects. Common methods for preparing nanoparticles are sol- gel, hydrothermal, and chemical co-precipitation. These techniques allow for precision synthesis. However these techniques often involve toxic chemical precursors, high temperature and consume a lot of energy. As a result it raises significant environmental and safety concerns hence green synthesis is now considered as a safer method of synthesis. It comprises the use of plant parts, microbial products, and biomolecules to synthesize nanoparticles in an eco-friendly way. Among them manganese dioxide (MnO_2) nanoparticles have frontline prospects due to their strong structure, multi oxidation states ($Mn^{2+}/Mn^{3+}/Mn^{4+}$), stimuli responsiveness , good bio-compatibility etc with wide range organisms. MnO_2 nanoparticles prepared through green route exhibit enzyme-mimetic catalytic activity and also show bright prospects in medical applications. They can cure ROS related disorders, generate oxygen under hypoxia conditions, as well as tumour microenvironment regulation. Applications include chemodynamic as well as photodynamic therapies, immunotherapy, and increasing magnetic resonance imaging contrast. This review focuses on recent advancements concerning green-synthesized MnO_2 nanoparticles' preparation focusing mainly on their biomedical uses and likely future developments.

Keywords: Green synthesis; MnO_2 nanoparticles; Biomedical applications; Characterization.

1. Introduction

The rapid progress in nanotechnology has led to the creation of materials with better surface reactivity, adjustable properties, and improved biological interactions [1]. These nanoscale features have induced the growth of extensive research into the use of nanoparticles in areas such as drug delivery systems, MRI contrast agents, biosensors, photodynamic therapy agents, environmental remediation products and catalytic applications [2]. Despite allowing for precise control over size and shape of particles created via methods like sol - gel, hydrothermal method and chemical co-precipitation still necessitate temperatures exceeding 100 - 200 °C as

well as high pressure conditions and/or employ toxic precursors leading to hazardous by-products; this control additionally comes at the expense of more complex synthesis protocols involving multi-step reactions system requiring long processing hours at elevated temperatures [3].

Green synthesis has become an eco-friendly, and economical approach that uses plant extracts, microbial metabolites, and biomolecules as reducing and stabilizing agents for the production of nanoparticles using green precursors at low temperature (<60–80 °C to prevent hazardous by-products) [4]. These nanomaterials have been found very effective in many applications such as more than 90% bacterial pathogens inhibition, superior modulation of reactive oxygen species (ROS), and significant antioxidant activity in vitro environments [5]. Among various nanomaterials, manganese dioxide (MnO_2) nanoparticles have drawn significant interest because of their structural stability, multivalent redox behavior, and enzyme-mimicking activity. [6]. MnO_2 nanoparticles can decompose hydrogen peroxide endogenously on a catalytic basis converting it into oxygen thereby alleviating hypoxia in tumor microenvironments leading to improved efficacy in photodynamic therapy, chemodynamic therapy, and radiotherapy [7]. Under acidic conditions, these particles release paramagnetic Mn^{2+} ions, which have been shown to enhance T1 MRI contrast in preclinical studies [8]. The MnO 2 nanoparticles are synthesized by environmentally benign methods, thus, making MnO 2 nanoparticles a green and multi-functional scaffold with scope of application in the biomedicines that are at the borderline between nano(scientific) foundational and translational medicine needs [9].

2. Biogenic Routes for Green Nanoparticle Synthesis

This green approach is a sustainable, ecologically sound and cost-effective alternative to the more commonly used chemical or physical methods [10]. This occurs via bioreductive processing of metal ions within plants, microorganisms or their isolated biomolecules as reducing, stabilizing and capping agents under eco-friendly chemistry [11]. The latter besides the reduced utilization of toxic reagents and high-energy inputs also offers the internal modification over nanoparticle surfaces for increased stability, solubility and biocompatibility contrives [12]. Various biogenic processes have been deeply scrutinized with each model showing individual mechanistic attributes and benefits [13].

