ADVANCED NANOTECHNOLOGICAL APPROACHES IN ENERGY, ENVIRONMENT, AND HEALTH

Editors

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OPENING THE GATE TO THE NANOWORLD: NANOTECHNOLOGY, SYNTHESIS TECHNIQUES, AND CHARACTERIZATION PRINCIPLES

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Introduction

Nanotechnology, as an interdisciplinary field focused on controlling matter at the atomic and molecular scale, has paved the way for groundbreaking innovations in both fundamental science and applied engineering. The unique optical, mechanical, electronic, and chemical properties of nanoscale materials enable behaviors not

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observed in their bulk counterparts, thereby facilitating the design of next-generation technologies.

Nanomaterials are functional nanostructures with at least one dimension within 1–100 nm range and can be constructed through their size and surface molecular configurations [1]. Parameters such as shape, particle size, structure, and surface area are determined the unique optical, electrical, magnetic, mechanical, and catalytic properties of these materials. Owing to these characteristics, nanomaterials have found widespread applications across biomedical engineering, electronics, energy storage, environmental technologies, and food packaging among many other fields [2].

In addition to the shape and size of nanomaterials, the synthesis methods employed can significantly influence their efficiency and activity. Comprehensive characterization of synthesized nanomaterials is essential for accurately determining their properties. Each synthesis technique presents distinct advantages, limitations, and application domains. Furthermore, a wide range of characterization methods is utilized to precisely evaluate the size, morphology, crystallinity and surface characteristics of nanomaterials. These techniques include electron microscopy (SEM, TEM), surface microscopy (AFM), crystal structure analyses (XRD, SAED), surface chemistry assessments (FTIR, XPS) and optical spectroscopy methods (UV–Vis, Raman, PL).

This chapter provides a detailed overview of nanomaterial synthesis approaches including physical, chemical, and biological pathways along with the characterization techniques used to analyze their structural and functional properties.

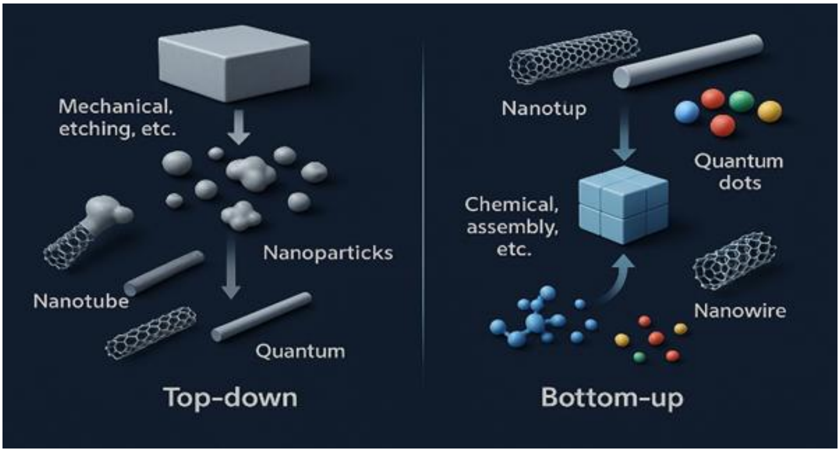
Synthesis Approaches for Nanomaterials

The synthesis approaches used for nanomaterials are generally classified into two main categories based on the phase of the starting material (Fig. 1):

Top-down approach: This approach involves converting bulk materials into nanoscale structures through mechanical, physical or chemical methods. In this strategy, the starting material is in the solid state.

Bottom-up approach: In this method, atoms or molecules are assembled in a controlled manner to construct the desired nanostructures. The starting material is typically in the liquid or gas state.

Figure 1. Synthesis approaches of nanomaterials



Top-Down Approaches

The top-down approach generally involves the processes listed below.

Mechanical Milling

Mechanical milling is a simple, widely used and cost-effective method for producing nanoscale materials through the milling of bulk solids. This technique offers high scalability for processed materials; however, the resulting particle size distribution is often heterogeneous. It is an effective approach for synthesizing nanoalloys, nanocomposites, and nanoquasicrystalline materials. Using mechanical milling, various Al/Ni/Mg/Cu-based nanoalloys, corrosion resistant spray coatings, oxide- and carbide-reinforced aluminum alloys, and numerous other nanocomposites have been synthesized with remarkably high yield [3]. Furthermore, when optimization parameters are precisely controlled, this method enables the production of polymeric, ceramic and metallic nanocomposite materials with diverse sizes and morphologies [4].

The literature also highlights mechanical milling as an environmentally benign technique that allows the homogeneous dispersion of nanoscale fillers into biodegradable polymers. Its advantages such as operation at low temperatures, the absence of solvents, and compatibility with nearly any polymer matrix facilitate the development of novel and functional materials. Additionally, the use of this method offers several benefits, including significant reduction of environmental waste, enhancement of compatibility between immiscible mixtures, and effective processing of recycled or waste-derived materials [5].

Lithography

Lithography is one of the most widely used techniques for creating micro and nanoscale patterns on material substrates. In other words, it is the process of transferring a desired pattern from a master slide, plate or mask onto another medium. Depending on the use of masks or templates, lithographic techniques are categorized into mask-based and maskless lithography. In mask-based lithography, patterns are simultaneously transferred over a large area using predefined masks or patterns [6]. Photolithography [7], soft lithography [8] and nanoimprint lithography (NIL) [9] are common examples of mask-based techniques. Maskless lithography, on the other hand, generates arbitrary patterns through serial writing without the need for a mask. Electron-beam lithography (EBL) [10], focused ion beam (FIB) lithography [11] and scanning probe lithography (SPL) [12] are among the primary maskless methods.

Photolithography is the most widely used lithographic technique in semiconductor fabrication. It relies on light to transfer geometric patterns from a mask onto a substrate coated with a light-sensitive chemical known as a photoresist. Because it operates based on optical exposure, photolithography is also referred to as optical lithography, and it has been a fundamental processing method in the semiconductor industry for decades [13].

Electron-beam lithography (EBL) has emerged in recent years as an advanced alternative to photolithography, addressing the need to fabricate smaller and finer structures on substrates. This technique uses a focused electron beam to produce features smaller than 10 nm. EBL enables the fabrication of highly complex and customized patterns with exceptionally high resolution [13].

Nanoimprint lithography (NIL) is a high-throughput, low-cost technique used to generate nanoscale patterns. One of its primary advantages is its ability to pattern features smaller than 10 nm with high efficiency and relatively low fabrication costs. However, NIL is considered a rigid, contact-based method; as a result, the molds used in patterning are prone to wear over time, requiring periodic replacement to ensure pattern fidelity [13].

Lithographic techniques are widely employed in the fabrication of micro-electromechanical systems (MEMS) and nano-electromechanical systems (NEMS) for creating structured and patterned surfaces [14]. As research continues to emphasize the importance of topographical cues in regulating cellular responses, lithography has become increasingly utilized in tissue engineering and biomaterials applications [15].

Laser Ablation

Laser ablation is an alternative synthesis technique to other physical and chemical methods for producing nanomaterials with high purity and reduced toxicity. In this method, when a target material is beamed with a laser pulse, the high energy causes the material to evaporate, leading to the formation of nanomaterials [16]. Since no chemicals or stabilizing agents are required in the synthesis of noble metal nanomaterials, this can be considered a green technique [17]. Using this method, various functional nanomaterials such as metal nanoparticles [18], carbon nanomaterials [19], oxide composites [20], ceramics, and oxide nanoparticles [21] can be produced.

Sputtering

Sputtering is a method in which nanomaterials are synthesized through the bombardment of solid surfaces with high energy particles such as plasma or gas. This method is considered highly effective for forming nanomaterial thin films [22].

The Arc Discharge Method

The arc discharge method holds great importance in the production of carbon-based nanomaterials, particularly fullerenes and graphene. In this technique, two graphite rods are placed inside a chamber where a specific helium pressure is maintained. Filling the chamber with pure helium is crucial, as the presence of moisture or oxygen in the environment inhibits fullerene formation. The arc discharge created between the tips of the graphite rods causes carbon atoms to evaporate at high temperature, initiating the conversion process into fullerenes [23].

This technique can also efficiently synthesize graphene nanostructures. The structural and electrical properties of the resulting graphene layers vary depending on the synthesis conditions. For example, graphene sheets produced through arc discharge exfoliation in a hydrogen atmosphere have been reported to possess higher electrical conductivity and superior thermal stability compared with those synthesized in an argon atmosphere [24].

Bottom-Up Approaches

Bottom-up methods rely on the controlled assembly of atoms or molecules to construct nanostructures.

Sol–Gel Method

The sol–gel method is a wet-chemical technique widely used for synthesizing high-quality metal oxide-based nanomaterials. It is referred to as “sol–gel” because the precursor material, initially in liquid form, is transformed into a sol phase and subsequently into a gel phase with a three-dimensional network structure. In this method, metal alkoxide compounds are typically dissolved in water or alcohol and transformed into a gel through hydrolysis or alcoholysis reactions accompanied by mixing and heating. The resulting gel, which is initially moist or wet, is processed using appropriate drying techniques depending on the desired material properties and application areas. For example, if the solution is prepared in an alcoholic medium, drying may be achieved by evaporating or burning the alcohol.

Dried gels are often converted into powder form and subjected to calcination. The sol–gel method is cost-effective and enables the production of high-purity materials at low reaction temperatures. Materials produced through this method may be used as molding precursors in ceramic synthesis, as interlayers between thin metal oxide films or in various industrial applications. Additionally, sol–gel-derived materials have wide applications in optics, electronics, energy, surface engineering, biosensors, pharmaceuticals, separation technologies (e.g., chromatography), surface coatings, building insulation, and functional textile production [25].

The main advantages of the sol–gel method include its ability to synthesize materials at low processing temperatures, produce high-purity and homogeneous structures, provide an economical and simple process, and enable the fabrication of composite and complex nanostructures [23].

Chemical Vapor Deposition

Chemical vapor deposition (CVD) is a technique in which materials are deposited onto substrates in the form of thin films through chemical reactions of vapor-phase precursors [26]. In other words, the gas phase precursor compounds are reacted on a solid surface under high temperature, pressure or plasma conditions to create nanostructured materials. This chemical method is widely used in the production of semiconductors, solid-state coatings and various nanomaterials. It is based on the conversion of vapor-phase precursors into solid products via chemical reactions occurring on the substrate surface. The resulting solid material accumulates as a thin film layer on the surface, while other by-products are removed as gases [27].

The CVD method is the most commonly used technique for synthesizing carbon nanotubes (CNTs). In this process, carbon sources such as acetylene (C_2H_2), ethylene (C_2H_4) or methane (CH_4) are reacted with Fe, Co or Ni catalysts. Carbon atoms are dissolved on the catalyst surface and rearranged to form cylindrical nanostructures. CNTs are used in electronics, composite materials, sensors and energy storage applications due to their high tensile strength, exceptional electrical conductivity and chemical stability [28–31].

Transition metal dichalcogenides are two-dimensional materials used in electronic and optoelectronic applications. Although several methods exist for producing 2D thin films, Zn-doped MoS_2 thin films were synthesized for the first time using the chemical vapor deposition method [32].

In this process, the selection of parameters such as temperature, pressure, gas flow rate and the chemical nature of precursor compounds is highly important. These parameters enable precise control of film thickness, crystal structure and surface morphology. This technique is particularly effective in materials science and nanotechnology for producing controlled film thicknesses, uniform surface coatings and high-purity materials [26].

The prominent advantages of CVD, include atomic-scale film thickness control, high-purity product formation, the ability to create multilayer structures and homogeneous coating of large surface areas. However, high processing temperatures and the use of toxic precursor gases introduce safety limitations.

Hydrothermal/Solvothermal Methods

The hydrothermal method is one of the best known and most widely used techniques for nanomaterial synthesis. It is performed in aqueous conditions using sealed reactors at temperatures and pressures above the normal boiling point of water. The solvothermal method is similar to the hydrothermal method, except that the synthesis is conducted in non-aqueous organic solvents [33]. Both methods are typically carried out in closed systems. Hydrothermal and solvothermal techniques are used to produce nanomaterials with various geometries, including nanowires, nanorods, nanosheets, and nanospheres [34–37].

In recent years, microwave-assisted hydrothermal synthesis has gained attention. This technique combines the advantages of both microwave and hydrothermal processes while reducing reaction time. Meng et al. (2016) [37] synthesized various functional nanomaterials including metal oxides, metal composite oxides, inorganic biomaterials (such as hydroxyapatite and calcium carbonate), and metal sulfides using microwave assisted hydrothermal synthesis. Additionally, CeO_2 nanostructures with electrochemical properties [38], ZnO nanoparticles used in piezoelectric nanogenerators [39], TiO_2 used in photoluminescence and catalysis, and $ZnO–ZrO_2$ nanocomposites used in photocatalysis have also been synthesized using this method [40].

Physical Vapor Deposition

The PVD method is a physical technique used in nanomaterial production, involving the transfer of vaporized material to the atomic level. In this environmentally friendly method, the source material to be deposited is heated and evaporated under vacuum at 10^{-2}–10^{-3} Pa. The vacuum environment allows vapor particles to reach the substrate directly and condense to form a thin solid film. This method enables the fabrication of ultrathin layers of nanomaterials. Additionally, it is used to deposit nanoscale thin films onto metal surfaces to enhance hardness and improve oxidation or corrosion resistance [41]. AgNPs [42] and GeNPs [43] used in electronic and optical devices have been produced using this technique.

Reverse Micelle Methods

The reverse micelle method is an effective technique for synthesizing nanomaterials with specific shapes and sizes [44]. When an oil-in-water emulsion is formed, normal micelles develop with hydrophobic tails oriented inward surrounding oil droplets. Conversely, in water-in-oil emulsions, reverse micelles form. In this system, the hydrophilic head groups of the surfactant molecules orient toward the water-containing core [23]. This aqueous core acts as a nanoreactor for nanoparticle synthesis. In other words, the system functions as a controlled microenvironment in which the nanomaterial is formed. The size of these nanoreactors can be controlled by adjusting the water-to-surfactant ratio, which directly influences the size of the synthesized nanoparticles. Reducing the amount of water results in smaller droplets and, consequently, smaller nanoparticles [45].

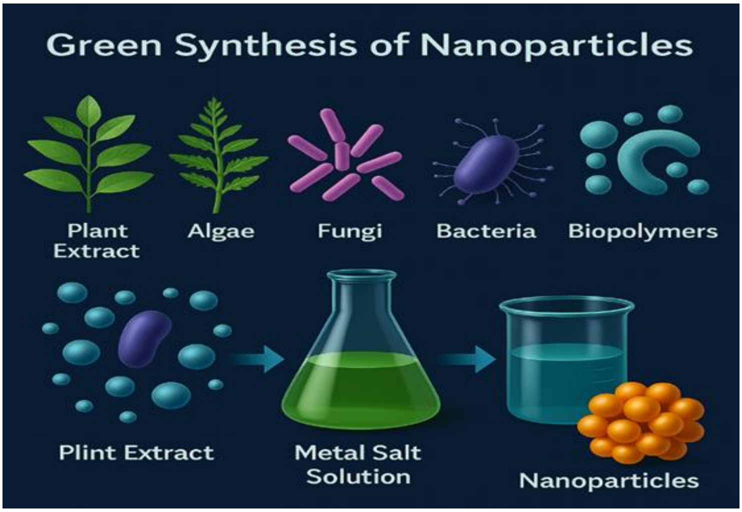
Thus, the reverse micelle method provides a simple and effective approach for producing monodisperse nanoparticles with precisely controlled size. Nanoparticles synthesized using this method exhibit high purity, uniform morphology, and narrow size distribution [46].

The reverse micelle method has been used to synthesize dielectric oxides of Ti and Zr [47,48], Zn oxalate [49,50], Fe oxalate [51], and Ni oxalate nanorods [52].

Green Synthesis Methods

Green synthesis aims to produce nanomaterials through environmentally friendly, non-toxic, and sustainable methods. This method typically uses natural reducing and stabilizing agents such as microorganisms, plant extracts, or biopolymers (Fig. 2). As a result, energy consumption, chemical waste, and environmental impact are minimized. The advantages of green synthesis include energy efficiency, low-cost production, product safety, affordability, and reduced waste. Due to these advantages, studies on nanomaterial synthesis through green methods have increased significantly in recent years.

Figure 2. Green synthesis methods



Microorganisms

Microorganisms (bacteria, algae, and fungi) are actively used in nanomaterial production to reduce the use of harmful and toxic chemicals. Microorganisms possess various reductase enzymes, which play an essential role in the reduction of metal salts into nanoparticles.

Nanoparticle synthesis using microorganisms can occur either intracellularly or extracellularly. In intracellular synthesis, ion transport takes place within the microbial cell, where the cell wall plays a crucial role. The positive charge of the metal interacts electrostatically with the negative charge of the cell wall. Enzymes present in the microbial cell wall reduce metal ions and enable the formation of stable nanoparticles [53].

In extracellular synthesis, microorganisms are first cultured under optimal conditions in a shaking incubator for 1–2 days. The biomass is then centrifuged and separated from the culture medium. The supernatant is collected and mixed with a metal salt solution for nanoparticle synthesis and further incubated [54]. The formation of nanoparticles is indicated by a visible color change in the culture medium. The synthesized nanoparticles are collected by high-speed centrifugation, carefully washed with ethanol/water, and then harvested [53].

Bacteria possess the ability to reduce metal ions, making them suitable for nanoparticle biosynthesis. Various bacterial species including Bacillus subtilis [55], Bacillus cereus [56], Escherichia coli [57], Pseudomonas aeruginosa [58], Klebsiella pneumoniae [59], and Lactobacillus casei [60] have been used to synthesize metallic and novel nanoparticles [61].

Fungi are also employed for the synthesis of metal or metal oxide nanoparticles. Due to the presence of intracellular enzymes, fungi act as biological agents in nanoparticle formation. Peptides, pigments, and polysaccharides which vary depending on the algal species serve as biomolecules responsible for the reduction of metals. Nanoparticle synthesis using algae occurs in a shorter duration compared with other biosynthesis methods [62].

A wide variety of nanomaterials with different types and properties have been synthesized using bacterial, algal, and fungal species with metals such as Ag, Au, Pd, Pt, Cu, Ni, Se, Ti, Fe, Co, and Zn. These materials have been applied in cancer therapy, pharmaceutical production, antibacterial and antifungal treatments, catalytic degradation, and tissue engineering [61–68].

Plant Extracts

The use of plant extracts in nanomaterial synthesis has gained significant attention in recent years as an environmentally friendly and sustainable production strategy. Plant extracts contain various biomolecules, including alkaloids, flavonoids, phenolic compounds, terpenoids, carbonyl groups, proteins, and enzymes. These compounds act as natural reducing and stabilizing (capping) agents in the reduction of metal ions and the stabilization of nanoparticles.

For example, metal nanoparticles such as Ag, Au, Cu, Fe_2O_3, and ZnO have been successfully synthesized using plant extracts from Azadirachta indica [69], Saintpaulia [70], Citrus lemon [71], Camellia sinensis [72], and Aloe vera [73]. Nanomaterials obtained through plant extract mediated synthesis are widely used in antimicrobial, anticancer, catalytic degradation, photocatalysis, drug delivery, and environmental remediation applications [61]. This method is considered both compatible with green synthesis principles and promising for the development of biologically functional nanostructures.

Biopolymers

Biopolymers are natural polymers containing chemically diverse macromolecules such as polysaccharides, polypeptides, polynucleotides, polyesters, and polyaromatics. These polymers are abundant in nature and are biodegradable, biocompatible, and non-toxic. Nanostructured components isolated from natural biomasses such as cellulose (sericin and fibroin nanoparticles), chitin, chitosan, silk, alginate, keratin, or collagen are served as building blocks for designing new biopolymer-based materials [74].

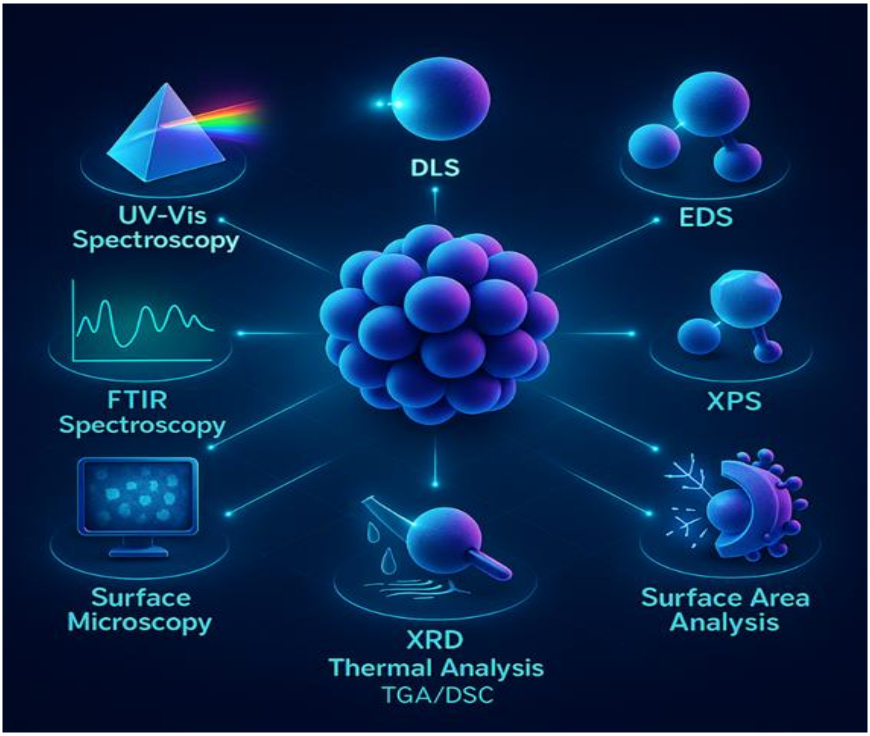
Biopolymeric nanomaterials are used in biomedical and agricultural applications. In biomedical contexts, biopolymer-based nanoparticles have potential uses in drug delivery and diagnostic systems, tissue engineering, and photodynamic and photothermal therapies. Bioactive molecules within nanomaterials can target specific sites (such as tumors) and exert localized effects. Additionally, nanoparticle-based delivery systems can improve drug stability, prolong therapeutic action, and allow for both enteral and parenteral administration. These features may prevent or minimize drug degradation, metabolism, and cellular efflux [74]. Biodegradable polymer nanomaterials also serve as unique carriers for delivering various drugs and vaccines into the human body [75].

In agriculture, they are used for pesticide delivery and rapid diagnosis of plant diseases [76]. The ecological non-toxicity of bio-based nanomaterials makes them particularly attractive for plant protection. Numerous studies have shown that biopolymeric nanomaterials enhance plant defense enzymes/genes and protect plants against pathogens [77,78]. Among these, chitosan and other carbohydrate-based nanoparticles have been demonstrated to be effective in plant protection [79,80].

Characterization Methods

To obtain information about the morphological, chemical, and physical properties of nanomaterials, analysis and characterization must be performed. These characterizations are conducted using numerous modern techniques, which are briefly described below (Fig. 3).

Figure 3. Characterization techniques of nanoparticles



Optical and Spectroscopic Techniques

UV–Vis Spectroscopy

UV-Vis spectroscopy is a type of absorption spectroscopy that measures how much ultraviolet or visible light is absorbed by a substance to determine its chemical composition. It is a simple and cost-effective characterization approach and a quantitative method used to identify functional groups present in nanomaterials. It is an effective and important tool for the characterization, analysis, identification, and examination of nanomaterials. When the energy required to excite an electron is absorbed by a molecule, this absorption is recorded as a spectrum using a UV-Vis spectrophotometer [41,81]. For example, $Zn(NO_3)_2$ exhibits an absorption spectrum at a maximum wavelength of around 300 nm, whereas nano-ZnO shows an absorption peak in the range of 340-370 nm [82].

Raman Spectroscopy

Raman spectroscopy is based on inelastic scattering (Raman scattering) that occurs when light interacts with matter. When a laser beam is directed at a sample, most photons are scattered elastically (Rayleigh scattering) with the same energy. However, a very small portion interacts with the vibrational modes of the molecules, gaining or losing energy; this is known as Stokes and anti-Stokes Raman scattering. These energy shifts act as a “fingerprint” of the vibrational energy levels of a material, producing unique Raman bands for each substance. Thus, Raman spectroscopy is a distinctive method for structural and chemical identification [81].

Raman spectroscopy is a powerful characterization technique for determining the chemical bonds, crystal structure, size-dependent effects, defect levels, and surface chemical modifications of nanomaterials [83]. It is the standard method for characterizing carbon-based nanomaterials such as graphene and is also widely used for characterizing metal oxides, nanotubes, nanobelts, and nanorods [84].

Fourier Transform Infrared Spectroscopy

Infrared spectroscopy (IR spectroscopy or vibrational spectroscopy) measures the interaction of infrared radiation with matter through absorption, emission, or reflection. This method enables the examination of inorganic and organic molecular bonds. The IR spectrum is produced by exposing a material to infrared radiation; depending on the molecular bonding characteristics, the material absorbs specific portions of the IR radiation. The molecular fingerprint of the material is determined through its infrared transmission and absorption. Functional groups present within the material can be identified using this technique [41,81].

Because titanium exhibits strong photocatalytic properties, the photocatalytic behavior of TiO_2 nanofibers in different phases has been examined using Fourier Transform Infrared Spectroscopy (FTIR). FTIR spectra confirmed the absence of carbon residues in the material [85].

X-ray Photoelectron Spectroscopy

X-ray Photoelectron Spectroscopy (XPS) is based on measuring the energy distribution of photoelectrons emitted when a material surface is irradiated with monochromatic X-rays. XPS is one of the most critical techniques for analyzing the surface composition and chemical states of nanostructured materials, as most properties at the nanoscale are governed by surface characteristics [81]. This method has been frequently used for the characterization of metal and metal oxide nanoparticles [86–88], carbon-based nanomaterials [89], composite nanostructures [90], and bio-nanomaterials [91].

Electron Microscopy Techniques

Scanning Electron Microscopy

Scanning electron microscopy (SEM) is an electron-optical technique that enables high-resolution imaging of material surfaces. Its fundamental principle involves scanning the sample surface with a focused electron beam and collecting the resulting signals with detectors. SEM is one of the primary techniques used for examining the morphology and chemical characteristics of nanoscale structures. It provides images with high depth of field, allowing the entire micrograph to remain in focus. SEM is often used together with Energy-Dispersive X-ray Spectroscopy (EDS/EDX) to determine elemental composition and orientation [81].

SEM is used to determine size distribution, particle shapes (spherical, rod-like, prismatic, polygonal), and agglomeration tendencies of metal and metal oxide nanomaterials [87,88,92], biopolymeric nanomaterials [74], N-graphene [89], nanocrystalline and nanocomposite materials [93].

Transmission Electron Microscopy

Transmission Electron Microscopy (TEM) operates by transmitting high-energy electrons through an ultrathin specimen, generating contrast after interactions with atoms within the sample. TEM is one of the most powerful direct-imaging tools for nanomaterials because it reveals particle size, shape, crystal structure, atomic arrangement, and internal defects. TEM provides detailed information on hollow structures, porosity, phase separation, atomic defects (dislocations, twinning), particle size, size distribution, shape analysis (spherical, rod-like, wire-like, sheet-like, core–shell), aggregation, and surface topography especially with the highest accuracy in systems <100 nm [41,81].

TEM is used for characterizing metal and metal oxide nanoparticles, graphene, carbon nanotubes, nanofibers, polymer and organic–inorganic hybrid nanomaterials, and magnetic nanomaterials.

Surface Microscopy

Atomic Force Microscopy

Atomic Force Microscopy (AFM) is a high-resolution microscopy technique that provides three-dimensional topographical images of a surface at atomic scale. Unlike SEM or TEM, AFM does not use an electron beam; instead, it relies on the physical interaction between a sharp probe tip and the sample surface. The probe has a nanometer thin tip to ensure resolution of surface features. AFM can be used on nearly all surfaces, whether conductive or insulating, and does not require vacuum conditions [81].

AFM is a powerful and versatile characterization technique used to analyze surface topography, morphology, mechanical properties, and electrical/magnetic characteristics of nanomaterials. It is especially indispensable in nanotechnology, biomaterials engineering, semiconductor technology, and thin-film research [94].

Crystal Structure Analyses

X-ray Diffraction

X-ray Diffraction (XRD) determines the atomic arrangement of materials by recording diffraction patterns produced when X-rays strike crystal lattice planes. XRD is one of the most widely used techniques for characterizing and analyzing nanomaterials. It is applicable to a wide range of crystalline, amorphous, powdered, and liquid nanomaterials. XRD is used to determine crystal structure, strain measuring, phase composition, structural properties, lattice distortions, defects, and to verify nanoparticle size and shape [41,74,81]. It is a distinctive technique for examining crystalline, amorphous, and polycrystalline materials at molecular and atomic levels.

It has been widely used in the characterization of numerous nanomaterials synthesized by different methods in the literature.

Selected Area Electron Diffraction

Selected Area Electron Diffraction (SAED) is an essential characterization technique integrated with TEM, enabling precise determination of the crystal structure of nanomaterials. SAED allows the examination of a specific micrometer-scale region within a sample. It is based on the elastic scattering of high-energy electrons by crystal lattice planes, producing diffraction patterns that provide direct information about crystallographic order. SAED reveals whether a sample is crystalline or amorphous, and its intrinsic structural properties [41]. In short, SAED is used together with TEM for crystallinity and phase analysis.

Thermal and Surface Area Analyses

Thermogravimetric Analysis

Thermogravimetric Analysis (TGA) is a thermo analytical technique that measures mass changes in a material as a function of temperature under a controlled atmosphere. The basic principle involves monitoring mass losses or gains due to decomposition, oxidation, removal of adsorbed water, dissolution, or evaporation while the sample is heated on an assay balance.

TGA measurements are typically performed under inert gas (N_2, Ar) or atmospheric (O_2, air) conditions. Under inert conditions, thermal stability and degradation mechanisms are examined; under oxidative conditions, combustion and oxidation behavior are determined. The technique produces mass-temperature or mass-time curves, with each mass-loss step corresponding to a specific chemical or physical event. Numerous metal oxide nanomaterials have been analyzed using TGA [81,95,96].

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) is a thermal analysis technique that measures heat-flow changes in a material under a controlled temperature program to analyze its physical and chemical transformations. A sample and reference material are subjected to the same heating rate; any endothermic (heat absorption) or exothermic (heat release) events are recorded as heat-flow differences. DSC is used to determine phase transitions, glass transition temperature (Tg), melting temperature (Tm), crystallization behavior, and thermal stability [97].

Brunauer–Emmett–Teller Surface Area Analysis

One of the primary indicators for determining whether a material can be considered a nanomaterial is its specific surface area. Because nanoparticles are extremely small, they exhibit a relatively high surface area per unit mass and therefore very high surface-to-volume ratios. Brunauer–Emmett–Teller (BET) analysis is widely used in nanomaterials where surface area and pore structure are critical.

BET measures the amount of gas physically adsorbed on a solid surface to determine specific surface area (m^2/g) and porosity characteristics (micro/mesopores). Nitrogen adsorption at 77 K is typically employed. As nanoparticle size decreases, surface area increases; thus, BET provides insight into the size-surface area relationship. The true density of nanomaterials and nanoparticles can also be measured using helium or nitrogen pycnometer [81].

Discussion and Application Perspectives

The synthesis and characterization of nanomaterials represent a rapidly evolving, multidisciplinary research field within materials science. Both traditional physical/chemical methods and biologically based green synthesis approaches now enable the production of nanomaterials with controlled morphology, high purity, and functional surface properties. Comparisons among synthesis techniques are made based on parameters such as cost-effectiveness, scalability, environmental impact, and product stability, with each method's advantages evaluated according to the intended application.

On the characterization side, integrating structural, morphological, chemical, and thermal analyses is critical for accurately interpreting nanomaterial performance. Complementary techniques such as XRD, TEM, XPS, BET, AFM, TGA-DSC provide researchers with a wide dataset ranging from atomic-scale resolution to surface energy and thermal stability. This multidimensional analytical capability forms the scientific basis for nanomaterial optimization in energy storage, catalysis, biomedical applications, and advanced sensor technologies.

From an application perspective, the potential uses of nanomaterials continue to expand. Sustainable production processes, biocompatible nanostructures, quantum-dot-based optoelectronic systems, metal–organic frameworks (MOFs), and atomically engineered 2D materials make it necessary to study synthesis–characterization relationships more deeply. Accordingly, automation, artificial-intelligence-assisted synthesis optimization, in-situ/operando characterization, and multiscale modeling approaches are expected to play a decisive role in the future development of the field.

In conclusion, nanomaterial synthesis and characterization remain essential research areas that not only accelerate technological innovation but also deepen fundamental scientific understanding. Progress in this field will depend on interdisciplinary integration and the closer coupling of characterization techniques with synthesis processes.

Future Perspectives and Conclusion

The field of nanomaterial synthesis and characterization has undergone rapid transformation in recent years, further accelerated by the integration of interdisciplinary innovations such as artificial intelligence, automation, green chemistry, and high-resolution imaging techniques. In the future, this field is expected to be reshaped by even more comprehensive, precise, and sustainable technologies.

The combination of autonomous and AI-assisted synthesis platforms with machine learning algorithms and robotic synthesis systems may enable real-time learning and optimization of reaction parameters. This advancement will allow the rapid fabrication of “designed” nanomaterials with tailored functional properties within minutes, significantly reducing trial-and-error processes and enhancing efficiency.

Environmental considerations will play a decisive role in the future of nanomaterial production, and fully green, biocatalytic, and zero-waste synthesis methods are expected to gain prominence. The use of plant extracts, microorganisms, enzymes, and biopolymers for non-toxic nanomaterial synthesis, along with next-generation biomimetic approaches capable of highly efficient production at low energy input without thermal processing, is anticipated to become widespread.

