International Journal of Science, Strategic Management and Technology
Volume **02** Issue **03** March-**2026** | ISSN: **3108-1762 (Online)** | Impact Factor: 3.8
An International, Peer-Reviewed, Open Access Scholarly Journal Indexed in recognized academic databases

Chitosan–Metal and Metal Oxide Nanocomposite Hydrogels: Synthesis Strategies, Antimicrobial Mechanisms, and Biomedical Applications

[1]*Varsha Elumalai, [1]Saqib Hassan, [3]Balachandar Vijayakumar

[1]Department of Biotechnology, Sathyabama Institute of Science and Technology, Chennai-600119, INDIA.

[2]Soft matter laboratory, Centre for Nanoscience and Nanotechnology, Sathyabama Institute of Science and Technology, Chennai-600119, INDIA.

https://doi.org/10.55041/ijsmt.v2i3.119

Cite this Article: Vijayakumar, V. E. S. H. B. (2026). Chitosan–Metal and Metal Oxide Nanocomposite Hydrogels: Synthesis Strategies, Antimicrobial Mechanisms, and Biomedical Applications. International Journal of Science, Strategic Management and Technology, *02*(03). https://doi.org/10.55041/ijsmt.v2i3.119

License: This article is published under the Creative Commons Attribution 4.0 International License (CC BY 4.0), permitting use, distribution, and reproduction in any medium, provided the original author(s) and source are properly credited.

Abstract

Chitosan–metal oxide nanocomposite hydrogels have emerged as promising multifunctional materials for biomedical and environmental applications due to their combined biocompatibility, antimicrobial activity, and tuneable physicochemical properties. Native chitosan hydrogels exhibit biodegradability and inherent antibacterial behaviour, yet their limited mechanical strength, structural stability, and moderate antimicrobial efficiency restrict advanced therapeutic use. Incorporation of metal-oxide nanoparticles such as ZnO, TiO_2, CuO, Fe_3O_4, MgO, and CeO_2 significantly enhances mechanical integrity, regulates swelling behaviour, and introduces multiple antibacterial mechanisms including reactive oxygen species generation, membrane disruption, and controlled ion release. This review summarizes recent advances in the design and fabrication of chitosan–metal oxide nanocomposite hydrogels with particular emphasis on microwave-assisted synthesis. Compared with conventional preparation methods, microwave processing enables rapid and uniform heating, controlled nucleation, improved nanoparticle dispersion, and reduced synthesis time, resulting in materials with enhanced reproducibility and performance. The antibacterial mechanisms of both chitosan and metal oxides and their synergistic effects are discussed along with physicochemical characteristics and safety considerations. Furthermore, major applications in wound healing, drug delivery, tissue engineering, dental care, water purification, and antimicrobial coatings are highlighted. Current challenges including nanoparticle aggregation, long-term toxicity, scalability, and regulatory barriers are critically analysed, and future perspectives such as smart responsive hydrogels, AI-guided optimization, and industrial-scale manufacturing are outlined. Overall, microwave-engineered chitosan–metal oxide nanocomposite hydrogels represent a versatile platform for next-generation antimicrobial and regenerative technologies.

Keywords: Nanomaterials; Environmental and ecofriendly; Metal oxide nanoparticles, Chitosan, Microwave technology.

1. Introduction

1.1 Background on biopolymer hydrogels

Biopolymer hydrogels are three-dimensional cross-linked polymeric networks capable of absorbing and retaining large quantities of water while maintaining structural integrity [1]. Their high-water content, softness, and permeability resemble the natural extracellular matrix, making them highly suitable for biomedical applications such as wound dressings, drug delivery

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

carriers, and tissue engineering scaffolds [2,12]. Unlike synthetic hydrogels, biopolymer-based hydrogels are derived from renewable biological sources and exhibit superior biocompatibility and biodegradability [1]. Natural polymers including alginate, gelatine, cellulose, and chitosan have therefore gained increasing attention in recent years. However, many biopolymer hydrogels suffer from weak mechanical strength, uncontrolled swelling, and limited antimicrobial performance, which restricts their direct use in advanced clinical environments [11]. Consequently, current research focuses on functional modification of natural polymer hydrogels to improve stability, durability, and biological activity.

1.2 Importance of chitosan as a bioactive polymer

Chitosan is a linear polysaccharide obtained by deacetylation of chitin, a naturally abundant biopolymer present in crustacean shells and fungal cell walls [3]. It contains reactive amino and hydroxyl functional groups that enable crosslinking, metal binding, and chemical modification [4]. Among natural polymers, chitosan is particularly valuable due to its intrinsic antibacterial activity, haemostatic behaviour, mucoadhesive nature, and ability to promote cell proliferation [4,6]. In acidic environments, protonated amino groups interact electrostatically with negatively charged bacterial membranes, leading to leakage of intracellular components and microbial inhibition [5]. Additionally, chitosan is non-toxic, biodegradable, and enzymatically degradable into harmless oligosaccharides, making it highly suitable for biomedical and pharmaceutical applications [3,4]. Because of these unique biological properties, chitosan hydrogels have been extensively investigated as wound healing materials, drug carriers, and antimicrobial coatings [6,12].

1.3 Limitations of native chitosan gels

Despite its advantages, native chitosan hydrogel exhibits several shortcomings that limit practical application. The polymer network generally possesses poor mechanical strength and becomes unstable under physiological conditions [6]. Rapid swelling and degradation lead to short functional lifetime in aqueous environments [11]. Furthermore, although chitosan shows antimicrobial activity, its effectiveness is often insufficient against resistant bacterial strains and biofilm formation [5]. The antibacterial effect is also strongly dependent on environmental pH, which restricts performance under neutral physiological conditions [5]. Another challenge is the lack of structural rigidity, making it difficult to maintain shape and durability in load-bearing biomedical applications [6]. These limitations necessitate reinforcement strategies to enhance stability and broaden antibacterial performance.

1.4 Advantages of metal-oxide incorporation

Incorporating metal oxide nanoparticles into chitosan hydrogels has emerged as an effective method to overcome these drawbacks [11]. Metal oxides such as zinc oxide, titanium dioxide, copper oxide, and magnesium oxide possess strong antimicrobial activity, chemical stability, and catalytic properties [7]. When embedded into the polymer network, they act as nanofillers that improve mechanical strength, thermal resistance, and structural integrity [11]. More importantly, they significantly enhance antibacterial activity through multiple mechanisms including reactive oxygen species generation, membrane disruption, and metal ion release [7,8]. The polymer matrix also prevents nanoparticle aggregation and reduces toxicity by controlling ion diffusion. As a result, chitosan–metal oxide nanocomposite hydrogels exhibit synergistic effects, combining the biocompatibility of the polymer with the potent antimicrobial activity of inorganic nanoparticles.

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

Table 1. Advantages metal-oxide incorporation

MONP	Key Properties and Applications in Chitosan Composites	Mechanism of Action
Zinc Oxide (ZnO)	Highly biocompatible, non-toxic, UV-blocking, strong antibacterial and antifungal activity, wound healing [4, 5].	Reactive Oxygen Species (ROS) generation, and Zn2+ ion release disrupting cell membranes [6].
Copper Oxide (CuO)	Excellent photocatalytic and potent broad-spectrum antibacterial activity, often used in conjunction with other oxides [7].	Cu2+ ion release, oxidative stress induction, and membrane damage [8].
Titanium Dioxide TiO2	High biocompatibility, photocatalytic activity (especially under UV light), anticorrosive properties [9].	Generation of highly reactive species (e.g., hydroxyl radicals) upon photoexcitation for contaminant degradation or enhanced antimicrobial action [10].
Iron Oxide Fe3O4	Superparamagnetic properties, essential for targeted drug delivery, Magnetic Resonance Imaging (MRI), and mechanical reinforcement [1, 11].	Magnetic guidance, mechanical reinforcement, potential for Fenton-like reactions.
Magnesium Oxide (MgO)	Primary non-toxic nanomaterial, effective antibacterial agent, potential for drug delivery [6, 12].	Release of alkaline Mg2+ ions and ROS generation; its high solubility avoids tissue residue issues [6].
Cerium Oxide CeO_2	Remarkable antioxidant properties (due to dual oxidation states Ce 3+ Ce4+, radical scavenging, and protective effects on cells [13].	Redox cycling and modulation of Reactive Oxygen Species (ROS).
Mixed/Hybrid Oxides	Combinations like ZnO/CuO or CuO-TiO2 are engineered to exploit synergistic effects, such as forming p-n heterojunctions to improve visible light harvesting and reduce electron-hole recombination in photocatalysis [7, 14].	Synergistic mechanisms combining ion release, ROS generation, and enhanced photocatalysis.

1.5 Why microwave engineering is emerging

The synthesis technique plays a crucial role in determining nanoparticle distribution and final material performance. Conventional heating methods rely on slow heat transfer from the surface to the interior, often producing non-uniform particles and aggregation within the hydrogel matrix [9]. Microwave-assisted synthesis has emerged as a promising alternative due to volumetric dielectric heating, where energy is directly absorbed by polar molecules throughout the reaction medium [9,10]. This results in rapid, uniform nucleation and controlled crystal growth within minutes [10]. Microwave processing reduces reaction time, minimizes energy consumption, and improves nanoparticle dispersion inside the polymer network [9]. The

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

method also limits excessive particle growth and enhances reproducibility, making it attractive for scalable fabrication of nanocomposite hydrogels.