2.1 Plant-Mediated Synthesis

One of the reasons why bio-synthesis is the preferred among green strategies is because phytochemicals are found in plenty in various parts of the plants like leaves, stems, roots, fruits, seeds and flowers [14]. Those natural biomolecules also flavonoids, polyphenols and terpenoids influence their bioactivity ‘promising’ them as a valuable source for green synthesis [15]. They include alkaloids, proteins, and reducing sugars that cooperatively perform activities such as reduction of metal ions/nucleation of nanoparticles/and stabilization of nanoparticles [16]. Bio-chemical composition of plant extracts directly affects nucleation kinetics, crystal growth rate and morphology as well as particle distribution [17]. The preparation parameters such as extract concentration pH temperature, metal salt precursor and incubation time can be used to control size, shape, morphology and dispersion characteristic

[18]. Researchers can modify these bio-synthesis factors continuously till desired particle size distribution shape formation is reached [19].
Capping of phytochemical-coated NPs is a promising means to achieve the diversification in NP morphologies which could be quasi-spherical, rod-like, sheet-like, or flower-like hierarchical structures [20]. The phytochemical capping not only prevents agglomeration but also provides surface functional groups for enhanced interaction with biological molecules, improved solubility and increased biocompatibility tendency [21]. In addition to these, nanoparticles possess multiple functionalities like antioxidant activity, antimicrobial efficacy, catalytic behavior and remediation versatility [22]. This process is practical in terms of application on large scale, cost- effective and does not result in formation of any hazardous product which makes it more favourable for sectors like medicine, agriculture and environmental technology [23].

2.2 Microbial-Mediated Synthesis

Nanoparticles are produced by microorganisms, such as bacteria, fungi, yeast and algae, both inside the cell and outside it [24]. Intracellular synthesis occurs when metal ions are taken up and enzymatic reduction within the cytoplasm takes place leading to nanoparticles of uniform size and crystallinity [25]. Extracellular synthesis is mediated through secreted enzymes, proteins and polysaccharides which make it easier to recover downstream [26]. The nanoparticles produced by microbes have narrow size distribution, colloidally stable forms with well-defined surfaces for functionalization that are suitable for various applications such as biomedical area, catalysis, biosensors and environmental applications [27].

2.3 Biomolecule-Assisted Synthesis

Some biomolecules such as amino acids, peptides, proteins, polysaccharides, and vitamins that act as reducing and stabilizing agents help in the directed synthesis of nanoparticles as well as their growth and functionalization [28]. Proteins and peptides contain functional groups to facilitate selective binding and surface passivation and polysaccharides contain steric stabilization measures to ensure aggregation is avoided [29]. It is concentrated on applications of high added value in such fields as targeted drug delivery, biosensors and immobilization of enzymes and theranostics where a particular application is needed, thus post-synthesis functionalization is necessary [30].

2.4 Hybrid Biogenic Strategies

Hybrid methods adopt several biogenic constituents that could be plant extracts and metabolic microbes or isolated biomolecules through the synergistic action during nanoparticle fabrication in their turn [31]. These strategies increase nucleation efficiency, yield and manufacture functionalized nanoparticles attaching suitable physicochemical and surface properties [32]. Hybrid biogenic nanoparticles are particularly useful for highly-complex applications that involve theranostics, biosensing, environmental decontamination and catalysis as they call for multi-functionality and high stability [33].
In a whole, biogenic technologies represent organic methods which are green, flexible, and can be effectively scaled for nanoparticle synthesis [34]. Strategies of using plants, microorganisms, and biomolecules allow to obtain controlled morphology and size of nanoparticles along with their functionalization while protecting the environment [35]. The

use of biological agents in the process provides functional-analog on the surface of a nanoparticle that significantly increases its performance and extends application areas of nanoparticles including medicine, environmental science as well as various nanotechnologies [36].