In the near future, the synthesis and characterization of nanomaterials are expected to evolve into faster, more efficient, and more environmentally friendly systems through the integration of advanced technology, sustainability principles, and computational methods. This transformation will not only broaden the boundaries of nanomaterials science but may also open the door to groundbreaking applications in medicine, energy, environmental engineering, and electronics.

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NANOCRYSTALLINE OXIDE PHASES IN GEOGENIC FORMATION-NANO-SCALE INVESTIGATION OF RARE EARTH ELEMENT ENRICHMENT IN SEDIMENTARY ROCKS

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Introduction

Rare Earth Elements (REEs) are a group of chemical elements comprising the lanthanide series (from lanthanum to lutetium) and yttrium (Y) [1]. These elements are indispensable for high-technology applications such as powerful permanent magnets used in wind turbines (specifically Neodymium, Nd, and Dysprosium, Dy), catalytic converters (Cerium, Ce), fiber optic cables, lasers, and modern electronic devices [2]. Due to their geopolitical and economic significance, REEs are classified as critical raw materials by many nations, making the investigation of

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reliable supply sources vital [3]. The REEs are typically divided into two main groups based on their atomic number: Light Rare Earth Elements (LREEs), spanning from La to Eu, which possess larger ionic radii; and Heavy Rare Earth Elements (HREEs), from Gd to Lu (often including Y), which have smaller ionic radii [4]. This size differentiation, a result of the Lanthanide Contraction, allows HREEs to form stronger complexes in aqueous solutions and on mineral surfaces due to their higher charge density. This phenomenon drives fractionation during geological processes, providing a key geochemical signature for understanding REE enrichment mechanisms [5].

In sedimentary rocks, REEs accumulate through two primary pathways: detrital (mechanical) origin and chemical/diagenetic origin. Detrital accumulation involves the physical weathering of REE-bearing parent rocks (e.g., refractory heavy minerals like monazite or zircon) and their subsequent mechanical transport and deposition [6]. Conversely, chemical/diagenetic accumulation the focus of this study occurs when REEs are dissolved from the water phase, transported in colloidal form, and then bound to newly forming minerals through chemical reactions during or after deposition (diagenesis) [7]. This mechanism is dominant in the formation of economically significant REE deposits such as phosphorites, black shales, and Fe-Mn oxide nodules. Understanding the specific chemical phases responsible for this concentration is crucial for resource exploration.

A critical, yet often overlooked, component in these chemical processes is the role of nanomineralogy. Over the last two decades, this emerging discipline has focused on examining geological materials at the nano-to-micrometer scale [8]. Nano-scale investigations surpass the resolution limits of conventional microscopic techniques, illuminating reactions at mineral-water interfaces, the precise binding sites of trace elements, and crystal growth mechanisms with unprecedented precision [9]. The exceptionally high surface area and resultant reactivity of nanocrystalline oxide phases (such as Fe and Mn oxyhydroxides) in sedimentary rocks play a significant role in scavenging and concentrating trace elements like REEs. Therefore, utilizing a nanotechnological approach is vital to elucidate the specific mechanisms driving the REE enrichment observed in these systems.

The principal objective of this chapter is to establish a comprehensive framework supporting the hypothesis that nanocrystalline oxide phases act as the key control mechanism for REE enrichment in sedimentary rocks. To achieve this, the scope of the chapter will encompass several core areas: exploring the geogenic formation pathways of Fe and Mn oxides at the nanoscale during diagenesis; illuminating the reactivity and mechanisms of REE binding, including surface adsorption and isomorphic substitution into the nanocrystal lattice; and discussing the advanced analytical techniques (such as HRTEM and XAS) necessary to validate these nano-scale interactions. This study serves as an important step toward understanding the nano-scale roles in geochemical cycles and advancing our scientific knowledge regarding the formation of critical raw material deposits.

Geogenic Formation of Nanocrystalline Oxide Phases in Sedimentary Environments

Formation and Stability of Oxide Phases

Key Geochemical Parameters Controlling Formation (pH, Eh, Temperature)

The formation, stability, and phase transformations of nanocrystalline oxide phases in sedimentary environments are primarily controlled by three fundamental geochemical parameters:

Oxidation-Reduction Potential (Eh): Eh directly determines the solubility of transition metals like Iron (Fe) and Manganese (Mn). Under oxidizing conditions (high Eh), Fe^{2+} and Mn^{2+} ions precipitate from solution, forming Fe(III) and Mn(IV) oxide/oxyhydroxide nanocrystals, respectively [10]. These solid phases dissolve under reducing conditions (low Eh).

Acidity-Basicity (pH): pH is the most critical factor controlling the precipitation boundaries of metal hydroxides and oxides [11]. Generally, an increase in pH (more alkaline environments) promotes the precipitation of these phases. Since the surface charge of Fe and Mn oxide nanocrystals is pH-dependent, pH also directly influences REE adsorption.

Temperature: Temperature affects solubility and reaction kinetics [12]. During diagenesis, an increase in temperature can accelerate the aging of nanocrystals and their transformation into more stable, larger crystalline phases, consequently altering their REE scavenging capacity.

Common Nanocrystalline Oxide Examples

The main nanocrystalline oxide phases playing a key role in REE enrichment in sedimentary environments include:

Iron Oxyhydroxides (Fe(III)): Goethite (α-FeOOH) and Lepidocrocite (γ-FeOOH) are the most common nanophases [13]. Due to their high specific surface area and reactive surface hydroxyl (-OH) groups, they are powerful REE adsorbents. As diagenesis progresses, these phases may transform through dehydration into the more stable Hematite (α-Fe_2O_3) nanocrystals.

Manganese Oxides (Mn(III/IV)): High-valence Mn oxides, such as Buserite, Birnessite, and Todorokite, possess layered or tunnel structures. Their exceptional ion exchange and adsorption capabilities make them among the most effective nanocrystals for REE scavenging.

Nanocrystal Growth and Aging Processes (Diagenetic Effect)

Crystallization and Recrystallization During Post-Depositional and Diagenetic Stages

Primary Fe and Mn precipitation in a sedimentary basin typically begins as very small, often amorphous or poorly crystalline, nanoparticles. Diagenesis the physical, chemical, and biological changes occurring after initial deposition determines the fate of these particles [15].

Ostwald Ripening: This process involves the dissolution of small, high-surface-energy nanocrystals and the re-precipitation of the dissolved components onto larger, more thermodynamically stable crystals [16]. This growth can lead to the incorporation of REE from the surface into the crystal lattice (inner-sphere complexation/isomorphic substitution), making the REE less mobile and more permanently sequestered from environmental changes.

Phase Transformation: The transformation, for instance, of amorphous Fe(III) hydroxides to Goethite and subsequently to Hematite, can fundamentally alter the REE's binding state and location. During these aging processes, some REE may be released, while others become trapped within the newly formed phases.

Morphological and Surface Area Properties of Nanocrystalline Phases

The morphology (shape: needle-like, plate-like, spherical) and, crucially, the specific surface area (SSA) of the nanocrystals are the most critical controllers of REE adsorption capacity [17].

High SSA: Nano-sized particles possess a significantly high SSA relative to their volume [18]. This translates to a vast number of reactive surface sites (hydroxyl groups) available for REE binding, multiplying the REE enrichment potential compared to macro-crystalline phases.

Morphological Effects: For example, needle-like Goethite nanocrystals exhibit different surface energies and REE binding sites than plate-like Hematite nanocrystals, which can influence the observed fractionation between LREE and HREE.

Nanocrystalline Oxide Source and Transport Mechanisms Dissolution-Precipitation Cycles

The source of the metal (Fe, Mn) for nanocrystalline oxide formation can stem from various inputs such as continental weathering, hydrothermal vents, and volcanic ash [19]. However, their formation within the sedimentary basin often involves a cycle of metal ion dissolution in the aqueous phase, followed by re-precipitation when chemical conditions become favorable (especially an increase in Eh). This continuous dissolution-re-precipitation cycle allows for the ongoing formation of nanocrystals and the scavenging of REE from the solution.

Colloidal/Suspension Transport and Filtration

The nano-sized oxide particles themselves can be transported over long distances not as dissolved ions, but in colloidal or suspension form [20].

Colloidal Transport: Nanoparticles, having adsorbed REE onto their surfaces, can remain suspended in the water column, thus acting as a mechanism for transporting and distributing REE across different areas of the basin.

Filtration and Aggregation: When conditions such as pH or salinity change, colloids may aggregate (flocculate), forming larger clusters that rapidly settle out of the water [21]. This aggregation step is critical in the swift and massive removal of REE from the solution, which helps to explain the abrupt and intensive REE enrichments observed in certain sedimentary rock types (e.g., black shales).

Mechanisms of REE Binding to Nanocrystalline Oxide Phases

REE Adsorption and Desorption on Nanocrystal Surfaces

Surface Complexation and Binding Strengths of REE

Adsorption is the most common and rapid mechanism by which REE bind to nanocrystalline oxide phases from aqueous solution [22]. Fe and Mn oxide nanoparticles offer a vast number of reactive surface sites due to their high SSA (Specific Surface Area).

The strength and type of adsorption depend on pH, the charge density of the REE ions (controlled by the Lanthanide Contraction), and the type of functional groups on the surface [23].

HREE, having smaller ionic radii and higher charge density compared to LREE, tend to bind to Fe and Mn oxide surfaces with higher affinity. This selective adsorption is the primary reason for the characteristic REE fractionation (LREE/HREE separation) observed in sedimentary rocks [24].

Desorption (release of REE from the surface) can be triggered by chemical changes such as a drop in pH or the presence of strong complexing ligands (e.g., bicarbonate, organic acids).

Formation of Inner-Sphere and Outer-Sphere Complexes

The molecular nature of adsorption determines how permanently REE are bound to the oxide surface:

Inner-Sphere Complexes: The REE ion binds to the surface atoms via direct chemical bonds (covalent or ionic) with no intervening water molecules [25]. These bonds are strong and permanent, ensuring the long-term immobilization of REE and explaining their immobility after diagenesis. They can be proven using high-resolution X-ray Absorption Spectroscopy (XAS).

Outer-Sphere Complexes: The REE ion binds to the surface through electrostatic attraction, maintaining one or more layers of water molecules between the ion and the surface [26]. These bonds are weaker and more susceptible to disruption by minor changes in pH or ionic strength.

During diagenetic aging processes, the transformation of weak outer-sphere complexes into more stable inner-sphere complexes plays a critical role in "locking" REE into sedimentary rocks.

Incorporation of REE into the Crystal Lattice (Isomorphic Substitution)

Compatibility of REE Ions with the Host Oxide Crystal

Isomorphic substitution is the process where a REE ion permanently enters the crystal lattice of the nanocrystalline oxide phase (e.g., Goethite or Birnessite) by replacing the host cation (Fe^{3+} or Mn^{4+}) [27]. This process occurs specifically during the precipitation and growth of the nanocrystals.

The REE ions (Ln^{3+}) must be compatible in terms of ionic radii with the host crystal cations, and the valance balance must be maintained (or balanced by accompanying substitutions).

When REE are incorporated this way, they become isolated from surface reactions. This makes REE the most stable form against dissolution and mobilization [28]. Nano-scale analyses using TEM and EDX provide evidence of this substitution by mapping the REE distribution within the crystal core.

Direct Precipitation of REE-Rich Nanophases

Enrichment of HREE in Small-Sized Minerals

In some cases, REE can be enriched not just as an adsorbate, but by forming their own nanometer-sized mineral phases [29]. This usually occurs in environments where REE concentrations are very high or where complexing ligands (e.g., phosphate) promote precipitation.

Especially HREE, due to their solubility and complexation tendencies, sometimes precipitate as REE phosphates (Monazite group) or REE carbonates (Bastnäsite group), but at the nano-scale [30].

The small ionic radius of HREE may lead them to thermodynamically favor smaller crystal structures. This direct precipitation can be a primary mechanism enabling REE to reach exceptionally high concentrations compared to other sedimentary minerals.

Role of Environmental Factors (Organic Matter, Carbonates, etc.) in REE-Oxide Interactions

The mechanism of REE binding to nanocrystalline oxides interacts complexly with other common phases in the sedimentary environment:

Organic Matter

Organic Matter (OM) can both increase REE mobility by complexing them in solution [31] and block REE binding sites by coating the Fe/Mn oxide surfaces. However, reducing species (like H_2S) formed from OM degradation can cause Fe oxide dissolution, leading to REE release.

Carbonates

Bicarbonate and carbonate ions are strong complexing agents for REE in aqueous solution, especially for LREE [32]. This complexation competes with REE adsorption onto Fe/Mn oxide surfaces, which can alter the resulting REE enrichment patterns

Clay Minerals

Clay minerals also offer REE adsorption sites, but the surface reactivity of nanocrystalline oxides is generally higher. A common synergistic effect is the coating of clay particles by Fe oxides, which makes the clay reactive.

Impact of Nanocrystalline Oxide Phases on REE Enrichment

Nano-Scale Investigation REE Fractionation (LREE/HREE Separation)

Selective Control of LREE and HREE by Different Oxide Phases

The most critical impact of nanocrystalline Fe and Mn oxides is their ability to modify the REE spectrum, causing a relative enrichment in a specific group (LREE or HREE). This fractionation arises because the difference in ionic radius, caused by the Lanthanide Contraction, becomes even more pronounced on nano-scale adsorption surfaces [33].

Mn Oxides HREE Selectivity: Nanocrystalline Mn oxides (especially layered phases like Birnessite) tend to adsorb HREE much more strongly than LREE due to their structural characteristics (lattice voids suitable for REE ion coordination and high negative surface charges) [34]. This explains the distinct positive Y/Ho and negative Ce anomalies observed in Mn nodules and HREE-rich crusts.

Fe Oxides Selectivity: Nanocrystalline Fe oxyhydroxides (Goethite, Lepidocrocite) generally bind both LREE and HREE strongly, though some studies suggest they may exhibit a slight selectivity toward HREE [35]. The aging and crystal growth of Fe oxide nanocrystals can change the REE fractionation pattern over time.

This selective control determines not only the quantity of REE enrichment but also its quality (the degree of enrichment of HREE, which are often of higher economic value).

Potential of Nanocrystalline Phases as an Rare Earth Element Source

The Role of Nanocrystals in Economically Significant Sedimentary REE Deposits

Nanocrystalline oxide phases act as active accumulation mechanisms, rather than passive carriers, in the formation of economically significant sedimentary REE deposits [36]. This role is critical in assessing potential REE resources.

Widespread Distribution and Large Volume: Fe and Mn oxide nanocrystals are extremely common in sedimentary basins and lateritic crusts. Even if the REE concentrations in individual nanocrystals are moderate, their widespread distribution throughout the rock volume makes them a globally large and important REE source.

Ease of Dissolution and Extraction: Nanocrystalline phases generally possess lower chemical stability compared to detrital minerals (Monazite, Zircon). This means that REE can be extracted relatively easily under low temperature and pH conditions (e.g., with dilute acids) [37]. This characteristic suggests that deposits containing nanocrystals may permit more sustainable and economic mining methods compared to challenging sources with complex mineralogy.

The presence of nanocrystalline phases can no longer be overlooked when evaluating the REE potential of a sedimentary deposit.

Case Studies (Selected Sedimentary Rock Types)

Nano-scale investigations conducted on specific sedimentary rock types are crucial for proving the role of nanocrystalline oxide phases in REE enrichment:

Phosphorites

Marine phosphorite deposits are globally important REE resources. While REE enrichment here is predominantly associated with the apatite mineral, the initial precipitation of Fe and Mn oxide nanocrystals during diagenesis, followed by the transfer of REE from these oxides into the apatite lattice (or the trapping of the nanocrystals themselves within the apatite), has been identified as a major mechanism [38]. REE fractionation patterns indicate that oxides preferentially select HREE first.

Black Shales

Organic matter-rich black shales have a huge potential as REE resources. REE are often associated with OM and clay here. However, in many cases, the association of REE with nanocrystalline pyrite (whose formation involves the reduction of Fe oxides) and diagenetic Fe oxide remnants has been detected at the nano-scale, proving the importance of the preceding oxide enrichment cycle [39].

Bauxites and Laterites

Bauxites and other lateritic crusts form from intensive chemical weathering of the parent rock. These environments contain high concentrations of nanocrystalline Fe oxides (Goethite, Hematite). REE enrichment in these deposits is strongly and directly correlated with the surface adsorption and isomorphic substitution capacity of these nanocrystalline Fe oxide phases [40]. The relative enrichment of HREE in lateritic bauxites is explained by the selectivity of Fe oxides.

Nano-Scale Characterization Techniques and Applications

High-Resolution Imaging Techniques

Transmission Electron Microscopy and High-Resolution TEM Applications

Transmission Electron Microscopy (TEM) is an indispensable tool for directly imaging the morphology, size, and structure of nanocrystalline phases. The High-Resolution TEM (HRTEM) mode, in particular, provides images at atomic resolution, offering key evidence for REE enrichment mechanisms [41].

Nanocrystal Morphology and Size: TEM confirms that sedimentary Fe and Mn oxides are nano-sized (typically 5-50 nm) and possess needle-like (Goethite) or layered (Birnessite) morphologies. This provides the fundamental data for calculating the reactive surface area available for REE binding.

HRTEM allows for the atomic-level examination **Crystal Lattice Observation:** of lattice fringe spacings, revealing the location of REE ions within the oxide crystal lattice (isomorphic substitution) or precipitation points on the surface [42]. This is especially important for monitoring phase transformations during aging processes (diagenesis).

Field Emission Scanning Electron Microscopy and Energy Dispersive X-ray Spectrometry

Field Emission Scanning Electron Microscopy (FE-SEM) provides high-resolution surface morphology and topography information. When combined with Energy Dispersive X-ray Spectrometry (EDX), it gains the capability to map the elemental composition (qualitative and semi-quantitative) of nanocrystals at the micron/nano-scale [43].

Elemental Mapping

The FE-SEM/EDX combination visualizes where REE (especially heavier elements like Ce, La) are enriched within the sedimentary matrix. It can directly prove that REE enrichment is spatially correlated with nanocrystalline clusters where Fe and Mn elements are highly concentrated [44].

Visible Nanophases

FE-SEM is ideal for examining the distribution and geometric relationships of nanocrystalline oxide phases that have aggregated (flocculated) during diagenesis within the host rock.

Surface Chemistry and Structural Analysis Techniques

X-ray Photoelectron Spectroscopy and Neutron Scattering

These techniques provide critical information regarding the surface chemistry and bulk structure of nano-scale materials:

Valence State via XPS: XPS analyzes the chemical and electronic states of elements on the sample's surface. It is vital for determining the valence state of Cerium (Ce) (Ce^{3+} or Ce^{4+}). The oxidation of Ce to Ce^{4+} in sedimentary rocks is directly linked to the high oxidative surface reactivity of Fe and Mn oxide nanocrystals and explains the formation of the negative Ce anomaly [45].

Neutron Scattering (Suggested Alternative: SR-XRD): While neutron scattering provides information particularly about magnetic structures or light atoms, Synchrotron-Source X-ray Diffraction (SR-XRD) is generally preferred for the structural analysis of nanocrystals. SR-XRD determines the crystal structure and size of nano-sized phases with much higher precision than laboratory XRD, thus establishing the definite identity of the nanocrystalline phase [46].

XANES/EXAFS (X-ray Absorption Spectroscopy) for Determining Binding States

XAS (X-ray Absorption Spectroscopy) techniques (XANES and EXAFS) are considered the gold standard for elucidating the mechanism of REE binding to nanocrystalline oxides at the molecular scale [47].

XANES (X-ray Absorption Near Edge Structure): Reveals the valence state and geometric symmetry of the absorbing atom. It identifies any valence changes in REE after binding to Mn or Fe oxides.

EXAFS (Extended X-ray Absorption Fine Structure): Precisely determines the atom type, number, and interatomic distance (bond length) of the first coordination shell around the REE ion [48]. This directly proves whether REE form inner-sphere complexes or outer-sphere complexes on the oxide surface, or if they undergo isomorphic substitution within the crystal lattice.

Nano-Scale Modeling and Simulation Techniques

Computer modeling is vital for complementing nano-scale experimental data and providing a deeper theoretical understanding of the mechanisms:

Density Functional Theory (DFT) Calculations

DFT is used to calculate the energy and stability of potential binding sites for REE ions on nanocrystalline oxide surfaces at the atomic level [49]. This helps predict how thermodynamically favorable inner-sphere complexation is.

Molecular Dynamics (MD) Simulations

MD simulations can dynamically model the adsorption/desorption kinetics of REE on nanocrystal surfaces and their interaction with water molecules over time. This aids in understanding the dynamic nature of surface reactions that are difficult to observe experimentally.

These modeling techniques ground experimental observations in a theoretical framework, offering a holistic understanding of REE-oxide interactions.

Nano-Scale Investigation of Rare Earth Element Enrichment and Multidisciplinary Applications of Nanotechnology

The accumulation of Rare Earth Elements (REEs) in sedimentary rock systems is a complex geochemical process characterized by the elements separating from solution and incorporating into solid mineral phases. Nano-scale mineralogical studies indicate that this accumulation is fundamentally controlled by nanocrystalline oxide and oxyhydroxide phases [50].

Control Mechanism and Specific Surface Area

The primary mechanism controlling REE accumulation is the high reactivity of Iron (Fe) and Manganese (Mn) oxyhydroxide nanoparticles formed during diagenesis (post-depositional chemical alteration) processes. Nanoparticles such as Goethite and Birnessite exhibit an extremely high Specific Surface Area (SSA). This high surface area increases reactivity, playing a key role in the transfer of REEs from the aqueous to the solid phase [51]

Fractionation and Lanthanide Contraction

Chemical separation, or fractionation, among the elements within the REE series is explained by the effect of Lanthanide Contraction. Heavy REEs (HREEs) have a smaller ionic radius and thus a higher charge density compared to Light REEs (LREEs) [50,52]. This phenomenon enables HREEs to form stronger and more stable complexes on mineral surfaces, driving geological enrichment.

Binding Mechanisms

The binding of REEs to nanocrystalline oxides occurs via two main pathways:

1. **Surface Adsorption:** A rapid and often reversible process where REE ions are physically or chemically attached to the nanoparticle surface.
2. **Isomorphic Substitution:** The entrapment of REE ions within the crystal lattice during diagenetic phase transformations.

High-resolution analytical techniques, particularly EXAFS (Extended X-ray Absorption Fine Structure) for determining interatomic distances, reveal the exact location of the REE ion on these surfaces [53].

Multidisciplinary Interactions of Nanotechnology

Nanotechnology is a critical, overarching process that integrates fundamental sciences like physics, chemistry, and biology with applied sciences such as engineering and medicine [54].

Biology and Medicine (Nanomedicine)

The application of nanotechnology to biological systems has led to revolutionary advancements in healthcare:

Targeted Drug Delivery: This is the most significant application. Nanocarriers (liposomes, polymer nanoparticles) are used to deliver drugs in high concentrations directly to targeted areas, such as cancerous cells, while minimizing harm to healthy tissues.

Diagnostics and Biosensors: Nano-scale sensors (biosensors) enable the monitoring of biological processes at the cellular level and facilitate the earlier and lower-cost detection of diseases (e.g., specific cancers or viruses)

Imaging: Gadolinium (Gd)-doped nanoparticles serve as MRI contrast agents, while Erbium (Er) and Neodymium (Nd)-doped nanocrystals are used as Upconversion Light materials, providing deep, high-resolution imaging in biological tissue. (55)

Current Research and Application Trends

Nanotechnology is a strategic field attracting intense R&D (Research and Development) investments and is expected to shape future technologies.

AI-Driven Materials Discovery: This is the most current deep technology trend. Artificial Intelligence (AI) and machine learning algorithms, combined with quantum simulations, enable scientists to discover and optimize new materials (nanocomposites, novel alloys) much faster than traditional methods.

Sustainability and Green Nanotechnology

Focuses on environmental challenges. Green Nanotechnology aims to produce nanoparticles using energy-efficient synthesis methods (e.g., Biological Synthesis) that generate minimal chemical waste. Applications include water purification, air filtration, and environmental clean-up (nanocatalysts).

Energy Solutions

Nanotechnology plays a critical role in energy storage (nano-electrodes for faster-charging lithium-ion batteries), energy generation (high-efficiency, low-cost solar cells), and energy saving (smart, insulating glass).

Global Investment and Strategy

Global investments in nanotechnology are increasing, and it is viewed as a strategic priority by regions such as the United States, China, and the European Union. Investments are flowing toward "deep tech" startups with the potential to radically change the market [50,52,54].

Concluion and Future Perspectives

Summary of Key Findings

This chapter examined the critical and previously overlooked nano-scale relationship between the geogenic formation of nanocrystalline oxide phases and REE enrichment in sedimentary rocks. The key conclusions of the chapter are as follows: The nano-sized phases of Fe and Mn oxides (e.g., Goethite, Birnessite) play a role as decisive as, if not more so than, the host rock mineralogy in the enrichment of REE (particularly HREE) in sedimentary rocks [56]. The high SSA of these nanocrystals provides an enormous adsorption capacity for REE. Furthermore, advanced characterization techniques (HRTEM, EXAFS) proved that REE are permanently bound to oxide surfaces via inner-sphere complexation and incorporated into the crystal lattice via isomorphic substitution during diagenesis, which explains the long-term immobilization of REE.

The ability of nanocrystalline Mn oxides to selectively enrich HREE compared to LREE forms the nano-scale basis for the economically valuable HRE fractionation observed in sedimentary REE deposits [57]. Moreover, REE bound to nanocrystalline phases are in a more easily leachable form than those bound to detrital minerals. Consequently, sedimentary deposits dominated by these phases should be considered important, new-generation resources for future REE supply.

Limitations and Gaps in Current Knowledge

Despite recent advancements in nanomineralogy, significant challenges and knowledge gaps remain in fully understanding REE-oxide interactions. Most current studies rely on controlled laboratory precipitation experiments or the examination of dry samples; thus, methodological constraints persist in observing how REE bind to nanocrystalline phases in natural sedimentary environments, in real-time and in situ [58]. Concurrently, precise kinetic and thermodynamic data for REE adsorption and desorption throughout the aging and diagenesis processes are still lacking for REE-oxide systems, making estimation difficult in complex natural solutions (in the presence of organic matter and various ligands) [59]. Finally, the often poorly crystallized or semi-amorphous nature of natural nanocrystalline oxide phases complicates the precise determination of REE binding sites and coordination numbers, even with advanced techniques like EXAFS.

Future Research Directions in Nanocrystalline Oxides and REE Enrichment Studies

To address the existing gaps, future research should focus on developing novel methodologies, such as Synchrotron X-ray techniques coupled with microfluidic cells that simulate REE complexation and nanocrystal growth [60]. This will allow for the real-time monitoring of REE binding dynamics on nano-surfaces. Additionally, the high HREE selectivity of Mn oxides should inspire material scientists and geologists to focus on engineering synthetic nanoparticles (biomimetic or geomiometic) capable of selectively adsorbing HREE (Dy, Tb) for recovery from low-concentration sources [61]. Deeper investigation into how biogeochemical processes alter nanocrystal morphology and, consequently, REE adsorption capacity is needed, as these processes are often driven by microorganisms [62]. Finally, theoretical studies using advanced

DFT and MD modeling must more accurately model the thermochemistry of REE-oxide surface interactions in complex multi-component systems. These research directions represent the next major breakthrough in the field of REE geochemistry and critical raw materials science.

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CARBON NANOSTRUCTURES: FULLERENES, CARBON NANO TUBES, AND GRAPHENE

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Introduction

Material science is continually breaking new ground thanks to the ability of carbon, the most versatile element in the periodic table, to form diverse geometric arrangements (allotropes). In addition to its traditional forms, which range from the three-dimensional (3D) perfect crystalline structure of diamond to the layered 3D structure of graphite, science and engineering in the 21st century have discovered new classes of carbon at the nanometer scale: Carbon Nanostructures (CNs). When scaled down to the nanometer range, quantum mechanical effects become dominant, and the material's optical, electronic, and mechanical properties diverge radically from their macro-scale counterparts [1,2]. This

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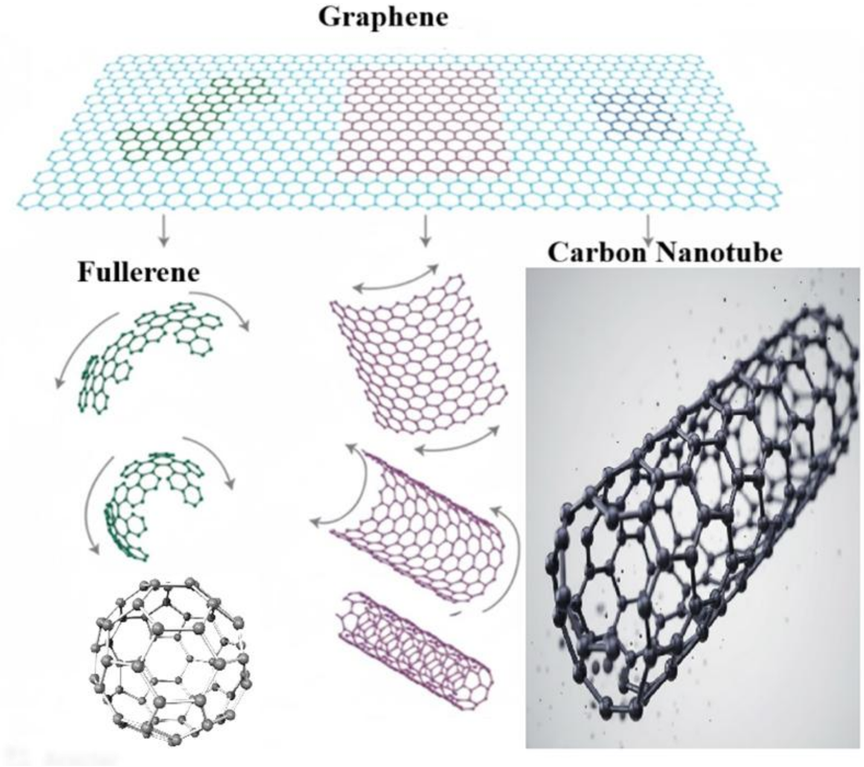
phenomenon is the fundamental factor that has made Carbon Nanostructures a driving force of modern technology.

Carbon Nanostructures (CNs) are fundamentally a class of nanomaterials in which carbon atoms are arranged in spherical, tubular, or planar forms. The three main members of the CN family-Fullerenes (0D), Carbon Nanotubes (CNTs) (1D), and Graphene (2D) are the most remarkable structures of this new era [1-3]. These structures, as illustrated in Figure 1, are formed by shaping their fundamental building block, the graphene sheet, into different geometries.

Figure 1. Schematic illustration of the formation of other carbon nanostructures (Fullerene and CNT) from Graphene [4]



Fullerene, the first discovered member of the Carbon Nanostructure (CN) family, is formed by the arrangement of carbon atoms in a closed-cage structure, typically in the shape of a sphere (Buckminsterfullerene, C_{60}). These structures, discovered in 1985 [5], possess a geometry like a standard soccer ball, composed of twelve pentagonal and twenty hexagonal rings. Due to their diameter of approximately one nanometre, they are classified as zero-dimensional (0D) materials. Despite their sp^2 hybridization, the strain introduced by the spherical form causes Fullerene molecules to exhibit different electronic behaviours compared to Graphene and CNTs, and they are generally semiconducting [6]. Their unique geometry and ability to act as electron acceptors have made them a popular research topic, particularly in organic solar cells and biomedical fields [7].

Carbon Nanotubes (CNTs), which became a major focus of interest in 1991, are fundamentally formed by rolling up a single graphene sheet into a seamless cylinder [8]. For this reason, CNTs are defined as one-dimensional (1D) structures. They are classified as either Single-Walled Nanotubes (SWCNTs) or Multi-Walled Nanotubes (MWCNTs), which consist of several concentric cylinders [9]. The revolutionary characteristic of CNTs is that the rolling angle (chirality) of the hexagonal lattice forming the cylinder directly determines the material's electrical property; this allows them to be either highly conductive (metallic) or semiconducting [10]. This controllable electronic structure makes CNTs ideal for transistors and sensors, while their incredibly high tensile strength makes them a fundamental component of lightweight and strong composite materials [11].

Graphene is considered the fundamental building block for carbon nanostructures. This two-dimensional (2D) planar material, formed by a single-atom-thick layer of carbon atoms arranged in a honeycomb lattice, constitutes the surface of C_{60} and the walls of CNTs [1,3]. Its isolation in 2004 [12] ushered in a new era in material science. It stands out among nanostructures for having the highest electron mobility and a zero-band gap (semi-metal) [2]. Graphene combines unique attributes such as transparent conductivity, superior thermal conductivity, and flexibility [1, 3].

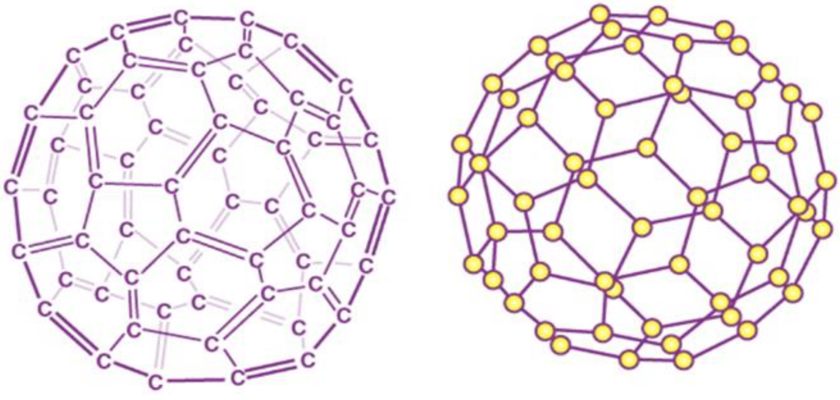
These three structures of varying dimensions (0D, 1D, 2D) showcase the incredible versatility of carbon and have opened the door to countless advanced technological applications, ranging from nanoelectronics and energy storage to biosensors and composite materials. This chapter will specifically examine the fundamental properties, synthesis methods, and technological potential of fullerene, CNTs, and graphene considering current research.