Table 2. Advantages of microwave engineering assisted synthesis

Advantage	Mechanism and Impact
Rapid Heating	Volumetric heating leads to extremely fast attainment of reaction temperature, drastically reducing synthesis time [8].
Uniform Energy Distribution	Minimizes temperature gradients, which is crucial for controlling the nucleation and growth of uniform nanoparticles [9].
Reduced Synthesis Time	Reactions that might take hours conventionally can be completed in minutes or even seconds, boosting throughput [8].
Controlled Nucleation and Particle Size	Rapid heating and short reaction times allow for kinetic control over the MONP formation, resulting in narrower size distribution and smaller, more uniform nanoparticles [10].
Energy Efficiency	Direct heating of the reactants results in less energy loss compared to heating an external furnace [8].

1.6 Scope and objectives of the review

This review focuses on recent developments in chitosan–metal oxide nanocomposite hydrogels synthesized using microwave-assisted techniques. The article discusses the structural characteristics of chitosan hydrogels, the role of metal oxide nanoparticles in improving physicochemical and biological properties, and the advantages of microwave processing over conventional methods. Particular emphasis is placed on antibacterial mechanisms, structure–property relationships, and biomedical applications including wound healing and drug delivery [11,12]. The objective is to identify current challenges and research gaps while providing insights into future design strategies for high-performance antimicrobial hydrogel systems suitable for advanced healthcare applications.

2. Chitosan as a Functional Biopolymer

2.1 Structure and physicochemical characteristics

Chitosan is a linear cationic polysaccharide composed of randomly distributed β-(1→4)-linked D-glucosamine and N-acetyl-D-glucosamine units derived from partial deacetylation of chitin [13,14]. The polymer contains primary amine ($–NH_2$) and hydroxyl (–OH) functional groups that make it chemically reactive and capable of forming hydrogen bonds, ionic interactions, and coordination complexes with metal ions [16]. Chitosan is insoluble in water and most organic solvents but becomes soluble in dilute acidic solutions (pH < 6.5) due to protonation of amino groups, resulting in a positively charged polyelectrolyte [15]. This cationic nature enables strong interaction with negatively charged biomolecules such as proteins, DNA, and microbial membranes. Chitosan also exhibits film-forming ability, viscosity control, and gel-forming capacity, making it a versatile biomaterial for biomedical and pharmaceutical applications [20]. Its physicochemical properties—including crystallinity, solubility, and swelling—depend on structural parameters such as degree of deacetylation and molecular weight [16].

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

2.2 Degree of deacetylation, molecular weight, and gel-forming ability

The performance of chitosan hydrogels is strongly influenced by its degree of deacetylation (DD) and molecular weight (MW). The degree of deacetylation determines the number of free amino groups present in the polymer chain. Higher DD increases positive charge density, improving solubility in acidic media, crosslinking efficiency, and biological activity [15,16]. Conversely, low DD results in reduced solubility and weaker intermolecular interactions.

Molecular weight governs viscosity, mechanical strength, and degradation rate of hydrogels. High molecular weight chitosan generally produces stronger but less flexible gels, while low molecular weight chitosan forms softer hydrogels with faster biodegradation [20]. Gel formation typically occurs through physical or chemical crosslinking mechanisms such as ionic interactions, hydrogen bonding, or covalent crosslinking agents [16]. The presence of abundant amino groups allows formation of three-dimensional networks capable of entrapping water molecules and bioactive compounds [20]. Therefore, tuning DD and MW is essential to tailor hydrogel properties for specific biomedical applications.

2.3 Antimicrobial and film-forming properties

Chitosan exhibits intrinsic antimicrobial activity against a wide range of Gram-positive and Gram-negative bacteria as well as fungi [17,18]. The primary mechanism involves electrostatic interaction between protonated amino groups and negatively charged microbial cell membranes, leading to increased permeability, leakage of intracellular components, and inhibition of nutrient transport [18]. In addition, chitosan can chelate essential metal ions and interfere with microbial enzyme activity and DNA replication [17].

Another important property is its excellent film-forming capability. Chitosan solutions can form transparent, flexible, and oxygen-permeable films after solvent evaporation, which is advantageous for wound dressings and protective coatings [19]. These films maintain a moist environment, support cell adhesion, and reduce infection risk. Because of these combined antimicrobial and barrier properties, chitosan is widely explored for biomedical coatings, packaging materials, and tissue engineering scaffolds.

2.4 Limitations of pure chitosan gels

Despite its beneficial biological properties, pure chitosan hydrogel has several limitations that restrict its direct clinical use. The mechanical strength of native chitosan gels is relatively low, causing deformation or dissolution in physiological conditions [21,22]. Excessive swelling leads to poor dimensional stability and short functional lifetime [20]. Furthermore, the antimicrobial activity of chitosan alone is moderate and strongly dependent on pH, becoming less effective near neutral physiological conditions [18].

Chitosan hydrogels also degrade rapidly and lack sufficient structural rigidity for long-term biomedical applications such as load-bearing tissue scaffolds or durable wound coverings [21]. These drawbacks have driven the development of composite systems, particularly incorporation of inorganic nanoparticles, to reinforce the polymer matrix and enhance antibacterial performance.

3. Metal-Oxide Nanoparticles (MONPs) in Chitosan Gels

3.1 Overview of Metal-Oxide Nanomaterials

Metal-oxide nanoparticles (MONPs) are inorganic nanomaterials widely incorporated into polymer matrices to enhance mechanical, thermal, and biological performance [32,33]. Their high surface-to-volume ratio, chemical stability, catalytic activity, and ability to generate reactive oxygen species (ROS) make them particularly effective antimicrobial agents [33].

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

When embedded in chitosan hydrogels, these nanoparticles act as nanofillers that reinforce the polymer network while simultaneously introducing bioactive functionality [32]. The polymer matrix stabilizes the nanoparticles, prevents aggregation, and controls ion release, thereby reducing toxicity and improving durability. As a result, chitosan–MONP nanocomposites exhibit synergistic properties combining polymer biocompatibility with inorganic antimicrobial potency.

Zinc Oxide (ZnO): Zinc oxide nanoparticles are among the most extensively studied metal oxides in biomedical hydrogels due to their biocompatibility and broad-spectrum antimicrobial activity [23,24]. ZnO nanoparticles generate reactive oxygen species such as hydroxyl radicals and superoxide ions, which damage bacterial cell membranes, proteins, and DNA [23]. In addition, released Zn^{2+} ions interfere with enzyme function and metabolic pathways [24]. Incorporation of ZnO into chitosan hydrogels significantly improves mechanical strength, UV-blocking ability, and antibacterial efficiency. ZnO-loaded hydrogels are widely explored for wound healing applications because they promote cell proliferation while preventing infection.

Copper Oxide (CuO): Copper oxide nanoparticles exhibit strong bactericidal activity even at low concentrations [25,26]. Their antimicrobial action mainly arises from Cu^{2+} ion release and oxidative stress generation, which disrupts bacterial respiration and membrane integrity [25]. In chitosan gels, CuO nanoparticles enhance structural rigidity and provide prolonged antibacterial action due to sustained ion diffusion from the hydrogel network. These nanocomposites are particularly effective against drug-resistant bacterial strains, making them promising materials for antimicrobial coatings and medical device protection [26].

Titanium Dioxide (TiO_2): Titanium dioxide nanoparticles are well known for their photocatalytic properties. Under light irradiation, TiO_2 produces reactive oxygen species capable of oxidizing organic molecules and microbial components [27]. When incorporated into chitosan hydrogels, TiO_2 provides photo-induced antibacterial activity, chemical stability, and improved mechanical performance. TiO_2-based hydrogels are attractive for self-sterilizing surfaces and environmentally responsive antimicrobial materials.

Iron Oxide (Fe_3O_4): Magnetite (Fe_3O_4) nanoparticles introduce magnetic responsiveness into chitosan hydrogels and are widely investigated for biomedical applications [28]. Besides moderate antibacterial activity, their major advantage lies in targeted drug delivery and externally controlled positioning using magnetic fields. Fe_3O_4-containing hydrogels can be directed to specific sites within the body, improving localized therapy and reducing systemic side effects. Additionally, they improve mechanical strength and allow repeated recovery or reuse in environmental applications.

Magnesium Oxide (MgO): Magnesium oxide nanoparticles possess good biocompatibility and relatively low toxicity compared to many metal oxides [29]. Their antibacterial mechanism involves membrane damage caused by alkaline surface reactions and reactive oxygen species formation [29]. In chitosan hydrogels, MgO nanoparticles improve swelling stability and support cell growth, making them suitable for tissue engineering scaffolds and wound dressings where mild antimicrobial activity and cytocompatibility are required.

Cerium Oxide (CeO_2): Cerium oxide nanoparticles exhibit unique redox cycling between Ce^{3+} and Ce^{4+} oxidation states, allowing them to act as antioxidant as well as antimicrobial agents [30]. Unlike other metal oxides that primarily generate oxidative stress, CeO_2 can regulate reactive oxygen species levels, reduce inflammation while still inhibit microbial growth. Incorporation into chitosan hydrogels produces multifunctional biomaterials capable of promoting tissue regeneration, reducing oxidative damage, and preventing infection simultaneously.

Mixed or Hybrid Oxides: Recent research explores hybrid or mixed metal oxide systems such as ZnO–CuO and ZnO–TiO_2. These combinations provide synergistic antibacterial effects by combining multiple mechanisms including ROS generation, ion release, and photocatalysis [31]. Embedding hybrid nanoparticles into chitosan hydrogels further improves stability, mechanical strength, and antimicrobial efficiency. Such multifunctional nanocomposite hydrogels are considered next-generation materials for advanced biomedical applications, offering broader antimicrobial spectrum and enhanced performance compared to single-oxide systems.