3. Determinant Parameters Governing Biogenic Nanoparticle Synthesis

The efficiency of biosynthesizing nanoparticles is a multifunctional complex, which is determined by physicochemical and biological factors that are responsible for the phenomena of nucleation, growth, morphology, size dispersity, surface chemistry and colloidal stability [37]. These factors need to be optimized to guarantee reproducibility, uniformity and functional efficacy of the processes in areas such as biomedical, catalytic or environmental applications [38]. The most important among them are the type and the concentration of biological reducing/stabilizing agents involved in the process; character of the metal precursor; conditions of reaction and macro environment properties [39].

3.1 Biological Reducing and Stabilizing Agents

The biosource (whether it is a plant extract, microbial metabolite or isolated biomolecule) and its type, concentration and bio-chemical composition directly define the nucleation and growth kinetics of a nanomaterial [40]. Phytochemicals such as flavonoids, polyphenols, terpenoids, proteins, reducing sugars among others carry on dual function; they reduce metal ions to elemental or oxide nanoparticles as well as stabilize the particles by capping/sternic hindrance [41]. These biomolecules cause havoc on the density of nucleation, growth rate and morphology of the particles due to their content and reactivity [42]. The lack of bio-molecular content could lead to partial reduction or uncontrolled aggregations, whereas the excess concentration could cause abnormal shapes or polydispersity, excessive capping which prevents the functioning of nanomaterials [43]. The diversity and structure of biomolecules have an impact on surface chemistry as well as providing functional groups which increase solubility, biocompatibility and post-synthesis functionalization possibility [44].

3.2 Synthesis Parameters

The pH, temperature, and incubation duration in the interaction environment can be referred to as the critical factors which deeply influence nanoparticle formation process [45]. The pH affects various aspects like ionization state of functional groups on biomolecules, reduction potentials, different dynamics of nucleation and growth of nanoparticles [46]. Ultra-acidic or high alkaline environments may completely change nucleation processes and/or affect shape, while also glycoside or precipitation of proteins can be observed; on the other hand, more neutral to mild conditions generally support noncomplicated formation of regular NPs [47]. The speed at which a molecule is reduced mediates biomolecule quantity, frequency of nucleation formation mediated by biomolecule and crystals growth rate [48]. Practically all temperatures are ideal to preserve biomolecular integrity besides promoting effective reduction; nevertheless very high temperatures may cause fast crystallization, as well as aggregation, degradation [49]. In like manner reaction time is an indicator for the degree of growth and aggregation; short periods lead to unfinished particle formation whereas long ones may result in many particles coagulation or even hierarchical aggregate's formation [50].

3.3 Metal Precursor Characteristics and Stoichiometry

Literally, the chemical nature, solubility and oxidation state of the metal precursor have a major contribution in the dynamical nucleation processes and nanoparticles' composition [51]. Although this may depend on other factors, typically precursors with high solubility and reactivity are reduced faster giving rise to smaller nanoparticles which have large surface area compared to those formed from less reactive salts that necessitate longer incubation periods or controlled environment [52]. Precursor-to-biomolecule ratio is of particular importance, which may result in an equilibrium that is either too low or too high, which may result in an incomplete reduction, aggregation or secondary particle growth but at a favorable stoichiometry all may be avoided as complete reduction takes place and biomolecular capping proceeds. [53].

3.4 Medium Properties and Agitation

The important factors to be considered also mainly include the types of solvents, ionic strength and mixing [54]. For instance, polar solvents like water will aid in ion mobility as well as enhance interaction of biomolecules with metal ions [55]. Ionic strength affects electrostatic stabilization; high ionic concentrations can shield charges with side effects to colloidal stability that decrease and aggregated particles emerge [56]. This is done gently to make sure that all molecules react uniformly distributed, preventing unwanted precipitation on a surface thus achieving homogenous nucleation and growth process [57]. Insufficient blending leads into heterogeneous particle size distributions and morphologies subsequently an excessive agitation could adversely affect fragile biomolecule-nanoparticle interactions [58].