Fullerenes

Fullerene is a groundbreaking member of the carbon allotrope family, characterized as zero-dimensional (0D) nanoforms where atoms are arranged in a spherical or cage-like structure around a polyhedral geometry [13]. This molecular structure represents a turning point in the scientific history of carbon nanostructures.

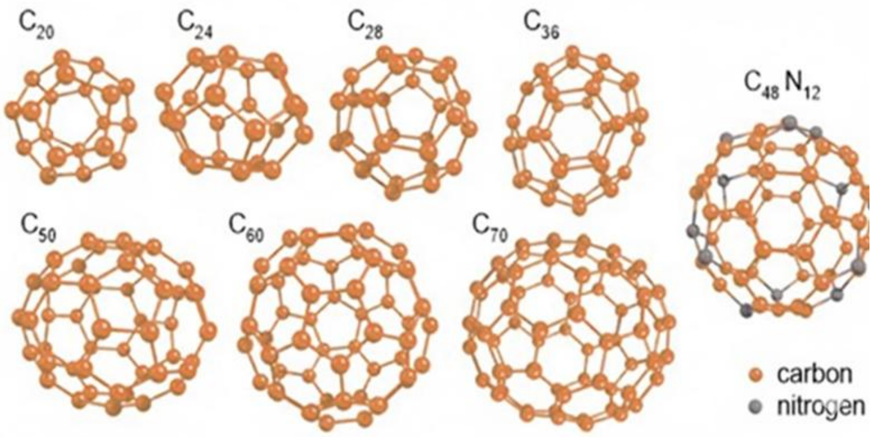
The discovery of Fullerenes is based on laser spectroscopy experiments conducted by Sir Harold W. Kroto, Robert F. Curl, Jr., and Richard E. Smalley at Rice University in 1985 [5]. They detected microscopic amounts of the C_{60} molecule through the laser vaporization of graphite in an inert atmosphere. This breakthrough earned them the 1996 Nobel Prize in Chemistry. Subsequently, in 1990, Krätschmer and colleagues successfully produced isolable quantities of C_{60} in the form of solid aggregates using the arc-discharge method [14]. The spherical geometry of the C_{60} molecule induces pyramidalization, causing the p-orbitals to project further toward the exterior surface of the sphere. This structural feature renders Fullerene an excellent electron acceptor and endows it with high electron affinity. This characteristic is fundamental to its application as an n-type material in organic solar cells. When solid C_{60} is doped with alkali metal atoms, such as potassium (K) or rubidium (Rb), the metal atoms intercalate into the interstitial voids of the Fullerene lattice, transferring electrons to the C_{60} molecules. For instance, in the K_3C_{60} form, the acquisition of three electrons per molecule results in the observation of superconductivity at low temperatures. This phenomenon stands as a striking example of how the electronic behaviours of a molecular structure can be precisely controlled through external doping.

Figure 2. Molecular structure of buckminsterfullerene C_{60}



The most well-known and stable member of the fullerene family, Buckminsterfullerene, is commonly referred to as the "buckyball" due to its resemblance to the geodesic domes designed by architect Buckminster Fuller. Topologically, the C_{60} molecule is similar to a soccer ball (a truncated icosahedron); its surface consists of 12 pentagonal and 20 hexagonal rings (Figure 3). In this structure, which adheres to Euler's law, every pentagon is surrounded only by hexagons [13]. Although C_{60} is the most extensively studied structure in the literature, many closed-cage molecules with varying numbers of atoms, ranging from C_{20} to C_{70}, are available. Fullerenes can be isolated as pure carbon structures or synthesized in heterofullerene forms, where some carbon atoms are substituted with heteroatoms such as nitrogen (as in $C_{48}N_{12}$) or boron [15].

Figure 3. Schematic representation of a heterofullerene structure (e.g., C48N12)



Solid-state structural studies have shown that C_{60} exhibits a face-centered cubic (fcc) lattice structure at room temperature [16]. The carbon atoms in Fullerene are connected by covalent bonds and are fundamentally in the sp^2 hybridization form. However, the curvature required by the spherical cage structure prevents the atoms from forming three bonds in the same plane, as in pure planar graphene. This situation leads to pyramidalization, which modifies the hybridization towards an intermediate state between pure sp^2 and sp^3 [17]. Two different covalent bond lengths are observed in the C_{60} molecule: 6–6 bonds (the short bonds connecting two adjacent hexagons, 1.38 Å) and 5–6 bonds (the long bonds connecting a pentagon and a hexagon, 1.45 Å). The pentagonal rings are essential as they provide the curvature necessary for the closure of the carbon cage [13].

Synthesis Methods

Various methods have been developed for the synthesis of fullerenes.

Arc Discharge: This method is based on generating a high-current arc between two graphite electrodes in an inert gas atmosphere, such as helium. It is the most common technique used for gram-scale production [14].

Flame Synthesis: Flame Synthesis is a scalable and cost-effective method used to produce fullerenes by the combustion of hydrocarbon fuels (such as benzene or acetylene) under carefully controlled conditions. This process involves optimizing parameters like fuel-to-oxygen ratio, pressure, and flame height/residence time to ensure that the soot generated contains a significant concentration of fullerenes. The combustion process creates carbon-rich intermediate species that subsequently assemble into the closed-cage C_{60} and higher fullerenes in the high-temperature zone of the flame. The fullerenes are then collected from the soot [18].

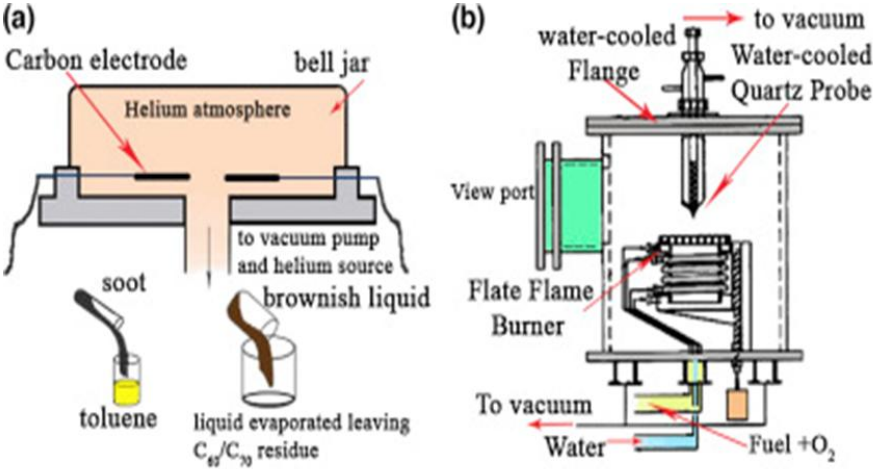
Chemical Vapor Deposition (CVD): Fullerenes can be synthesized through the thermal decomposition of hydrocarbon gases at high temperatures. This method has the potential to provide better control over production parameters [18].

Physical and Chemical Properties

The pyramidalization of fullerene significantly differentiates the molecule's properties from planar sp^2 structures like graphene [17]. Pyramidalization causes the p-orbital lobes to extend further towards the outer surface of the sphere, leading to a high electron affinity. This characteristic makes C_{60} an effective electron acceptor. The C_{60} exhibits semiconducting properties with a band gap of approximately 1.7eV. When doped with metal atoms (e.g., alkali metals), the conductivity of C_{60} changes, and a superconducting phase can be achieved [19].

Compared to planar graphene, the strain resulting from pyramidalization increases the chemical reactivity of fullerene toward addition reactions. The hollow nature of the molecules for the formation of encapsulation derivatives, such as endohedral fullerenes (where atoms or small molecules are trapped inside the cage) [15].

Figure 4. Schematic illustration of the arc discharge (a) and flame synthesis (b) methods used for Fullerene production [18]



Application Areas

The superior electronic properties and chemical reactivity of fullerenes have enabled their evaluation in a wide range of applications [7, 20]. Fullerenes and their derivatives are widely used as n-type materials in organic solar cells due to their high electron accepting properties [21]. They show potential as powerful antioxidants, drug delivery systems, and photodynamic therapy agents. Promising results have been reported, particularly in cancer treatment and neurological diseases [22, 23]. Their high surface area and reactive surfaces allow them to be used as catalysts or catalyst supports in heterogeneous catalysis [15]. Fullerene-based materials are being investigated as electrode materials for supercapacitors and batteries [24].

Carbon Nanotubes (CNTs)

One-dimensional (1d) cylindrical carbon allotropes

Carbon Nanotubes (CNTs) are cylindrical and one-dimensional (1D) nanoforms positioned between the spherical (0D) structure of fullerene and the planar (2D) structure of graphene. Their fundamental structure is formed by rolling up a graphene sheet seamlessly onto itself to create a tube [8]. These hollow structures, with diameters in the nanometer scale (1 nm to 100 nm) and a length-to-diameter ratio that can exceed 10^6, offer revolutionary properties for industrial and scientific fields due to their unique tubular geometry.

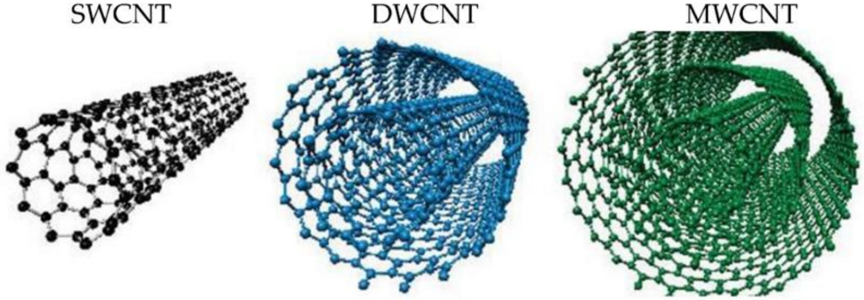
Structural Characteristics and Classification

CNTs are primarily divided into two main classes based on the number of wrapped graphene layers around the axis:

Single-Walled Carbon Nanotubes (SWCNTs): Formed by the rolling up of a single layer of graphene atoms into a seamless cylinder. Their diameters are typically around 1-2 nm.

Multi-Walled Carbon Nanotubes (MWCNTs): Consist of multiple concentric cylinders nested within each other, separated by van der Waals forces. Their diameters can range from 5-100 nm.

Figure 5. Single-walled (SWCNT), double-walled (DWCNT), and multi-walled (MWCNT) nanotubes [9]



Chirality and Electronic Properties

The most critical structural parameter of a CNT is its chirality, which is the angle at which the graphene sheet is rolled up to form the tube. This parameter is defined by the chiral vector (n,m) and fundamentally determines the electrical behaviour of the CNT (Figure 6). The electronic behaviour of Carbon Nanotubes (CNTs) is entirely dictated by their nanoscale rolling angle, defined by the chirality vector (n,m). This represents a unique quantum mechanical effect that is absent in macro-scale materials. The atomic symmetry along the tube axis in Armchair (n,n) nanotubes invariably results in metallic conductivity, positioning the CNT as a theoretically perfect molecular wire. Both Zigzag (n,0) and Chiral (n,m) tubes, however, typically exhibit semiconducting properties. A crucial exception to this is observed in Zigzag tubes: if the index n is a multiple of three (i.e., n=3k, where k=1, 2, 3...), that specific nanotube will also acquire metallic properties. This precise rule necessitates the challenging process of sorting and selective synthesis of nanotubes for electronic applications, as current synthesis methods commonly yield a complex mixture of both metallic and semiconducting species.

Synthesis Methods

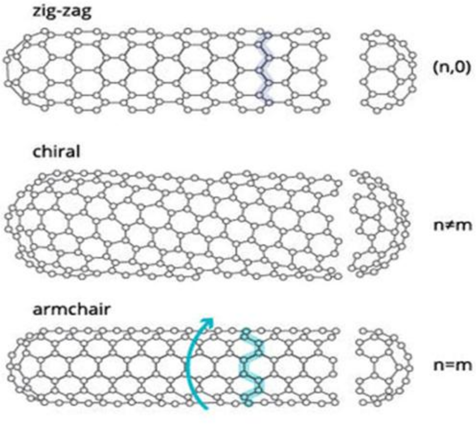
Three primary methods are employed to produce CNTs:

Arc Discharge: This method relies on the formation of CNTs in a plasma environment generated between graphite electrodes. It provides high-quality CNTs but is difficult to control.

Laser Ablation: CNTs are obtained by the laser vaporization of a graphite target and subsequent condensation in an inert gas flow. It is suitable to produce high-purity SWCNTs (Single-Walled Carbon Nanotubes).

Chemical Vapor Deposition (CVD): This is the most suitable and widespread method for industrial-scale CNT production. It is based on the decomposition of a carbon-containing gas (such as methane or ethylene) over nanoscale metal catalysts (like Fe, Ni, or Co) at high temperatures (600-1000 °C). The catalyst is critical in controlling the CNT's diameter and growth direction [25].

Figure 6. Classification of carbon nanotubes based on chirality (rolling angle): Zigzag, Armchair, and Chiral structures [10]



Applications

These superior properties have opened a wide range of applications for CNTs. They are incorporated into polymer, metal, or ceramic matrices to create lightweight, high-strength, and conductive composites used in aerospace, automotive, and sports equipment [27]. Due to their ability to form both p-type and n-type transistors, they are used in the development of nano-transistors and flexible electronic devices [10, 28]. The combination of high surface area and excellent conductivity makes CNTs ideal electrode materials for supercapacitors and lithium-ion batteries [29]. Since the adsorption of chemical or biological molecules on their surfaces changes their conductivity, they are excellent candidates for ultra-sensitive chemical and biosensors [30].

Toxicity and Safety Concerns

The increasing production and use of CNTs have raised concerns regarding potential health and environmental risks. Their fibrous morphology has led to worries that they may cause asbestos-like pathological effects. Research indicates that CNTs exhibit varying toxicological profiles depending on properties such as length, diameter, purity, and surface chemistry. Effects such as inflammation, fibrosis, and granuloma formation in the lungs have been reported [31, 32]. Therefore, the development of standardized risk assessment protocols is of critical importance for the safe management of CNTs throughout their entire lifecycle (production, use, and disposal) [33].

Graphene

Two-dimensional (2d) planar carbon allotrope

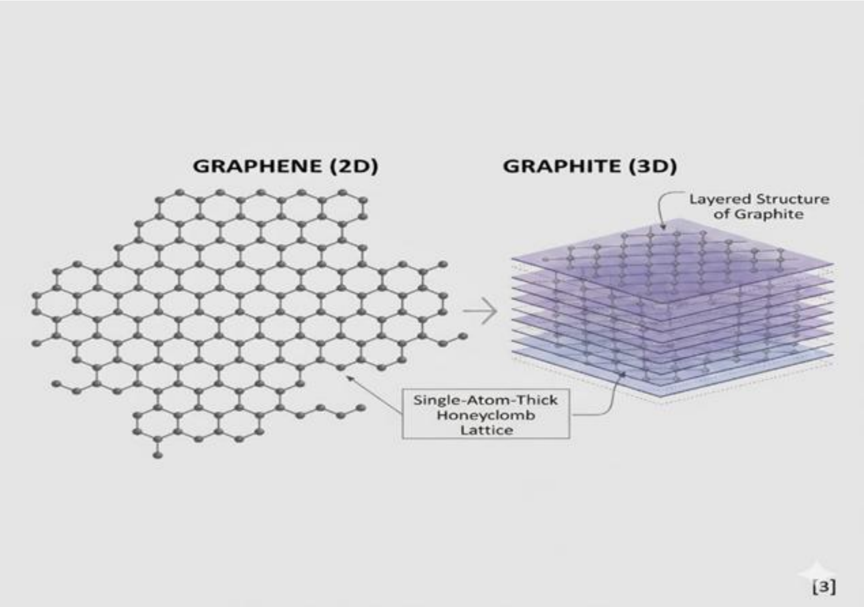
Graphene is the fundamental building block of the carbon nanostructures family. It is a planar, hexagonal (honeycomb) lattice structure composed of sp^2-hybridized carbon atoms arranged in a single-atom-thick layer. This structure is the thinnest known material and the pioneer of the two-dimensional (2D) material class [1, 3].

Structural Characteristics

Graphene was first discovered in 2004 by Andre Geim and Konstantin Novoselov by isolating it from graphite layers using a simple mechanical exfoliation (Scotch Tape) method [12]. This groundbreaking work was honoured with the 2010 Nobel Prize in Physics.

Graphene is one of the strongest materials known, proven to be approximately 200 times stronger than steel [11]. It is an excellent heat conductor [26]. Graphene's unique electronic properties stem directly from its atomic-scale honeycomb lattice. In the electronic band structure of graphene, the conduction band and the valence band meet at six specific points in momentum space, known as Dirac points. This tangency results in a zero-band gap, classifying the material as a semi-metal. Near these Dirac points, electrons effectively behave as massless Dirac fermions. This quantum mechanical behaviour allows the electrons to travel at an astonishing velocity of approximately 10^6 m/s roughly 1/300 th the speed of light. This exceptionally high electron mobility makes Graphene an ideal candidate for developing significantly faster and higher-frequency nano electronic devices compared to conventional silicon-based materials.

Figure 7. The single-atom-thick honeycomb lattice of Graphene and its layered structure in Graphite [3]



Synthesis Methods

Scalable production methods are critical for the translation of Graphene into industrial applications. The principal methods are summarized in Figure 8.

Top-Down Methods

Mechanical Exfoliation: A high-quality but low-yield method [12].

Liquid-Phase Exfoliation (LPE): The delamination of graphite into its layers using ultrasonication in an appropriate solvent. This method offers potential for large-scale production.

Graphene Oxide (GO) Reduction: The reduction of Graphene Oxide (obtained by oxidizing graphite with strong oxidizers) using chemical, thermal, or electrochemical methods.

This is a low-cost and scalable method, but the resulting reduced graphene oxide (rGO) contains structural defects [36].

Bottom-Up Methods

Chemical Vapor Deposition (CVD): This is the most industrially promising method, offering the potential to produce large-area, high-quality films at the meter scale. It is typically grown from carbon sources like methane on copper or nickel foils [25, 37].

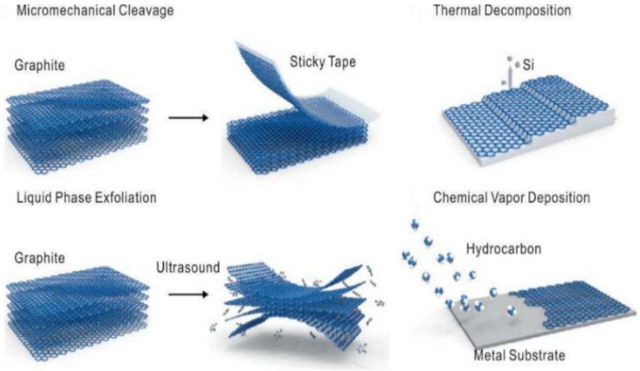
Epitaxial Growth: Involves heating crystalline surfaces, such as silicon carbide (SiC), at high temperatures, causing the silicon on the surface to sublime and leave behind graphene layers [38].

Chemical Vapor Deposition (CVD) stands as the most industrially promising method for achieving scalable graphene production, typically executed on transition metal surfaces such as copper (Cu) or nickel (Ni). The choice of substrate critically influences the resulting graphene film quality and thickness. Due to the limited solubility of carbon in copper, the CVD process on Cu predominantly favors surface precipitation, enabling the controlled growth of single-layer graphene (SLG). Conversely, nickel exhibits a high carbon solubility, leading to significant carbon dissolution into the bulk metal at high temperatures. During the cooling stage, this dissolved carbon precipitates out, resulting in the formation of multi-layer graphene (MLG) films. In parallel, top-down methods, such as Liquid-Phase Exfoliation (LPE) and Graphene Oxide (GO) Reduction, provide solution processability, making them highly suitable for large-scale production of inks, coatings, and polymer composites. However, Reduced Graphene Oxide (rGO), obtained through the chemical reduction of GO, inherently retains structural defects and residual oxygen functional groups. This compromise in material integrity results in diminished electronic performance compared to the pristine, high-quality graphene produced via CVD. Therefore, the strategic selection of the synthesis method is paramount, and must be dictated by the specific application requirements, whether for high-performance nanoelectronics (favoring CVD) or energy storage/composite materials (often utilizing rGO/LPE).

Application Areas

Graphene's unique multifunctional character makes it a fundamental material for a wide spectrum of applications. The combination of transparency and conductivity makes it ideal for foldable displays, touch panels, and solar cells [39]. Its high electron mobility makes Graphene ideal for high-frequency transistors and ultra-fast electronic applications [28]. It is used as an electrode material in supercapacitors and batteries to enhance energy and power density [29]. The addition of even small amounts to polymers significantly improves their mechanical, thermal, and electrical properties [27]. Its high surface area and electronic sensitivity enable the development of high-precision sensors capable of detecting biomolecules such as DNA and proteins [30]. Graphene oxide (GO), in particular, is used in drug delivery systems [40].

Figure 8. Comparative schematic of the main methods used for Graphene production [35]



Comparison of Carbon Nanostructures and Hybrid Materials

Although Fullerene, CNTs, and Graphene are composed of the same element, they exhibit distinct properties due to their varying dimensionality and geometry. The table below compares these three structures.

Hybrid Materials

The integration of nanostructures is frequently utilized to overcome the limitations of a single component. Hybrid materials, which combine the superior properties of structures with different dimensionalities, create new functionalities.

CNT-Graphene Hybrids: CNTs grown vertically on a graphene surface (referred to as "pillared graphene") combine both the electronic conductivity of the 2D plane and the high surface area of the 1D tube. This three-dimensional architecture is ideal for applications, especially in energy storage (supercapacitors) and high-performance sensors [41, 42].

Fullerene-Graphene Hybrids: Fullerene's electron acceptor property is combined with graphene or graphene oxide (GO) matrices to create synergistic effects in photovoltaic or catalytic systems. GO, in particular, can act as a carrier to disperse fullerene molecules more efficiently in biological or chemical systems [43].

Table 1. Comparison of carbon nanostructures

Property	**Fullerene (0D)**	**Carbon Nanotube (1D)**	**Graphene (2D)**
Geometry	Spherical (Cage)	Cylindrical (Tube)	Planar (Sheet)
Hybridization	Intermediate between sp^2 sp^3	sp^2	sp^2
Band Gap	Semiconducting 1.7 eV	Metallic or Semiconducting	Semi-metal (Zero)
Key Advantage	Electron acceptor, solubility	High strength, chirality-dependent electronic properties	Superior electron mobility, transparency
Key Disadvantage	Low mechanical strength	Difficulty in chirality control, toxicity concerns	Lack of a band gap, challenges in scalable production

Conclusion and Future Perspectives

Carbon nanostructures (Fullerene, CNTs, and Graphene) have instigated a revolution in materials science over the last three decades. The unique electronic, mechanical, and thermal properties of these materials, which can be controlled at the atomic level, have made them fundamental candidates for countless technological applications. However, two primary challenges must be overcome for the CN era to reach its full potential: scalability and functionalization. Future research and industrial developments will focus on addressing these challenges. It will be critical to develop more cost-effective production of high-quality Graphene and CNT films at the metric scale using methods like CVD, and to advance transfer-free integration techniques [35, 37]. This will facilitate the widespread adoption of CNs into the semiconductor industry.

The future of CNs lies not in their singular structures, but in hybrid systems. The integration of these structures of varying dimensions will maximize both surface area and electron transfer rate, enabling the emergence of next-generation materials for ultra-efficient batteries, supercapacitors, and catalytic systems [41]. Furthermore, the unique quantum mechanical behaviours of these materials are opening a new horizon for future computing technologies, such as quantum computing and spintronics. Their biocompatibility and sensitivity also hold the potential to revolutionize fields like wearable sensors, smart drug delivery systems, and bioelectronic interfaces [30, 40]. Carbon nanostructures will not only improve existing technologies but will fundamentally shape the technology of the future by opening the door for scientists to perform precise material engineering at the atomic level.

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BIOLOGICAL INTERACTIONS AND BIOMEDICAL APPLICATIONS OF METAL OXIDE NANOPARTICLES

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Introduction

Metal oxide nanoparticles (MONPs) are highly versatile nanomaterials with broad industrial and biomedical applications owing to their large surface area, chemical stability, ion-release capacity, and vigorous photocatalytic activity. At the nanoscale, their optical, magnetic, electrical, and catalytic properties are significantly enhanced, supporting potent antibacterial, antifungal, anticancer, and other biomedical effects. MONPs interact with biological systems through mechanisms such as ROS generation, membrane damage, and disruption of DNA and protein structures. Surface functionalization further enables the conjugation of drugs, enzymes, and antibodies, making them valuable platforms for targeted

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therapies. Among the numerous MONPs, this chapter focuses on iron, zinc, titanium, silver, copper, and gold nanoparticles.

Iron Oxide Nanoparticles

Iron oxide nanoparticles (IONPs), mainly composed of Fe_3O_4 and γ-Fe_2O_3, are extensively utilized magnetic nanomaterials owing to their pronounced magnetism, superparamagnetic characteristics at dimensions of approximately 10–20 nm, and remarkable biocompatibility [1–3]. Their minimal toxicity, biodegradability, and efficient metabolic elimination, combined with a large modifiable surface area, facilitate conjugation with biomolecules and stabilization through lipidic or polymeric coatings, thereby enhancing colloidal stability and mitigating immune responses [3,4]. IONPs exhibit broad applicability in biomedical fields, serving in antimicrobial and anticancer therapies, magnetic hyperthermia, site-specific drug delivery, cell labeling, nucleic acid purification, biosensing, and magnetic resonance imaging (MRI) diagnostics [1,2,5–7]. Beyond biomedicine, they are employed in catalysis, wastewater remediation, magnetic separation, and energy-related technologies. Their overall functionality is influenced by parameters such as particle size, shape, crystal phase, and surface engineering. In summary, Fe_3O_4 and γ-Fe_2O_3 nanoparticles constitute vital magnetic nanomaterials with adjustable physicochemical properties and proven biological safety, making them indispensable across diverse scientific, clinical, and industrial domains.

Evaluation of the Antimicrobial Potential of Iron Oxide Nanoparticles

IONPs display strong antibacterial effects dependent on particle size, surface charge, and coating. In the 10–50 nm range, their high surface reactivity enables membrane penetration and structural disruption [8,9]. Positively charged chitosan-coated

IONPs interact with negatively charged bacterial membranes, increase ROS production, and effectively inhibit *E. coli* and *B. subtilis*. Similarly, surface-modified FeO NPs suppress both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*, *P. aeruginosa*) bacteria via ion release, membrane damage, and metabolic interference [6].

Their antibacterial mechanism relies on Fe^{2+}/Fe^{3+}-driven Fenton reactions that generate hydroxyl radicals (•OH), leading to oxidative injury of lipids, proteins, and DNA. Under UV or visible light, photoactivated IONPs further enhance ROS generation [5,10]. Electrostatic interactions compromise membrane integrity, while released ions inhibit key enzymes and trigger DNA strand breaks [11,12]. Additionally, IONPs prevent biofilm formation by hindering bacterial adhesion and degrading the extracellular polymeric substance (EPS) matrix; their magnetic properties enable localized targeting and enhance biofilm disruption [13,14]. In summary, IONPs function as broad-spectrum antimicrobial agents through ROS production, membrane and enzyme disruption, and biofilm inhibition, making them promising for antibacterial coatings, wound dressings, and implant surface applications.

Evaluation of the Antifungal Potential of Iron Oxide Nanoparticles

IONPs exhibit antifungal activity by disrupting both cell membranes and intracellular processes. Despite the rigid chitin and β-glucan cell wall, Fe_3O_4 and Fe_2O_3 NPs destabilize this structure and interact with ergosterol-rich membranes, increasing permeability and causing ion leakage, metabolic imbalance, and vacuolar swelling [10,15,16]. Released Fe ions amplify the generation of reactive oxygen species (•OH, $O_2^{\bullet-}$), inducing lipid peroxidation, DNA and protein oxidation, and mitochondrial dysfunction in *Candida* and *Aspergillus* species. Reported MIC values range from 62.5 to 500 µg/mL for FeO NPs against major *Candida* strains, mainly via membrane disruption and oxidative stress [16].

IONPs also inhibit fungal spore germination by adsorbing onto spore surfaces, blocking water and nutrient uptake, and disrupting intracellular iron balance through excess radical formation or enzyme inhibition [17,18]. More than 80% reduction in spore germination has been documented for *Penicillium* and *Trichothecium* species [10]. In summary, IONPs serve as effective antifungal agents by inducing membrane damage, generating ROS, suppressing spore germination, and disturbing iron metabolism.

Evaluation of the Anticancer Potential of Iron Oxide Nanoparticles

IONPs are potent nanotherapeutics in cancer treatment due to their superparamagnetism, high surface area, and biocompatibility. In acidic tumor environments, FeO NPs dissolve rapidly, releasing Fe^{2+}/Fe^{3+} ions that drive Fenton reactions and generate ROS, leading to mitochondrial collapse, ATP loss, cytochrome-c release, apoptosis (p53, Bax, caspase-3), DNA damage, and cell-cycle arrest [1,20].

They also enable magnetic hyperthermia: alternating magnetic fields heat IONPs to 42–46 °C, causing damage to membranes and proteins and enhancing chemotherapy by increasing tumor perfusion and drug uptake [21]. Surface-modified IONPs can deliver anticancer drugs, antibodies, and ligands with high tumor specificity. Oleic acid–Pluronic–coated Fe_3O_4 nanoparticles efficiently load hydrophobic agents, and numerous studies report the successful delivery of drugs such as doxorubicin and paclitaxel [19]. Overall, IONPs provide ROS-mediated cytotoxicity, hyperthermia, DNA damage, and targeted delivery, making them powerful platforms for modern cancer therapy.

Biomedical Prospects and Applications of Iron Oxide Nanoparticles

IONPs are versatile theranostic nanomaterials owing to their superparamagnetism, surface tunability, and low toxicity [22]. Their magnetic responsiveness enables targeted drug delivery, allowing external-field–guided transport of chemotherapeutics, insulin, nucleic acids, and growth factors [23]. SPIONs also function as MRI contrast agents, providing high-resolution imaging of tumors and inflammation [1,24].

Beyond imaging and delivery, IONPs support cell labeling, magnetic separation, biosensing, and tissue engineering, facilitating precise tracking and isolation in stem-cell and immune research [11,25,26]. Their ROS-generating ability contributes to wound healing, antimicrobial coatings, and biofilm inhibition, while surface modifications enhance biocompatibility [27]. Overall, IONPs integrate targeted delivery, imaging, hyperthermia, biosensing, and antimicrobial functions, making them valuable nanoplatforms for modern diagnostics and therapy.

Zinc Oxide Nanoparticles

Zinc oxide nanoparticles (ZnO NPs) are wide-bandgap semiconductors characterized by high stability, low toxicity, and large surface area [28]. At the nanoscale, they exhibit enhanced photocatalytic activity, UV absorption, and electron-transfer efficiency. Commonly synthesized via zinc-ion hydrolysis and thermal treatment, their properties can be tuned by Mg^{2+} or Al^{3+} doping, which improves catalytic performance beyond that of TiO_2 in some cases [29,30].

ZnO NPs show strong antibacterial, antifungal, and anticancer effects through ROS generation, Zn^{2+} release, membrane disruption, and genotoxic stress. Their biocompatibility and easy functionalization enable use in bioimaging, tissue regeneration, wound healing, biosensing, drug delivery, and antiviral applications [28,29,31]. Overall, the performance of ZnO NPs depends on size, morphology, crystal structure, and surface chemistry. With high stability, UV absorption, and tunable photocatalytic activity, they serve as multifunctional materials for environmental, energy, pharmaceutical, and biomedical applications.

Evaluation of the Antimicrobial Potential of Zinc Oxide Nanoparticles

ZnO NPs, as wide-bandgap semiconductors, exhibit potent antibacterial activity through ROS generation, Zn^{2+} release, membrane disruption, and DNA/protein damage [32]. Photoactivated ZnO produces $\bullet OH$, $O_2\bullet^-$, and H_2O_2, leading to lipid peroxidation, membrane destabilization, and cytoplasmic leakage. Internalized Zn^{2+} further inhibits essential enzymes and induces oxidative DNA lesions, impairing replication [33].

ZnO NPs also reduce adhesion and suppress biofilms, particularly on implant surfaces, improving antibiotic efficacy [34]. Biogenic ZnO NPs show vigorous activity against Gram (+) and Gram (–) bacteria, supported by phytochemical synergy. Mahamuni-Badiger et al. (2020) demonstrated marked antibacterial and antibiofilm effects against *P. aeruginosa*, *S. pneumoniae*, *L. monocytogenes*, and *E. coli* [35]. Overall, ZnO NPs function as effective antimicrobial agents for wound dressings, dental applications, implant coatings, and antimicrobial surfaces.

Evaluation of the Antifungal Potential of Zinc Oxide Nanoparticles

ZnO NPs exhibit strong antifungal effects by disrupting the fungal cell wall and ergosterol-rich membrane, increasing permeability, and disturbing ion balance. Internalized Zn^{2+} ions promote ROS generation that damages lipids, proteins, and DNA, causing metabolic collapse in *Candida* and *Aspergillus* species [32]. Elevated membrane permeability and ionic imbalance are consistently observed.