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

3.2 Rationale for Incorporating MONPs

The incorporation of metal-oxide nanoparticles (MONPs) into chitosan hydrogels is primarily driven by the need to overcome the mechanical and biological limitations of native polymer networks. Chitosan alone provides biocompatibility and mild antimicrobial activity, but its structural fragility and moderate antibacterial performance restrict long-term biomedical use. Embedding inorganic nanofillers within the polymer matrix creates hybrid organic–inorganic systems with multifunctional properties.

Enhanced antimicrobial action: MONPs exhibit strong antibacterial activity through multiple mechanisms including reactive oxygen species (ROS) generation, oxidative stress induction, and membrane disruption. When dispersed within a hydrogel network, nanoparticles remain localized at the material surface and continuously interact with microbes. The hydrogel also maintains a moist microenvironment that facilitates diffusion of antimicrobial species, leading to prolonged bacterial inhibition compared to free nanoparticles.

Increased mechanical strength: Nanoparticles act as reinforcing agents within the polymer network. They form physical crosslinking points through hydrogen bonding, electrostatic attraction, or coordination with amino groups of chitosan. These additional junctions restrict polymer chain mobility and significantly improve tensile strength, elasticity, and resistance to deformation. As a result, nanocomposite hydrogels maintain structural integrity under physiological conditions.

Improved structural stability: Incorporation of MONPs reduces excessive swelling and slows hydrogel degradation. The nanoparticles occupy free volume inside the matrix and limit water penetration, leading to controlled swelling behaviour. This improves dimensional stability and extends functional lifetime, which is essential for wound dressings and implantable materials.

Ion-release mediated bioactivity: Many metal oxides release biologically active ions such as Zn^{2+}, Cu^{2+}, or Mg^{2+}. These ions participate in cellular signalling pathways, stimulate tissue regeneration, and inhibit microbial metabolism. The hydrogel matrix regulates ion diffusion, enabling sustained release rather than sudden exposure, thereby enhancing therapeutic efficiency while minimizing toxicity.

Synergistic antibacterial effects: The combination of chitosan and MONPs produces a cooperative antimicrobial mechanism. Chitosan disrupts the negatively charged bacterial membrane, increasing permeability, while nanoparticles penetrate more easily and generate oxidative damage. This dual action improves effectiveness against resistant bacteria and reduces the required nanoparticle concentration.

3.3 Potential Risks

Despite the advantages, incorporation of MONPs also introduces safety and performance concerns that must be carefully addressed before clinical application.

Cytotoxicity: At high concentrations, nanoparticles may damage mammalian cells through oxidative stress and mitochondrial dysfunction. Smaller particle size increases reactivity and may lead to undesired interactions with healthy tissues. Therefore, optimizing nanoparticle loading and dispersion is essential to maintain biocompatibility.

Excessive ion release: Although controlled ion release promotes antimicrobial activity, uncontrolled release can produce toxicity and inflammatory responses. Burst release during early swelling stages may harm surrounding tissues. Proper crosslinking density and particle encapsulation strategies are required to regulate ion diffusion.

Aggregation issues: Nanoparticles have a natural tendency to agglomerate due to high surface energy. Aggregation reduces active surface area, decreases antimicrobial efficiency, and creates structural defects within the hydrogel. Uniform dispersion

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

methods—such as in-situ synthesis or rapid heating techniques—are necessary to maintain consistent performance and reproducibility.

4.1 Conventional Preparation Methods

Traditional preparation techniques rely on solution chemistry and polymer crosslinking to incorporate MONPs into the chitosan network.

Sol–gel method

The sol–gel process involves hydrolysis and condensation of metal precursors within the polymer solution. Metal salts are converted into oxide nanoparticles while simultaneously forming a three-dimensional hydrogel network. This approach produces uniform dispersion because nanoparticles are generated inside the polymer matrix rather than added externally. The method allows precise control over porosity and is commonly used for ZnO, TiO_2, and MgO-based hydrogels [44,45].

In situ precipitation In situ precipitation is one of the most widely used methods for preparing nanocomposite hydrogels. Metal ions are introduced into dissolved chitosan and converted to nanoparticles by adjusting pH or adding a precipitating agent. The polymer chains act as stabilizing templates preventing particle agglomeration. This method improves particle–polymer interaction and enhances antibacterial efficiency due to intimate interfacial contact [46,47].

Chemical crosslinking: Chemical crosslinkers such as glutaraldehyde, genipin, or tripolyphosphate create covalent or ionic bridges between chitosan chains. Nanoparticles can be incorporated during crosslinking to form reinforced networks. Crosslinking improves mechanical strength, decreases solubility, and regulates swelling behaviour. However, residual crosslinking agents may affect cytocompatibility if not properly removed [46,47].

Freeze–thaw and freeze-drying: Freeze–thaw cycles create physical crosslinks through hydrogen bonding and crystalline domain formation. Freeze-drying further removes water to generate highly porous scaffolds. These methods produce interconnected pores beneficial for tissue engineering and wound healing, allowing oxygen diffusion and cell migration [48].

Sono chemical methods: Ultrasonic irradiation induces cavitation bubbles that collapse and generate localized high temperature and pressure. This energy promotes nanoparticle formation and uniform dispersion within the chitosan solution. Sono chemical synthesis often produces smaller particles and prevents aggregation compared to mechanical stirring [49].

4.2 Microwave Engineering

Microwave-assisted fabrication has emerged as a powerful alternative to conventional heating because it directly couples electromagnetic energy with the reacting molecules, enabling rapid and homogeneous reactions.

4.2.1 Principles of microwave-assisted synthesis

Microwave radiation interacts with polar molecules and ions through dipole rotation and ionic conduction. Instead of heating the vessel surface first, energy is generated inside the material, producing volumetric heating. This accelerates nucleation reactions and promotes uniform particle growth within the hydrogel matrix [50–52].

4.2.2 Advantages over conventional preparation

Rapid heating: Microwave irradiation heats the entire solution instantly, eliminating thermal gradients and reducing reaction time from hours to minutes [50,53].

Uniform energy distribution: Volumetric heating ensures homogeneous nucleation, resulting in narrow particle size distribution and improved dispersion in the polymer network [52].

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

Reduced synthesis time: Fast reaction kinetics shorten gelation and nanoparticle formation steps, enabling one-pot synthesis [50,53].

Controlled nucleation and particle size: Quick supersaturation favors nucleation over growth, producing smaller and more stable nanoparticles [51,52].

Energy efficiency: Microwave heating minimizes heat loss to surroundings and consumes less energy compared to conventional oil-bath or furnace heating [53].

4.2.3 Microwave-assisted fabrication routes

Microwave-assisted nanoparticle formation: Metal precursors are converted into MONPs directly within chitosan solution under microwave irradiation, producing highly dispersed nanocomposites [51,52].

Microwave-induced gelation of chitosan: Microwave exposure accelerates polymer chain interaction and crosslinking reactions, allowing rapid hydrogel formation without prolonged heating [50].

Composite gel formation with pre-formed MONPs: Pre-synthesized nanoparticles can be uniformly distributed into chitosan during microwave treatment, improving interfacial bonding and reducing aggregation [52].

4.3 Emerging and Hybrid Methods

Recent advances aim to improve sustainability, precision, and scalability of hydrogel fabrication.

Green synthesis (plant extracts, biominerals): Biological reducing agents from plants or biomolecules can generate nanoparticles inside chitosan matrices without toxic reagents, improving biocompatibility [54].

3D printing of chitosan-MONP gels: Additive manufacturing enables fabrication of patient-specific scaffolds with controlled porosity and architecture for tissue engineering applications [55].

Photo crosslinking and click chemistry: Light-activated or click reactions provide rapid and cytocompatibility gelation with precise control over crosslink density and mechanical properties [56].

Microfluidic-assisted gel formation: Microfluidic platforms allow continuous production of uniform hydrogel particles and injectable systems with controlled size distribution [57].

5. Structural, Physicochemical, and Mechanical Properties

Incorporation of metal-oxide nanoparticles (MONPs) into chitosan hydrogels significantly alters the internal architecture and bulk properties of the polymer network. The final performance of nanocomposite hydrogels depends on nanoparticle dispersion, polymer–particle interaction, and crosslink density. These factors influence porosity, swelling behaviour, mechanical strength, thermal stability, and morphological characteristics [58,60]. Microwave-assisted fabrication further modifies these parameters by controlling nucleation kinetics and network homogeneity [66–68].

5.1 Influence of Metal-Oxide Incorporation on Chitosan Matrix

Chitosan contains amino and hydroxyl functional groups capable of interacting with metal oxides through hydrogen bonding, electrostatic attraction, and coordination bonding. When nanoparticles are introduced into the hydrogel matrix, they act as multifunctional junction points within the polymer network [58,60]. This interaction restricts polymer chain mobility and transforms the soft hydrogel into a reinforced hybrid structure.

The inorganic phase also modifies crystallinity. Nanoparticles serve as nucleation sites that reorganize polymer chains, producing semi-crystalline regions within the otherwise amorphous chitosan matrix. As a result, nanocomposite hydrogels

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

display improved dimensional stability, reduced solubility, and enhanced resistance to deformation under physiological conditions [61,62].

5.2 Changes in Porosity, Swelling Behaviour, and Stability

Porosity is a critical factor governing oxygen diffusion, nutrient transport, and bacterial interaction. The presence of MONPs influences pore formation during gelation by occupying free volume and altering polymer packing density. Typically, nanoparticle addition produces smaller but more uniform pores, resulting in a controlled diffusion environment [59,63].

Swelling behaviour is strongly dependent on crosslink density. Pure chitosan hydrogels absorb large amounts of water due to abundant hydrophilic groups. After MONP incorporation, swelling ratio decreases because nanoparticles create additional physical crosslinks and limit polymer expansion [58,63]. Reduced swelling improves structural integrity and prevents premature degradation.