4. Analytical Techniques for Characterization

Knowledge about biologically produced nanoparticles can be obtained in order to discover their structural, morphological, optical and functional properties [59]. The main function of the described techniques is the size, morphology and aggregation of nanoparticles using SEM and TEM; the crystalline phase and structural purity of materials analyzed with XRD; surface functional groups and biomolecular capping investigated with FTIR technique; optical behavior and colloidal stability observed by UV–Vis spectroscopy; hydrodynamic size distribution and zeta potential analysis assessed by DLS [60]. Individually each of them provides a great insight into nanoparticle structure as well as its surface chemistry which is very important for biomedical as well as industrial applications [61].

4.1 Zeta Potential and Particle Size Analysis

One of the most important physicochemical parameters i.e., the particle size, has quite an impact on the nanomaterial properties such as reactivity, cellular uptake, biodistribution, and drug delivery [62]. Smaller particles generally have a higher reactivity area and better biological interactions while larger aggregates may decrease the effectiveness [63]. Techniques such as dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA) in hydrodynamic size, polydispersity, shape factor and colloidal distribution can be performed rapidly if required; SEM and TEM morphology imaging for aggregation/ crystallization visualisation which complement to size data are provided high resolution [64]. Particle size

determination is important for relating the effect of synthesis process parameters to its bioactive or catalytic function [65].

Zeta potential that is expressed as the surface charge of nanoparticles in suspension, is at the same time one of key factors for colloidal stability [66]. Nanoparticles having high absolute zeta potential repel themselves which help prevent aggregation while low ones may cause clustering and reduce dispersion stability [67]. Zeta potential also affects biomolecule adsorption/interactions with cell membranes and cellular internalization; those are highly important for biomedical applications including drug delivery, imaging, and antimicrobial activity [68]. Interactive assessment of particle size and zeta potential offers a detailed insight into nanoparticle physicochemistry to aid designers in building on existing ideas or creating new approaches to the development, optimization, or functionalization of suitable biocompatible nanomaterials which has been presented as a more effective approach than conducting individual analysis on each property [69].

4.2 Scanning Electron Microscopy (SEM)

SEM provides significant information about surface morphology, structural arrangement and aggregation behavior of biogenically synthesized MnO_2 nanoparticles [70]. Micrographs displayed mostly quasi-spherical, rod- or needle-like and sheet-like morphologies with at times hierarchical assemblies such as flower-like or networked structures formed via biomolecule-mediated oriented attachment [71]. Rough, porous, or wrinkled surfaces result from adsorbed biomolecules which act as capping agents to limit particle blend and produce polycrystalline regions with amorphous layers [72].

Primary particles are typically within tens of nanometers and secondary aggregates are larger among other things, resulting from partial stabilization and polydisperse nucleation [73]. The behavior of aggregation is reliant on the coating levels of biomolecules and also their electrostatic stabilization [74]. SEM, otherwise known as a combination of spectroscopic and crystallographic analysis, provides a mechanistic understanding of nucleation coupled with facet-sensitive growth and hierarchical assembly [75]. These structural characteristics have direct functional implications that comprise catalytic activity, capacity to carry load of drugs, redox property, antimicrobial effectiveness and general biomedical performance of green-synthesized MnO_2 nanoparticles [76].