Their large surface area facilitates spore adsorption, blocking water and nutrient uptake and inhibiting germination. Photocatalytically produced ROS further damage mitochondria and induce apoptosis-like cell death. Biogenic ZnO NPs containing phytochemicals enhance these effects, while interactions with fungal polysaccharides weaken the cell wall and suppress spore germination in *Penicillium* and other phytopathogens [36–38]. In summary, ZnO NPs function as efficient antifungal agents with potential use in topical treatments, dental coatings, food preservation, and agricultural fungicides.

Evaluation of the Anticancer Potential of Zinc Oxide Nanoparticles

ZnO NPs show strong potential in cancer therapy as both cytotoxic agents and drug carriers. In the acidic tumor microenvironment, they rapidly dissolve, releasing Zn^{2+} ions that, together with ROS generation, induce mitochondrial dysfunction, ATP depletion, and apoptosis via p53, Bax, and caspase activation [33]. Their semiconductor properties further enhance ROS production under light, intensifying oxidative stress beyond cellular repair capacity.

The large surface area of ZnO NPs allows efficient drug loading and controlled release, reducing toxicity to healthy cells [39,40]. Studies, including Pal and Pareek (2021), demonstrate enhanced ROS-mediated tumor inhibition, particularly when combined with photodynamic therapy. ZnO NPs exhibit selective cytotoxicity toward cancer cells, causing DNA damage, cell cycle arrest, and apoptosis, as shown by Asif et al. (2023) [40,41]. Overall, ZnO NPs represent promising multifunctional platforms for cancer treatment, offering targeted drug delivery and potent ROS-driven anticancer activity.

Biomedical Prospects and Applications of Zinc Oxide Nanoparticles

ZnO NPs possess broad biomedical potential owing to their biocompatibility, low toxicity, UV-blocking properties, and ease of surface modification. They are applied in bioimaging, tissue engineering, wound healing, implant and dental coatings, and drug-delivery systems [42]. ZnO NPs enhance the antimicrobial and anticariogenic performance of dental materials, promote dentin remineralization, and serve in dermatological and sunscreen formulations due to their strong UV absorption [34].

Their excellent electron-transfer capacity supports biosensing applications for detecting glucose, cholesterol, and tumor biomarkers [43]. ZnO NPs also contribute to drug delivery, tissue regeneration, phototherapy, and antiviral defense by inhibiting viral entry and replication [41,44]. Overall, ZnO NPs function as versatile diagnostic and therapeutic nanomaterials, with biocompatibility, controlled dissolution, and adjustable surface chemistry enabling diverse uses in medical devices, biosensors, and advanced therapeutic systems.

Copper Oxide Nanoparticles

Copper oxide nanoparticles (CuO/Cu_2O NPs) have garnered attention due to copper's low cost, high availability, and enhanced nanoscale optical, catalytic, and electrical properties [45–47]. Cu_2O serves as a semiconductor in catalysis and electrochemical systems, while CuO NPs exhibit vigorous redox activity and superior catalytic efficiency. Their variable Cu^{+}/Cu^{2+} states, ion-release capacity, and ROS generation underpin their antibacterial, antifungal, and anticancer activities, supporting applications such as wound dressings, implant coatings, drug delivery, and biosensing [46, 48, 49]. Industrially, CuO NPs function as catalysts, electrode materials, and combustion enhancers, aided by their versatile redox behavior [50]. Overall, CuO NPs are multifunctional nanomaterials with broad biomedical and industrial relevance.

Evaluation of the Antimicrobial Potential of Copper Oxide Nanoparticles

CuO NPs exhibit strong, broad-spectrum antibacterial activity due to their high surface area, Cu^{+}/Cu^{2+} redox states, and surface reactivity. Their antimicrobial action involves membrane disruption, Cu^{2+} ion release, and ROS generation, which increase permeability, cause cytoplasmic leakage, and trigger metabolic failure [51,52]. Internalized Cu^{2+} binds sulfhydryl groups and inhibits key enzymes such as NADH dehydrogenase and fumarase, impairing energy metabolism; Cu_2O rapidly deactivates fumarase A, while CuO elevates superoxide levels, accelerating cell death [51,53].

Cu^{+}/Cu^{2+} redox cycling produces ROS—superoxide, hydroxyl radicals, and peroxides—causing irreversible protein oxidation, DNA damage, and lipid peroxidation [52,54]. Accumulated near membranes, CuO NPs intensify oxidative stress, especially in Gram-positive bacteria (*S. aureus*, *B. subtilis*) [52]. They also disrupt the EPS matrix, limiting adhesion and biofilm formation [52,55]. In summary, CuO NPs are potent antibacterial nanomaterials suitable for use in textiles, implant coatings, wound dressings, and surface disinfection applications.

Evaluation of the Antifungal Potential of Copper Oxide Nanoparticles

CuO NPs display potent antifungal effects by damaging the fungal cell wall and membrane, disrupting ionic homeostasis, and inducing oxidative stress. Cu^{2+} ions bind to chitin- and β-glucan–rich wall components and interact with ergosterol membranes, weakening structure, increasing permeability, and causing ion imbalance [56]. Released Cu^{2+} targets the mitochondrial electron transport chain, elevating ROS production; generated hydroxyl and superoxide radicals lead to lipid peroxidation, protein denaturation, and DNA fragmentation, resulting in metabolic collapse in *Candida* and *Aspergillus* species [56,57].

CuO NPs also suppress spore germination by adsorbing onto spore surfaces and limiting water and nutrient uptake [58]. Green-synthesized CuO NPs containing phytochemicals further enhance antifungal efficacy against both clinical and phytopathogenic fungi [54]. In summary, CuO NPs exert antifungal action through cell wall and membrane disruption, ROS generation, mitochondrial damage, and spore inhibition, making them promising materials for food preservation, agriculture, dental coatings, textiles, and medical applications.

Evaluation of the Anticancer Potential of Copper Oxide Nanoparticles

CuO NPs demonstrate strong, selective cytotoxicity against cancer cells through Cu^{2+}/Cu^{+} ion release and nanoparticle-induced

ROS generation [59]. In the acidic tumor microenvironment, CuO dissolves rapidly, producing high copper ion concentrations that drive Fenton-like reactions, leading to mitochondrial membrane collapse, cytochrome c release, ATP depletion, and caspase-mediated apoptosis [22,60].

Their preferential accumulation in cancer cells—attributed to higher metabolic rates and metal sensitivity—enhances selectivity. Studies report that CuO NPs cause DNA double-strand breaks, cell cycle arrest (G0/G1 or G2/M), and activation of p53, Bax, and caspase-3, resulting in strong cytotoxic effects in lines such as MCF-7, HeLa, and A549 [57,61]. Their photocatalytic nature also boosts ROS formation under light exposure, mimicking photodynamic therapy. Additionally, surface-modified or magnetically engineered CuO NPs can function as targeted nanocarriers, allowing controlled drug release and tumor-specific delivery [62,63]. Overall, CuO NPs combine potent ROS-driven cytotoxicity with targeted delivery capability, making them promising multifunctional agents for advanced cancer therapy.

Biomedical Prospects and Applications of Copper Oxide Nanoparticles

CuO NPs are versatile biomedical materials with high catalytic activity, ion-release capacity, and large, easily functionalized surfaces. They exhibit strong antimicrobial effects, supporting use in implant coatings, wound dressings, and medical textiles [59,64]. By promoting fibroblast growth and angiogenesis, CuO NPs also aid tissue regeneration and wound repair [65]. Their excellent electron-transfer ability enhances biosensors for glucose, cholesterol, and tumor detection [43,66], while photocatalytic ROS generation under UV/visible light prevents biofilm formation and surface contamination [22]. CuO NPs are further explored in drug delivery, photodynamic therapy, and cancer hyperthermia [60,67].

Green-synthesized variants offer improved biocompatibility, though controlled ion release remains critical for safety. Overall, CuO NPs serve as multifunctional nanomaterials with strong diagnostic and therapeutic potential.

Silver Oxide Nanoparticles

Silver oxide nanoparticles (Ag_2O NPs) are semiconductor nanomaterials with high surface area, efficient Ag^+ release, and strong photocatalytic activity, providing potent antimicrobial, antifungal, and anticancer effects [68–71]. Green synthesis using plant extracts or biopolymers yields biocompatible NPs that retain silver's enzyme-inhibiting and ROS-generating properties [15,72].

Their action involves membrane disruption, ionic imbalance, and oxidative stress, enhanced by photocatalytic and SPR effects [71]. These features support applications in wound healing, implant coatings, biosensors, photodynamic therapy, and environmental remediation. Overall, green-synthesized Ag_2O NPs are sustainable, multifunctional nanomaterials with broad diagnostic and therapeutic potential [73,74].

Evaluation of the Antimicrobial Potential of Silver Oxide Nanoparticles

Ag_2O NPs display potent, broad-spectrum antibacterial activity driven by high surface reactivity, efficient Ag^+ ion release, and photocatalytic ROS generation. Ag^+ ions interact with thiol-containing membrane proteins, disrupt enzymatic activity, and compromise membrane integrity, leading to cytoplasmic leakage and metabolic failure [73,75]. Their wide-bandgap semiconductor properties enhance light-induced ROS production ($\bullet OH$, $O_2\bullet^-$, H_2O_2), causing oxidative damage to DNA, proteins, and lipids, ultimately resulting in cell death [75,76].

Gram-negative bacteria permit easier nanoparticle penetration, while Gram-positive species are more affected by Ag^+-mediated wall disruption; smaller Ag_2O NPs show greater membrane affinity and antibacterial potency [71]. Additionally, Ag_2O NPs degrade biofilm EPS, preventing adhesion and increasing bacterial susceptibility to antibiotics [77]. Overall, Ag_2O NPs act as powerful antimicrobial agents suitable for use in wound dressings, implant coatings, water purification, and antimicrobial surfaces.

Evaluation of the Antifungal Potential of Silver Oxide Nanoparticles

Ag_2O NPs show strong antifungal activity by disrupting fungal cell walls and membranes. Ag^+ ions bind to ergosterol-rich membrane regions, increasing permeability and disturbing ion balance, while also weakening chitin- and β-glucan–based wall layers [74,78].

Under light, Ag_2O generates high ROS (•OH, $O_2^{\bullet -}$, H_2O_2), causing lipid peroxidation, protein/DNA damage, mitochondrial dysfunction, and cell death in fungi such as *Candida* spp. and *Aspergillus* spp. [71,79]. Ag_2O NPs also adsorb onto spores, inhibiting water/nutrient uptake and suppressing germination [76,80]. Green-synthesized forms often enhance these effects, and antifungal potency depends on the NP size, charge, and Ag^+ release [74, 81]. Through these mechanisms, Ag_2O NPs serve as potent antifungal agents for food preservation, agricultural fungicides, dental coatings, and medical devices.

Evaluation of the Anticancer Potential of Silver Oxide Nanoparticles

Ag_2O NPs exhibit strong and selective anticancer activity through Ag^+ ion release and photocatalytically generated ROS. In the acidic tumor microenvironment, the rapid dissolution of Ag_2O

elevates Ag^+ levels, triggering Fenton-like reactions, mitochondrial depolarization, ATP loss, cytochrome c release, and the activation of p53/Bax/caspase–3–mediated apoptosis. Ag_2O and Ag NPs also induce DNA double-strand breaks, G0/G1 or G2/M arrest, and accumulation of oxidative damage in tumor cells [71].

Their SPR-driven ROS production enhances efficacy under light, supporting photodynamic therapy [82,83]. Silver-based NPs additionally inhibit MDR efflux pumps, increasing intracellular drug levels, while exhibiting selective toxicity toward cancer cells due to their higher metabolic and metal-ion sensitivity [84]. Overall, Ag_2O NPs function as direct cytotoxic agents and multifunctional nanoplatforms for light-activated and targeted anticancer therapies.

Biomedical Prospects and Applications of Silver Oxide Nanoparticles

Ag_2O NPs are multifunctional, biocompatible materials with high surface area, efficient ion release, and strong photocatalytic and antimicrobial activity, supporting broad biomedical use [85]. They promote wound healing, prevent infections, and inhibit biofilms on implant surfaces [85].

Their high electron-transfer ability enhances biosensors for glucose, cholesterol, and tumor markers [84], while Ag_2O/Ag systems also show antiviral, water-purifying, and detoxifying effects useful in dental, pharmaceutical, and environmental applications [81,86–90]. Green-synthesized, phytochemical-stabilized Ag_2O NPs improve compatibility, enable targeted delivery, and reduce toxicity [91,92]. Under visible light, their photocatalytic properties drive pollutant degradation. Overall, Ag_2O NPs serve as versatile materials for diagnostic, therapeutic, and environmental applications.

Titanium Dioxide Nanoparticles

Titanium dioxide nanoparticles (TiO_2 NPs) are wide-bandgap semiconductors with strong light absorption, surface reactivity, and photocatalytic activity, supporting applications in purification, self-cleaning coatings, solar cells, and hydrogen generation [93,94]. Their performance depends on crystal phase and morphology, while green synthesis provides sustainable, biocompatible options [95,96]. Under UV or visible light, TiO_2 produces ROS (•OH, $O_2•^-$) that degrade pollutants and damage microbial membranes and DNA, giving it potent antibacterial and antifungal properties for sterilization, coatings, and water treatment [97–102]. Light-activated TiO_2 also induces ROS-mediated apoptosis (p53, Bax, caspase-3), enabling use in photodynamic therapy and targeted drug delivery [93].

In biomedicine, TiO_2 NPs serve in implants, wound dressings, biosensors, and dermatological products due to their antimicrobial, UV-protective, and electron-transfer features [103,104]. Overall, TiO_2 NPs unite photocatalytic efficiency, biocompatibility, and tunable surfaces, making them versatile for environmental and biomedical use.

Evaluation of the Antimicrobial Potential of Titanium Dioxide Nanoparticles

TiO_2 NPs exhibit strong antibacterial activity through their semiconductor properties and high photocatalytic ROS generation. Under UV or visible light, electron–hole pairs produce •OH, $O_2•^-$, and singlet oxygen, causing lipid peroxidation, protein damage, and DNA disruption, ultimately leading to bacterial death [100,105].

Antibacterial efficacy depends on surface charge, particle size, and crystalline phase—especially anatase, which enhances membrane interaction, facilitates penetration in Gram (–) bacteria, and weakens peptidoglycan in Gram (+) species [102]. TiO_2 NPs also disrupt biofilm EPS matrices, reducing adhesion and improving antibiotic response. Light-assisted TiO_2 photocatalysis effectively decreases microbial load, supporting its use in water purification, surface sterilization, and medical device coatings. Overall, TiO_2 NPs act as efficient antimicrobial agents for hospital infection control and environmental bioremediation [22,30].

Evaluation of the Antifungal Potential of Titanium Dioxide Nanoparticles

The antifungal activity of TiO_2 NPs stems from their ability to damage fungal cell walls and membranes. Under UV or visible light, photoactivated TiO_2 generates ROS (•OH, $O_2•^-$) that oxidize membrane lipids and proteins, increase permeability, and cause cytoplasmic leakage, making *Candida* and *Aspergillus* particularly sensitive [106].

TiO_2 NPs also interact with chitin and β-glucan layers, weakening the cell wall, while their adsorption onto spores limits water and nutrient uptake, inhibiting germination [107]. Smaller anatase-phase particles show the strongest photocatalytic antifungal effects and effectively suppress phytopathogenic fungi [108]. Overall, TiO_2 NPs act as efficient antifungal nanomaterials applicable in agriculture, food packaging, dental coatings, and medical devices.

Evaluation of the Anticancer Potential of Titanium Dioxide Nanoparticles

TiO_2 NPs act as potent nanotherapeutic agents through photocatalytic and oxidative mechanisms that induce selective cancer cell death. In the tumor microenvironment, photoactivated TiO_2 generates ROS, causing mitochondrial collapse, cytochrome-c release, ATP depletion, and caspase-mediated apoptosis via p53, Bax, and caspase-3 activation [109,110].

Hybrid TiO_2 nanostructures with surface plasmon resonance (SPR) enhance ROS production and improve photodynamic and photothermal therapy efficiency. Their selectivity arises from cancer cells' high metabolism and oxidative stress sensitivity. Surface-functionalized TiO_2 NPs also enable targeted delivery, controlled release, and overcome multidrug resistance [109]. Overall, TiO_2 NPs are promising anticancer platforms for photodynamic therapy, drug delivery, and combination treatments.

Biomedical Prospects and Applications of Titanium Dioxide Nanoparticles

TiO_2 NPs are widely applied in biomedicine owing to their biocompatibility, surface stability, strong photocatalytic activity, and ease of modification. In implant coatings, they prevent bacterial adhesion and biofilm formation, lowering infection risks, especially in orthopedic devices. In wound dressings, TiO_2 NPs promote regeneration, enhance oxygenation, and accelerate healing through antimicrobial action [111,112]. Their excellent electron-transfer ability enhances biosensors for detecting glucose, tumor markers, and other diagnostic molecules, while their strong UV absorption supports safe use in dermatological sunscreens [43]. Surface-functionalized TiO_2 NPs also enable controlled drug delivery and targeted therapy.

Beyond medicine, TiO_2 NPs serve as effective photocatalysts in environmental cleanup, water purification, and sterilization. Overall, their multifunctionality makes TiO_2 NPs valuable nanoplatforms for diagnostic, therapeutic, and environmental applications.

Gold Oxide Nanoparticules

Au/Au$_2$O NPs are versatile, biocompatible nanomaterials with tunable physicochemical and SPR-based optical properties, enabling broad diagnostic and therapeutic use in cancer, infectious diseases, tissue engineering, and targeted drug delivery [113,114]. Their antimicrobial activity—via membrane disruption, ion imbalance, ROS generation, and light-induced photothermal/photocatalytic effects—supports applications in wound dressings, implant and dental coatings, and antimicrobial surfaces [55,115].

In oncology, Au$_2$O NPs induce selective ROS- and hyperthermia-mediated apoptosis, while functionalized Au NPs enable targeted, controlled drug delivery and improved therapeutic efficacy [114,116]. They also serve as sensitive SPR-based biosensors for nucleic acids, proteins, pathogens, and tumor markers, and contribute to tissue repair and immune modulation. Green-synthesized Au NPs offer enhanced biocompatibility for pharmaceutical and implant applications [117–119]. Overall, Au/Au$_2$O NPs act as multifunctional theranostic platforms with strong diagnostic and therapeutic potential.

Evaluation of the Antimicrobial Potential of Gold Oxide Nanoparticules

AuO NPs exhibit strong, broad-spectrum antibacterial activity driven by surface plasmon resonance (SPR)-induced reactivity, membrane interaction, and high biocompatibility. Their direct contact with bacterial membranes disrupts lipid bilayers, increases permeability, and causes ion imbalance and membrane potential collapse, impairing cellular metabolism [55,120]. Under visible or near-infrared light, their photosensitivity enables photothermal and photocatalytic ROS generation (•OH, O_2•⁻), leading to lipid, protein, and DNA oxidation and rapid bacterial death in both Gram-negative and Gram-positive species [121]. Green-synthesized Au NPs containing phytochemicals enhance membrane affinity and antibacterial efficiency.

Smaller or surface-functionalized particles penetrate membranes more effectively and show synergistic effects with antibiotics against resistant strains [74]. Overall, AuO NPs act as potent antimicrobial agents applicable in wound dressings, implant coatings, sterilization systems, water purification, and antimicrobial surfaces.

Evaluation of the Antifungal Potential of Gold Oxide Nanoparticules

AuO NPs exhibit strong antifungal activity by disrupting fungal cell walls and membranes while inducing oxidative stress. Their interaction with ergosterol-rich regions alters membrane fluidity, increases permeability, and causes ion imbalance and cytoplasmic leakage [122]. Concurrent oxidative damage to chitin and β-glucan structures results in vacuole swelling, metabolic arrest, and cell death.

Under light exposure, their photocatalytic properties enhance ROS generation, leading to lipid, protein, and DNA oxidation, producing rapid fungicidal effects against *Candida* and *Aspergillus* species [55]. Green-synthesized Au NPs rich in phytochemicals further strengthen wall adhesion and inhibit spore germination, blocking early colonization. Overall, AuO NPs act as potent antifungal nanomaterials applicable in food preservation, agricultural fungicides, dental coatings, and medical device surfaces.

Evaluation of the Anticancer Potential of Gold Oxide Nanoparticules

AuO NPs are multifunctional anticancer nanotherapeutics that induce selective cytotoxicity through ion-release–driven oxidative stress and light-activated effects. In the acidic tumor microenvironment, increased Au^+/Ag^+ ion release and ROS generation cause mitochondrial depolarization, ATP loss, cytochrome c release, DNA damage, and p53/Bax/caspase-3–mediated apoptosis, leading to G1 or G2/M arrest and rapid tumor cell death [123,124]. Their surface plasmon resonance (SPR) properties enable efficient conversion of visible or NIR light into localized hyperthermia (42–45 °C), selectively destroying tumor tissue, while SPR-enhanced ROS generation amplifies photodynamic therapy and acts synergistically with chemotherapeutics [116,125].

Surface modification further allows targeted delivery, controlled release, and reduced systemic toxicity; engineered Au NPs also inhibit metastasis, suppress angiogenesis, and help overcome multidrug resistance [121,126]. Overall, AuO NPs combine cytotoxic, photothermal, photodynamic, and targeted-delivery functionalities, establishing them as advanced nanoplatforms for modern cancer therapy.

Biomedical Prospects and Applications of Gold Oxide Nanoparticules

AuO NPs possess excellent biocompatibility, unique SPR-based optical properties, and tunable surface chemistry, making them highly valuable for advanced biomedical use. Their optical and electronic characteristics enhance signal transduction in SPR biosensors, allowing ultrasensitive detection of DNA, proteins, pathogens, and tumor biomarkers [117,118,127].

In wound dressings and implant coatings, Au NPs promote tissue repair and inhibit biofilms, while in tissue-engineering scaffolds, they support cell proliferation and improve electrical conductivity for neural, cardiac, and artificial skin applications. Their modifiable surfaces enable targeted, controlled drug delivery with high payload capacity, tumor specificity, and low systemic toxicity [128]. SPR-driven photothermal conversion also enables localized, minimally invasive tumor ablation.

Green-synthesized, phytochemical-stabilized Au NPs further enhance compatibility for use in pharmaceuticals, tissue engineering, and implant materials [118]. Overall, AuO NPs function as multifunctional nanomaterials with wide-ranging diagnostic and therapeutic potential.

Future Prospect: Metal Oxide Nanoparticles

In the future, the controlled and safe use of MONPs in biological systems is expected to expand further through the development of targeted drug delivery systems, photodynamic and magnetic hyperthermia-based cancer therapies, novel antimicrobial strategies against antibiotic resistance, and environmentally friendly green synthesis approaches. In particular, biocompatible coating techniques and surface functionalization strategies that minimize toxicity will play a crucial role in promoting the sustainable application of these NPs in medicine, biotechnology, and environmental technologies.

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NANOTECHNOLOGY IN FOOD TECHNOLOGY

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Introduction

Nanotechnology has emerged in recent years as a multidisciplinary and strategically significant field positioned at the forefront of scientific research and industrial applications. The unique physical, chemical, and biological properties that appear at the nanometer scale enhance the functionality of materials and enable the development of entirely new applications. By designing and controlling structures within the range of 1–100 nm, nanotechnology confers macroscopic materials with novel

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functionalities that are not observed in their bulk forms. Phenomena such as increased surface-to-volume ratio, quantum confinement, and interfacial effects lead to striking changes in reactivity, color, mechanical, and barrier properties [1–3]. In this respect, nanotechnology has become a transformative science and technology branch with applications extending far beyond material science and engineering to include health, energy, environment, agriculture, and food systems [3–10].

The food industry is one of the primary sectors directly benefiting from the innovative approaches offered by nanotechnology. Food safety, quality, shelf life, nutritional value, and sensory attributes are all factors that must be continuously improved in accordance with consumer expectations. In this context, nanotechnology provides remarkable opportunities in areas such as food processing, packaging, quality control, biosensor applications, and the development of functional foods. Through nanoencapsulation techniques, for instance, bioactive compounds can be protected and released in a controlled manner, thereby enhancing the functional properties of foods. Similarly, the integration of nanomaterials into packaging technologies contributes to improved food safety and prolonged shelf life of products [11–13].

The main drivers behind the use of nanotechnology in food applications include: (i) preservation and enhancement of nutrient bioavailability, (ii) extension of shelf life and improvement of safety, (iii) development of smart/active packaging and rapid quality control systems, and (iv) reduction of food waste in alignment with sustainability goals [14,15].

Globally, the market size of food nanotechnology has shown a consistent increase since the late 2010s, with packaging and responsive sensor technologies leading the segment. In Türkiye, research has accelerated through TÜBİTAK-funded projects and university-based UYG-AR/NANO centers, focusing both on materials (chitosan, cellulose, biopolymers) and applications (packaging, encapsulation, nanosensors). Nevertheless, consumer confidence, ethical labeling, and regulatory frameworks are equally significant and must be addressed through comprehensive risk assessment and standardization according to EFSA, FDA, and OECD guidelines.

This chapter examines the classification of nanomaterials used in foods, the role of nanotechnology in food processing, and its current applications in food production and quality assurance. Moreover, it discusses the potential advantages, risks, and regulatory dimensions of nanotechnology in the food sector, presenting a holistic overview of its impact and implications.

Classification of Nanomaterials in Foods

Nanotechnology offers revolutionary innovations in various areas of the food industry. At the core of these innovations lie the characteristics and classification of the nanomaterials used. Nanomaterials employed in food applications are generally classified into three main categories: organic, inorganic, and carbon-based nanomaterials. Each category provides distinct properties and application potentials.

Organic Nanomaterials

Organic nanomaterials are derived from biological sources or synthesized using biological components. They are well known for their biocompatibility and biodegradability. In the food industry, these materials are primarily utilized in nutrient delivery systems and stabilization of functional food components. Examples include liposomes**,** nanocapsules, and nanolipids. By facilitating the controlled release of nutrients, these materials can enhance the nutritional value and extend the shelf life of food products [18].

Inorganic Nanomaterials

Inorganic nanomaterials consist mainly of metal and metal oxide nanoparticles, which are favored in food packaging due to their antimicrobial properties. Silver (Ag), zinc oxide (ZnO), titanium dioxide (TiO_2), and silica (SiO_2) nanoparticles are among the most widely used inorganic nanomaterials in food packaging. These materials prevent spoilage, extend product shelf life, and enhance food safety [19].

Carbon-Based Nanomaterials

Carbon-based nanomaterials are composed of carbon atoms arranged in specific structural configurations and are notable for their high surface area and electrical conductivity. In the food industry, they are primarily applied in sensor technologies and food quality monitoring systems. Materials such as graphene, carbon nanotubes, and carbon quantum dots have potential applications in the monitoring and quality assessment of food products [19].

The classification of nanomaterials used in food systems represents a critical step in understanding their properties and potential applications. Each type of nanomaterial offers distinct advantages as well as potential risks. Therefore, a comprehensive understanding of the characteristics and classification of these materials is essential for the safe and effective application of nanotechnology in the food industry.

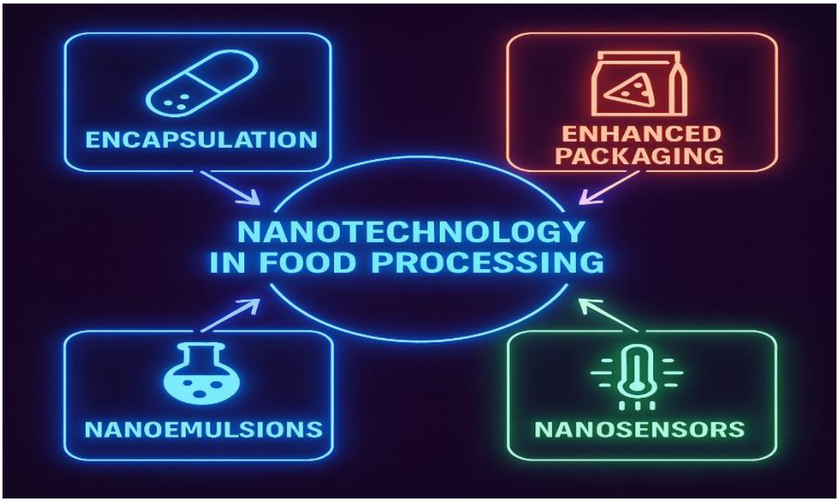
Nanotechnology in Food Processing

Nanostructured food components have been developed to improve the taste, texture, and consistency of food products (Fig. 1).

Applications of nanotechnology in the food sector help to extend the shelf life of products and reduce food losses caused by microbial contamination. Currently, nanocarrier systems are widely used to transport food additives without altering the basic morphology of food materials. The particle size directly affects the distribution of bioactive compounds in the human body; for example, certain cell types can efficiently absorb only submicron-sized nanoparticles, while larger microparticles cannot be absorbed effectively [20,21].

An ideal delivery system should possess three fundamental properties: **(i)** accurate and efficient delivery of the active compound to the target site, **(ii)** controlled release of the active substance at the desired time and rate, and **(iii)** long-term stability of active compounds under storage conditions.

Figure 1. Nanotechnology in food processing



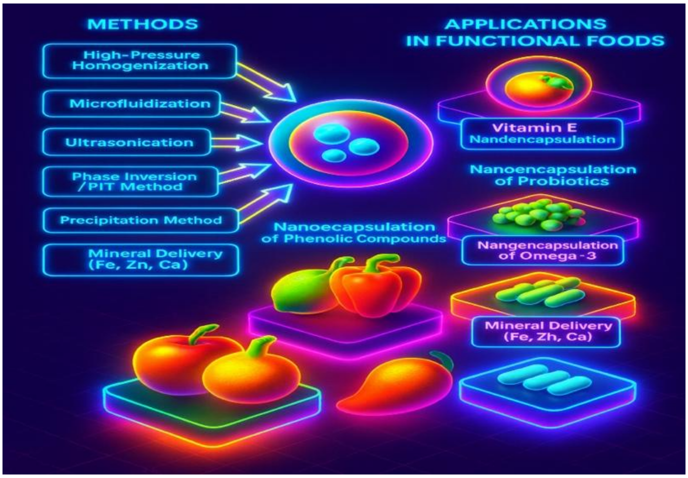
Nanotechnological approaches including encapsulation, emulsions, biopolymer matrices, simple solutions, and colloidal combinations offer highly effective delivery systems that meet these criteria [20,22]. Furthermore, nanopolymers have the potential to replace conventional packaging materials, improving both durability and functionality. Nanosensors, on the other hand, are increasingly utilized to detect contaminants, mycotoxins, and microorganisms in foods, thereby enhancing food safety and traceability [18].

Nanoencapsulation and Food Additives

Fundamental Principles and Techniques

Nano Nanoencapsulation refers to the incorporation of bioactive compounds (such as vitamins, minerals, polyphenols, carotenoids, probiotics, and flavor molecules) into nanoemulsions, nanoliposomes, polymeric nanoparticles, solid lipid nanoparticles (SLN/NLC), dendrimers, or nanomicelles [23–26]. The main production techniques are summarized below (Fig.2).

Figure 2. Nanoencapsulation and food additives



High-Pressure Homogenization

High-pressure homogenization (HPH) is a technique in which liquids are forced through narrow orifices under very high pressure, generating strong shear forces. This process reduces particle size and enhances emulsion stability. In the food industry, it is particularly effective for encapsulating active compounds and stabilizing emulsions [27].

Microfluidization

Microfluidization uses microchannels to propel liquids at high velocities, creating strong shear forces that reduce droplet size to the nanometer scale and ensure uniform particle distribution. It is widely applied in the preparation of emulsions and active compound delivery systems in food formulations [28].

Ultrasonication (Sonication)

Ultrasonication involves applying sound waves at high frequencies within a liquid medium, causing the formation and collapse of microscopic bubbles a phenomenon known as cavitation. This mechanical action reduces particle size and enhances emulsion stability. Ultrasonic-assisted encapsulation is commonly used to improve the bioavailability and stability of phytochemicals and other bioactive compounds in foods [29].

Phase Inversion Temperature Method

The phase inversion temperature (PIT) method relies on changes in the hydrophilic lipophilic balance (HLB) of surfactants as a function of temperature. A mixture of water, oil, and surfactant is heated and then cooled in a controlled manner to form a nanoemulsion. During heating, the surfactant's HLB value changes, inducing a phase inversion, which in turn triggers nanoemulsion formation [30].

Precipitation Method

This technique is based on the precipitation of a dissolved compound through solvent exchange or by adding a reactive agent, leading to solid particle formation. It is particularly used for encapsulating bioactive compounds such as polyphenols and vitamins and is favored for being cost-effective and operationally simple [31–33].

Ionic Gelation Method (Chitosan/Alginate Systems)

Ionic gelation is based on the reaction of cationic polysaccharides such as chitosan with negatively charged compounds (e.g., tripolyphosphate) to form gel structures. This method is extensively used for encapsulating biologically active compounds and has demonstrated high biocompatibility [31–33].

Nanoprecipitation Method

Nanoprecipitation involves the rapid change or evaporation of a solvent in which an active compound is dissolved, leading to its precipitation in solid form. It is particularly applicable for encapsulating lipophilic compounds in nanoformulations [31–33].

Applications of Nanoencapsulation in Functional Foods

Nanoencapsulation is a highly effective technique used to enhance the stability, controlled release, and bioavailability of biologically active compounds. This technology plays a vital role in the design of functional foods.

Vitamin E Nanoencapsulation

Vitamin E is a powerful antioxidant that prevents cellular damage and contributes to health maintenance. However, its poor water solubility and susceptibility to oxidation limit its efficiency in food systems. Granata et al. (2025) demonstrated that nanoencapsulated vitamin E improved oxidation resistance and prolonged the shelf life of fruit-based beverages [34].