Furthermore, nanocomposite hydrogels exhibit enhanced stability in aqueous environments. The inorganic phase slows hydrolytic degradation and maintains scaffold integrity over extended periods, which is essential for wound healing and implant applications [62].

5.3 Mechanical Reinforcement by MONPs

Metal-oxide nanoparticles function as nanofillers that reinforce the polymer matrix similarly to composite materials. They transfer applied stress across the hydrogel network and prevent crack propagation. Mechanical parameters such as tensile strength, compressive modulus, and elasticity significantly increase after nanoparticle addition [58,61,65].

The reinforcement mechanism arises from strong interfacial bonding between the chitosan chains and nanoparticle surfaces. Uniform dispersion results in effective load transfer, whereas aggregated particles act as defects [64]. Therefore, particle size and distribution directly determine mechanical performance.

Higher mechanical strength enables nanocomposite hydrogels to withstand handling, implantation, and physiological movement without structural failure, expanding their usability in biomedical fields [58,65].

5.4 Thermal Properties

Thermal stability of chitosan hydrogels improves considerably upon MONP incorporation. Pure chitosan undergoes thermal degradation at relatively low temperatures due to depolymerization and dehydration reactions. Nanoparticles delay degradation by restricting polymer chain motion and acting as heat-resistant barriers [58,62].

Thermogravimetric behaviour typically shows increased degradation temperature and reduced weight loss rate in nanocomposite hydrogels, indicating stronger intermolecular interactions and enhanced resistance to thermal decomposition [62]. Improved thermal stability is particularly beneficial during sterilization processes and storage.

5.5 Morphology (SEM/TEM, Particle Dispersion)

Microscopic characterization reveals structural transformation after nanoparticle incorporation. Scanning electron microscopy commonly shows porous three-dimensional networks in pure chitosan gels, while nanocomposites exhibit more compact and organized structures [64,65].

Transmission electron microscopy confirms nanoparticle size and dispersion within the matrix. Ideally, nanoparticles are uniformly distributed and embedded within pore walls, ensuring effective reinforcement and antibacterial contact. Agglomeration leads to heterogeneous regions and deteriorates performance [64].

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

Surface roughness also increases in nanocomposite hydrogels, which can enhance bacterial interaction and improve antimicrobial efficiency [58].

5.6 Influence of Microwave Engineering on Structural Characteristics

Microwave-assisted synthesis significantly affects structural features of chitosan-MONP hydrogels. Rapid volumetric heating promotes instantaneous nucleation and prevents uncontrolled particle growth, resulting in smaller and more uniformly distributed nanoparticles [66,67].

The fast reaction kinetics also produce homogeneous crosslinking throughout the hydrogel rather than localized surface gelation. Consequently, microwave-fabricated hydrogels typically exhibit: narrower particle size distribution, improved nanoparticle dispersion, uniform pore architecture, enhanced mechanical strength, controlled swelling behaviour

These improvements arise from simultaneous nanoparticle formation and gelation under microwave irradiation [66–68]. The stronger polymer–particle interface directly enhances antibacterial performance and long-term stability.

6. Antibacterial Mechanisms and Performance

The antibacterial performance of chitosan–metal oxide nanoparticle (MONP) hydrogels arise from the combination of organic polymer activity and inorganic nanoparticle reactivity. Unlike traditional antibiotics that rely on a single biochemical pathway, nanocomposite hydrogels employ multiple simultaneous mechanisms such as membrane disruption, oxidative stress, ion release, and intracellular damage [74]. This multi-targeted approach reduces the probability of bacterial resistance and makes these materials highly promising for biomedical applications including wound healing, coatings, and infection-preventing implants.

6.1 Antibacterial Mechanisms of Chitosan

Chitosan exhibits intrinsic antimicrobial activity due to its polycationic nature. In acidic and physiological environments, amino groups of chitosan become protonated, allowing strong interaction with negatively charged bacterial cell walls [69,70].

Electrostatic interaction: Positively charged chitosan binds to negatively charged components of bacterial membranes such as lipopolysaccharides and teichoic acids. This interaction increases membrane permeability and disrupts ion balance, impairing essential cellular processes [69,70].

Membrane disruption: Adsorption of chitosan onto the cell surface forms a polymeric film that blocks nutrient transport and causes leakage of intracellular components including proteins and nucleic acids, ultimately leading to cell death [71].

Chelation of metals: Chitosan can bind trace metals required for microbial enzyme activity. By sequestering essential ions, the polymer inhibits metabolic pathways and prevents microbial growth [72].

Reactive oxygen species (ROS) contribution: Although chitosan itself is not a strong ROS producer, interaction with bacterial surfaces can induce oxidative stress, especially when combined with inorganic particles [69].

6.2 Antibacterial Mechanisms of MONPs

Metal-oxide nanoparticles contribute stronger bactericidal activity than the polymer matrix. Their nanoscale size enables penetration into bacterial cells and interaction with intracellular components [73,74].

ROS generation: Many metal oxides catalyse formation of reactive oxygen species such as hydroxyl radicals, superoxide radicals, and hydrogen peroxide, leading to oxidative damage of biomolecules [73,75].

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

Metal ion release: Nanoparticles gradually release metal ions (e.g., Zn^{2+}, Cu^{2+}, Fe^{2+}), which interfere with enzymatic reactions and disrupt cellular respiration pathways [75].

Interaction with bacterial membranes and proteins: Nanoparticles adsorb onto cell surfaces and penetrate cell walls due to their small size and high surface energy, causing physical membrane damage and protein denaturation [77].

DNA damage: Once inside the cell, nanoparticles and ROS interact with nucleic acids, leading to strand breakage and inhibition of replication [76].

6.3 Synergistic Antibacterial Properties of Chitosan–MONP Gels

Combining chitosan with MONPs produces cooperative antibacterial action that is significantly stronger than either component alone [74].

Enhanced ROS generation: Chitosan improves nanoparticle stability and dispersion, exposing more active surface area and intensifying oxidative stress [73,74].

Multi-mechanism bacterial killing: The polymer disrupts membrane permeability while nanoparticles enter the cell and generate intracellular damage, preventing bacterial adaptation [74].

Anti-biofilm potential: Biofilms protect bacteria from antibiotics through extracellular polymeric substances. Chitosan weakens biofilm adhesion while nanoparticles penetrate and destroy embedded bacteria [78,79].

Broad-spectrum activity: The combined system is effective against both Gram-positive and Gram-negative bacteria due to differences in killing pathways [69,74].

6.4 Microwave Effects on Antibacterial Performance

Microwave-assisted synthesis further enhances antibacterial performance by improving structural uniformity and nanoparticle activity.

Improved nanoparticle dispersion: Rapid volumetric heating prevents particle aggregation and distributes nanoparticles uniformly within the hydrogel matrix [80,81].

Enhanced ROS-related activity: Microwave-generated nanoparticles typically possess smaller size and higher surface reactivity, leading to increased oxidative species production [80].

Increased gel crosslinking and stability:Uniform crosslinking strengthens the hydrogel network, enabling sustained ion release and prolonged antimicrobial action without excessive toxicity [81].

7. Biomedical and Environmental Applications

Chitosan–metal oxide nanocomposite hydrogels combine biodegradability, antimicrobial activity, adsorption capability, and structural tunability. Because the organic matrix provides biocompatibility while metal oxides introduce catalytic and antibacterial functionality, these materials are widely explored in both biomedical and environmental fields. Their ability to maintain moisture, release active ions, and interact with biological or chemical contaminants makes them multifunctional platforms for healthcare and pollution control technologies.

7.1 Biomedical Applications

Wound Healing and Antibacterial Dressings

An ideal wound dressing should maintain a moist environment, allow oxygen exchange, absorb exudates, and prevent infection [82]. Chitosan hydrogels naturally promote haemostasis and cell adhesion due to their cationic nature [83], while incorporated

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

metal oxides enhance antimicrobial efficiency [84]. The nanocomposite hydrogel acts as a protective barrier that continuously releases antibacterial species and suppresses microbial colonization.

Additionally, metal ions such as zinc and copper support tissue regeneration by stimulating collagen synthesis and angiogenesis [83]. The porous structure enables nutrient diffusion and accelerates epithelial cell proliferation. As a result, nanocomposite hydrogels shorten healing time and reduce inflammation compared with conventional dressings [82].

Drug Delivery: Chitosan-based nanocomposite hydrogels are promising controlled drug delivery carriers because their swelling behaviour can be tuned by crosslinking density and nanoparticle loading [85]. The polymer network can encapsulate antibiotics, anti-inflammatory agents, or growth factors and release them gradually through diffusion and matrix degradation [86].

Metal oxides also act as functional regulators by altering pore size and providing pH-responsive or stimulus-responsive release behaviour [85]. The combination enables localized therapy, minimizes systemic side effects, and maintains therapeutic concentration over extended durations. These systems are particularly useful for infection treatment and post-surgical care [86].

Dental Applications: In dentistry, microbial biofilms are responsible for caries, pulp infections, and implant failure. Chitosan–MONP hydrogels are used as antimicrobial coatings for dental implants, root canal sealants, and periodontal treatments [87]. Their antibacterial activity inhibits oral pathogens while the polymer matrix promotes adhesion to tooth structures.

Furthermore, remineralizing ions released from metal oxides support enamel repair and dentin regeneration [88]. The materials also show compatibility with oral tissues, making them suitable for long-term dental applications.