4.3 Transmission Electron Microscopy (TEM)

In nanobiotechnology, TEM offers the possibility to get high resolution insights into the morphology inside, crystalline nature and nanoscale architecture of biogenic MnO_2 nanoparticles, which in turn complete the surface level observation obtained from SEM [77]. TEM images usually depict nanostructures with well defined lattice fringes that validate/corroborate crystalline MnO_2 phase formation under relatively mild bio-mediation conditions [78]. This work has revealed primary particles as ultrafine quasi-spherical nanocrystallites and elongated rod-/wire-like structures, which show anisotropic growth through selective adsorption of biomolecules on certain crystallographic planes [79]. Also note the presence ultrafine sheet-like or flake-like morphologies that corresponds to layered MnO_2 phases formed by stacking or oriented assembly of MnO_6 octahedra [80]. In HRTEM, the high resolution TEM helps to support the crystallinity of the sample by clearly showing lattice

fringes [81]. Furthermore, in SAED (selected area electron diffraction) patterns show that there are concentric rings which means that this nanomaterial is polycrystalline also they show that there are many nucleation sites during synthesis [82]. The amorphous organic layers around the crystalline domains indicate adsorption of plant-, microbial- or biomolecule-derived compounds as reducing, stabilizing and capping agents [83]. They perform protective functions since they prevent growth of particles, over-aggregation and increase colloidal stability [84]. According to observation of aligned nanostructures along certain directions the mechanisms behind growth of nanoparticles can be proposed [85]. It is clear that these structures have direct implications towards functional performances such as redox activity, cellular uptake, drug-loading capacity and antimicrobial efficiency [86]. From such a description we can conclude that TEM imaging confirms nanoscale integrity as well crystallographic orientation bioorganic structuring of synthesized MnO2 nanoparticles to point to the mechanistic and functional benefits bio-mediated synthesis strategies offer [87].

4.4 X-ray Diffraction (XRD)

XRD is a key technique to verify the crystalline phase, structural integrity, and order of biogenic MnO_2 nanoparticles at long-range order [88]. Under green synthesis methods, MnO_2 are usually observed to form diffraction patterns with broad peaks that can be attributed to δ-, α-, or γ-MnO_2 representations, depending on the starting materials, concentration of precursors and the type of reducing agents [89]. Peak broadening or partial amorphousness is suggested to be an indicator of nanocrystallinity, whereas the presence of well-defined peaks in the diffraction pattern is an indication of a successful phase formation [90]. Small crystallites with surface-bound biomolecules enlarge further as overlapping peaks and slightly differentials of location of such overlap signals, create disorder of signals in nanostructure lattice dynamics [91]. The Scherrer equation provides a reasonable estimate of the size of such small crystallites and it also underlines the controlled nucleation of the process when the synthetic is in green [92]. Absence of impurity peaks serves to confirm high phase purity and the chelating nature of biomolecules as they synthesize [93]. Structural characteristics among others reduced crystallite size and lattice defects promote redox functionality performance [94]. Hence, XRD patterns are employed for insight on the fine structural refinement and functional enhancement of biogenic MnO_2 nanoparticles [95].

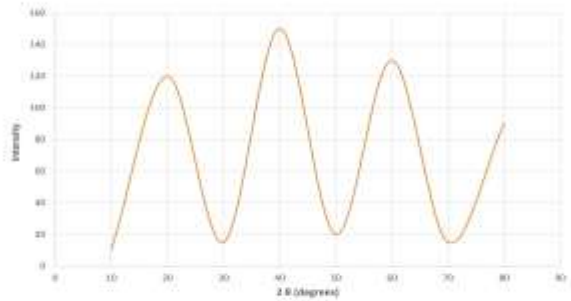

Figure 1 : XRD pattern of biogenically synthesized MnO_2 nanoparticles showing broad diffraction peaks, confirming nanocrystalline and phase purity.