Nanoencapsulation of Probiotics

Probiotics are live microorganisms that support gut health but are sensitive to harsh gastrointestinal conditions such as gastric acid and bile salts. Arratia-Quijada et al. (2024) reported that nanoencapsulation significantly improves probiotic survival throughout the gastrointestinal tract, thereby enhancing their biological activity [35].

Omega-3 (EPA/DHA) Nanoencapsulation

Omega-3 fatty acids are essential compounds known for their cardioprotective effects. However, their high susceptibility to oxidation and low stability restrict their practical applications in foods. A project reported by CORDIS (2019) showed that omega-3 nanoencapsulation in bakery products effectively prevented oxidation and enhanced nutritional value [36].

Nanoencapsulation of Phenolic Compounds

Phenolic compounds are well-recognized antioxidants with various health benefits, yet their bioavailability and stability are limited by environmental factors. Su et al. (2022) highlighted that nanoencapsulation improves the functionality of phenolics in food matrices by enhancing both their stability and release properties [37].

Nanoencapsulation of Spirulina

Spirulina is a microalga known for its high protein and vitamin content. However, its direct use may limit its effectiveness in the digestive system. In a study conducted by Almeida et al. (2021), the nanoencapsulation of Spirulina for the development of functional foods enhanced the bioavailability of this compound and improved the nutritional value of the product [38].

Curcumin, Resveratrol, and Quercetin

These three polyphenolic compounds possess strong antioxidant and anti-inflammatory properties but suffer from poor solubility and low stability under light, pH, and enzymatic conditions. Nanocarrier systems improve their bioavailability and stability in food formulations [38,39].

Vitamins D, K_2, and B_{12}

Certain vitamins, particularly the fat-soluble vitamins D and K_2, as well as the water-soluble vitamin B_{12}, have attracted significant interest in functional food applications. However, their effective distribution, absorption, and stability remain limited in conventional formulations, and nanotechnology has been shown to overcome these challenges [40,41].

Specifically for vitamin B_{12}, the study titled "From Nutrient to Nanocarrier" explored the dual role of the B_{12} molecule as both a nutrient and a carrier, demonstrating its ability to bind with other compounds within nanocarrier systems for therapeutic and preventive purposes. The study emphasized that such systems exhibit promising biocompatibility and intracellular targeting capabilities, highlighting their potential in advanced food and biomedical applications [42].

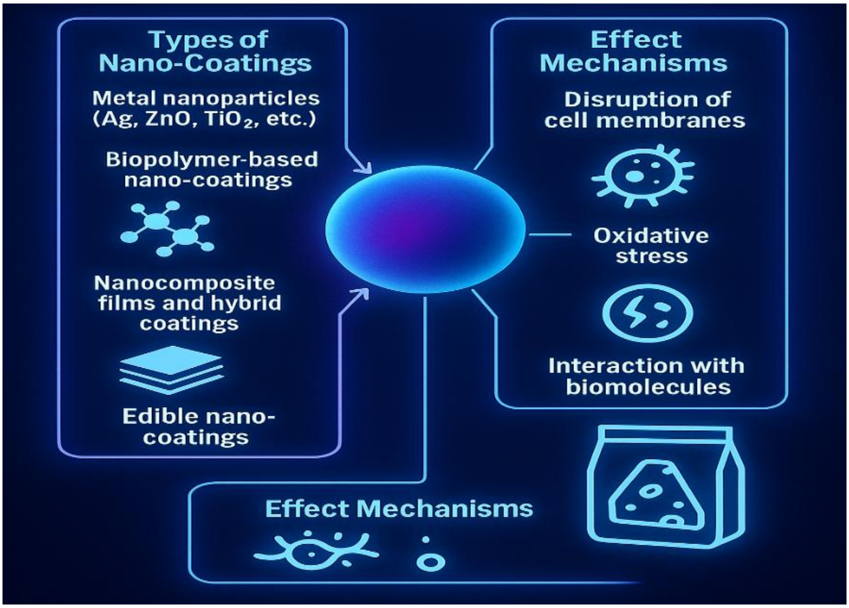
Mineral Delivery (Fe, Zn, Ca)

Minerals are often used in functional foods to address deficiencies, but challenges such as poor bioavailability, undesirable taste, and interactions with other food components remain significant. Nanoencapsulation or gelation/ionic bonding techniques can alleviate these issues by enhancing stability and improving controlled release [43].

Antimicrobial Nanocoatings and Food Packaging

In recent years, research on imparting antimicrobial properties to food packaging materials has intensified, aiming to enhance food safety, extend shelf life, and reduce the risk of contamination by foodborne pathogens (Fig. 3). Owing to their high surface area, size-dependent physicochemical characteristics, and ability to provide targeted functionality, nanotechnology-based systems have become a focal point in active and intelligent packaging design [44,45].

Figure 3. Antimicrobial nanocoatings and food packaging



Common Types of Nanocoatings and Their Mechanisms of Action Metallic Nanoparticles (Ag, ZnO, TiO_2, etc.)

Silver nanoparticles (AgNPs) exhibit broad-spectrum antimicrobial activity through multiple mechanisms, including disruption of cell wall and membrane integrity, ion release, and the generation of reactive oxygen species (ROS). AgNP-containing nanocomposite films and coatings have been shown to effectively reduce microbial loads on food surfaces and extend product shelf life. Nevertheless, concerns remain regarding AgNP toxicity, nanoparticle migration, and environmental implications [46,47].

Zinc oxide (ZnO) and titanium dioxide (TiO_2) nanoparticles are also commonly used due to their antimicrobial and UV-protective properties. Through photocatalytic activity, these nanoparticles reduce microbial growth on surfaces, providing an additional preservation mechanism in packaging systems [45,48,49].

Biopolymer-Based Nanocoatings

Chitosan a biopolymer known for its natural antimicrobial activity, film-forming capacity, and biodegradability has become an attractive material for nano-enabled food packaging. In nanoscale forms (such as chitosan nanoparticles, nanofibrils, or electrospun fibers), it serves both as a carrier and an active component. Chitosan-based nanocoatings reduce microbial proliferation, limit oxidative degradation, and improve the mechanical and barrier properties of packaging films [8,50,51].

Nanocomposite Films and Hybrid Coatings

Nanocomposite films are developed by incorporating nanoparticles (Ag, ZnO, TiO_2), essential oils, phenolic compounds, or enzymes into polymer matrices (such as PLA, PCL, chitosan, and cellulose derivatives). These systems exhibit controlled release, enhanced mechanical strength, and improved barrier performance. Notably, biogenic or plant-derived nanoparticles are gaining attention as sustainable alternatives in antimicrobial packaging applications [45,52].

Edible Nanocoatings

Edible coatings typically polysaccharide- or protein based are applied as ultra-thin nanofilms or emulsion layers to the surfaces of fruits, vegetables, and fresh produce. These coatings effectively reduce microbial growth and water loss while maintaining visual and textural quality. In addition to improving consumer safety, they provide an environmentally friendly alternative to conventional non-biodegradable packaging [53,54].

Use of Nanoparticles in Nutraceuticals

The application of nanotechnology in the field of nutraceuticals (dietary supplements and functional foods) has shown promising developments, particularly in improving bioavailability, stabilization, controlled release, and targeted delivery of micronutrients. However, these applications also raise important concerns regarding safety, regulation, and **long-**term biological effects.

Bioavailability and Stabilization

Nanoparticles due to their small size (1–100 nm), high surface-to-volume ratio, and modifiable surface chemistry can significantly improve the absorption of poorly soluble micronutrients such as vitamin A, vitamin B_{12}, folic acid, and iron. A recent review emphasized that nanoparticle systems enhance the bioavailability of such micronutrients but require rigorous safety assessment before widespread adoption [55].

Similarly, the study *"Application of Nanoparticles in Human Nutrition"* reported that nanocarrier systems enhance the water solubility, thermal stability, and oral bioavailability of active ingredients, highlighting their growing potential in human nutrition [56].

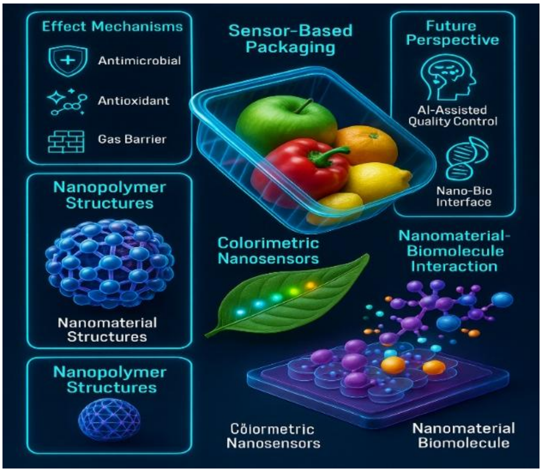
Types of Nanoformulations

Nanoformulation strategies used in nutraceutical development include nanoemulsions, lipid-based nanoparticles, nanocapsules, polymeric nanoparticles, and layered nanocomposites. Nanoencapsulation allows for the incorporation of vitamins, minerals, and antioxidants into food matrices without negatively affecting taste, color, or texture [56]. In the context of mineral delivery, nanocarrier systems (such as iron or zinc-based complexes) have also been shown to improve nutrient absorption and bioavailability [55,57].

Shelf-Life Extension and Quality Control

Extending shelf life and maintaining quality are critical objectives for ensuring both consumer safety and food waste reduction. Traditional packaging methods often fall short due to oxygen and moisture permeability, microbial contamination, and light- or heat-induced degradation. Nanotechnology-based active and intelligent packaging systems have emerged as effective solutions to overcome these limitations (Fig. 4).

Figure 4. Shelf life extension and quality control



Nanomaterials for shelf-life enhancement: The integration of nanoparticles and nanostructured materials into packaging systems provides multiple advantages, including enhanced barrier, antimicrobial, and antioxidant properties, as well as real-time monitoring capabilities.

Barrier enhancement: Films containing nanofillers such as ZnO, Ag, and TiO_2 nanoparticles minimize the permeation of oxygen, carbon dioxide, and water vapor, thereby reducing oxidative degradation and moisture loss [55,58–60].

Antimicrobial and antioxidant activity: Packaging films embedded with AgNPs and ZnO nanoparticles inhibit the growth of spoilage and pathogenic microorganisms, preserving product safety and extending shelf life [11,14,60].

Smart monitoring and control: Nanosensors, gas sensors, and time–temperature indicators enable real-time detection of spoilage processes and provide feedback on storage conditions, supporting proactive quality control and supply chain management [44,61].

Quality Control Aspects

In addition to shelf-life extension, nanotechnology contributes significantly to the preservation of organoleptic and microbiological quality:

Preservation of sensory attributes: such as color, texture, and freshness: Nano-films help minimize water loss, softening, and browning during storage [11,59,62].

Reduction of microbial load: thereby ensuring food safety and lowering the risk of spoilage or toxin formation [14,44].

Migration and safety monitoring: The potential migration of nanoparticles from packaging to food matrices poses a key safety concern. Thus, packaging design, nanoparticle selection, and migration testing have become essential components of quality assurance [14,60].

Safety, Toxicology, and Ethical Issues

While the use of nanotechnology in food production, packaging, and preservation systems is rapidly increasing, it simultaneously brings forth a series of safety, regulatory, and ethical challenges that must be critically addressed.

Safety and Toxicology Concerns

The extremely small size, high surface-to-volume ratio, and unique cellular-level interactions of nanoparticles indicate that their effects on human health may differ significantly from those of conventional materials. For example, a systematic review reported that the use of nanomaterials in food production and processing poses potential risks, including allergenic reactions, heavy metal ion release, and nanoparticle migration from packaging materials into foods [63].

Furthermore, the migration of nanoscale materials from packaging to food, their subsequent absorption in the gastrointestinal system, and parameters such as systemic biocompatibility are not yet fully understood [58,64]. This scientific uncertainty can undermine consumers' confidence in the overall safety of nano-enabled food systems, highlighting the necessity of ongoing risk assessment and toxicological evaluation.

Regulatory Framework

A specific, internationally accepted regulatory framework for the use of nanotechnology in food and packaging applications has not yet been fully developed. In both the European Union (EU) and the United States, current regulations for chemicals and packaging materials are often adapted for nanoscale materials rather than being designed specifically for them.

A review noted that Europe currently lacks a dedicated nanotechnology regulation, creating ethical and regulatory ambiguities regarding its application in food systems [65]. This absence of comprehensive legislation constitutes a critical gap in consumer protection, as standardized testing protocols for nanoparticle migration, component interactions, and long-term biological effects are still underdeveloped [66].

Consequently, a harmonized international framework addressing toxicology, environmental safety, and migration limits is essential to ensure the responsible implementation of nanotechnology in the food sector.

Ethical and Social Considerations

The integration of nanotechnology into the food and packaging sectors is not merely a technical issue but also encompasses significant ethical, social, and economic dimensions. Ethical analyses highlight four main principles: **(i)** providing consumers with transparent information and the right to make informed choices (autonomy), **(ii)** ensuring fair distribution of benefits and risks (justice), **(iii)** preventing potential harm (nonmaleficence), and **(iv)** promoting sustainability and environmental responsibility [65].

Consumer attitudes toward nano-enabled food products remain divided. A study found that acceptance of nanotechnology in the food sector is directly related to risk perception, safety concerns, and access to accurate information [67]. Additionally, unequal access to technology and its benefits may exacerbate economic disparities, creating what has been termed a "nano-divide", a phenomenon increasingly discussed in the ethical discourse surrounding emerging technologies [68].

Consumer Confidence, Legal Compliance, and Standardization

Consumer confidence is a decisive factor in the widespread adoption of nanotechnology in food and packaging applications. Inadequate or misleading labeling can raise suspicion and skepticism about the use of nanoscale materials. Therefore, labeling, transparency, and public awareness are indispensable elements of responsible nanotechnology governance.

Research indicates that deficiencies in the ethical labeling of nano-enabled food packaging negatively affect consumer perceptions and trust [69]. The migration of nanoparticles from packaging to food matrices is among the most critical technical and regulatory issues. Studies emphasize that the migration of ions or nanoparticles from nanocomposite films must be controlled and limited; however, most current testing methods were not specifically developed for nanoscale systems [58].

Furthermore, the lack of standardization and the absence of comparable testing methodologies are considered significant obstacles to both technology transfer and regulatory harmonization [66]. Developing unified global standards and validated analytical methods is thus a prerequisite for advancing both consumer safety and industrial innovation.

Future Perspectives and Conclusion

The integration of nanotechnology into food technology has led to revolutionary progress in functional food development, packaging safety, quality control, and shelf-life enhancement. In particular, nanoencapsulation enables the targeted delivery of biomolecules while protecting them against environmental factors such as oxidation, heat, and pH fluctuations, thereby increasing the bioavailability of bioactive compounds. In addition, smart nanosensors allow real-time monitoring of microbial spoilage, offering a valuable approach to improving consumer safety.

In the near future, the optimization of nanoactive packaging materials with superior oxygen, ethylene, and moisture barrier properties is expected to further extend the shelf life of fresh produce and contribute to reducing global food waste. Research on biopolymer-based nanoparticles suggests the potential for eco-friendly and sustainable packaging solutions that align with circular economy goals. Moreover, in the context of personalized nutrition, nano-biotechnology may enable the development of micronutrient delivery systems tailored to individual metabolic requirements.

However, the integration of nanotechnology into the food chain also brings regulatory and ethical challenges. Long-term assessments of nanoparticle toxicity, the establishment of standardized protocols, and the strengthening of consumer acceptance remain vital research priorities. Without regulatory frameworks emphasizing safety, transparency, and ethical accountability, the widespread and responsible implementation of nanotechnology will remain limited.

In conclusion, the application of nanotechnology in the food sector is expanding rapidly, offering innovative solutions for sustainable production, safe consumption, and functional product innovation. Nevertheless, the success of this transformation depends on the coordinated progress of scientific research, industrial practices, and regulatory mechanisms. A balanced integration of these domains will ensure that nanotechnology continues to evolve as a cornerstone of safe, sustainable, and intelligent food systems.

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NANOTECHNOLOGY AND ITS APPLICATIONS IN HORTICULTURAL CROPS

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Introduction

The term 'nanotechnology' emanates from the Greek word nano, meaning 'dwarf.' The advent of nanotechnology is closely associated with the historic remark of Nobel laureate Richard Phillips Feynman [1], who stated, *'There is plenty of room at the bottom*.' Nanotechnology refers to the science, engineering, and technological applications that take place at the nanoscale (roughly 1 to 100 nanometers) [2–6]. Indeed, nanoparticles possess demonstrably different properties than bulk materials owing to their exceptionally high surface-to-volume ratios [5–8]. Additionally, the quantum phenomena occurring at the nanoscale significantly enhance the catalytic activity of any molecule, element, or material [5,7,9–11].

Due to these factors, nanoparticles have found extensive applications in various fields, including communication technologies, electronics, textiles, the automotive industry,

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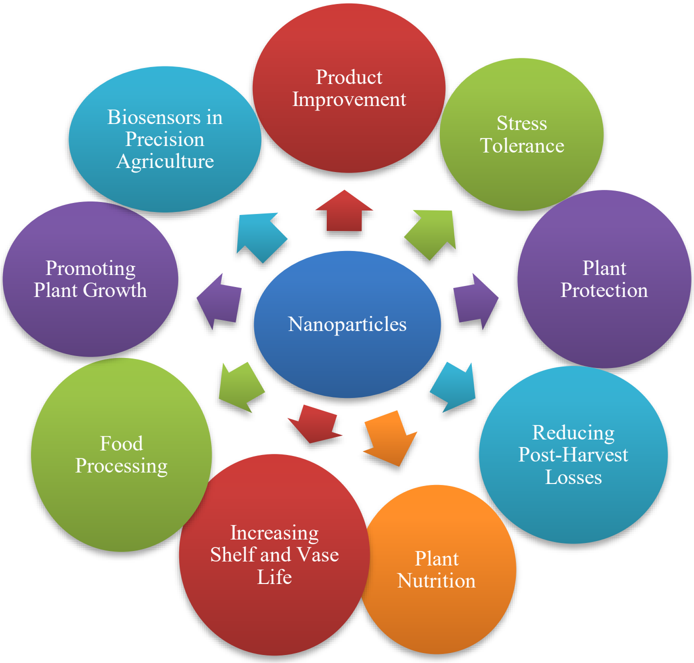
biomedical devices, environmental technologies, biotechnology, and renewable energy. In agriculture, new nanomaterials have presented great potential for developing new plant varieties through genetic engineering and hybrid breeding, as well as highly effective agrochemicals for plant nutrition and protection [12,13]. Furthermore, the application of nanomaterials enhances food processing and packaging, improves food safety, increases the efficacy of fertilizers and pesticides, reduces environmental contamination, and improves nutraceutical production [14,15]. In agriculture, particularly in horticultural crop production, the application areas of specially designed nanoparticles are illustrated in (Figure 1).

Figure 1. Major application areas of nanoparticles in agricultural production and food systems. Redrawn and adapted from Rana et al. [16]



Nanotechnology is a field that has been in existence for over two decades [17]. Over the years, it has evolved into a sophisticated tool for various scientific fields, including chemistry, physics, medicine, materials science, aerospace, pharmaceuticals, agriculture, food science, and even horticulture [18]. Horticulture, itself a branch of agricultural science, can be defined as the art and science of cultivating and managing fruits, vegetables, flowers, and ornamental plants.

Ensuring food and nutrition security for the growing global population under rapidly changing global climate conditions is becoming increasingly challenging. In this context, the adoption of innovative approaches such as nanotechnology and biotechnology to increase productivity and reduce post-harvest losses is emerging as an important strategy. The use of nanomaterials in horticulture plays a critical role in reducing post-harvest losses in ornamental plants, fruits and vegetables, as well as increasing product yield and quality. Losses of up to 30% occur, particularly in developing countries, due to microbiological and physiological deterioration. Antimicrobial nanomaterials, nano-packaging and nanofilm technologies can reduce these losses to 5–10 per cent levels, thereby improving food preservation. Furthermore, nanopesticides and nanofertilisers offer higher target specificity, efficacy and safety compared to synthetic chemicals, which are harmful to the environment and human health, as well as being expensive and inefficient.

A significant amount of literature has reported the influence of nanomaterials on enhancing the yield, quality, and postharvest stability of different agricultural crops [12,13]. Even as the prospect of nanotechnology in agriculture is now widely reviewed, no comprehensive evaluation has thus far focused solely on enhancing yield and quality, and reducing postharvest losses of horticultural crops through the application of nanomaterials. Therefore, the objective of this chapter is to review the recent literature concerning the use of nanotechnology in improving productivity, quality, and preservation of horticultural crops, and also discuss the future direction in the field.

The Role of Nanomaterials in Enhancing Growth and Development in Agricultural Production

Nanoparticles are solid colloidal structures that can encapsulate or adsorb active agents such as bioactive compounds. In agriculture, nanofertilizers are cost-effective and environmentally friendly inputs that enhance nutrient use efficiency and crop yield. They deliver nutrients through nanoparticle coatings in nanoporous materials, polymer encapsulation, or nanoscale emulsions. These systems enable slow, controlled, and target-specific nutrient release, reducing losses and improving plant uptake efficiency.

For instance, ZnO nanoparticles enhance the yield of peanut (*Arachis hypogaea*) [19]. Similarly, the application of SiO_2 nanoparticles enhances plant biomass and increases the levels of biomolecules, such as chlorophyll, proteins, and phenolics, in maize kernels [20]. Low concentrations of carbon nanotubes enhance root growth in hexaploid wheat [21], and also cell growth in mustard (*Brassica juncea*) [22], black gram (*Phaseolus mungo*) [23], rice (*Oryza sativa*) [24], and tobacco (*Nicotiana tabacum*), by up to 16% [25]. The application of TiO_2 and SiO_2 nanomaterials enhances nitrate reductase activity, which appears to encourage seed germination and seedling growth in soybean [26]. Like field crops, the application of nanomaterials also supports growth and development in horticultural crops.

In horticultural production, nanofertilizers are used to enhance vegetative growth, pollination efficiency, and floral productivity, which, in turn, improve fruit tree yield and the overall quality of the crops [27,28]. Under saline irrigation conditions, nano-calcium supplementation enhances vegetative growth and leaf chlorophyll content in blueberry plants [29]. Similarly, foliar nano-boron application enhances the levels of chlorophyll and nutrients such as N, P, K, Mn, Mg, B, Zn, and Fe in mango trees [30]. Foliar nano-zinc application to mango trees improves fruit weight and number, yield, leaf chlorophyll and carotenoid content, and the content of various nutrients like N, P, K, and Zn [27].

Similarly, the application of nano-boron and nano-zinc fertilizers improves fruit quality by increasing fruit number, total soluble solids (TSS), maturity index, total sugars, and total phenolics in pomegranate [31].

Nanofertilizers

A fertilizer is defined herein as any inorganic or organic substance, other than liming materials, that is added to the soil or applied to the plant tissue for the purpose of supplying one or more nutrients essential to plant nutrition [32,33]. Nutrient sources may either be obtained from natural deposition or manufactured through an industrial process. In modern agriculture, the application of fertilizers is crucial for increased crop yields. One of the greatest inefficiencies in fertilizer application for crops is related to nutrient losses from applied fertilizers through various routes of discharge, which commonly contribute to environmental pollution and increase the production cost.

A significant recent development in reducing such nutrient losses has been the synthesis and use of nanofertilizers. Nanofertilizers can be prepared by loading plant nutrients onto nanomaterials, coating nutrient molecules with a thin layer of nanomaterial, or manufacturing nutrients in nanoscale emulsions. Nanofertilizers and nanobiofertilizers, which utilize both natural and synthetic materials, have been demonstrated to enhance bioavailability and soil fertility more effectively than conventional fertilizers [34].

The key characteristics of nanofertilizers include: (i) an individual particle size of approximately 100 nm; (ii) a volume dimension on the order of 100 nm; and (iii) environmental safety and durability of the nanoproduct.

Another important characteristic of nanofertilizers is their ability to maintain a nanoscale size and aggregation behavior during interaction with either soil particles or plant roots. The reactivity of nanofertilizers is mainly influenced by the shape and size of the nanoparticles [35]. The key benefits of nanofertilizers include improved nutrient use efficiency, controlled release of active components, and minimal residual effects on soil biodiversity [36]. Nanofertilizers can be categorized primarily into two large subgroups based on their distribution, nutrient balance, and the amount required by plants: macronutrient nanofertilizers and micronutrient nanofertilizers.

Macronutrient Nanofertilizers

Macronutrients are the essential elements necessary for plant growth in relatively higher amounts for better growth and productivity. To enhance the nutrient use efficiency, one or more of these nutrients have generally been mixed with nanoparticles, allowing specifically balanced levels of nutrients to reach the target crops while providing added benefits and reducing the total input [34,37]. Macronutrient nanofertilizers are composed of one or more nutrient elements enveloped within specific nanoparticles. The global use of N, P, and K fertilizers in crop production is estimated to reach 265 million tons by 2020 [38].

Other examples of nanofertilizers are zeolites, mesoporous silica nanomaterials, and hydroxyapatite, which act as nano-enabled sources of nitrogen and can be classified as slow- or controlled-release nanofertilizers. Some of these nanofertilizers have shown positive impacts on improving plant performance and productivity [39, 40]. One example of a biocompatible nanofertilizer is a nanoscale suspension of water-phosphorite particles with a size from 60 to 120 nm.

However, further research is still needed to elucidate the exact modes of interaction between applied nanofertilizers and plants, soils, plant microbiota, and the environment as a whole. The environmental fate of nanofertilizers requires a comprehensive investigation for their safe application. The overall cost-effectiveness and market accessibility of nanofertilizers will also facilitate the wider adoption of these new agrochemicals.

Micronutrient Nanofertilizers

The micronutrients are implicated in the biosynthesis of proteins and carbohydrates, as well as hormonal regulation, for instance, auxins, thereby playing crucial roles in plant defense against pathogen and pest attacks [41]. Zinc-based nanofertilizers have been reported to be advantageous for several horticultural crops, including peas, cucumbers, spinach, tomatoes, eggplants, peppers, coriander, and onions [42–47]. Additionally, the application of zinc nanoparticles in pearl millet (*Pennisetum americanum* L.), a field crop rather than a horticultural crop, has resulted in an approximate 38% increase in grain yield. This was accomplished with enhancements in shoot height (15%), root length (4%), root area (24%), chlorophyll accumulation (24%), total soluble protein in leaf and plant biomass (39%), and total biomass (12%) as compared with the control [48].

Significant yield improvement has also been reported in rice, wheat, maize, sugarcane, potato, sunflower, and Brassica species after the application of Zn nanoparticles [40]. Iron (Fe)-based nanofertilizers have been found to enhance yield in various horticultural crops such as cucumber, lettuce, and garden peas [49–51]. Another important micronutrient, copper (Cu), is an imperative component for plant growth and development. The application of Cu nanoparticles at proper concentrations significantly enhances the physiological development of several horticultural crops, such as lettuce and tomato [52–53, 56]. On the contrary, the higher doses of Cu may induce phytotoxic effects in some plant species [50, 54–58].

Mn also plays a crucial role in the physiological and metabolic activities of plants. As a cofactor, it regulates several enzymatic activities and enhances plant tolerance to various environmental stresses. Nano-Mn fertilizers improve the growth and yield of plants, particularly in soils deficient in this micronutrient [59].

The recommended doses of micronutrients for the optimal growth and productivity of horticultural crops depend on the soil analysis; thus, this needs to be done before recommending or applying any nano-enabled micronutrient fertilizer.

Nanopesticides

Insect pests are among the most important limiting factors in crop productivity, and their management is imperative. Conventional methods of pest control rely heavily on the application of chemical pesticides, which pose environmental hazards and increase production costs [60]. Nano-processing of water can enhance the efficacy of pesticides when these are diluted with it. Nanopesticides control pests more effectively than conventional pesticide formulations, resulting in costs that can be reduced by almost half [61].

Most nanopesticides are environmentally benign, with highly target-specific and controlled-release formulations. These formulations greatly enhance the efficacy of pesticides while substantially reducing residue levels and environmental contamination. In this regard, high-polymeric nano- and microcapsule formulations, prepared using light-, moisture-, temperature-, enzyme-, and soil pH-responsive materials, display controlled release and protective properties. Nanopesticide formulations enhance droplet adhesion on plant surfaces, which enables an improvement in the distribution and bioactivity of the active ingredient. Their higher efficacy is due to their small size, high wettability, improved droplet pliability, and improved adsorption on targets.

Insecticidal performance can be further improved by nano-encapsulation, which protects the active pesticidal agent with a thin protective nanoscale coating. The resulting efficacy is greatly improved with reduced pesticide needs and less environmental pollution. As one recent example, hollow clay nanotubes called halloysite also have emerged as a nanopesticide carrier system that greatly reduces pesticide usage to control a target pest [62].

Nanoinsecticides

Nanoencapsulation enables the controlled release of chemical agents via biodegradation, dissolution, osmotic pressure, and pH-responsive diffusion, increasing the efficiency in insect pest management [63]. Garlic oil–loaded nanoparticles act effectively in controlling *Tribolium castaneum* [64]. Nanoencapsulated insecticides are commonly species-specific, which reduces the amount to be used compared to traditional pesticides.

Treatment of wheat with nanostructured alumina for three days resulted in significantly higher mortality of two major pests, *Rhyzopertha dominica* and *Sarocladium oryzae* [65]. The insecticide ethiprole encapsulated in poly (lactic acid) and polycaprolactone nanospheres demonstrated that the enhanced insecticidal activity resulted not from controlled release, but from improved cellular penetration of the active ingredient due to the small nanospherical size [66].

An in vivo assay using Spodoptera littoralis larvae demonstrated that novaluron nanoparticles were toxic at concentrations equivalent to the commercial formulation [67]. Nanoformulations, including commercial CR formulations of imidacloprid, were evaluated for their potential to control major soybean pests, such as stem fly (*Melanagromyza sojae*) and whitefly (*Bemisia tabaci*). Many CR formulations demonstrated superior pest management compared to non-CR industrial products. In addition, some CR formulations outperformed non-CR insecticides or untreated controls in terms of crop yield [68]. Similarly, CR formulations containing imidacloprid and carbofuran showed better *leafhopper* (*Amrasca biguttula Ishida*) and *aphid* (*Aphis gossypii*) management in potato as compared to their non-CR counterparts.

The control of fruit fly populations can also be environmentally friendly through pheromone-based approaches. Nano-pheromones represent a very effective method for trapping and monitoring pests in both guava and mango orchards. A nano-gel with methyl eugenol and a low-molecular-weight organic gelator, like all-trans tri (p-phenylene vinylene) bis-aldoxime, exhibits high stability at ambient conditions, shows reduced volatilization, and ensures optimal pheromone release [69]. This nano-pheromone gel was found to rapidly capture pests in guava and mango orchards. For instance, it effectively controlled the notorious fruit fly *Bactrocera dorsalis*, which is causing severe damage to these crops.

Nanofungicides

Traditionally, fungal diseases have been managed using a chemically diverse battery of fungicides, including dicarboximides, copper salts, dithiocarbamates, dinitrophenols, triazoles, thiabendazole, organotin compounds, and thiocarbamates. However, many of these fungicides exhibit insufficient target specificity. Nanotechnology enables targeted specificity through nano-enabled fungicide formulations.

Recently, Kumar et al. [70] developed a nanoformulation of a widely used industrial fungicide containing 25% trifloxystrobin and 50% tebuconazole to control *Macrophomina phaseolina*, a fungal pathogen with a broad host range. The nanoform exhibited enhanced inhibitory activity, characterized by altered hyphal morphology, destruction of hyphal cells, and abnormal sclerotia formation.

In another study, Antonoglou et al. [71] prepared a cost-effective Cu–Zn bimetallic nanoparticle to control *Saccharomyces cerevisiae*. The metallic nanofungicide exhibited higher antifungal activity compared to conventional treatments, without significant effects on photosystem II in tomato leaves.

Nanonematicides

Chemical control of nematode pests remains extremely difficult. Aldicarb, fenamiphos, fosthiazate, and oxamyl are some of the common nematicides applied in agricultural fields [72]. However, due to the rapid release of toxic active ingredients from these chemicals, they pose a threat to both human health and the environment [73]. Recently developed nanotechnological methods offer hope for overcoming such difficulties. For instance, silver nanoparticles exhibited strong control against *Meloidogyne incognita* and *M. graminis* [74]. In another study, green-synthesized silver nanoparticles were found to be more effective than standard chemical nematicides in controlling *M. javanica* in eggplant [75].

Enhancing Postharvest Quality Attributes of Horticultural Crops Using Nanomaterials

Because most ornamental plants, fruits, and vegetables are highly perishable, their shelf life declines quickly when kept at room temperature. While various traditional preservation methods are available, they are often costly, offer limited success in maintaining postharvest quality, or leave behind unwanted residues. Thanks to the versatile functional properties of nanomaterials, nanotechnology-based strategies for extending shelf life demonstrate strong potential in addressing the shortcomings of conventional preservation techniques.

Nanofilms and Coatings

Nanofilms act as antimicrobial protective layers and can carry metallic nanoparticles (NPs). These advanced materials help reduce respiration rates, slow down spoilage and discoloration, maintain storage stability, and extend the shelf life of horticultural produce. Edible nanofilms, in particular, have been suggested as a practical solution for preserving the physicochemical qualities of horticultural products during storage and distribution.

Recently, Dubey et al. developed a nanocomposite edible film made from glycerol, aloe vera gel, and ZnO nanoparticle (ZnO-NP) suspensions [76]. Among the various formulations tested, those containing ZnO nanoparticles were particularly effective in extending the shelf life and preserving the quality of mangoes stored at room temperature for up to nine days. These films helped reduce weight loss, maintained lower levels of total soluble solids, increased titratable acidity and ascorbic acid content, preserved pH, and improved both film thickness and permeability.