Tissue Engineering (Cartilage, Bone, Skin): Tissue engineering scaffolds require a combination of mechanical strength, porosity, and biological activity [89]. Chitosan provides a biodegradable extracellular matrix–like structure, whereas metal oxides improve mechanical stability and cellular signalling.

For bone regeneration, nanoparticles release ions that stimulate osteoblast differentiation and mineral deposition [90]. In cartilage repair, hydrogels support chondrocyte growth by maintaining hydration and elasticity [89]. For skin regeneration, the porous network enables fibroblast migration and collagen formation [83]. The tuneable degradation rate allows the scaffold to gradually degrade as new tissue forms [89].

7.2 Environmental Applications

Water Purification: Chitosan contains amino groups capable of binding organic pollutants and microorganisms [91]. When combined with metal oxides, the hydrogel gains catalytic and antimicrobial functionality [93]. These materials remove dyes, pharmaceutical residues, and pathogens from contaminated water through adsorption and oxidative degradation mechanisms.

The porous structure provides high surface area and allows repeated usage after regeneration, making the system suitable for sustainable water treatment technologies [91].

Heavy Metal Adsorption: Nanocomposite hydrogels efficiently capture toxic metal ions such as lead, cadmium, chromium, and arsenic [92]. Chitosan chelates metal ions through coordination with amino groups, while metal oxide particles provide additional adsorption sites and sometimes redox transformation of contaminants [92,93].

The synergy improves adsorption capacity, selectivity, and reusability. This property is especially important for industrial wastewater treatment and environmental remediation [92].

Antimicrobial Coatings: Chitosan–MONP hydrogels can be applied as thin coatings on medical devices, packaging materials, and surfaces prone to microbial contamination [94]. The coating prevents bacterial attachment and biofilm formation by continuously releasing antimicrobial ions and maintaining an unfavourable surface charge for microbes.

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

Such coatings are useful in hospitals, food storage systems, and water distribution networks, reducing infection risk and improving hygiene safety [94].

8. Safety, Toxicology, and Biocompatibility

The incorporation of metal-oxide nanoparticles (MONPs) into chitosan matrices significantly enhances functional performance; however, biomedical application requires careful evaluation of toxicity and biological safety. The interaction of nanoparticles with living tissues depends on their size, concentration, dissolution behaviour, and synthesis route. While chitosan itself is highly biocompatible, metal oxides may induce oxidative stress, inflammation, or cellular damage if not properly controlled [95,108].

8.1 Cytotoxicity Concerns of MONPs

Metal-oxide nanoparticles may generate reactive oxygen species (ROS) when exposed to aqueous biological environments, leading to oxidative stress, lipid peroxidation, and mitochondrial dysfunction in mammalian cells [95,97]. ZnO and CuO nanoparticles are particularly known to release ions and produce intracellular oxidative damage, which can disrupt membrane integrity and protein function [96,98]. TiO_2 nanoparticles, although relatively stable, may still cause cellular stress depending on particle size and exposure duration [99].

Embedding MONPs within a chitosan hydrogel significantly reduces direct cellular exposure by immobilizing particles inside the polymeric network, thereby lowering cytotoxicity while maintaining antibacterial activity [104]. Thus, the nanocomposite structure acts as a protective regulator that balances antimicrobial performance and cellular compatibility.

8.2 Dose-Dependent Toxicity

Nanoparticle toxicity is strongly concentration-dependent. At low concentrations, released metal ions may promote cellular signalling and tissue regeneration, whereas higher concentrations lead to apoptosis and necrosis [100]. Studies on ZnO nanoparticles demonstrate selective toxicity: bacteria are inhibited at concentrations that remain tolerable to mammalian cells [100,101].

Particle size also plays a critical role; smaller nanoparticles possess higher surface energy and dissolve more rapidly, increasing ion release and toxic potential [102]. Therefore, optimizing nanoparticle loading inside the hydrogel matrix is essential to achieve therapeutic effectiveness without damaging surrounding tissues.

8.3 Influence of Synthesis Method on Safety

The synthesis route directly affects nanoparticle surface chemistry, crystallinity, and residual impurities, which in turn determine biological safety. Chemically synthesized nanoparticles may contain toxic reagents or stabilizers, while green-synthesized particles prepared using plant extracts often show improved biocompatibility and reduced oxidative damage [103].

Encapsulation within nanocomposite hydrogels further enhances safety by controlling particle dispersion and limiting burst ion release [104]. Uniformly distributed nanoparticles prevent local accumulation, reducing inflammatory responses and improving long-term stability in physiological environments.

8.4 In Vitro and In Vivo Biocompatibility Studies

Biocompatibility of chitosan–MONP hydrogels is commonly evaluated through standardized cytotoxicity assays such as ISO 10993-5 testing [105]. Most studies report high cell viability, good fibroblast adhesion, and enhanced proliferation when nanoparticle concentration remains within optimized limits [106].

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

In vivo experiments further demonstrate favourable biological response, including reduced inflammation, accelerated tissue regeneration, and enhanced wound closure [107]. The presence of chitosan improves cellular attachment and extracellular matrix formation, while controlled metal-ion release stimulates healing pathways [108].

Overall, when properly engineered, chitosan-MONP nanocomposites exhibit acceptable biosafety profiles and are considered promising candidates for clinical biomedical applications.

9. Challenges and Research Gaps

Despite the rapid progress in chitosan–metal oxide nanocomposite hydrogels, several scientific and technological limitations still restrict their transition from laboratory studies to large-scale clinical and industrial use. Current research mainly demonstrates short-term antibacterial efficiency and material characterization, whereas long-term safety, manufacturing reproducibility, and regulatory acceptance remain insufficiently addressed. Identifying these gaps is essential for guiding future investigations and improving practical implementation.

9.1 Difficulty in Controlling Nanoparticle Dispersion

Uniform dispersion of metal-oxide nanoparticles inside the chitosan matrix is one of the most critical challenges. Nanoparticles possess high surface energy and tend to agglomerate during synthesis or drying processes [109]. Aggregation reduces active surface area, weakens antibacterial efficiency, and produces structural defects such as pore collapse or heterogeneous mechanical regions within the hydrogel.

Although in-situ synthesis and microwave heating improve distribution, complete stabilization is rarely achieved, especially at higher nanoparticle loadings. Future work must focus on surface functionalization, polymer–particle interface engineering, and advanced mixing techniques to obtain stable nanoscale dispersion throughout the hydrogel network [110].

9.2 Stability and Reproducibility Issues

Many reported nanocomposite hydrogels show promising laboratory performance but suffer from batch-to-batch variability. Small changes in pH, temperature, polymer molecular weight, or precursor concentration significantly alter gelation behaviour and particle nucleation, resulting in inconsistent porosity, swelling ratio, and antimicrobial performance [110,111].

Long-term storage stability is also poorly understood. Hydrogels may undergo dehydration, structural shrinkage, or gradual nanoparticle migration over time [111]. Therefore, standardized fabrication parameters and quality-control protocols are required to achieve reproducible material properties suitable for commercial production.

9.3 Incomplete Understanding of Long-Term Toxicity

Most toxicity studies evaluate short-term cytocompatibility using in-vitro assays, but chronic exposure effects remain largely unknown. Slow ion release, nanoparticle degradation products, and possible accumulation inside tissues could produce delayed inflammatory or oxidative responses [112,113].

In addition, interactions with immune systems, microbiome imbalance, and environmental release after disposal have not been sufficiently investigated. Long-duration in-vivo studies, degradation pathway analysis, and pharmacokinetic evaluations are essential to establish safe exposure limits for clinical application [118].

9.4 Scale-Up Limitations for Microwave Synthesis

Microwave-assisted synthesis provides rapid heating and uniform nucleation at laboratory scale; however, scaling this technique to industrial production is challenging. Microwave penetration depth decreases with increasing reaction volume, leading to uneven heating and inconsistent nanoparticle formation [114,115].

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

Large-scale reactors also require precise power control, pressure management, and material compatibility, which increases equipment complexity and cost. Developing continuous-flow microwave reactors or hybrid heating systems is necessary to maintain the advantages of microwave processing while enabling mass production [115].

9.5 Regulatory and Standardization Barriers

For biomedical applications, regulatory approval requires comprehensive safety data, reproducible manufacturing protocols, and standardized characterization methods. Currently, no universally accepted guidelines exist for evaluating nanocomposite hydrogels, particularly regarding nanoparticle release limits and long-term exposure effects [116,117].

Differences in international regulations further complicate commercialization. Establishing standardized testing procedures, reporting formats, and material classification frameworks will be crucial for translating chitosan–MONP hydrogels from research prototypes into clinically approved products [118].

10. Future Perspectives

Chitosan–metal oxide nanocomposite hydrogels have demonstrated significant promise in antibacterial therapy, regenerative medicine, and environmental remediation. However, future research is expected to move beyond passive materials toward intelligent, adaptive, and clinically translatable systems. Emerging interdisciplinary approaches combining materials science, artificial intelligence, and advanced manufacturing will play a major role in transforming these nanocomposites into next-generation functional biomaterials.

10.1 Smart and Stimuli-Responsive Chitosan–MONP Gels

Future hydrogels will increasingly function as *responsive therapeutic systems* rather than static dressings or coatings. By integrating responsive linkages and functional nanoparticles, chitosan–MONP gels can be designed to react to environmental triggers such as pH, temperature, enzymes, light, or infection-related biochemical signals [119,120].

For example, infected wounds typically exhibit acidic pH and elevated bacterial enzyme activity. A smart hydrogel could selectively release antimicrobial ions or drugs only under these pathological conditions, minimizing damage to healthy tissue [121]. Similarly, temperature-sensitive gels may undergo sol–gel transition at body temperature, enabling injectable therapies that solidify in situ. Light-responsive nanoparticles may also enable externally controlled antimicrobial activation or on-demand drug release.