4.5 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy is a powerful quality instrument that can be used to determine the type of functional groups responsible for reduction, stabilization and surface functionalization of biogenic produced MnO_2 MPs [96]. Bands in the low-wavenumber region (~500–750 cm^{-1}) display the typical absorption peaks which are connected with manganese atoms' oscillations within the MnO_6 octahedral coordination structures, hence seem to support the presence of manganese dioxide frameworks [97]. Further, in 900 – 1100 cm^{-1} and 1200-1500cm^{-1} specific bands resulted from C–O, C–N and C–C stretching and this depict organics constitute from plant extracts, microbial metabolites or their bioreducing agents are adsorbed on NPs faces [98]. The presence of polyphenols, alcohols oxidation burst absorptions at 3200-3600 $cm^{-}1$; whereas peak appeared at around 1600-1650 $cm^{-}1$ temperatures carbonyl or amide bonds, this means there is proteins, enzymes or secondary metabolites involved in capping and stabilization [99].

Peak shifts indicate that functional groups are binding to the surface of MnO_2 which governs reduction and stabilization [100]. FTIR gives us proof that molecules from organisms change surfaces [101]. It shows that a coating forms which helps the particles stay separate from each other, and makes sure they do not stick together when they are in the human body [102]. This proof tells us that the changes on the surfaces are important for the way MnO2 behaves in the body and that there are great things about green ways of making MnO2 [103].

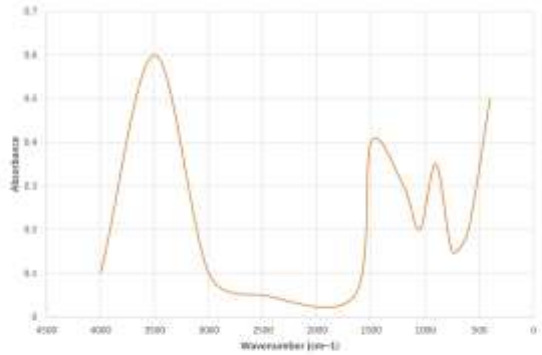

Figure 2 : FTIR analysis confirming biomolecule – mediated synthesis and surface functionalization of MnO_2 nanoparticles.

4.6 UV–Visible spectroscopy

UV–Vis spectroscopy is among the techniques often used to study functions including absorption spectrum, electronic states, and colloid stability of biogenically synthesized MnO_2 nanoparticles [104].The formation of MnO_2 is clear from a new broad absorption band at 320-380 nm which is ascribed to the ligand-to-metal charge transfer of O^{2-} ligands onto Mn^{4+} centers in MnO_6 octahedra [105]. The surface chemistry and biomolecular capping, the position and shape of the band will depend upon nanoparticle size, crystallinity, surface chemistry, and biomolecular capping; sharp or broad bands suggest uniform formation and polydispersity respectively [106]. The intensity of absorbance indicates the quantity of nanoparticles in solution – which can be exploited to follow biosynthesis kinetics [107].

As per the Tauc plot, the band gap energy (Eg) of the MnO_2 NPs falls within the range of 1.5 - 2.5 eV is depicted by size-dependence, by surface defects and functionalization patterns

[108]. Optoelectronic properties of these materials directly affect electrochemical behavior which in turn affects catalytic activities, and biomedicine applications such as redox reactions, (in particular, the modulation of reactive oxygen species, oxidative stressors, and photo-assisted therapy) are areas where this information may be used [109]. In total UV–Vis spectroscopy not only serves as a proof for basic MnO_2 formation but also as an applicational characteristic for their electronic configuration/structure related optical properties at application level along with other methods of characterization to determine quality and functionality of nanoparticles [110].

5. Biomedical Applications of Manganese dioxide Nanoparticles

MnO_2 has been widely used in biomedical fields due to its easy-to-adjust redox function, good biological compatibility and sensitivity to body changes [111]. When the interface activity of MnO_2 nanoparticles increases, MnO2 can interact with the body, and even participate in the process of body regulation and disease response [112].

Such functions make MnO_2 nanostructure play a role in the antibacterial field, tumor therapy, biosensing and diagnostic imaging [113]. It can also catalyze endogenous hydrogen peroxide into molecular oxygen to relieve hypoxia, thus improving the efficiency of oxygen therapy [114]. With the enzyme-like properties, MnO_2 nanostructure can artificially regulate the reactive oxygen species for microbial killing and cell protection [115]. Due to the above structural characteristics, MnO_2-based nanomaterials can be used as a high-level platform for controlled drug release, and can be applied to diagnostic and therapeutic systems [116].