Chitosan-based nano-components have been widely reported to enhance postharvest quality and shelf life in horticultural products. For instance, chitosan combined with procyanidin effectively reduces mold and yeast growth, maintains fruit firmness, and increases antioxidant activity in blueberry (*Vaccinium myrtillus*) [77]. In mango (*Mangifera indica* L.), chitosan treatments retard the aging process by reducing water loss and firmness degradation [78], while chitosan combined with spermidine activates defense mechanisms against anthracnose, leading to increased firmness and delayed decay [79]. Similarly, chitosan application in guava (*Psidium guajava*) lowers weight loss, respiration rate, and oxidative processes, while enhancing firmness [80].

In grape (*Vitis vinifera*), chitosan enriched with salicylic acid stimulates defense-related enzymes such as chitinase, lyase, and glucanase, concomitantly reducing respiration, weight loss, and decay incidence [81]. Composite coatings based on chitosan, carboxymethyl cellulose, and *Mentha spicata* essential oil exhibit strong antimicrobial effects and positively influence titratable acidity, weight loss, water vapor resistance, pH, and respiration rate in strawberry (*Fragaria*) [82]. Likewise, chitosan coatings incorporating *Mentha villosa* or *Mentha piperita* essential oils inhibit spore germination and mycelial growth, thereby preserving sensory and physicochemical quality in cherry (*Prunus avium*) and tomato (*Solanum lycopersicum*) during storage [83].

Comparative studies in tomato further demonstrate that chitosan outperforms propolis and thyme essential oil by better preserving total carotenoids and flavonols, while both thyme and chitosan maintain total soluble sugars and propolis is more effective in conserving terpenes and organic acids; overall, chitosan provides the most comprehensive quality preservation [84]. Beyond chitosan-based systems, nano-zinc oxide (nano-ZnO) has shown strong antimicrobial efficacy, extending the storage life of freshly cut apple (*Malus domestica*) by approximately six days [85] and significantly reducing microbial spoilage while increasing shelf life in carrot (*Daucus carota* L.) [86].

Nano-Packaging

Packaging and processing are key factors in extending the shelf life and preserving the quality of food products [87]. Globally, a significant amount of food is lost each year due to the absence of proper packaging knowledge and technologies. Among modern advancements, nano-enabled food processing and packaging are considered among the most effective solutions. These approaches utilize nanomaterials to enhance and maintain the quality and longevity of food.

Active nano-packaging materials include metallic nanoparticles, such as silver (Ag), copper (Cu), titanium dioxide (TiO_2), and magnesium oxide (MgO) [88], as well as edible antimicrobial nanocomposite films and gas scavengers [89]. For instance, adding silver nanoparticles (Ag-NPs) to packaging materials can help extend the shelf life of fruits and vegetables by absorbing ethylene gas [90]. Since oxygen speeds up the spoilage of fresh produce, incorporating gas-scavenging nanoparticles into packaging and processing materials helps maintain quality and storage stability by preventing oxidative reactions [91]. Nanocrystalline TiO_2, in particular, has been shown to act as an oxygen scavenger in food packaging and processing applications [92].

Kasaai [93] reported that using nano-silica (nano-Si) as a surface coating in food packaging improved both the quality and storage life of horticultural products. Packaging materials enhanced with silver nanoparticles (Ag-NPs) can further extend shelf life by reducing microbial activity [94]. In addition to Ag-NPs, other nanomaterials such as ZnO-NPs, TiO_2-NPs, MgO-NPs, CuO, chitosan nanoparticles, carbon nanotubes, and quantum dots are commercially valuable for their antimicrobial properties and their effectiveness in preserving the quality and extending the shelf life of stored fruits, vegetables, and exported food products [91,95–97].

Nanomaterials for Enhancing Postharvest Quality Attributes of Fruits

The primary objective of utilizing nano-based strategies to enhance fruit stability and quality is to improve postharvest attributes in horticultural crops, particularly fruits and vegetables [98,99]. Recently, both organic and synthetic nanoparticle-based coatings, such as chitosan, silica (Si), titanium dioxide (TiO_2), and their composites, have been applied to short-shelf-life fruits. These nanomaterials help extend the shelf life of fruits, such as Chinese bayberry [100], loquat [101], and strawberry [99], by enhancing their mechanical strength and antimicrobial properties.

The following subsections highlight various nanoparticles that show potential in extending the postharvest shelf life of agricultural produce and summarize their respective effects.

Silver Nanoparticles

The impact of various types of silver nanoparticles (Ag-NPs) on extending the shelf life of fruits is well established. Agriculturally rich nations, such as China, India, Brazil, and the United States, widely use Ag-NPs to extend the storage life of fresh produce. In India, ranked as the world's second-largest producer of fruits and vegetables, different Ag-based nanostructures are commonly applied to help maintain freshness and improve the storability of harvested crops.

For instance, A-Ag nanoparticles have been shown to extend the shelf life of lemon (*Citrus aurantifolium*) and apple (*Malus domestica*) [102]. In another study, Chowdappa [103] found that chitosan-based Ag-NP composites significantly reduced postharvest losses in fresh mangoes by enhancing quality through their antifungal effects. Kumar et al. [104] reported that combining Ag-NPs with biocompatible coating materials like chitosan and glycol extended the storage life of red grapes for up to 14 days. Additionally, incorporating Ag nanostructures into organic polymer coatings improved the mechanical strength of the coating films [104].

Like India, China extensively utilizes silver nanoparticles (Ag-NPs) to enhance the freshness and storage capacity of fruits and vegetables [94]. Thanks to their strong antimicrobial properties, Ag-NPs help maintain the quality of cherry tomatoes for up to 15 days. In Brazil, biologically synthesized Ag-NPs produced using *Myxobacteria virescens* extract have also been applied to extend the shelf life of fresh apples [105]. These bioactive nanoparticles are synthesized directly onto paper and incorporated into the packaging of fruits. The paper-embedded Ag-NPs exhibit strong antibacterial activity and can extend apple shelf life by up to two weeks [105].

Hexanal

Hexanal ($C_6H_{12}O_6$) is a volatile, aroma-producing compound naturally generated during fruit ripening. It works by reducing enzymatic activity on the fruit surface, which in turn lowers ethylene production and helps limit postharvest diseases [106]. Because of these properties, hexanal is commercially applied as a preharvest spray or postharvest dip to extend fruit freshness by 2–3 weeks without compromising quality.

Treating mangoes after harvest with a 0.02% hexanal solution (2 liters per kilogram of fruit) for 10 minutes, followed by dry storage, has been shown to lower ethylene production, reduce physiological weight loss and soluble solids, and increase chlorophyll content. This treatment effectively delays ripening by at least two days under ambient conditions (25 ± 0.8 °C and 60 ± 10% relative humidity) [107].

Enhancing Postharvest Quality of Cut Flowers

Cut flowers hold both ornamental and commercial value, but their vase life is often short due to high levels of microbial contamination [108,109]. Early wilting typically results from microbial growth and vascular blockages that hinder water uptake and transport, leading to water imbalance in the stems [110,111]. As a result, preventing microbial infections and stem blockage is essential. Several studies have shown that nano-silver can significantly extend the vase life of cut flowers [111–114].

Graphene oxide (GO) is a prominent carbon-based nanoparticle that resembles graphene and features a high concentration of oxygen-containing groups along with a large surface area. These properties make it highly effective for nutrient delivery, offering strong potential for use in slow-release fertilizers [115].

Nanomaterials in Food Processing

Food processing techniques are used to enhance flavor and preserve the quality of food products over longer periods. However, methods like radioactivity, high hydrostatic pressure, and ohmic heating are generally not considered ideal for food preservation

[116]. In contrast, the use of nanoparticles and related technologies in food processing is growing rapidly.

Nanotechnology-based approaches have been increasingly integrated into food processing due to their ability to improve quality, stability, and nutritional value. Among these, nanoencapsulation techniques using nano-capsules enhance the stability of food components by protecting them against oxidation and preserving sensitive compounds, while also enabling aroma formation, controlled moisture release, and pH-dependent slow release, thereby improving bioavailability and overall effectiveness [117]. Similarly, nanoencapsulation via nano-liposomes is effective in masking undesirable odors or components in foods and enhances product quality by facilitating the transport and controlled delivery of enzymes, aromas, and related functional compounds [118].

Nanoemulsion systems also play a crucial role in modern food processing. Colloidosomes are widely used to support the fortification of foods with essential vitamins and minerals, ensuring that targeted food products are enriched with the desired nutrients [119]. Nano-coatings derived from nanoemulsions contribute to the superior quality of processed foods by improving their structural and functional attributes [120]. Certain commercial nanoemulsion applications, such as Daily Boost formulations, are specifically employed for the nano-encapsulation of vitamins and bioactive compounds to enhance their stability and functionality in food matrices [121]. More broadly, nanoemulsions are commonly applied in products such as salads, flavored oils, desserts, beverages, and other food systems to improve food safety and overall quality [122]. In addition, nanoemulsions formulated with compounds such as brominated vegetable oil, ester gum, dammar gum, and sucrose acetate isobutyrate enhance the dispersion, stability, and bioavailability of nutrients in processed foods [123].

Nanosensors in Horticultural Crops

A nanosensor is any device that can convert data about the behavior and characteristics of nanoparticles at the nanoscale into measurable signals at the macroscopic level [124]. These sensors are vital for real-time monitoring of field crops, tracking plant growth, and detecting the presence of pests and diseases.

Nanomaterials used in sensor development include metal nanotubes, nanowires, nanofibers, nanocomposites, nanorods, and nanostructured polymers, as well as various forms of carbon, such as carbon nanotubes, graphene, and fullerenes [125]. Nanosensors equipped with these materials allow for real-time monitoring, helping to reduce the overuse of pesticides and fertilizers in crop production. This not only minimizes environmental pollution but also cuts down overall production costs.

Integrating nanosensors into agriculture is transforming traditional practices into smart agriculture, an approach that is more energy-efficient and environmentally sustainable. In horticultural production, smart agricultural technologies include:

(i) nanoformulation-based delivery systems for fertilizers and pesticides that improve nutrient distribution and surface wettability [126];

(ii) nanodetectors for tracking pesticide and fertilizer residues; and

(iii) remote sensing systems for monitoring disease outbreaks and crop development. Nanosensors are also used in horticulture to detect soil moisture levels, identify pesticide residues, assess nutrient needs, and monitor pest presence.

Conclusion and Future Prospects of Nanotechnology in Agriculture

Nanotechnology is a cutting-edge tool in modern agriculture that supports sustainable crop production. In horticulture, it has considerable potential, as various nanomaterials are used to improve productivity and quality while reducing postharvest losses in fruits and vegetables. By utilizing the functional properties and targeted delivery capacity of nanomaterials, nanotechnology enhances overall crop performance and helps minimize the excessive and inefficient use of chemical fertilizers and pesticides. Nanomaterials are generally easy to fabricate, cost-effective, and environmentally friendly, allowing their production without significant ecological damage. In horticultural systems, nanotechnology plays a crucial role in improving quality and extending the shelf life of fresh and processed fruits, vegetables, and cut flowers. In addition, nanosensors are increasingly applied to monitor soil moisture, detect pesticide residues, assess nutrient requirements, and identify crop pests, enabling more precise and sustainable crop management. However, improper or uncontrolled application of nanomaterials may pose risks to both plants and the environment. Therefore, responsible and research-based use of nanotechnology is essential. Science-driven application strategies are required to reduce postharvest losses while ensuring food safety and quality.

Overall, the adoption of nanotechnology has been shown to promote agricultural growth by increasing yields, lowering production costs, and reducing postharvest losses, while maintaining product quality and shelf life. Under conditions of global population growth and climate change, achieving food and nutritional security will increasingly depend on access to beneficial nanomaterials, supported by thorough safety assessments in real agricultural environments. The responsible expansion of nanotechnology will contribute to climate-resilient horticulture by reducing postharvest losses and improving the overall quality of agricultural produce.

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INTERSECTION OF SUPERCONDUCTIVITY AND NANOTECHNOLOGY

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Introduction

Nanotechnology and superconductivity represent two of the most innovative and rapidly evolving frontiers in modern materials science. The intersection of these disciplines enables the emergence of groundbreaking applications in electronics and energy technologies. Nanotechnology offers approaches based on the control of matter at the atomic and molecular scales [1], allowing for the design of materials with physical and chemical properties unattainable through conventional methods. Specifically, below the 100 nm scale, phenomena such as surface dominance, quantum confinement, and interface effects become prominent to significant changes in fundamental properties including conductivity, magnetism, and mechanical strength [2, 3].

The understanding of these nano-scale effects is determined by quantum mechanics (QM). This quantum world, where energy and similar quantities appear in discrete values, was shaped by

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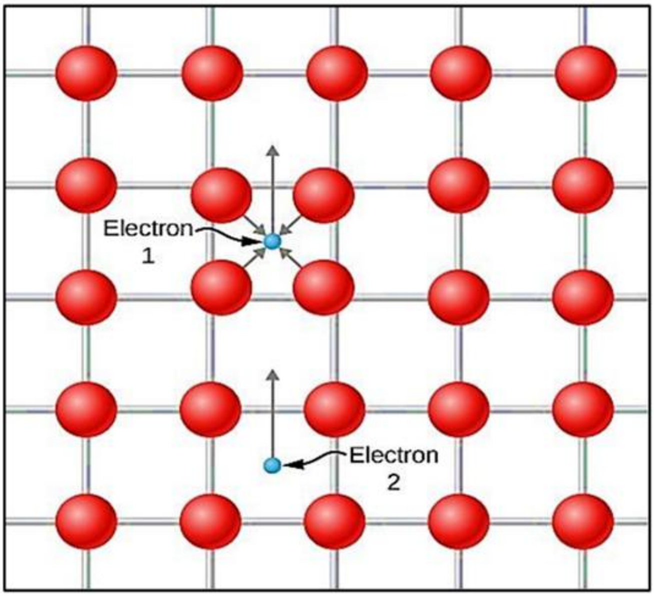
Planck′s solution to black-body radiation and Einstein′s explanation of the photoelectric effect, achieving its modern structure in the 1920s. The probabilistic description provided by the wave function is essential for understanding the behavior of atomic-scale systems. Many of today's electronic components, such as transistors, LEDs (light-emitting diodes), lasers, and microprocessors, are directly based on quantum principles; thus, the development of nanotechnology is inherently linked to this QM framework.

Superconductivity is a purely quantum-origin phase state, characterized by the absolute loss of electrical resistance below a certain critical temperature (T_c) and the effective expulsion of an external magnetic field, Meissner Effect [4, 5]. Discovered by H. K. Onnes in 1911, the microscopic explanation for this phenomenon was provided in 1957 by the BCS theory, which posited that the collective movement of phonon-mediated Cooper pairs enables lossless current transport [6]. The formation of Cooper pairs is shown in Figure 1 [7]. Cooper pairs can move freely within the crystal without undergoing any process that would lead to electrical resistance, and this results in superconductivity.

Advances in nanotechnology have added a new dimension to this field by enabling the control of superconductive quantum processes at the nanoscale. Nanostructured superconductors, such as nanowires, ultrathin films, multilayer super-lattices, and quantum dots, play a critical role in both fundamental research into quantum behavior and practical device technologies [8]. Changes observed in the critical temperature, critical current density (J_c), and flux pinning mechanisms as dimensions shrink directly influence the design of quantum information processing components, high-sensitivity measurement systems, and low-loss energy devices.

Figure 1. Formation of a Cooper pair via electron–phonon interaction



The fabrication techniques used for these structures generally require the combined application of both top-down and bottom-up approaches. Methods such as electron beam lithography and focused ion beam processing provide precise nano patterning, while techniques like MBE (molecular beam epitaxy), CVD (chemical vapor deposition), and atomic layer deposition enable the production of thin films with high crystalline quality. Understanding the properties of superconducting structures relies on the integrated use of advanced characterization methods such as TEM (transmission electron microscopy), AFM (atomic force microscopy), SQUID (superconducting quantum interference device) magnetometry, and low-temperature electrical measurements [9].

One of the most intense application areas for nanotechnological engineering is high-temperature superconductors

(HTS). In complex oxides like BSCCO (Bi-Sr-Ca-Cu-O) and REBCO ($REBa_2Cu_3O_{7-x}$), nano-scale defect control is crucial for optimizing flux pinning centers and enhancing the critical current density (J_c). HTS-based sensors, quantum circuit elements, fast electronic components, and optoelectronic devices are strong candidates for future technologies because of their high speed, low energy consumption, and high sensitivity [10, 11].

This study aims to present a comprehensive, contemporary perspective on the nanometric-level engineering of superconducting materials by addressing the effects of nanotechnology on superconductivity, the quantum processes that emerge at the nanoscale, production approaches, and application potentials within an integrated framework.

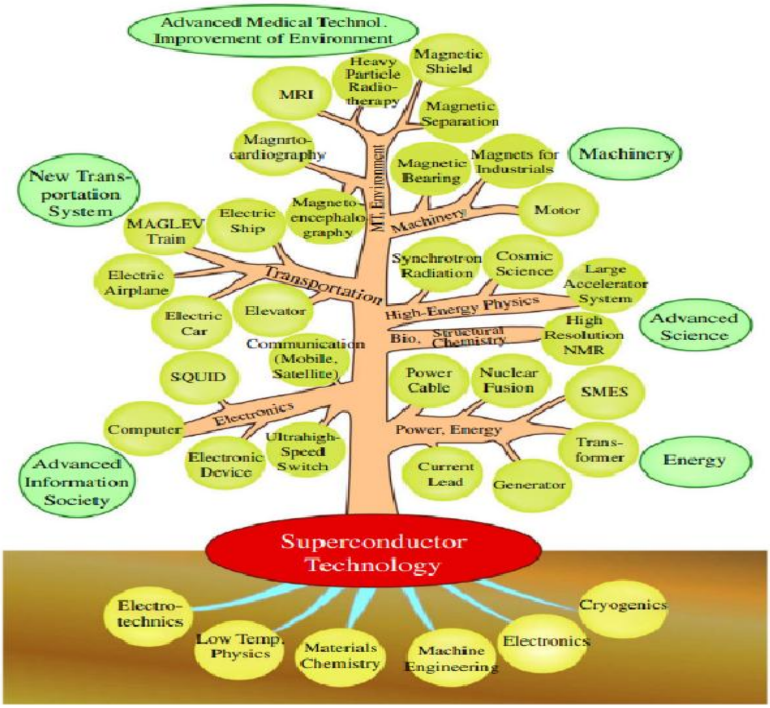
Energy Systems and Environmental Applications

The development trajectory of superconducting technology can be viewed as a growth tree, extending from fundamental scientific discoveries to groundbreaking practical applications. The roots of this tree are grounded in the basic quantum knowledge underpinning superconductivity's origins, while its fruits represent the diverse range of application areas that continue to multiply each year.

HTSs play a central role in this evolution. The proportion and prevalence of HTS materials in various application sectors are continuously increasing, which demonstrates the maturity of the technology. In this context, it is clear that HTS materials are rapidly moving beyond the development stage and transitioning into the mass production phase for a variety of practical applications.

As global energy and environmental issues gain importance and the need for advanced medical technologies deepens, HTS technology is expected to make significant contributions to these critical areas in the near future. This advancement proves that superconductivity is not merely a laboratory subject, but also a cornerstone for future technological solutions. Figure 2 illustrates, through a visual metaphor, the technological evolution of superconductivity, starting from its fundamental principles (the roots) and extending to the diverse application outcomes (the branches and fruits) achieved [12].

Figure 2. The future of superconducting applications



The interaction between nanotechnology and superconductivity offers innovative solutions to two critical problems facing modern energy infrastructure: the reduction of energy losses and the development of environmentally friendly technologies. Nano-engineered superconductors enable the improvement of fundamental superconducting parameters, including critical temperature (T_c), critical current density (J_c), and critical magnetic field (H_c). This capability ensures high efficiency and sustainability in energy transmission, conversion, and environmental applications [13, 14].

Nanoelectronic, a sub-discipline of nanotechnology, focuses on the design and integration of electronic devices, chips, and circuits at the nanometer scale. The continued miniaturization of transistors in integrated circuits has revolutionized electronic technology, enabling the development of chips with memory densities reaching 1 terabyte per square inch. This advancement is poised to significantly enhance the storage capacity of memory units. Furthermore, progress in nanoelectronic has improved the screen technologies used in electronic systems, yielding substantial gains in energy consumption, weight, and thickness. Since nanoelectronic overcomes the scaling limitations of conventional Complementary Metal-Oxide-Semiconductor (CMOS) technology, it is often viewed as a disruptive technology [8, 15]. Moreover, developments in nanotechnology have found extensive use not only in electronic, information, and biomedical applications but also across numerous other aspects of modern life. Nano-sized materials themselves exhibit superior mechanical and physical properties due to their fine-grained structures and high grain boundary volume fractions [16].

Life Sciences and Health Technologies

Superconducting nanotechnology represents an emerging paradigm in biomedical diagnostics and therapeutic monitoring, offering unprecedented gains in sensitivity and precision. Superconducting devices grounded in quantum-architecture principles exhibit exceptional capability in detecting and characterizing the extremely weak magnetic fields generated by physiological processes. Organs such as the human brain and heart produce biomagnetic fields on the order of femto Tesla (10^{-15} T) because of their intrinsic electrophysiological activity. The non-invasive detection and analysis of these ultra-low-amplitude signals hold substantial clinical significance, encompassing early diagnosis, functional mapping, and pre-operative planning [17].

SQUIDs (Superconducting Quantum Interference Devices) constitute the most sensitive magnetic flux detectors known to date [18]. Advances in nanoscale fabrication have enabled the miniaturization and performance enhancement of these systems, leading to the development of NanoSQUIDs-next-generation sensors integrating Josephson junctions within superconducting nano-rings (e.g., Nb, NbN). Nanoscale geometric optimization of these junctions markedly improves flux coupling efficiency, facilitating the detection of magnetic field fluctuations at or below the 10^{-15} T regime.

Nano-SQUID-based platforms have found two principal medical applications: magnetoencephalography (MEG) and magneto-cardiography (MCG) [19].

MEG enables the measurement of neuronal magnetic fields with magnitudes around 10^{-14} T, providing millisecond-level temporal resolution. This capability is essential for localizing epileptogenic zones, investigating cognitive dynamics, and performing high-precision pre-surgical cortical mapping [20, 21].

MCG, in contrast, measures magnetic fields associated with cardiac electrophysiological activity in a fully non-invasive manner. Owing to their superior sensitivity, NanoSQUIDs can detect these fields without significant attenuation by intervening tissues, thereby supporting the early diagnosis of arrhythmias, ischemia, and other cardiac pathologies.

Compared with conventional EEG and ECG systems, these technologies offer substantially higher accuracy because they measure magnetic signals directly and therefore exhibit reduced susceptibility to tissue-induced distortions. High-field magnetic resonance imaging (MRI) systems incorporating nanostructured superconducting magnets represent one of the most powerful non-invasive imaging modalities in modern medicine. The performance of high-resolution MRI is intrinsically linked to the strength, homogeneity, and stability of the magnetic field generated by the system, placing superconducting magnets at the core of MRI technology.

In traditional MRI platforms, NbTi coil windings are increasingly being replaced by nanotechnology-enhanced high-temperature superconducting (HTS) thin films and coated conductors. Through methods such as nano-engineered precipitate phases, defect engineering, and the formation of nano-columnar structures, the critical current density (J_c) of HTS materials can be significantly enhanced [22]. These improvements enable the generation of stronger magnetic fields using smaller and lighter coils, simplify cryogenic infrastructure, improve field homogeneity-and consequently image quality-and provide more stable magnetic characteristics in ultra-high-field (UHF) MRI systems operating at 7 T and above.

Nanotechnology also enables sub-micrometer precision in the fabrication of coil windings and structural supports, thereby minimizing magnetic field inhomogeneities and ensuring a more stable field distribution throughout the imaging volume.

Nanotechnological superconductors offer transformative advancements in medical imaging and diagnostics. The femtotesla-level sensitivity of NanoSQUIDs facilitates the detection of neuronal and cardiac activity with previously unattainable detail, enabling the identification of pathologies such as stroke, tumors, and multiple sclerosis even at very small lesion sizes. Additionally, nanostructured superconducting coils support the development of portable MRI systems suitable for clinical environments such as operating rooms and intensive care units. These superconductivity-based technologies open new avenues for real-time monitoring of biological processes at the molecular scale, providing innovative diagnostic and assessment tools for modern medicine.

Magnetic resonance imaging (MRI) has made significant contributions to the detailed visualization of soft tissues-such as blood, organs, vasculature, and bone structures-since its introduction into clinical practice. When a strong magnetic field is applied to the human body, different tissues can be distinguished from one another with high clarity [23, 24]. MRI technology exploits this principle to generate cross-sectional images of the body, enabling the identification of various tissue types and their associated abnormalities.

MRI often allows the diagnosis of internal diseases with no exploratory surgery or exposure to high doses of X-rays. Consequently, the frequency of exploratory surgical procedures has decreased substantially in modern clinical practice [25].

However, MRI systems remain more costly than other imaging modalities such as ultrasonography and X-ray computed tomography (CT). This is primarily because of the superconducting magnets at the core of MRI systems. Owing to their high magnetic-field strength and stability, superconducting magnets enable exceptional image quality-performance levels unattainable with conventional copper-based magnets. The field strength and homogeneity required for MRI cannot be practically achieved using traditional electromagnetic systems.

High magnetic-field homogeneity and stability are critical to achieving clinically acceptable spatial resolution, diagnostic accuracy, and imaging speed. Superconducting materials uniquely fulfill these stringent requirements, making them indispensable components of modern MRI scanners.

As a result, MRI has become an essential diagnostic tool in contemporary medicine, particularly due to its superior soft-tissue imaging capabilities. Moreover, it remains the only superconducting technology currently deployed on a broad commercial scale [26].

Among the most advanced cancer treatment modalities, proton therapy and heavy-ion therapy are fundamentally dependent on superconducting technology. The particle accelerators used in these treatments propel protons or heavy ions to velocities approaching the speed of light. The precise, millimeter-scale steering and focusing of these high-energy particle beams require superconducting magnets, which play a pivotal role in ensuring accurate dose delivery to the tumor target [27].

Advances in nanotechnology have facilitated the development of superconducting wires with enhanced critical current density (J_c). These next-generation conductors enable the design of accelerator magnets that are smaller, lighter, and more energy-efficient. As a result, the installation cost and physical footprint of proton therapy centers can be reduced, improving the accessibility of these treatment modalities.

Targeted drug delivery-transporting therapeutic agents exclusively to diseased tissues while preventing damage to healthy structures-is a central goal for increasing treatment efficacy. In this approach, drugs are bound to nanoscale magnetic particles (nanocarriers). After systemic administration, these nano-drug complexes can be actively guided to the desired location using strong, localized magnetic field gradients generated by externally applied superconducting magnets [28].

Magnetic field strengths and gradients that far exceed the capabilities of conventional magnets can be generated only through superconducting coil systems. This capability enables the highly accurate delivery of nano-therapeutics to targeted tissue sites.

In the discovery and development of new pharmaceutical compounds, understanding the atomic-level chemical structure of candidate molecules is of paramount importance. Such structural elucidation relies on Nuclear Magnetic Resonance (NMR) spectroscopy, a technique that requires exceptionally strong and stable magnetic fields to resolve molecular configurations. The world′s highest-performance NMR instruments are constructed using superconducting magnets, which routinely operate at frequencies of 800 MHz and above, corresponding to magnetic fields on the order of 18.8 Tesla [29].

The extraordinary strength and stability of these magnetic fields enable the characterization of nanoscale drug components with atomic-level resolution and high analytical precision, significantly accelerating pharmaceutical research and development workflows.

The Future of Nanostructured High-Temperature Superconductors

HTSs represent one of the most compelling research areas in condensed matter physics, characterized by their complex crystal structures and quantum mechanisms that remain not fully elucidated. The emergence of zero resistance and the Meissner effect at relatively higher temperatures renders these materials unique for critical applications in energy transmission, medical imaging, and quantum information processing [4]. Specifically, the enhanced stability, improved flux pinning capacity, and higher critical temperatures of nanostructured superconductors play a determinant role in the development of scalable and reliable qubit architectures [30].

The potential of superconducting nanotechnology, however, is shaped by engineering constraints, including the efficiency of cryogenic systems, manufacturing scalability, the reduction of AC losses, and material brittleness. The requirement for reliable cooling at the 77 K level in HTS-based systems has made the design of new-generation micro-coolers and hybrid cryogenic interfaces strategic [31]. Similarly, the need for flawless nanostructure homogeneity increases the importance of precise positioning of flux pinning centers and the nano-porous architectures developed in REBCO films [32]. The ability to substantially reduce AC losses through optimization in multilayer HTS tapes is an important development that improves material performance and expands potential application areas [33].

In the field of quantum information processing, superconducting nanotechnology, through high-precision nanofabrication approaches that increase coherence times, has positioned Josephson-based qubits as one of the strongest candidates for scalable quantum processors [34]. Correspondingly, the achievement of single-molecule magnetic moment sensitivity with NanoSQUID technology signals the beginning of a new era in biomedical diagnostics [35]. The resistance-free information transfer offered by superconducting nanowires takes on a critical role in the construction of sustainable, low-energy data centers.

Nanobiotechnology is creating a transformative paradigm shift in healthcare with its wide range of applications, extending from diagnosis to therapy. The controlled design of the size, shape, and surface chemistry of nanocarriers allows for the improvement of drug pharmacokinetic and pharmacodynamic profiles, increased bioavailability, and more effective application of targeted therapies. Nanostructures compatible with molecular and cellular scales enable the development of new-generation drugs, diagnostic techniques, and high-precision sensors, opening the door to early disease diagnosis and personalized treatment strategies [36].

Nevertheless, uncertainties regarding the toxicity, biocompatibility, and long-term safety profiles of nanomaterials remain a critical area of research for the technology's clinical integration. The optimization of fundamental properties such as the shape, diameter, and surface charge of nanoparticles through advanced synthesis and characterization methods will strengthen the therapeutic efficacy of nanobiotechnology. The adaptation of nanorobots, quantum dots, and other innovative platforms to biomedical applications will accelerate through the deepening of industry-academia collaboration. Overall, these multi-dimensional developments in nanobiotechnology will enable the emergence of more precise, effective, and sustainable solutions in healthcare, forming the building blocks of future medical practices [37].

Nanostructured superconducting materials play a pivotal role in the advancement of quantum computer technology due to their superior properties, such as higher critical temperatures, enhanced flux pinning capabilities, and reduced energy losses. These materials provide a fundamental infrastructure for the production of stable, scalable, and highly efficient qubits required for practical quantum computers. Although challenges such as material stability, complexity of manufacturing processes, and large-scale integration persist, current research and technological advancements in nanostructured superconductors offer a promising outlook for the future of quantum computers [30, 38].

The resurgence of superconductivity is facilitating the emergence of radical and unconventional applications across diverse sectors, ranging from nanotechnology, computer and communication technologies, and information processing to the entertainment industry, clean energy, and transportation systems. This broad expansion underscores that the history of superconductivity is full of unexpected developments and that it remains an exciting research area in physics with open fundamental questions.

This study specifically addresses the BSCCO compound, known as the first high-temperature superconductor that does not contain rare-earth elements. BSCCO's superior performance, particularly in optoelectronic industries, has led to its widespread use in modern technologies. This innovative approach signals a significant transformation across virtually every discipline of science and engineering, with the potential to influence many facets of human life in the future. In essence, BSCCO and similar high-temperature superconductors set the stage for the development of new-generation devices and technologies that offer higher efficiency, thus carrying the potential to significantly improve human activities and quality of life [7].

Ultimately, superconducting nanotechnology is not merely about the development of new materials; it is a multi-dimensional research axis that accelerates the global energy transition, strengthens the foundations of quantum technologies, and enhances biomedical precision.

Future studies focusing on nanostructure engineering, cryogenic efficiency, and the fundamental physics of quantum architecture will determine the transformative capacity of this field. These advancements will position superconducting nanotechnology as a strategic nexus in the scientific and technological infrastructure of the 21st century.

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INNOVATIVE APPROACHES FOR WATER SECURITY AND WASTE MANAGEMENT: NANOTECHNOLOGY-BASED MEMBRANE PROCESSES

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Introduction

Clean and safe drinking water is considered a basic human right; however, growing water scarcity and contamination around the world are making access to it more challenging. Despite the fact that water covers nearly two-thirds of our planet, only a very small portion about 0.3% of the total available water is fresh and usable for the needs of the world’s 8.1 billion people. As freshwater resources are depleted, water scarcity threatens human activity. Current water treatment systems cannot meet the growing demand. Approximately 2 billion people lack safe water, the vast majority of whom rely only on basic water services. Recent advances in nanoscience offer numerous solutions to alleviate the need for scarcity or pollution control. Water, a crucial resource for human survival, is becoming increasingly important with the growth of

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industry. Water is a valuable resource that supports economic growth and human well-being. Developed nations are undertaking large-scale projects to prevent and treat water pollution. In this context, the potential of nanotechnology (NT) for water treatment has excited many researchers, and numerous articles have been published on the topic of nanomaterials and NT for chemical water production and wastewater treatment. This significant interest stems from the numerous benefits, properties, and capabilities that NT offers in addressing the ever-increasing challenges related to water quality, availability, and sustainability. In this context, the adoption of highly advanced NT into traditional process engineering offers new technological advancements for water and wastewater technology processes. NT offers long-term potential by improving filtration materials, improving water quality, and reducing costs. Nanomaterials designed at the nanoscale (below 100 nanometers) play a key role in these advances. Here are some of the recent developments in nanomaterials for water and wastewater treatment processes, including nanoadsorbents, nanometals, membranes, and nanobased materials such as photocatalysts. Membrane-based technologies have attracted considerable attention in NT application areas. Research involving membrane-based technologies has recently been increasingly explored in traditional water and wastewater treatment processes to meet the growing demand for clean water and minimize negative environmental impacts. Membrane-based water treatment and purification systems have been recognized as a revolutionary method. Membrane systems have played a significant role in both industrial and domestic water treatment by effectively removing unwanted substances from water. Membrane systems can be described as semi-permeable membrane structures. This permeable membrane structure allows water molecules to pass through while retaining dissolved substances, particles, microorganisms, and chemical contaminants.