Such dynamic behaviour will improve treatment precision, reduce antibiotic overuse, and extend material lifetime, making hydrogels more compatible with personalized and minimally invasive medicine.

10.2 AI-Guided Nanoparticle Optimization

Artificial intelligence and machine learning are expected to revolutionize biomaterial development by predicting material performance prior to experimental fabrication. Chitosan–MONP systems contain numerous tuneable variables, including nanoparticle size, concentration, surface charge, crosslinking density, and synthesis conditions. Traditional trial-and-error optimization is time-consuming and inefficient.

AI models can analyse large experimental datasets to identify relationships between structural parameters and biological performance such as antibacterial efficiency, cytotoxicity, and degradation rate [122]. Predictive algorithms may guide the selection of optimal compositions and synthesis parameters, significantly accelerating material discovery. In the future, automated laboratories integrated with machine learning could design hydrogels tailored for specific pathogens or clinical conditions [123].

10.3 Personalized Biomedical Gels

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

Personalized medicine aims to tailor treatments according to patient-specific physiological conditions. Chitosan nanocomposite hydrogels offer an adaptable platform for individualized therapies because their mechanical strength, degradation rate, drug loading, and ion release profile can be easily tuned [124].

Patient-specific wound dressings could be fabricated based on infection severity, healing rate, or comorbidities such as diabetes. Injectable gels may deliver customized growth factor combinations depending on tissue regeneration requirements. Additionally, hydrogels could incorporate patient-derived cells or biomolecules to enhance compatibility and reduce immune reactions [125].

The integration of biosensors into hydrogels may allow real-time monitoring of infection markers, pH changes, or inflammation, enabling feedback-controlled therapy directly at the treatment site.

10.4 Hybrid Metal-Oxide and Organic Nanostructures

Future research is expected to move toward multi-component nanostructures that combine metal oxides with organic nanomaterials such as graphene derivatives, biopolymers, or bioactive molecules. Hybrid systems can integrate complementary functions within a single material [126].

For instance, metal oxides provide antimicrobial activity, while carbon-based nanomaterials offer electrical conductivity and mechanical reinforcement. Such conductive hydrogels could stimulate cell proliferation in nerve or muscle regeneration [127]. Incorporating bioactive peptides or natural antioxidants may further enhance healing while reducing oxidative damage to host tissues.

By combining multiple nanoscale functionalities, these hybrid hydrogels could perform simultaneous infection control, tissue regeneration, and biosensing — representing a transition toward multifunctional therapeutic platforms.

10.5 Pathways Toward Industrial Manufacturing

For practical translation, scalable production methods must be developed without compromising material uniformity. Continuous-flow microwave reactors, automated mixing systems, and standardized precursor formulations are potential approaches to achieve reproducible fabrication [128]. Process optimization should focus on consistent nanoparticle dispersion, controlled crosslinking, and long-term storage stability.

Regulatory acceptance will require validated safety protocols, reproducible quality control, and standardized characterization procedures. Advanced fabrication technologies such as additive manufacturing and 3D printing may further enable customizable biomedical hydrogel production [129,130]. Collaboration between researchers, clinicians, and industry partners will be necessary to bridge the gap between laboratory prototypes and commercial biomedical products.

Conclusion

Chitosan–metal oxide nanocomposite hydrogels represent an important class of multifunctional biomaterials that integrate the biological advantages of natural polymers with the physicochemical performance of inorganic nanomaterials. Throughout this review, the structural characteristics of chitosan, the functional contributions of various metal-oxide nanoparticles, and the influence of fabrication techniques—particularly microwave-assisted synthesis—have been discussed in relation to antibacterial efficiency and material performance.

Native chitosan hydrogels provide biodegradability, biocompatibility, and inherent antimicrobial activity, yet their weak mechanical strength and limited long-term stability restrict advanced biomedical usage. The incorporation of metal-oxide nanoparticles significantly enhances structural integrity, regulates swelling behaviour, and introduces multiple antibacterial mechanisms including membrane disruption, ion release, and oxidative stress induction. The resulting hybrid systems exhibit synergistic effects that improve microbial inhibition while maintaining biological compatibility when appropriately optimized.

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

Among fabrication strategies, microwave-assisted synthesis has emerged as a promising method due to rapid volumetric heating, uniform nanoparticle nucleation, reduced reaction time, and improved dispersion within the polymer matrix. These advantages allow better control over particle size and hydrogel architecture compared with conventional preparation approaches. Consequently, microwave-engineered nanocomposite hydrogels demonstrate improved reproducibility, enhanced antibacterial activity, and more predictable physicochemical properties.

The materials show broad applicability in wound healing, drug delivery, tissue engineering, dental care, water purification, and antimicrobial coatings. However, challenges remain regarding nanoparticle aggregation, large-scale fabrication, long-term toxicity evaluation, and regulatory standardization. Addressing these limitations requires interdisciplinary efforts combining materials science, toxicology, engineering design, and clinical validation.

Future developments are expected to focus on smart responsive hydrogels, personalized therapeutic systems, hybrid multifunctional nanostructures, and scalable manufacturing processes. With continued optimization and standardized safety assessment, chitosan–metal oxide nanocomposite hydrogels have strong potential to transition from laboratory research to practical biomedical and environmental technologies, contributing to next-generation antimicrobial materials and sustainable healthcare solutions.

References

1. Ahmed, E. M. (2015). Hydrogel: Preparation, characterization, and applications: A review. *Journal of Advanced Research*, 6, 105–121.

2. Caló, E., & Khutoryanskiy, V. V. (2015). Biomedical applications of hydrogels: A review of patents and commercial products. *European Polymer Journal*, 65, 252–267.

3. Rinaudo, M. (2006). Chitin and chitosan: Properties and applications. *Progress in Polymer Science*, 31, 603–632.

4. Dash, M., Chiellini, F., Ottenbrite, R. M., & Chiellini, E. (2011). Chitosan—A versatile semi-synthetic polymer in biomedical applications. *Progress in Polymer Science*, 36, 981–1014.

5. Kong, M., Chen, X. G., Xing, K., & Park, H. J. (2010). Antimicrobial properties of chitosan and mode of action. *International Journal of Food Microbiology*, 144, 51–63.

6. Jayakumar, R., Prabaharan, M., Sudheesh Kumar, P. T., Nair, S. V., & Tamura, H. (2011). Biomedical applications of chitin and chitosan-based nanomaterials. *Biotechnology Advances*, 29, 322–337.

7. Dizaj, S. M., Lotfipour, F., Barzegar-Jalali, M., Zarrintan, M. H., & Adibkia, K. (2014). Antimicrobial activity of metal oxide nanoparticles. *Materials Science & Engineering C*, 44, 278–284.

8. Jones, N., Ray, B., Ranjit, K. T., & Manna, A. C. (2008). Antibacterial activity of ZnO nanoparticle suspensions. *FEMS Microbiology Letters*, 279, 71–76.

9. Kappe, C. O. (2004). Controlled microwave heating in modern organic synthesis. *Angewandte Chemie International Edition*, 43, 6250–6284.

10. Bilecka, I., & Niederberger, M. (2010). Microwave chemistry for inorganic nanomaterials synthesis. *Nanoscale*, 2, 1358–1374.

11. Gaharwar, A. K., Peppas, N. A., & Khademhosseini, A. (2014). Nanocomposite hydrogels for biomedical applications. *Biotechnology Advances*, 32, 971–983.

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

12. Boateng, J. S., Matthews, K. H., Stevens, H. N., & Eccleston, G. M. (2008). Wound healing dressings and drug delivery systems: A review. *Journal of Pharmaceutical Sciences*, 97, 2892–2923.

13. Kumar, M. N. V. R. (2000). A review of chitin and chitosan applications. *Reactive & Functional Polymers*, 46, 1–27.

14. Younes, I., & Rinaudo, M. (2015). Chitin and chitosan preparation from marine sources. *Marine Drugs*, 13, 1133–1174.

15. Roberts, G. A. F. (1992). *Chitin Chemistry*. Macmillan Press.

16. Pillai, C. K. S., Paul, W., & Sharma, C. P. (2009). Chitin and chitosan polymers: Chemistry, solubility and fiber formation. *Progress in Polymer Science*, 34, 641–678.

17. Hosseinnejad, M., & Jafari, S. M. (2016). Evaluation of antibacterial activity of chitosan. *Food Hydrocolloids*, 61, 1–11.

18. Raafat, D., & Sahl, H. G. (2009). Chitosan and its antimicrobial potential – a critical review. *Microbial Biotechnology*, 2, 186–201.

19. Elsabee, M. Z., & Abdou, E. S. (2013). Chitosan based edible films and coatings. *Materials Science & Engineering C*, 33, 1819–1841.

20. Berger, J., Reist, M., Mayer, J. M., Felt, O., & Gurny, R. (2004). Structure and interactions in chitosan hydrogels. *European Journal of Pharmaceutics and Biopharmaceutics*, 57, 35–52.

21. Bhattarai, N., Gunn, J., & Zhang, M. (2010). Chitosan-based hydrogels for controlled drug delivery. *Advanced Drug Delivery Reviews*, 62, 83–99.

22. Kołodziejska, I., & Sikorski, Z. E. (2012). Properties of chitosan and its application. *Food Chemistry*, 132, 1–7.

23. Sirelkhatim, A., Mahmud, S., Seeni, A., et al. (2015). Review on zinc oxide nanoparticles: antibacterial activity and toxicity mechanism. *Nano-Micro Letters*, 7, 219–242.