5.1 Microbial Targeting and Inactivation Mechanisms

Controlled generation of reactive oxygen species, such as hydroxyl radicals and superoxide anions by MnO_2 NPs, can cause oxidative stress, which is a key antibacterial mechanism of MnO_2 NPs [117]. Highly reactive oxygen species can indiscriminately attack bacterial membranes, proteins, and nucleic acids, disrupting the vital process of bacterial metabolic activity and replication [118]. Furthermore, small dimensions and high surface energy can establish close contact at the bacterial cell envelope, which can destabilize the membrane by electrostatic interaction [119]. In addition to the chemical oxidative effects, direct interfacial interactions between MnO_2 NPs and bacterial membranes could achieve a direct antimicrobial effect by inducing membrane deformation, increased permeability, and leakage of cytoplasmic contents [120]. Multiple antibacterial actions reduce the potential for resistance development while broadening the spectrum of antimicrobial effects [121]. The above mechanisms encourage the use of MnO_2 -based nanostructures in wound dressings, antimicrobial surface coatings, and infection-control systems [122].

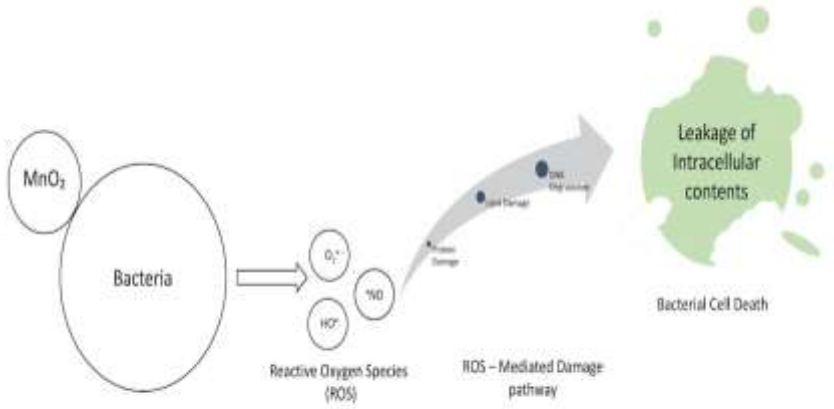

Figure 3 : Antibacterial Mechanism Of MnO_2 Nanoparticle

5.2 Redox-Modulating Activity

MnO_2 nanoparticles show strong antioxidant activity, which is a result of their internal enzyme-mimetic characteristics [123]. They can act similarly to the catalase and superoxide dismutase enzymes that are present in living beings, and effectively break down O_2 radicals, especially hydrogen peroxide, into harmless components [124]. Owing to the redox-controlled catalytic mechanisms, MnO_2 nanomaterials can mediate against the excessive O_2 radicals in cells, which cause oxidative harm to cell signalling pathways and structures [125]. MnO_2 nanoparticles can prevent cell membrane breakdown, protein denaturation, and DNA damage by neutralizing O_2 radicals and oxidative stress [126]. They have significant antioxidant activity, especially in cases such as inflammation, neurodegeneration, and tissue damage, that produce excessive amounts of O_2 radicals [127]. Therefore, manganese dioxide nanostructures have been incorporated into several nanotherapeutic platforms to alleviate oxidative stress, reduce inflammation, and improve cell viability and proliferation [128].