This chapter comprehensively reviews the progress made in water treatment technology using nanotechnology-based materials, with particular emphasis on applications of nanomaterials, including nanotechnology-based membranes and their composites. Furthermore, this review examines various nanotechnology-based water treatment techniques and provides a summary of advances in water and wastewater treatment technologies using various nanomaterials.

Integration of Nanotechnology into Membrane Technology

Nanotechnology has the potential to drive significant large-scale changes since nanostructures are far smaller than conventional bulk materials. At the atomic and molecular level, as well as across interfaces, the interactions of energy and matter become evident on the nanometer scale. In fact, advancements in nanotechnology have already produced gradual yet transformative impacts across various industries, reshaping traditional approaches and systems.

Membranes and nanoporous adsorbents developed through nanotechnology can achieve more efficient and eco-friendly separations compared to conventional thermal or phase-based methods. Designing an effective membrane requires carefully maintaining a balance between permeability and selectivity allowing the targeted substance to pass while preventing the movement of unwanted compounds. Additionally, these membranes must be suitable for large-scale production and possess long-term durability to ensure economic sustainability. Recent progress in nanoscale fabrication focuses on improving consistency and scalability. Materials such as zeolites, graphene oxide, metal oxides, metal–organic frameworks (MOFs), nanofibers, and carbon nanotubes offer promising alternatives to traditional thermal distillation processes. Furthermore, nanotechnology-enabled nanoporous membranes can achieve chemical separations based on zeolites and their micro- and nanopores through adsorption, ion exchange, or catalysis. It minimizes the need for energy-intensive thermal changes in cost-effective processes and is already being used in many areas, including hydrocarbon separation [1]. Nanotechnology has significantly influenced separation technologies, with reverse osmosis being a prime example. Today, large-scale desalination primarily relies on polymer-based nanoscale membranes. Although desalination expenses remain closely tied to energy consumption, advances in membrane technology since the 1990s have helped lower overall costs by nearly threefold. Furthermore, the latest nanofiltration membranes have become viable alternatives to reverse osmosis, offering potential energy reductions of up to 29% [2].

Membrane-focused nanotechnology represents a key approach for water purification and treatment worldwide. Although membrane separation techniques do not directly manipulate structures at the atomic or molecular scale, they incorporate principles of nanoscience and utilize nanomaterials and nanocomposites to enhance separation efficiency and water purification performance. The integration of nanomaterials in these systems provides notable benefits and improvements to membrane-based technologies [3].

With the growing adoption of hybrid energy generation methods, the reliance on environmental resources for energy production has been significantly reduced [4]. Nonetheless, the advancement of sustainable materials remains limited by factors such as natural resource availability and economic policies. Since energy plays a central role in achieving sustainability goals, membrane-based systems are gaining prominence as promising tools for producing cleaner and more sustainable energy [5]. In contrast to conventional separation technologies, membrane-based methods require lower energy input, produce fewer emissions, and rely on smaller amounts of chemicals thereby decreasing total CO_2 output and minimizing environmental harm [6]. The following section examines key elements of membrane technology that contribute to building a sustainable future.

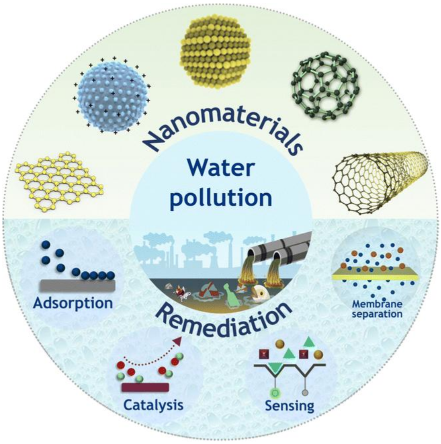
Membrane technologies are being adopted across a wide range of industrial fields, such as gas purification, wastewater treatment, chemical and pharmaceutical manufacturing, food and beverage processing, hemodialysis, and textile production [7-10]. Membrane technology plays a vital role in advancing sustainability through its applications in desalination, wastewater recycling, clean drinking water production, and overall water purification [11].

Figure 1. Diagram showing different strategies for membrane sustainability [11]

Basic Concepts of Nanotechnology

The distinctive chemical, physical, and optical characteristics of nanomaterials, along with their innovative application through nanotechnology, have created new opportunities and advancements in the field of water treatment research and related technologies (Figure 2). For instance, functional nanomaterials' superior light absorption capabilities make them highly suitable for applications such as solar-driven photothermal water treatment, membrane distillation using nanophotonics, and water disinfection, among others. In addition, conventional water treatment techniques often rely on toxic chemicals for disinfection, leading to the formation of harmful byproducts, and use large amounts of iron- and aluminum-based coagulants that are typically discarded in landfills and seldom recycled. By contrast, integrating nanotechnology into water treatment can minimize these toxic impacts while enhancing operational efficiency and sustainability, allowing for multiple regeneration cycles without compromising performance [12].

Figure 2. Schematic representation of various nanomaterials and their applicability in different water treatment processes [3]



Research in nanotechnology is focused on enhancing current water treatment methods and creating entirely new approaches. Yet, developing sustainable and economically viable nanostructured water treatment solutions requires a thorough understanding of the pollutants involved and the factors affecting them. Designing nanomaterials for specific applications involves precise control over their size, electronic characteristics, and functional properties. Nanomaterials have shown exceptional potential for selectively targeting a wide range of environmental contaminants, even at trace levels. Consequently, establishing permissible pollutant limits is essential for choosing the most suitable nanomaterial or technology to achieve an effective water treatment system [3].

Membrane Types Modified with Nanotechnology

The use of nanotechnology in membrane technologies has led to significant improvements in critical properties such as separation efficiency and fouling resistance in recent years. Nanotechnological approaches implemented through the incorporation of nanomaterials into the membrane matrix or surface modification are paving the way for next-generation solutions for both polymeric and inorganic membranes. In this context, the classification and performance comparison of membrane types modified with nanotechnology has become a fundamental research area in modern membrane engineering [13].

- Polymeric membranes

Polymeric membranes, which can be either symmetric or asymmetric, are commonly employed for gas separation. Symmetric membranes, also known as isotropic membranes, feature a consistent composition, porosity, and void structure across their entire thickness. Thanks to their adjustable chemical composition, structural design, and performance properties, polymeric membranes have become highly adaptable for numerous industrial applications. By tailoring the chemistry of the polymers, these membranes can provide a broad spectrum of separation, purification, and filtration functions. Polymeric symmetric membranes provide benefits including low production costs and straightforward manufacturing processes. Nevertheless, they may be limited in terms of separation performance, selectivity, and durability under extreme conditions [14]. Composed of organic polymers, these membranes are widely used for industrial-scale separation applications because they can be easily scaled up and fabricated. Common fabrication methods include phase inversion, stretching, electrospinning, and channel etching [15].

- Ceramic membranes

Ceramic membranes, often preferred in micro- and ultrafiltration applications, offer thermal strength and high mechanical properties. They are essentially porous and have a similar structure to polymeric membranes. Despite their high investment costs, ceramic membranes can be widely used in conditions where polymeric membranes are not suitable. Compared to polymeric membranes, their mechanical resistance and permeate flux are higher than ceramic membranes. Ceramic membranes are more resistant to pressure, high temperatures, and a wide pH range. Polymeric membranes can be used in separation processes involving acids, bases, oxidative/corrosive chemicals, and strong solvents. Because ceramic membranes have high chemical stability and can be cleaned with concentrated and strong chemicals, they can be cleaned and reused repeatedly. Their high mechanical, chemical, and thermal resistance, coupled with their ability to be cleaned and reused, give ceramic membranes a long life and have become widely used in many industrial applications [16].

- Composite (nanocomposite) membranes

In recent years, nanotechnological methods have been used in the production of composite membranes. These studies are particularly widespread in the field of nanocomposite membrane production. Nanocomposite membranes can be organic-organic,

organic-inorganic, or inorganic-inorganic mixtures. The most common example of nanocomposite membranes is the incorporation of nanostructured materials such as silver, TiO_2, and zeolite into polymeric materials.

Composite membranes consist of three layers. The outer and inner layers are made of microporous polyethylene. Between these two layers is a 1 μm thick, non-porous polyurethane layer. The non-porous layer is used to allow the pressurized gas substrate to diffuse across the membrane surface without creating bubbles [17, 18].

- Hybrid membranes

"Hybrid membrane" or "organic-inorganic hybrid membrane" is a general term used for membrane materials formed by combining polymeric (organic) and inorganic (e.g., ceramic, metal oxide, nanoparticle) components [19]. These membranes aim to combine the advantages of organic membranes, such as ease of processing and low cost, with the advantages of inorganic membranes, such as high thermal, chemical and mechanical resistance [20].

Nanomaterial Types and Their Effects on Membrane Performance

Nanomaterials can be broadly classified into four main groups: carbon-based materials, metal-based materials, dendrimers, and composites. Nanomaterials within these categories, synthesized in controlled ways, exhibit superior functions thanks to their unique structural and physical properties, which are in high demand in many fields such as imaging, thermal management, mechanical strength, medicine, and industry.

- Carbon-Based Nanomaterials:

Carbon-based nanomaterials are among the most interesting and researched material groups in nanotechnology. Graphene, composed of a single layer of carbon atoms arranged in a two-dimensional honeycomb lattice, is characterized by superior electrical conductivity, high thermal conductivity, and exceptional mechanical strength. Carbon nanotubes (CNTs), on the other hand, are obtained by rolling graphene sheets into a cylindrical shape and possess very high tensile strength. These properties make them widely used in many sectors, including electronics, composites, and aerospace.

- Metal-Based Nanomaterials

Metal-based nanomaterials are a broad group of materials that include various metal nanoparticles, such as gold, silver, and iron oxide. These materials are notable for their unique optical, electrical, and catalytic properties. For example, gold nanoparticles are valuable in sensor technologies and medical imaging applications due to their surface plasmon resonance properties. Silver nanoparticles, on the other hand, are used in medical devices, textiles, and hygiene products due to their antibacterial properties.

- Semiconductor Nanomaterials

Semiconductor nanomaterials offer significant advantages in electronic devices by striking a balance between conductive and insulating properties. Quantum dots, small semiconductor crystals with strong light-emitting properties, are used in display technologies, bioimaging, and even cancer treatment. Furthermore, nanowires and nanorods are promising materials for high-efficiency electronic components and solar energy systems.

- Ceramic Nanomaterials

Ceramic-based nanomaterials offer excellent mechanical strength, heat resistance, and electrical stability. Titanium (TiO_2)

nanoparticles, thanks to their strong photocatalytic properties, are used in self-cleaning surfaces and water and air purification systems. Furthermore, ceramic nanocomposites, with their high strength and lightweight advantages, are preferred in the aerospace, automotive, and defense industries.

- Polymer-Based Nanomaterials

Polymer-based nanomaterials are notable for their lightweight structure and easy formability. Nanoparticles produced from biopolymers such as polylactic acid (PLA) and polyethylene glycol (PEG) play an important role in drug delivery systems, tissue regeneration applications, and biocompatible nanotechnological solutions. These materials offer sustainable alternatives in both biomedical and environmental applications.

Application Areas

Membranes are defined as barriers that exhibit selective permeability between two distinct phases. Their distinctive permeability to specific contaminants makes them valuable as effective separation materials. Advantages such as the high quality of purified water obtained with membrane systems, their compact design, small space requirements, low construction requirements, compatibility with automation, and minimal chemical use make this technology attractive. However, membrane surface fouling and clogging are among the primary problems that reduce system efficiency and limit the widespread use of the technology. Water scarcity resulting from increasing global population and industrialization have increased the importance of more advanced treatment technologies, innovative membrane processes, and material development efforts aimed at improving membrane performance.

Membrane technologies are widely used in many different areas such as drinking water supply, domestic and industrial wastewater treatment, gas separation processes, electrochemical applications, blood and urine dialysis in the biomedical field, oxygen transfer, and controlled drug release with membrane-based sensor systems [21]. Some of these applications are as follows;

- Water and Wastewater Treatment

Desalination: As local watersheds around the world deplete, communities have turned to alternative water sources, water recycling, water imports, and desalination. Desalination is the process of removing excess salts and other dissolved chemicals from seawater, reducing salt concentrations to or below the World Health Organization's drinking water limit of 500 ppm. While desalination has been around for centuries, it has gained prominence in recent decades.

Desalination of brackish and seawater has since grown rapidly worldwide [21]. In 2013, there were more than 17,000 active desalination plants in 150 countries, providing approximately 80 x 106 m^3 of water per day to 300 million people. By 2015, production capacity had increased to almost 97.5 x 106 m^3 per day [23]. The supply of desalinated water is expected to increase to 192 x 106 m^3 per day by 2050.

Despite its widespread use, desalination remains controversial because it is an expensive way to produce water. It also has numerous environmental impacts, including high greenhouse gas emissions and waste products that can impact marine habitats [24].

Removal of micropollutants (dyes, heavy metals, pharmaceuticals): In water and wastewater treatment, micropollutants (organic compounds present in very low concentrations but capable of causing significant impacts on life and ecosystems) such as endocrine disruptors, pharmaceuticals, and pesticides are becoming a growing environmental problem. In this context, membrane technologies stand out as an important separation tool.

Micropollutants, mainly pharmaceuticals, personal care products, industrial chemicals, pesticides, polycyclic aromatic hydrocarbons, and metallic trace elements, have been widely detected in different waste streams at a wide range of concentrations from a few nanograms to micrograms per liter [25]. With the rapid increase in the application of synthetic products such as pharmaceuticals, cosmetics, and pesticides, it is estimated that more than 100 micropollutants have been detected in municipal wastewater. For example, hospital wastewater is considered a significant contributor to antibiotics in the environment [26]. Porous MF and UF membranes cannot retain micropollutants, but their slight removal can be achieved through adsorption by the membrane materials and retention by fouling layers [27].

Fouling control and recyclable membranes: In membrane treatment systems, fouling control and recyclable membrane strategies are two critical and complementary areas. Through fouling control, membrane performance is maintained and its lifespan is extended, resulting in improved end-of-life module condition and, consequently, reuse or recycling options. Reuse reduces environmental impact and provides economic benefits. While research in these areas is promising, the sustainability of fouling control, particularly in real-scale applications, and the widespread adoption of recycling strategies are still under development.

Membrane fouling (surface and pore clogging and accumulation), one of the most critical operational issues in the widespread use of membrane systems, directly impacts system performance. For example, membrane fouling leads to reduced flow, increased pressure, increased energy consumption, increased cleaning frequency, and shortened membrane life [28].

Fouling mechanisms include events such as narrowing or clogging of membrane pores, adsorption of solutes onto the membrane surface and pores, cake layer formation on the active layer, and concentration polarization [28].

- Gas Separation Applications

Separating specific components from gas mixtures is now of great importance in areas such as carbon dioxide capture (CO_2 capture), natural gas purification, and oxygen or nitrogen production. In this area, membrane technologies offer advantages such as small footprint, low energy consumption, and continuous operation compared to traditional processes, making them an important option for gas separation [29].

Membrane gas separation technology is in its nascent stage, with much research and pilot applications underway. However, for widespread industrial use, the following are critical:

- Membrane materials must offer both high flow and selectivity, as well as durability.
- Optimizing module and system designs in terms of energy, flow, and pressure conditions.
- Determining membrane solutions suitable for the gas source (composition, pressure, temperature, contaminants) for the application.

Conducting economic analyses: ensuring the membrane system investment, operating costs, and energy consumption are competitive with traditional technologies. Therefore, if your project utilizes gas separation membranes, factors such as membrane material selection, module type, operating conditions, and process optimization must be carefully considered from the outset.

- Energy Applications

Membrane technologies play a significant role in the energy sector today, with many objectives including reducing greenhouse gas emissions, supporting the hydrogen economy, producing oxygen or nitrogen, and utilizing gradient energies. For example, it has been reported that membrane systems are increasingly being utilized in energy conversion and energy saving processes [30].

Membrane processes have the potential to offer lower energy consumption, reduced chemical usage, and more compact system structures than traditional conversion/separation technologies. For example, membrane separation systems have been evaluated as having a smaller energy footprint compared to traditional methods [30].

It is emphasized that membranes are critical components in advanced energy applications such as hydrogen production, purification and energy storage systems (e.g., fuel cells, flow batteries) [31].

- Biomedical and Pharmaceutical Applications

In recent years, membrane applications in the medical field have seen continuous development [32]. Membranes are typically described as porous films that serve as barriers between two adjacent phases, enabling selective transport of certain substances from one phase to another [33]. In the biomedical field, membranes are commonly utilized for applications such as tissue engineering, purification processes, and the development of implants and scaffolds. They are also employed in controlled-release systems for active compounds and in diagnostic tools, including sensors and various testing platforms [34].

The use of polymeric membranes in tissue engineering has been widely explored because of their biocompatibility, strong mechanical properties, and potential to support the repair and regeneration of damaged tissues or organs [35]. Another key biomedical application of polymeric membranes is in the design of drug or protein delivery systems, including the targeted delivery of molecules such as antibiotics [36]. In these systems, the active substances diffuse through the polymeric membrane, enabling controlled and site-specific drug release [37].

Latest Developments and Trends

Recent trends indicate that membrane technologies are being redefined not only for their separation efficiency but also as smart, environmentally friendly, digital, and sustainable systems. Smart membranes are becoming more responsive to environmental changes, while nanocomposite structures provide multifunctionality. 3D printing and artificial intelligence are accelerating design processes to create personalized solutions, while green synthesis and recycling approaches are minimizing environmental impact. In the future, the integration of these technologies is expected to lead to the widespread adoption of longer-lasting, self-renewing, and energy-efficient membrane systems.

Smart (stimulus-responsive) membranes developed in recent years can dynamically change their permeability, surface wettability, or selectivity properties by responding to external stimuli such as temperature, pH, light, magnetic field, or chemical concentration. These membranes are particularly prominent in areas such as drug delivery, water treatment, and sensor applications [38]. Membranes can adapt to environmental changes through the addition of smart segments to polymer chains or surface functionalization methods [39]. However, long-term stability, performance loss in repeated stimulation cycles, and scalable production are still important research topics.

Nanocomposite membranes, obtained by integrating nanofillers such as graphene, metal-organic cages (MOFs), carbon nanotubes (CNTs), and TiO_2 into the membrane matrix, improve the permeability-selectivity balance and simultaneously impart antifouling, antibacterial, or photocatalytic properties [40]. These multifunctional structures have been reported to exhibit high performance in energy production and environmental treatment applications. However, the homogeneity of the nanomaterial distribution, mechanical integrity, and risks of nanoparticle leakage must be carefully evaluated.

3D printing technologies enable precise control of membrane geometry and the fabrication of complex internal channel structures. This allows for the development of module designs with optimized flow dynamics [41]. Furthermore, artificial intelligence (AI) and machine learning (ML) approaches offer innovative solutions in areas such as membrane material selection, pore structure optimization, and fouling prediction. These integrated approaches have the potential to shorten membrane design time and increase cost-effectiveness.

As an alternative to traditional chemical methods, membrane production using environmentally friendly and biobased materials has gained prominence in recent years. Plant-derived polymers (cellulose, chitosan, lignin) and biobased nanoparticles are being used to reduce toxic solvents and achieve sustainable production goals [42]. This approach contributes to the development of safe and environmentally compatible materials, particularly for biomedical and drinking water applications. Within the sustainability framework, membrane lifecycle management (LCA) and post-use (EoL) recovery are becoming increasingly important. Recycling used reverse osmosis (RO) or nanofiltration (NF) membranes through chemical regeneration or downcycling methods reduces costs and waste. Furthermore, studies on the production of new membranes from recycled polymer waste offer a future vision compatible with circular economy principles [43].

Conclusion and Recommendations

In recent years, the rapid advancement of nanotechnology has driven revolutionary innovations in membrane technologies. Although traditional membrane systems are extensively used across industries such as water treatment, gas separation, food processing, and energy production, they often encounter challenges over time, including performance deterioration, fouling, limited selectivity, and low permeability. Nanotechnology has proven to be a powerful approach for addressing these limitations.

Nanomaterials significantly enhance membrane performance thanks to their properties such as high surface area, unique surface functions, superior mechanical strength, and chemical stability. In particular, carbon-based nanomaterials (graphene, carbon nanotubes), metal oxide nanoparticles (TiO_2, ZnO, SiO_2), silver nanoparticles, and inorganic nanoadditives such as zeolites are used to increase water permeability, resist fouling, and enhance selective separation capacity by incorporating them into the membrane structure.

Nanotechnology-modified membranes can be conferred hydrophilic or hydrophobic properties by controlling surface morphology and roughness, optimizing targeted performance parameters in various processes such as water treatment and gas separation. Furthermore, nanocomposite membranes enable selective ionic or molecular permeation, improving energy efficiency and reducing operating costs.

Today, nanotechnology-enabled membrane systems demonstrate broad application potential, particularly in wastewater treatment, seawater desalination, the food industry, pharmaceutical production, and energy conversion (fuel cells, electrodialysis). However, the long-term environmental impacts of nanomaterials, production costs, and scalability remain significant areas requiring research and development.

In conclusion, nanotechnology-modified membranes represent a new era in both efficiency and sustainability, pushing the boundaries of conventional membrane technologies. This approach holds great potential for protecting water resources, increasing energy efficiency, and making industrial processes more environmentally friendly in the future.

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APPLICATIONS OF NANOTECHNOLOGY IN MEDICINE (NANOMEDICINE)

Murat ÇAVUŞ[1]

Introduction

Among the scientific and technological revolutions of the twenty-first century, nanotechnology serves as an interdisciplinary bridge with its structure that allows for the control of matter at the atomic and molecular levels. Nanotechnological approaches offer innovative solutions that transcend the limits of conventional methods, particularly in the solution of global problems such as energy, environment, and health. "Nanomedicine," which is the health component of this triad, is defined as the integration of nanotechnology into medical diagnosis, treatment, and preventive medicine practices. Today, nanotechnology has ceased to be merely a theoretical science confined to the laboratory; as seen in the mRNA vaccines developed during the COVID-19 pandemic, it has transformed into a clinical reality that directly affects global public health [1]. This chapter aims to examine the areas of use of nanotechnology in medicine, its basic principles, and its complex

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interactions with biological systems. Nanomedicine offers solutions across a wide spectrum, from improving the pharmacokinetic properties of drug molecules to the molecular-level imaging of diseased tissues and increasing the precision of surgical interventions. However, the success of this technology in the clinic depends on the ability of nanomaterials to overcome biological barriers and on a correct understanding of the "nano-bio" interface established with living systems.

What is Nanomedicine? (History and Basic Concepts)

Nanomedicine, in its most fundamental definition, is the use of engineered materials that have similar dimensions to the nanometer-scale (1-100 nm) building blocks of biological systems (DNA, proteins, cell membranes) for the purpose of monitoring, repairing, constructing, and controlling diseases [2]. One nanometer is one-billionth of a meter (10^{-9} m). This scale is the dimension where biological processes naturally occur; for example, the diameter of a DNA helix is approximately 2 nm, while a hemoglobin molecule is about 5 nm in size. This dimensional compatibility allows nanotechnological tools to interact directly and precisely with biological targets.

The fundamental advantage of nanomedicine lies in the fact that when matter is reduced to the nanometer scale, it exhibits physical, chemical, and optical properties that are completely different from those at the macro scale (such as a gold ingot). Possessing enormous surface areas relative to their volumes makes it possible for the surfaces of nanoparticles to be functionalized with drug molecules, targeting ligands, or imaging agents [3]. This situation allows nanomaterials, unlike classical drugs, to exhibit "smart" behaviors within the body; for example, it enables the release of the drug only in cancerous tissue or the detection of a specific biomarker.

Historical Perspective

The conceptual foundations of nanotechnology are based on the talk titled "There’s Plenty of Room at the Bottom" given by the famous physicist Richard Feynman at the American Physical Society meeting in 1959. In that speech, Feynman foresaw a future in which atoms could be manipulated individually. However, the term "Nanotechnology" was first used by Norio Taniguchi in 1974 to describe the process of processing materials atom by atom or molecule by molecule [3].

The first concrete steps in the medical field were taken in the 1960s with Alec Bangham’s discovery of liposomes (bilayer phospholipid vesicles). Liposomes are considered the "Trojan Horse" of nanomedicine; because they encapsulate drugs, ensuring their safe transport within the body. As a fruit of these studies, in 1995, the FDA approved the first nanotechnology-based drug, Doxil® (PEGylated liposomal doxorubicin). Doxil is a formulation in which the cancer drug doxorubicin is trapped inside a liposome, thereby reducing its toxic effect on the heart and prolonging its circulation time [4].

The 2000s marked a transition period from passive carriers to "smart" nanosystems capable of active targeting. Abraxane® (albumin-bound paclitaxel), approved in 2005, proved the success of protein-based nanotechnology. Finally, the Pfizer/BioNTech and Moderna vaccines developed against the SARS-CoV-2 virus in 2020 demonstrated to the whole world that lipid nanoparticles (LNPs) could successfully deliver genetic material (mRNA) to the human cell, initiating a new era in the history of nanomedicine [1].

Basic Concepts

The theoretical framework of nanomedicine relies on three fundamental concepts that distinguish it from traditional medicine.

The first is Targeted Drug Delivery, which involves directing the therapeutic agent exclusively to the diseased tissue, such as a tumor or infection site, via nanoparticles, rather than allowing it to disperse throughout the body via systemic circulation. This approach significantly enhances the efficacy of the drug while minimizing systemic side effects [5]. Beyond delivery, nanomedicine introduces the concept of Theranostics, a term derived from the combination of "Therapy" and "Diagnostics." This paradigm refers to the utilization of a single nanoparticle platform for the dual purpose of imaging (diagnosis) and treating the disease. For instance, magnetic nanoparticles can function as contrast agents for MRI while simultaneously destroying tumor cells by generating heat under a magnetic field [6]. Furthermore, nanotechnology enables Personalized Medicine by facilitating the development of treatment strategies tailored to a patient's specific genetic profile or the molecular characteristics of the disease, such as specific nanoparticles designed to target cancer stem cells [7].

Biological Barriers and Nano-Bio Interactions

The success shown by a nanoparticle in a laboratory environment (in vitro) may not always be repeatable in clinical application (in vivo). The fundamental reason for this is the complex physiological structure of the human body and the multi-layered defense mechanisms it develops against foreign substances. The greatest struggle of nanomedicine is to overcome the biological barriers encountered until the therapeutic agent is delivered to the target region. In this process, the nanoparticle's size, shape, surface charge, and chemistry are critical parameters determining its interaction with biological systems [8].

Nano-Bio Interface and Protein Corona

The moment nanoparticles enter the blood circulation, they instantly interact with proteins in the blood plasma (albumin, immunoglobulins, fibrinogen, etc.). This protein layer covering the surface of the nanoparticle is called the "Protein Corona". The protein corona hides the original chemical identity of the nanoparticle and gives it a new "biological identity". Cells see and recognize not the nanoparticle, but this protein layer outside it [4]. Electrostatic forces play a major role in this interaction. Biological macromolecules are generally charged structures, and the surface charge (zeta potential) of the nanoparticle determines which proteins will adhere to the surface [8]. The protein corona can increase the size of the nanoparticle, prevent it from binding to its targets, or cause it to be noticed more quickly by immune system cells (opsonization).

Reticuloendothelial System and Clearance

One of the body's main defense mechanisms, the Reticuloendothelial System (RES) or by its new name, the Mononuclear Phagocytic System (MPS), is the first major barrier nanomedicine must overcome. The liver (Kupffer cells) and spleen are filled with macrophages tasked with detecting and destroying foreign particles circulating in the blood. If the surfaces of nanoparticles are not modified appropriately (e.g., hydrophobic surfaces), they are marked by opsonin proteins and are phagocytosed within seconds, being cleared from circulation (clearance) [4]. To overcome this barrier, the "Invisibility Cloak" strategy is applied in nanotechnology. By coating the surface of nanoparticles with hydrophilic polymers like Polyethylene Glycol (PEG) (PEGylation), the adhesion of proteins to the surface is prevented, and the circulation time of the particle is extended [5].

Cellular Barriers and Uptake Mechanisms

Even if the nanoparticle reaches the target tissue (e.g., a tumor), in order to exert its therapeutic effect, it generally needs to cross the cell membrane and internalize into the cytoplasm or nucleus. Since the cell membrane acts as a natural barrier possessing a selectively permeable structure [9], the uptake of nanoparticles typically occurs via endocytosis. However, the specific endocytic pathway utilized is largely determined by the physicochemical properties of the particle, such as size and charge. For instance, particles in the 100–200 nm size range are generally internalized via clathrin-mediated endocytosis, whereas smaller particles may utilize caveolae-mediated pathways. Furthermore, surface charge plays a critical role; positively charged (cationic) nanoparticles penetrate the cell more easily by engaging in electrostatic interactions with the negatively charged cell membrane. Nevertheless, it is important to note that at high concentrations, these cationic particles can compromise membrane integrity and induce cytotoxicity [8, 10].

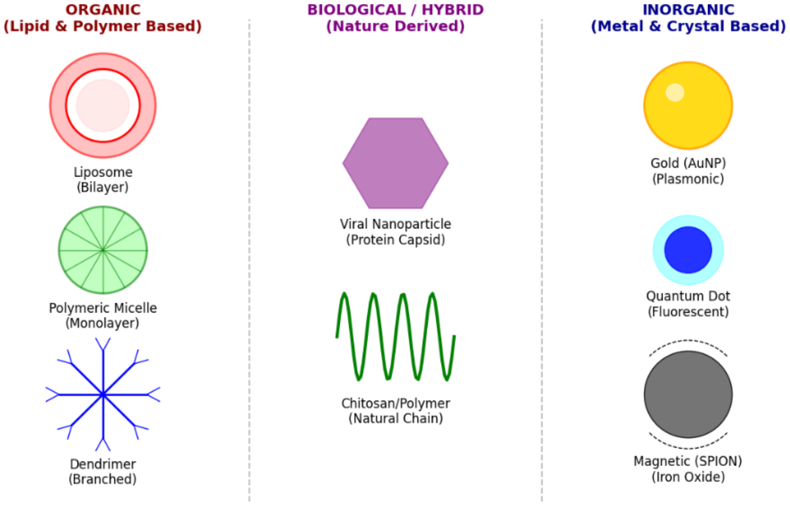
Physiological and Pathological Barriers

Specific barriers also exist according to the type of disease. The most challenging of these is the Blood-Brain Barrier (BBB) encountered in the treatment of brain diseases. Tight junctions between endothelial cells in brain capillaries prevent the passage of 98% of drugs into the brain. Nanotechnology aims to overcome this barrier by using receptor-mediated transcytosis methods to transport drugs for Alzheimer's, Parkinson's, or brain tumors [2]. Consequently, although nanotechnology offers revolutionary opportunities in medicine, the transfer of this potential to the clinic depends on managing the dynamic relationship of nanomaterials with biological barriers. In the following sections, specific diagnostic and treatment strategies developed to overcome these obstacles will be detailed.

Nanomaterials Used in Medical Applications

The success of nanomedicine is directly dependent on the physicochemical properties of the material selected during the design phase. A nanomaterial's chemical composition, size, shape, surface charge, and hydrophobic/hydrophilic balance determine its fate in biological systems. Nanomaterials used in medical applications are generally classified into three main categories as shown in Figure 1: (1) Organic (polymeric and lipid-based) systems, (2) Inorganic (metal and semiconductor) systems, and (3) Bio-based or hybrid systems. Each class has its own unique advantages and limitations in terms of "pharmacokinetic profile" (distribution in the body) and "biocompatibility" [8].

Figure 1. Basic classes of medical nanomaterials: Organic (left), biological/hybrid (middle), and inorganic (right) structures (Created by the author)



Organic Nanoparticles

Organic nanoparticles are structures composed of synthetic or natural polymers and lipids, which are generally biocompatible and biodegradable. This group represents the family that finds the most extensive application in clinical nanomedicine and hosts the majority of products that have received FDA approval. Their most significant feature is their capacity to encapsulate and transport both water-soluble (hydrophilic) and insoluble (hydrophobic) drugs [1].

Among organic nanoparticles, Liposomes are considered the one of the earliest developed nanocarriers of nanomedicine and arguably the most mature technology in the clinic. Structurally, they are spherical vesicles composed of phospholipid bilayers similar to the natural cell membrane. This architecture grants them a unique "dual transport" capability: hydrophilic drugs can be carried in the liposome's aqueous core, while hydrophobic drugs are sequestered within the fatty membrane layer (Figure 1) [4]. While the primary advantage of liposomes is their low toxicity, "naked" liposomes face the challenge of rapid recognition by Reticuloendothelial System (RES) cells in blood circulation, leading to breakdown in the liver. To overcome this, liposome surfaces are often coated with Polyethylene Glycol (PEG) polymers to create "Stealth" liposomes; Doxil® (doxorubicin-loaded liposome) stands as the first and most successful example of this technology in cancer treatment. Furthermore, Lipid Nanoparticles (LNP), the most advanced iteration of liposome technology, play a revolutionary role in vaccine development—a topic detailed in the context of new generation vaccines. LNPs utilize ionizable lipids to successfully deliver negatively charged mRNA molecules to the cytoplasm by overcoming the electrostatic repulsion of the cell membrane [1, 8].