24. Raghupathi, K. R., Koodali, R. T., & Manna, A. C. (2011). Size-dependent bacterial growth inhibition by ZnO nanoparticles. *Langmuir*, 27, 4020–4028.

25. Ren, G., Hu, D., Cheng, E. W., Vargas-Reus, M. A., Reip, P., & Allaker, R. P. (2009). Characterisation of copper oxide nanoparticles for antimicrobial applications. *International Journal of Antimicrobial Agents*, 33, 587–590.

26. Azam, A., Ahmed, A. S., Oves, M., Khan, M. S., Memic, A., & Möller, M. (2012). Antimicrobial activity of metal oxide nanoparticles against Gram-positive and Gram-negative bacteria. *International Journal of Nanomedicine*, 7, 6003–6009.

27. Fujishima, A., Zhang, X., & Tryk, D. A. (2008). TiO_2 photocatalysis and related surface phenomena. *Surface Science Reports*, 63, 515–582.

28. Laurent, S., Forge, D., Port, M., et al. (2008). Magnetic iron oxide nanoparticles: synthesis, stabilization, and biomedical applications. *Chemical Reviews*, 108, 2064–2110.

29. Sawai, J. (2003). Quantitative evaluation of antibacterial activity of magnesium oxide powder. *Journal of Chemical Engineering of Japan*, 36, 954–956.

30. Das, M., Patil, S., Bhargava, N., et al. (2007). Cerium oxide nanoparticles: applications and prospects in nanomedicine. *Nanomedicine*, 2, 755–767.

31. Zhang, L., Pornpattananangkul, D., Hu, C. M. J., & Huang, C. M. (2010). Synergistic antibacterial activity of metal oxide nanoparticle combinations. *Applied Microbiology and Biotechnology*, 86, 1237–1245.

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

32. Gaharwar, A. K., Peppas, N. A., & Khademhosseini, A. (2014). Nanocomposite hydrogels for biomedical applications. *Biotechnology Advances*, 32, 971–983.

33. Rai, M., Yadav, A., & Gade, A. (2009). Silver and metal oxide nanoparticles as antimicrobial agents. *Biotechnology Advances*, 27, 76–83.

34. Gaharwar, A. K., Cross, L. M., Peak, C. W., et al. (2019). 2D nanomaterials in biomedical applications: nanocomposite hydrogels. *Advanced Materials*, 31, 1900332.

35. Hetrick, E. M., & Schoenfisch, M. H. (2006). Reducing implant-related infections: antibacterial biomaterials. *Chemical Society Reviews*, 35, 780–789.

36. Dizaj, S. M., Lotfipour, F., Barzegar-Jalali, M., et al. (2014). Antimicrobial activity of metal oxide nanoparticles. *Materials Science & Engineering C*, 44, 278–284.

37. Hajipour, M. J., Fromm, K. M., Ashkarran, A. A., et al. (2012). Antibacterial properties of nanoparticles. *Trends in Biotechnology*, 30, 499–511.

38. Jones, N., Ray, B., Ranjit, K. T., & Manna, A. C. (2008). Antibacterial activity of ZnO nanoparticles. *FEMS Microbiology Letters*, 279, 71–76.

39. Zhang, L., Pornpattananangkul, D., Hu, C. M. J., & Huang, C. M. (2010). Nanoparticles in medicine: therapeutic applications and safety concerns. *ACS Nano*, 4, 5840–5854.

40. Nel, A., Xia, T., Mädler, L., & Li, N. (2006). Toxic potential of nanomaterials. *Science*, 311, 622–627.

41. Shi, J., Votruba, A. R., Farokhzad, O. C., & Langer, R. (2010). Nanotechnology in drug delivery and tissue engineering. *Nano Letters*, 10, 3223–3230.

42. Cho, W. S., et al. (2012). Metal oxide nanoparticles induce inflammatory responses. *Particle and Fibre Toxicology*, 9, 17.

43. Bhattacharjee, S. (2016). DLS and zeta potential: nanoparticle aggregation behaviour. *Journal of Controlled Release*, 235, 337–351.

44. Brinker, C. J., & Scherer, G. W. (2013). *Sol–Gel Science: The Physics and Chemistry of Sol–Gel Processing*. Academic Press.

45. Stöber, W., Fink, A., & Bohn, E. (1968). Controlled growth of monodisperse silica spheres. *Journal of Colloid and Interface Science*, 26, 62–69.

46. Rinaudo, M. (2006). Chitin and chitosan: properties and applications. *Progress in Polymer Science*, 31, 603–632.

47. Dash, M., Chiellini, F., Ottenbrite, R. M., & Chiellini, E. (2011). Chitosan—A versatile semi-synthetic polymer in biomedical applications. *Progress in Polymer Science*, 36, 981–1014.

48. Hassan, C. M., & Peppas, N. A. (2000). Structure and morphology of freeze–thawed hydrogels. *Macromolecules*, 33, 2472–2479.

49. Suslick, K. S. (1990). Sonochemistry. *Science*, 247, 1439–1445.

50. Kappe, C. O. (2004). Controlled microwave heating in modern organic synthesis. *Angewandte Chemie International Edition*, 43, 6250–6284.

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

51. Bilecka, I., & Niederberger, M. (2010). Microwave chemistry for inorganic nanomaterials synthesis. *Nanoscale*, 2, 1358–1374.
52. Horikoshi, S., & Serpone, N. (2013). *Microwaves in Nanoparticle Synthesis: Fundamentals and Applications*. Wiley.
53. Polshettiwar, V., & Varma, R. S. (2010). Green chemistry by microwave irradiation. *Green Chemistry*, 12, 743–754.
54. Iravani, S. (2011). Green synthesis of metal nanoparticles using plant extracts. *Green Chemistry*, 13, 2638–2650.
55. Murphy, S. V., & Atala, A. (2014). 3D bioprinting of tissues and organs. *Nature Biotechnology*, 32, 773–785.
56. DeForest, C. A., & Anseth, K. S. (2011). Cytocompatible click-based hydrogels. *Nature Chemistry*, 3, 925–931.
57. Whitesides, G. M. (2006). The origins and future of microfluidics. *Nature*, 442, 368–373.
58. Gaharwar, A. K., Peppas, N. A., & Khademhosseini, A. (2014). Nanocomposite hydrogels for biomedical applications. *Biotechnology and Bioengineering*, 111, 441–453.
59. Ahmed, E. M. (2015). Hydrogel: preparation, characterization, and applications. *Journal of Advanced Research*, 6, 105–121.
60. Dash, M., Chiellini, F., Ottenbrite, R. M., & Chiellini, E. (2011). Chitosan—A versatile semi-synthetic polymer in biomedical applications. *Progress in Polymer Science*, 36, 981–1014.
61. Díez-Pascual, A. M., & Díez-Vicente, A. L. (2016). ZnO-reinforced polymer nanocomposites for biomedical applications. *ACS Applied Materials & Interfaces*, 8, 17902–17920.
62. Szymańska, E., & Winnicka, K. (2015). Stability of chitosan—a challenge for pharmaceutical applications. *Marine Drugs*, 13, 1819–1846.
63. Rinaudo, M. (2006). Chitin and chitosan: properties and applications. *Progress in Polymer Science*, 31, 603–632.
64. Tang, B., et al. (2012). Preparation and characterization of chitosan/ZnO nanocomposite hydrogels. *Carbohydrate Polymers*, 89, 1030–1036.
65. El-Fawal, G. F., Abu-Serie, M. M., Hassan, M. A., & Elnouby, M. (2017). Hydroxyapatite/chitosan nanocomposite scaffold characterization. *Materials Science and Engineering C*, 79, 673–681.
66. Bilecka, I., & Niederberger, M. (2010). Microwave chemistry for inorganic nanomaterials synthesis. *Nanoscale*, 2, 1358–1374.
67. Horikoshi, S., & Serpone, N. (2013). *Microwaves in Nanoparticle Synthesis: Fundamentals and Applications*. Wiley.
68. Polshettiwar, V., & Varma, R. S. (2010). Green chemistry by microwave irradiation. *Green Chemistry*, 12, 743–754.
69. Kong, M., Chen, X. G., Xing, K., & Park, H. J. (2010). Antimicrobial properties of chitosan and mode of action: A state of the art review. *International Journal of Food Microbiology*, 144, 51–63.
70. Raafat, D., & Sahl, H. G. (2009). Chitosan and its antimicrobial potential. *Biomacromolecules*, 10, 131–137.
71. Helander, I. M., Nurmiaho-Lassila, E. L., Ahvenainen, R., et al. (2001). Chitosan disrupts bacterial cell membrane permeability. *International Journal of Food Microbiology*, 71, 235–244.
72. Liu, H., Du, Y., Wang, X., & Sun, L. (2004). Chitosan kills bacteria through metal chelation. *Carbohydrate Polymers*, 56, 243–250.
73. Dizaj, S. M., Lotfipour, F., Barzegar-Jalali, M., et al. (2014). Antimicrobial activity of metal oxide nanoparticles. *Materials Science & Engineering C*, 44, 278–284.
74. Hajipour, M. J., Fromm, K. M., Ashkarran, A. A., et al. (2012). Antibacterial properties of nanoparticles. *Trends in Biotechnology*, 30, 499–511.
75. Jones, N., Ray, B., Ranjit, K. T., & Manna, A. C. (2008). Antibacterial activity of ZnO nanoparticles. *FEMS Microbiology Letters*, 279, 71–76.
76. Zhang, L., Pornpattananangkul, D., Hu, C. M. J., & Huang, C. M. (2010). Nanoparticles in medicine: therapeutic applications and safety. *ACS Nano*, 4, 5840–5854.
77. Morones, J. R., Elechiguerra, J. L., Camacho, A., et al. (2005). Nanoparticles damage bacterial membranes. *Nanotechnology*, 16, 2346–2353.
78. Hall-Stoodley, L., Costerton, J. W., & Stoodley, P. (2004). Bacterial biofilms: from environment to infectious disease. *Nature Reviews Microbiology*, 2, 95–108.