5.3 Smart Drug Delivery Systems

MnO2 nanoparticles are a promising drug delivery platform because of their stimulus-responsive properties and suitable physicochemical properties [129]. The major advantage of MnO_2-based nanocarriers is their acidity sensitivity [130]. When exposed to acidic pathological microenvironments, such as tumor tissues, MnO_2 will degrade and release drugs inside or on their surface in a site-specific, controlled, and long-term manner [131]. Degradation of the MnO_2 carrier also generates molecular oxygen, which can release oxygen into hypoxic tissues to enhance the effectiveness of oxygen-dependent treatments [132]. The large surface area of MnO_2 nanoparticles also enables a high drug-loading efficiency [133]. Modification with polymers, antibodies, or specific ligands enhances the cellular uptake of MnO_2 nanoparticles and allows targeting of specific organs, tissues, or cells of interest [134]. Overall, these features highlight the potential of MnO_2 drug delivery systems for controlled and specific drug delivery applications [135].

5.4 Tumor Microenvironment Modulation and Therapeutics

MnO_2 nanoparticles play a versatile therapeutic role in the field of oncology by virtue of active tumor microenvironment remodulation [136]. One major issue with the treatments of these kinds of cancers is that they are often found in solid tumors. [137]. These solid tumors have low oxygen levels and a high concentration of hydrogen peroxide; which makes radiotherapy and photodynamic therapy inefficient at destroying such tumours [138].This kind of cancer is one reason why this type of tumor is hard to treat since it can be difficult to get rid of a tumor that has no blood vessels as means for drugs to reach into it [139].

Besides oxygenation, the identical catalytic tactic enhances results of cytotoxic radicals in photodynamic processes, which leads to enhanced tumor ablation [140]. The changes in local pH could be accomplished by MnO_2 nanoparticles as well, improving malignant cell sensitivity [141]. Therefore, simultaneously controlling the level of hypoxia, redox state and acidity in the tumor microenvironment, MnO_2-based nanostructures is an effective adjuvant to enhance conventional cancer therapy [142].

6. Future Perspectives

Green synthesis can be used to make nanoparticles of MnO 2 in a more environmentally friendly and biocompatible method to form useful nanostructures [143]. Researchers must pay close attention to the size, shape, crystallinity and surface charge of the nanoparticles in order to achieve optimum results with their catalyst, antimicrobial and medical applications [144]. It has been established that nucleation and growth of the nanoparticles can be influenced by an extensive number of factors, including but not limited to the number of biological extracts, pH, molarity of the precursor, temperature, reaction time and mixing conditions. [145]. Statistical strategies like design-of-experiments can help figure out the best conditions for making MnO_2 nanoparticles with different plant, microbial, and biomolecular sources [146]. Using advanced techniques, such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), X-ray diffraction (XRD), and FTIR, can help with the characterization of the shape, size, composition, and surface chemistry of the nanoparticles [147]. Additionally, high-resolution TEM, atomic force microscopy (AFM), Raman mapping, X-ray absorption spectroscopy, and in situ spectroscopic methods can provide a better understanding of how the nanoparticles form and how biogenic components are involved in reducing, stabilizing, and surface functionalization [148].

7. Conclusion

The green method of synthesis of manganese dioxide nanoparticles is a completely eco-friendly, low-priced and everlasting contrast to specious chemical and physical methods only through bio-resources which are plant extracts, microbial metabolites, and biomolecules that convert ion metals into seeds for metal reduction, nucleation, or stabilization. The complete characterization demonstrates that formation of nanoparticles with their morphologies regulated crystallinity in the nano dimensions level and discrete optical and structural properties without the presence of catalytic, redox and biomedical applications functionality. These biogenically synthesized nanoparticles are quite versatile in the antimicrobial activity, antioxidant therapy, targeted drug delivery system, cancer theranostics and environmental remediation applications while biocompatibility is achieved by natural capping agents

decreasing cytotoxicity. Although meeting with difficulties in mechanistic elucidation, long-term biosafety analysis, and scalable production, green synthesis stands as a flexible and sustainable method of producing multifunctional MnO_2 nanomaterials that have high prospects in biomedical and environmental applications.

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