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

79. Wu, M. C., Deokar, A. R., Liao, J. H., et al. (2013). Graphene-based antimicrobial materials. *ACS Nano*, 7, 1281–1290.
80. Bilecka, I., & Niederberger, M. (2010). Microwave chemistry for inorganic nanomaterials synthesis. *Nanoscale*, 2, 1358–1374.
81. Horikoshi, S., & Serpone, N. (2013). *Microwaves in Nanoparticle Synthesis: Fundamentals and Applications*. Wiley.
82. Boateng, J. S., Matthews, K. H., Stevens, H. N., & Eccleston, G. M. (2008). Wound healing dressings and drug delivery systems: A review. *Journal of Pharmaceutical Sciences*, 97, 2892–2923.
83. Dash, M., Chiellini, F., Ottenbrite, R. M., & Chiellini, E. (2011). Chitosan—A versatile semi-synthetic polymer in biomedical applications. *Progress in Polymer Science*, 36, 981–1014.
84. Raghavendra, G. M., Jayaramudu, T., Varaprasad, K., Sadiku, R., & Ray, S. S. (2017). Development of smart antimicrobial hydrogels based on chitosan and metal oxide nanoparticles for biomedical applications. *Carbohydrate Polymers*, 186, 46–54.
85. Ahmed, E. M. (2015). Hydrogel: Preparation, characterization, and applications—A review. *Journal of Advanced Research*, 6, 105–121.
86. Peppas, N. A., Hilt, J. Z., Khademhosseini, A., & Langer, R. (2006). Hydrogels in biology and medicine: From molecular principles to biomedical applications. *Advanced Materials*, 18, 1345–1360.
87. Shrestha, A., Zhilong, S., Gee, N. K., & Kishen, A. (2010). Nanoparticulates for antibiofilm treatment and effect on bacterial viability in endodontic infections. *Journal of Endodontics*, 36, 1035–1040.
88. Xu, H. H., Weir, M. D., Sun, L., & Moreau, J. L. (2011). Nanocomposite dental materials with calcium phosphate nanoparticles for remineralization. *Dental Materials*, 27, 762–769.
89. O'Brien, F. J. (2011). Biomaterials and scaffolds for tissue engineering. *Materials Today*, 14, 88–95.
90. Bose, S., Roy, M., & Bandyopadhyay, A. (2012). Recent advances in bone tissue engineering scaffolds. *Trends in Biotechnology*, 30, 546–554.
91. Crini, G., & Badot, P. M. (2008). Application of chitosan for dye removal from aqueous solutions. *Progress in Polymer Science*, 33, 399–447.
92. Vakili, M., Rafatullah, M., Salamatinia, B., et al. (2014). Application of chitosan and its derivatives as adsorbents for dye removal. *Carbohydrate Polymers*, 113, 115–130.
93. Rinaudo, M. (2006). Chitosan: Properties and applications. *Progress in Polymer Science*, 31, 603–632.
94. Kong, M., Chen, X. G., Xing, K., & Park, H. J. (2010). Antimicrobial properties of chitosan and mode of action. *International Journal of Food Microbiology*, 144, 51–63.
95. Nel, A., Xia, T., Mädler, L., & Li, N. (2006). Toxic potential of materials at the nanolevel. *Science*, 311, 622–627.
96. Xia, T., Kovochich, M., Liong, M., et al. (2008). Mechanism of toxicity of ZnO and CeO_2 nanoparticles. *ACS Nano*, 2, 2121–2134.
97. Fu, P. P., Xia, Q., Hwang, H. M., Ray, P. C., & Yu, H. (2014). Mechanisms of nanotoxicity: Generation of reactive oxygen species. *Journal of Food and Drug Analysis*, 22, 64–75.
98. Karlsson, H. L., Cronholm, P., Hedberg, Y., et al. (2008). Cell membrane damage induced by CuO nanoparticles. *Chemical Research in Toxicology*, 21, 1726–1732.
99. Shi, H., Magaye, R., Castranova, V., & Zhao, J. (2013). Titanium dioxide nanoparticles toxicology review. *Particle and Fibre Toxicology*, 10, 15.
100. Reddy, K. M., Feris, K., Bell, J., et al. (2007). Selective toxicity of ZnO nanoparticles to bacteria and cancer cells. *Applied Physics Letters*, 90, 213902.
101. Franklin, N. M., Rogers, N. J., Apte, S. C., et al. (2007). Comparative toxicity of nanoparticulate ZnO. *Environmental Science & Technology*, 41, 8484–8490.
102. Fadeel, B., & Garcia-Bennett, A. E. (2010). Understanding nanoparticle toxicity. *Advanced Drug Delivery Reviews*, 62, 362–374.
103. Iravani, S. (2011). Green synthesis of metal nanoparticles using plants. *Green Chemistry*, 13, 2638–2650.

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.

104. Gaharwar, A. K., Peppas, N. A., & Khademhosseini, A. (2014). Nanocomposite hydrogels for biomedical applications. *Biotechnology and Bioengineering*, 111, 441–453.
105. ISO 10993-5 (2009). Biological evaluation of medical devices — Tests for in vitro cytotoxicity.
106. Balagangadharan, K., Dhivya, S., & Selvamurugan, N. (2017). Chitosan based nanocomposites for tissue engineering. *International Journal of Biological Macromolecules*, 104, 1378–1387.
107. Augustine, R., et al. (2016). Electrospun PCL/ZnO nanocomposite membranes for wound healing. *ACS Applied Materials & Interfaces*, 8, 30092–30103.
108. Dash, M., et al. (2011). Chitosan—A versatile biomaterial for tissue engineering and drug delivery. *Progress in Polymer Science*, 36, 981–1014.
109. Bhattacharjee, S. (2016). DLS and zeta potential – What they are and what they are not? *Journal of Controlled Release*, 235, 337–351.
110. Gaharwar, A. K., Peppas, N. A., & Khademhosseini, A. (2014). Nanocomposite hydrogels for biomedical applications. *Biotechnology and Bioengineering*, 111, 441–453.
111. Ahmed, E. M. (2015). Hydrogel preparation and applications. *Journal of Advanced Research*, 6, 105–121.
112. Nel, A., Xia, T., Mädler, L., & Li, N. (2006). Toxic potential of nanomaterials. *Science*, 311, 622–627.
113. Fadeel, B., & Garcia-Bennett, A. E. (2010). Understanding nanoparticle toxicology. *Advanced Drug Delivery Reviews*, 62, 362–374.
114. Horikoshi, S., & Serpone, N. (2013). *Microwaves in Nanoparticle Synthesis*. Wiley-VCH.
115. Bilecka, I., & Niederberger, M. (2010). Microwave chemistry for inorganic nanomaterials synthesis. *Nanoscale*, 2, 1358–1374.
116. Rauscher, H., Roebben, G., Mech, A., et al. (2019). Concepts used in the EU definition of nanomaterial. *JRC Technical Reports*.
117. ISO/TR 10993-22 (2017). Biological evaluation of medical devices — Guidance on nanomaterials.
118. Fadeel, B., Farcal, L., Hardy, B., et al. (2018). Advanced tools for nanomaterial safety assessment. *Nature Nanotechnology*, 13, 537–543.
119. Koetting, M. C., Peters, J. T., Steichen, S. D., & Peppas, N. A. (2015). Stimulus-responsive hydrogels. *Materials Science and Engineering R*, 93, 1–49.
120. Wei, M., Gao, Y., Li, X., & Serpe, M. J. (2017). Stimuli-responsive polymers and applications. *Polymers*, 9, 1–23.
121. Yang, Y., et al. (2020). Smart hydrogel-based drug delivery systems. *Chemical Society Reviews*, 49, 4233–4256.
122. Butler, K. T., Davies, D. W., Cartwright, H., Isayev, O., & Walsh, A. (2018). Machine learning for materials science. *Nature*, 559, 547–555.
123. Stokes, J. M., et al. (2020). A deep learning approach to antibiotic discovery. *Cell*, 180, 688–702.
124. Ashley, E. A. (2016). Towards precision medicine. *Nature Reviews Genetics*, 17, 507–522.
125. Mura, S., Nicolas, J., & Couvreur, P. (2013). Stimuli-responsive nanocarriers for drug delivery. *Nature Materials*, 12, 991–1003.
126. Geim, A. K., & Novoselov, K. S. (2007). The rise of graphene. *Nature Materials*, 6, 183–191.
127. Shin, S. R., et al. (2016). Graphene-based materials for tissue engineering. *Advanced Drug Delivery Reviews*, 105, 255–274.
128. Bilecka, I., & Niederberger, M. (2010). Microwave chemistry for inorganic nanomaterials synthesis. *Nanoscale*, 2, 1358–1374.
129. Gross, B. C., Erkal, J. L., Lockwood, S. Y., Chen, C., & Spence, D. M. (2014). Evaluation of 3D printing in biotechnology. *Analytical Chemistry*, 86, 3240–3253.
130. Rengier, F., Mehndiratta, A., von Tengg-Kobligk, H., et al. (2010). 3D printing in medical applications. *International Journal of Computer Assisted Radiology and Surgery*, 5, 335–341.

© Author(s). This work is peer-reviewed, openly published, and permanently archived
This article is openly accessible and reusable with proper attribution.