Another significant class is Polymeric Micelles, which are nanostructures formed by the self-assembly of amphiphilic block copolymers in an aqueous environment. Above a certain concentration known as the Critical Micelle Concentration (CMC), these molecules spontaneously form spherical structures by orienting their hydrophobic tails inward and their hydrophilic heads outward [8]. The hydrophobic core of the micelle serves as an ideal reservoir for water-insoluble anticancer drugs, protecting them from the external environment during transport. The outer shell, usually consisting of hydrophilic polymers like PEG, ensures the micelle remains suspended in water. Typically, smaller than liposomes (10–100 nm), polymeric micelles possess an advantage in penetrating deep into tumor tissue via the EPR effect. Moreover, polymer chemistry allows for the creation of "stimuli-responsive" smart micelles that degrade and release their cargo upon sensing specific environmental triggers, such as the acidic pH ($pH < 6.5$) of the tumor microenvironment [10].

Distinct from the self-assembled structures are Dendrimers, which are highly symmetric, hyper-branched polymers that grow outward from a central core in a regular, tree-like fashion. Unlike linear polymers, dendrimers are synthesized with precise control, allowing for exact determination of their molecular weights and sizes (monodispersity) [8]. The surface of a dendrimer presents numerous functional groups (e.g., amine, carboxyl) that can be utilized like a "Swiss Army Knife": a cancer drug can be conjugated to one branch, an imaging agent to another, and a targeting ligand to a third. This multifunctionality makes dendrimers an excellent platform for theranostics. While PAMAM (polyamidoamine) dendrimers are the most commonly used type, their high positive charge density can induce cytotoxicity by damaging cell membranes. Therefore, surface modifications such as acetylation or PEGylation are critically important in clinical applications to mask these charges and ensure safety [10].

Inorganic Nanoparticles

Inorganic nanomaterials consist of metals (gold, silver), metal oxides (iron oxide), or semiconductors (quantum dots).

Possessing more stable structures compared to their organic counterparts, these particles stand out especially in diagnostic imaging and physical treatment methods (hyperthermia) due to their unique optical, magnetic, and electrical properties (Figure 1).

Among metal-based systems, Gold Nanoparticles (AuNPs) are particularly prominent. While gold is chemically inert and yellow at the macro scale, reducing it to the nanoscale (1–100 nm) imparts a unique optical property called Surface Plasmon Resonance (SPR), resulting from the resonance of free electrons with light. Thanks to this property, AuNPs can strongly absorb and scatter visible light and near-infrared (NIR) rays [11]. In medicine, these optical properties are utilized for high-contrast imaging in lateral flow tests (e.g., rapid pregnancy tests) and microscopy. Furthermore, their capacity to convert absorbed light energy into heat renders them indispensable for Photothermal Therapy (PTT) applications, which will be elaborated further [12].

Another critical metal-based nanomaterial is Silver Nanoparticles (AgNPs), known historically for antimicrobial properties but exhibiting significantly enhanced efficacy at the nanoscale due to increased surface area. AgNPs function by adhering to the bacterial cell wall to disrupt membrane integrity and entering the cell to inhibit respiratory enzymes. Additionally, the released silver ions (Ag^+) interact with bacterial DNA and proteins, thereby halting replication [13]. Consequently, AgNPs are widely used in wound dressings, burn creams, catheter coatings, and dental filling materials to prevent infection. However, careful dosing is required due to potential toxicity to mammalian cells and environmental accumulation [14].

In the realm of metal oxides, Superparamagnetic Iron Oxide Nanoparticles (SPIONs), consisting of magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3) cores, play a vital role. The term "superparamagnetic" indicates that these particles become magnetized only under an external magnetic field and lose this property when the field is removed, a feature crucial for medical safety as it prevents intravascular aggregation and occlusion [6]. SPIONs serve three primary functions: they enhance image clarity as T2-weighted contrast agents in Magnetic Resonance Imaging (MRI); enable magnetic targeting by collecting drug-loaded particles in tumor regions via external magnets; and facilitate magnetic hyperthermia, where particles vibrating under an alternating magnetic field (AMF) generate frictional heat to destroy tumor cells.

Finally, Quantum Dots (QDs) represent semiconductor nanocrystals ranging from 2 to 10 nm in size. Their most striking feature is the quantum confinement effect, where they emit fluorescent light in different colors depending on their size; for instance, a 2 nm QD emits blue light, while a 6 nm one emits red light. This tunable fluorescence allows for multiplexing, enabling the simultaneous imaging of multiple biological targets with a single light source [15]. Although they offer superior brightness and photostability compared to organic dyes, toxicity concerns regarding heavy metals (Cd, Se) in first-generation QDs have shifted current research focus toward non-toxic Carbon Quantum Dots and Graphene Quantum Dots.

Bio-based and Viral Nanoparticles

The future of nanomedicine is evolving from synthetic materials towards materials that "mimic nature" (biomimetic) or are obtained directly from nature. This approach aims to minimize immunological side effects while maximizing biocompatibility. Prominent among these bio-based materials are Chitosan and Polysaccharide-Based Nanoparticles. Chitosan, derived from the exoskeleton of crustaceans (e.g., shrimp, crab) via a deacetylation process, stands out as the sole cationic (positive-charged) polysaccharide found in nature. This unique positive charge facilitates strong electrostatic interactions with negatively charged cell membranes and mucosal layers, a property known as mucoadhesion. Such features render chitosan unique, particularly for drug transport to the brain via the intranasal route or in oral drug applications [5, 10]. Furthermore, chitosan nanoparticles exhibit pH sensitivity; they swell in acidic environments, such as tumor tissue, to release their drug payload. Being biodegradable, they are enzymatically broken down into non-toxic components and excreted from the body. Additionally, chitosan hybrids produced using plant extracts via green synthesis methods (e.g., Silver-Chitosan) represent modern wound-healing materials that combine eco-friendliness with high antimicrobial efficacy [10].

In parallel with polysaccharide-based systems, nanomedicine exploits the structural precision of Viral Nanoparticles (VNPs) and Virus-Like Particles (VLPs). Millions of years of evolution have refined viruses into biological "nanorobots" specialized in transporting genetic material into cells. Nanomedicine harnesses this natural ability by stripping viruses of their disease-causing properties. VNPs are essentially protein capsids obtained by removing the virus's genetic material (RNA/DNA), creating "hollow cages" that serve as natural nanocontainers for drug loading (Figure 1) [16]. VNPs derived from plant viruses, such as the Tobacco Mosaic Virus (TMV) or Cowpea Mosaic Virus (CPMV), are considered safe as they do not infect humans. Structurally, they possess an extremely symmetrical and uniform (monodisperse) size distribution, a level of standardization that is challenging to achieve with synthetic methods. Through genetic engineering, cancer-recognizing ligands can be chemically attached to the outer surface of the capsid, while drug molecules are loaded into the interior. This technology, termed "natural nanotechnology," offers exceptional precision in targeted drug delivery [16].

Nanodiagnostics: Early Diagnosis of Diseases

The oldest and unchanging rule of medicine is this: "Early diagnosis saves lives". However, traditional diagnostic methods (biochemical tests, microscopic examinations) can yield results when disease symptoms become clinically visible or when the number of pathogens exceeds a certain threshold in the body. Nanodiagnostics aims to change this paradigm and detect diseases "before they give symptoms," that is, at the level of a single molecule or a single cell. Diagnostic applications of nanotechnology challenge the limits of classical methods in terms of sensitivity, specificity, and speed [17]. Nanodiagnostic systems are basically examined in two main categories: (1) In vitro nanobiosensors detecting biomarkers in extracorporeal fluids (blood, urine, saliva), and (2) In vivo imaging agents imaging diseased tissue within the body. In this section, new generation diagnostic technologies moved from the laboratory environment to the bedside (point-of-care) and the working principles behind them will be detailed.

Nanobiosensors and Working Principles

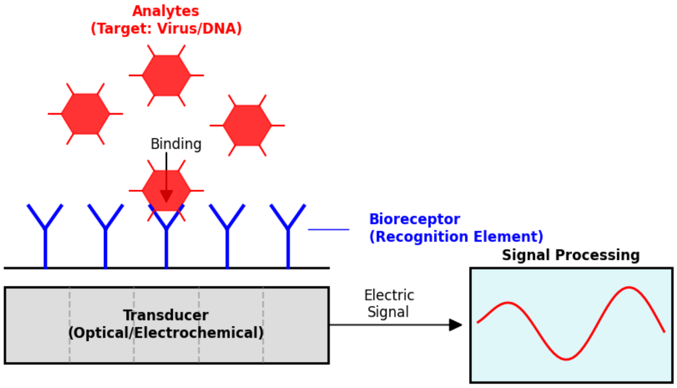
A biosensor is an analytical device that converts a biological reaction into a measurable electrical, optical, or thermal signal. The best-known example of classical biosensors is the glucometers used by diabetics. Nanobiosensors, on the other hand, pull detection limits to femtomolar (10^{-15} M) or even attomolar (10^{-18} M) levels thanks to the modification of the sensor surface with nanomaterials (gold nanoparticles, carbon nanotubes, graphene, etc.). This is a sensitivity equivalent to detecting a drop of ink in the ocean [17]. A nanobiosensor consists of three basic components as illustrated in Figure 2:

1. Bioreceptor (Recognition Element): It is the antibody, enzyme, aptamer, or DNA probe that binds

specifically to the target analyte (virus, cancer protein, DNA sequence).

2. Transducer: It is the part that converts the biochemical interaction (binding event) into a processable signal. The most critical role of nanomaterials begins here; because the high surface/volume ratio of nanomaterials allows more bioreceptors to bind per unit area and accelerates electron transfer.
3. Signal Processor: It is the electronic circuit that converts the resulting signal into data that the user can understand.

Figure 2. Schematic representation of the biosensor recognition and transduction mechanism (Created by the author)



Schematic Diagram of a Biosensor

Among the various transduction mechanisms, Electrochemical Nanobiosensors operate by measuring current (amperometric), potential (potentiometric), or impedance (impedimetric) changes resulting from the interaction between the target molecule and the bioreceptor. In these systems, carbon-based nanomaterials like Carbon Nanotubes (CNT) and graphene act as "electron highways" due to their excellent electrical conductivity. For instance, binding of a cancer antigen to an antibody on the sensor surface alters the electron flow, a change that is amplified thousands of times by nanomaterials. This amplification enables the early-stage detection of cancer markers (e.g., PSA, CA-125) at extremely low concentrations [18]. A significant advantage of these sensors is their potential for miniaturization and integration into portable "Lab-on-a-chip" systems, while paper-based microfluidic variants offer cost-effective and rapid diagnostic solutions, particularly for resource-limited regions [19].

In the realm of optical detection, Optical Biosensors rely on changes in light-matter interaction, such as absorption, reflection, refraction, or fluorescence. The most advanced technology in this field involves sensors based on Surface Plasmon Resonance (SPR). SPR is a phenomenon where light striking a metal surface (usually gold or silver) at a specific angle induces the vibration of free electrons (plasmons) [11]. In SPR sensors, the binding of a biomolecule to the surface causes a precise change in the refractive index, allowing for real-time monitoring of the binding event without the need for dyes or markers (label-free). Recent advancements as of 2025 utilize "Plasmonic Imaging" (SPRi) technology, capable of detecting single exosomes or circulating tumor cells (CTCs). Furthermore, the Localized SPR (LSPR) effect of gold nanoparticles significantly enhances sensitivity, enabling the diagnosis of infections with very low viral loads even during the incubation period [11, 17].

Next-Generation Diagnostic Tools: Quantum Sensors and Aerogel-Based Systems

As the limits of nanotechnology are pushed, new generation diagnostic tools emerge where the rules of classical physics are replaced by quantum mechanics rules, offering the promise of monitoring biological processes at atomic resolution. Leading this frontier are Quantum Biosensors, which carry measurement sensitivity to theoretical limits by utilizing phenomena such as quantum superposition and entanglement. Diamond Nitrogen-Vacancy (NV) Centers represent the most prominent example of this technology. These defects, formed by a nitrogen atom replacing a carbon atom in the diamond crystal lattice with an adjacent vacancy, create a structure that preserves its quantum properties even at room temperature [15]. NV centers are extremely sensitive to magnetic fields, capable of detecting the field generated during the firing of a single neuron or the structural changes during the folding of a single protein. This technology holds the potential to map brain activities (Magnetoencephalography - MEG) with much higher resolution than currently possible or to detect cardiac arrhythmias at the cellular level, paving the way for high-resolution imaging using portable devices without the need for massive MRI magnets [15].

Parallel to quantum advancements, Aerogel-Based Biosensors are redefining non-invasive diagnostics. Often referred to as "frozen smoke," aerogels are extremely light and porous solids composed of approximately 99% air. Nanotechnology-enabled silica, carbon, or polymer-based aerogels possess enormous surface areas (over 1000 m^2/g), making them excellent candidates for applications such as breath analysis [20]. Since human breath contains volatile organic compounds (VOCs) that serve as biomarkers for diseases like lung cancer or diabetes, the spongy structure of aerogels allows them to capture these gas molecules at extremely low concentrations (parts per billion). In operation, carbon or metal-oxide doped aerogels interact with captured gas molecules, creating a measurable change in electrical resistance. This technology heralds a new diagnostic era where detecting complex diseases could be as simple and non-invasive as "blowing a breath" [20].

In Vivo Imaging and Contrast Agents

Detecting disease outside the body (in vitro) is merely the first step; however, visualizing the location, size, and spread of the pathology inside the body (in vivo) is essential for effective treatment planning. Existing imaging techniques such as MRI, CT, and Ultrasound often fail to detect early-stage tumors or metastases due to insufficient tissue contrast. Nanoparticles address this limitation by acting as advanced contrast agents that significantly sharpen the resolution and sensitivity of these devices.

In the realm of soft tissue imaging, Magnetic Resonance Imaging (MRI) is considered the gold standard, yet its sensitivity can be enhanced further. Superparamagnetic Iron Oxide Nanoparticles (SPIONs) improve contrast by shortening the T2 relaxation times of water protons in their vicinity through the creation of a strong magnetic moment. This effect ensures that regions of nanoparticle accumulation, such as tumors, appear darker and more distinct in MRI scans [6]. Unlike traditional gadolinium-based agents, SPIONs are biocompatible and integrate into the body's natural iron metabolism. Furthermore, by coating their surfaces with tumor-specific ligands for active targeting, they can be transformed into "smart contrast agents" that selectively highlight cancerous tissue, enabling the detection of even millimeter-sized metastases.

While optical imaging offers the advantages of being harmless and providing real-time monitoring, it is traditionally limited by tissue depth. Quantum Dots (QDs) are overcoming this barrier, replacing organic dyes due to their size-tunable fluorescence emission, high brightness, and photostability [12]. Particularly, QDs emitting in the Near-Infrared (NIR) region facilitate imaging of deeper tissues by operating within the "optical window" (650–900 nm) where biological tissues are relatively transparent. A critical application of this technology is "Tumor Painting," where injected QDs cause cancerous tissue to glow during surgery. This guidance allows surgeons to clearly distinguish tumor boundaries, ensuring the complete removal of malignant tissue while preserving healthy structures [15].

For dense tissues like bone, Computed Tomography (CT) utilizing X-rays is highly effective, though it often lacks sufficient soft tissue contrast. Gold Nanoparticles (AuNPs), with their high atomic number (Z=79) and electron density, absorb X-rays significantly more strongly than conventional iodine-based contrast agents. This property allows AuNPs to remain in circulation longer, providing detailed mapping of vascular structures (angiography) and tumor vasculature. Additionally, AuNPs offer a theranostic advantage by focusing radiation on the tumor during radiotherapy (radiosensitization), thus combining diagnosis and treatment [11, 21]. Consequently, nanodiagnostics enhances the sensitivity and speed of medical diagnosis across a broad spectrum, ranging from sensors capable of detecting single molecules to illuminated nanoparticles guiding surgical precision, ultimately maximizing treatment success by identifying diseases before symptoms manifest.

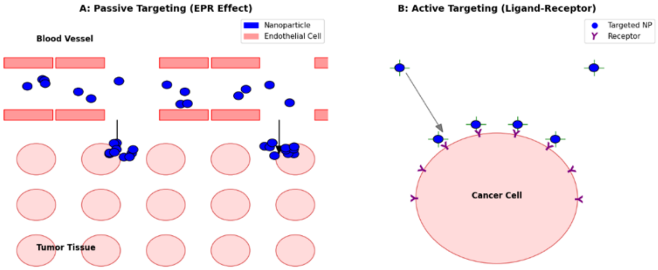
Nanotherapeutics And Targeted Drug Delivery Systems

One of the biggest paradoxes of medicine is that the treatment itself can sometimes be as destructive as the disease. Traditional pharmacotherapy, especially chemotherapeutics used in cancer treatment, is distributed systemically when given to the body and affects both diseased and healthy cells indiscriminately. This situation can lead to dose-limiting toxicity, serious side effects (hair loss, bone marrow suppression, organ failure), and ultimately the discontinuation of treatment. Nanotherapeutics are "magic bullets" developed to solve this problem, aiming to deliver drug molecules only to the target tissue by trapping them inside nano-sized carriers. This approach protects healthy tissues and maximizes treatment efficacy while increasing the bioavailability of the drug [2]. The success of nanotherapeutic systems depends on how well we can control the journey of the drug inside the body. This control is carried out mainly through two main strategies: Passive and Active targeting.

Drug Delivery Mechanisms: Passive (EPR) and Active Targeting

The arrival and accumulation of a nanoparticle in tumor tissue following intravenous injection is not a random occurrence; rather, it relies on precise mechanisms jointly determined by tumor biology and particle physics, as illustrated in Figure 3. The primary mechanism, known as Passive Targeting, is driven by the "Enhanced Permeability and Retention (EPR)" effect. Tumors are characterized by uncontrolled and rapid growth, necessitating the secretion of signals like VEGF to trigger angiogenesis. However, these hastily formed vessels possess irregular, wide fenestrations ranging from 100 nm to 2 microns, unlike the tight junctions of healthy vasculature. Concurrently, the lymphatic drainage system within the tumor is often impaired or non-existent [8]. These two anomalies synergize to create the EPR effect: the vascular permeability allows 20–200 nm sized nanoparticles to leak through the fenestrations into the tumor tissue, while the lack of lymphatic drainage ensures their retention within the tissue (Figure 3A). Despite forming the basis of passive targeting, the EPR effect is subject to significant variability due to tumor heterogeneity and does not guarantee cellular internalization, which necessitates further strategies [5].

Figure 3. Comparison of drug delivery mechanisms: (A) Passive targeting via the EPR effect, and (B) Active targeting via specific ligand-receptor interaction (Created by the author)



To overcome the limitations of passive accumulation, Active Targeting employs a "key-lock" approach by equipping the nanoparticle surface with specific ligands that bind to receptors overexpressed on target cells (Figure 3B). This modification prolongs retention in the tumor tissue and facilitates receptor-mediated endocytosis. Principal targeting ligands include Monoclonal Antibodies, such as Trastuzumab targeting the HER2 receptor, which offer the highest specificity. Alternatively, Aptamers—folded DNA or RNA sequences—provide a smaller, cost-effective, and less immunogenic option compared to antibodies. Small molecules like vitamins also play a crucial role; for instance, Folic Acid is widely used because rapidly dividing cancer cells possess significantly more folate receptors than normal cells, causing them to avidly internalize folate-coated nanoparticles [10].

Beyond spatial localization, effective therapy requires temporal control, a concept realized through Stimuli-Responsive (Smart) Release. An ideal nanotherapeutic must retain its payload during circulation and release it solely at the target site. To achieve this, "Smart" nanoparticles have been developed to respond to specific internal stimuli. For example, pH-sensitive systems utilize polymers like chitosan that swell or dissolve in the acidic environment of tumor tissue and intracellular endosomes (pH 5.0–6.5), triggering drug release. Similarly, enzyme-sensitive systems employ linkers that are selectively cleaved by tumor-secreted enzymes, such as matrix metalloproteinases, ensuring the drug is liberated only within the malignant microenvironment [22].

Nanomedicine in Cancer Treatment: Chemotherapy and Targeting Cancer Stem Cells

Cancer is not a single entity but a complex ecosystem containing not only rapidly dividing tumor cells but also Cancer Stem Cells (CSCs) responsible for tumor recurrence. Nanomedicine offers advanced strategies to combat this disease on both fronts. In the realm of Nano-Chemotherapy, a significant challenge is that most classical chemotherapy drugs (e.g., Paclitaxel, Doxorubicin, Cisplatin) are hydrophobic, meaning they do not dissolve in water. Consequently, administering these drugs requires toxic solvents like Cremophor EL, which often lead to serious allergic reactions. Nanoparticles such as liposomes and micelles solve this by dissolving hydrophobic drugs within their cores, transforming them into safe, water-based formulations. A prominent example is Abraxane®, a formulation of paclitaxel combined with human serum albumin. Since albumin is a protein that tumor cells require as a nutrient, they uptake the drug-loaded nanoparticle under the guise of "food." This "Trojan horse" approach significantly increases drug efficacy while eliminating solvent-derived side effects [4].

While traditional chemotherapy effectively shrinks the bulk tumor mass, recurrence is common months or years later. The primary drivers of this relapse are Targeting Cancer Stem Cells (CSCs), which reside deep within the tumor and exhibit resistance to chemotherapy. Functioning like "queen bees," CSCs possess the ability to self-renew, differentiate into various cell types, and reinitiate tumor growth. As highlighted by Ertas et al. (2021), CSC resistance stems from three main mechanisms: transporter proteins (efflux pumps) that eject drugs from the cell, a hypoxic niche located far from blood vessels that limits drug access, and highly efficient DNA repair mechanisms [7]. Nanotechnology addresses these challenges with specialized targeting strategies. One such strategy is CD44 Targeting; since the CD44 receptor is overexpressed on CSC surfaces, nanoparticles coated with its natural ligand, Hyaluronic Acid (HA), can bind directly to CSCs to deliver therapeutic agents. Another approach is Combination Therapy, where nanoparticles co-deliver chemotherapy drugs and genetic materials (e.g., siRNA) to dismantle resistance mechanisms simultaneously—for instance, silencing drug efflux pumps before releasing the lethal drug. Finally, Niche Targeting leverages the small size of nanoparticles to penetrate deep, hypoxic tumor regions inaccessible to free drugs, effectively striking CSCs in their hidden sanctuaries [7].

Physical Treatment Methods: Magnetic and Photothermal Hyperthermia

The most revolutionary aspect of nanomedicine is that it can not only transport drugs but also destroy the tumor using its own physical properties. "Hyperthermia" (overheating) is the process of killing tumor cells by exposing them to temperatures of 42-45°C. Cancer cells are much more sensitive to heat than healthy cells due to weak vascular structures and insufficiency of heat shock proteins.

One prominent method utilizing this principle is Magnetic Hyperthermia, which is performed using Superparamagnetic Iron Oxide Nanoparticles (SPIONs). After these particles are injected into the tumor tissue or targeted, a high-frequency Alternating Magnetic Field (AMF) is applied from outside the patient's body. Under the effect of the magnetic field, SPIONs generate heat via two mechanisms: Néel Relaxation, where the magnetic moment (spin) inside the nanoparticle constantly changes direction to align with the external magnetic field and loses energy during this time; and Brown Relaxation, where the nanoparticle itself physically rotates within the fluid it is in and creates friction heat. This method provides a great advantage in the treatment of tumors deep in the body (e.g., Glioblastoma in the brain) because the magnetic field passes harmlessly through human tissues. As stated by Gholami et al. (2020), surface modification of SPIONs (e.g., silica or polymer coating) both prevents clumping of particles and increases heat production efficiency (Specific Absorption Rate - SAR) [6]. In clinical studies, it has been shown that magnetic hyperthermia significantly increases survival rates when combined with radiotherapy [6].

Alternatively, Photothermal Therapy (PTT) utilizes materials like Gold Nanoparticles (AuNPs), carbon nanotubes, or graphene that convert light into heat. The basis of this method lies in the Surface Plasmon Resonance (SPR) property of metallic nanoparticles. After particles accumulate in the tumor, a Near-Infrared (NIR) laser (700–1100 nm wavelength) is directed at the region. NIR light passes through tissue and blood with minimum absorption, a phenomenon known as the "Biological Window." However, gold nanoparticles strongly absorb this light and radiate intense heat to their surroundings within seconds. This localized heat burns (ablation) only the cancer cells in the millimeter area where the nanoparticles are located, leaving surrounding tissues undamaged. PTT's biggest advantage is its suitability for the "See and Treat" (Theranostic) approach. Since gold nanoparticles are also contrast agents, the doctor can first turn on the laser at low power to visualize the exact location of the tumor, then increase the power to destroy it. Furthermore, bio-degradable PTT agents developed in recent years (e.g., Prussian Blue nanoparticles or organic polymers) have enhanced the safety profile of this treatment by eliminating the risk of long-term metal accumulation [12, 23].

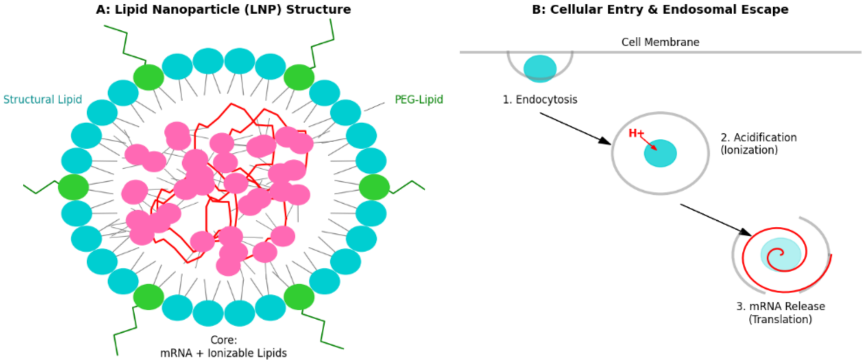
New Generation Vaccine Technologies and Gene Delivery

The year 2020 has gone down in history as a turning point where nanomedicine ceased to be a "promised technology" and became a "life-saving necessity" in modern medical history. The BioNTech/Pfizer and Moderna vaccines developed against the global pandemic caused by the SARS-CoV-2 virus are not only a biology victory but also a nanotechnology engineering marvel. The mRNA technology at the center of these vaccines relies on the safe delivery of genetic material to the human cell. However, injecting "naked" (unprotected) nucleic acids (DNA or RNA) into the body is medically inefficient; because these molecules are broken down within seconds by nuclease enzymes in the blood and cannot enter the cell due to the negative charge of the cell membrane. The key technology solving this problem is nanovectors that package the genetic code and deliver it to the target [1]. Nanomedicine-based gene delivery not only develops vaccines against infectious diseases; it also allows for genetic disorders called "incurable" (e.g., Cystic Fibrosis, Spinal Muscular Atrophy) to be corrected at the root with gene therapy. In this section, Lipid Nanoparticles, pivotal role in the pandemic response and viral/non-viral vector systems shaping the future of gene therapy will be examined.

Lipid Nanoparticles (LNPs) and mRNA Vaccines

Lipid Nanoparticles (LNPs) are nano-carriers developed for the transport of nucleic acids, representing a more advanced and complex derivative of liposomes. While classical liposomes can be described as "bubbles filled with water," LNPs are denser and more stable structures where lipids and nucleic acids are organized in a complex internal arrangement. The success of COVID-19 vaccines relies heavily on precise engineering in the chemical design of these particles [2]. In an mRNA vaccine, while the genetic code provides the blueprint for the virus's "Spike" protein, the core technology enabling its delivery is the LNP sphere, approximately 80–100 nm in size, that encapsulates it. As stated by Jain and Sharma (2021) and illustrated in Figure 4A, a clinically successful LNP consists of four fundamental components [1]. The most critical of these is the Ionizable Cationic Lipid. According to Muthukumar's (2023) "physics of charged macromolecules" principles, a positively charged lipid is required to package negatively charged mRNA [8]. However, to avoid the toxicity associated with permanently charged lipids, scientists developed pH-sensitive "ionizable" lipids. These molecules become positively charged in acidic environments ($pH < 6$), such as during production or inside cellular endosomes, allowing them to bind mRNA tightly, but revert to a neutral state in blood circulation (pH 7.4) to ensure safe transport. This core is stabilized by PEG-Lipids, which form a "hydrophilic shield" to prevent aggregation and immune clearance (Stealth effect), along with Phospholipids (DSPC) and Cholesterol that provide structural integrity and facilitate membrane fusion.

Figure 4. Structure and delivery mechanism of LNPs. (A) mRNA-loaded core within a PEGylated lipid shell. (B) Endocytosis and pH-dependent release of mRNA into the cytoplasm (Endosomal Escape) (Created by the author)



Upon administration, the function of LNPs extends beyond transport; they must successfully deliver the mRNA into the cytoplasm, the cell's protein production center. This intracellular journey unfolds in three key steps as depicted in Figure 4B. First, the cell engulfs the LNP into a vesicle known as an endosome via Endocytosis. This leads to the most critical stage, Endosomal Escape. As the cell attempts to digest the foreign material, the interior of the endosome becomes acidic. Sensing this pH drop, the ionizable lipids within the LNP revert to a positively charged state and interact with the negatively charged endosomal membrane, causing it to rupture. Finally, in the Translation phase, the released mRNA enters the cytoplasm where it is read by ribosomes to produce the viral protein, which the immune system subsequently identifies as an antigen [1, 2]. This sophisticated mechanism stands as a prime example of how nanotechnology can precisely manipulate biological processes at the molecular level.

Viral and Non-Viral Vectors for Gene Therapy

While vaccines are used to introduce a foreign protein to the body; Gene Therapy is used to change or repair a damaged or missing gene. This process is much more difficult than vaccination because the genetic material usually needs to reach the cell nucleus and remain permanent there. Nanomedicine offers two different carrier (vector) strategies for this purpose: Nature's own nanorobots, Viruses, and human-made Synthetic Nanoparticles.

Viral vectors represent nature's engineering; millions of years of evolution have specialized viruses in inserting genetic material into cells. Scientists have transformed them into safe carriers by removing the disease-causing replication genes and substituting them with therapeutic genes. Adeno-Associated Viruses (AAV) are utilized in most of the FDA-approved gene therapies today, such as Luxturna for blindness treatment and Zolgensma for SMA treatment. AAVs are approximately 20–25 nm in diameter, can infect non-dividing cells like neurons, and can remain inside the nucleus without integrating into the human genome. Another viral vector type, Adenoviruses, is widely used in COVID-19 vaccines (e.g., Oxford/AstraZeneca, Sputnik V). Since they create a very strong immune response, they are ideal for vaccines but can be disadvantageous for long-term gene therapy. Despite their efficiency, the biggest problem of viral vectors is immunogenicity. The body can produce antibodies against the virus capsid itself, which makes repeating the treatment impossible. Additionally, the gene size that can be loaded into viruses is limited due to low cargo capacity, and production costs are remarkably high [16].

The safety concerns and production limitations of viral vectors have necessitated the development of completely synthetic "Non-Viral" systems, demonstrating the power of nanomedicine. These systems are produced in the laboratory with nanotechnological methods, stimulate the immune system less, and can theoretically carry genes of unlimited size. Cationic Polymers, with Chitosan and Polyethyleneimine (PEI) being the leaders, form nano-sized particles by wrapping the negatively charged DNA/RNA helix like a ball of yarn, a process known as polyplex formation. Chitosan, due to being biocompatible and biodegradable, is promising especially in gene delivery via the mucosal route (nose). Swain and Biswal (2023) emphasize that chitosan nanocomposites protect genes from enzyme attack and increase cellular uptake [10]. Furthermore, Inorganic Nanoparticles such as Gold nanoparticles (AuNPs) and Magnetic nanoparticles can be utilized as gene carriers. Especially in the "Gene Gun" method, DNA-coated gold particles are fired at high speed into the tissue to provide gene transfer. Similarly, magnetic particles can be collected in the desired tissue by applying an external magnetic field, a technique known as Magnetofection.

The final frontier in gene therapy is the gene editing technology CRISPR/Cas9, which repairs the defective gene in situ instead of replacing it. However, the CRISPR system (Cas9 protein and guide RNA) is a large macromolecular complex that is very difficult to transport into the cell. Nanomedicine solves this problem by packaging CRISPR components into LNPs or gold nanoparticles. In recent studies [2], it has been shown that LNP-transported CRISPR systems successfully corrected sickle cell anemia and some hereditary liver diseases in mouse models by over 90%. This serves as proof that nanotechnology has become a tool capable of rewriting our genetic destiny. Consequently, the boundary between vaccines and gene therapy has blurred thanks to nanotechnology. Whether to gain immunity against a virus or to repair a faulty gene, the solution passes through delivering the right genetic code to the right address with the right nano-courier.

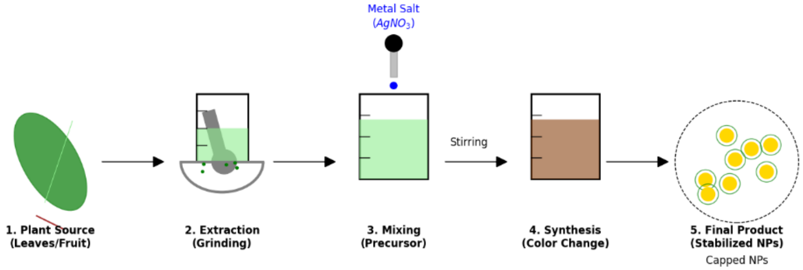
Sustainable Nanomedicine: Green Synthesis Approaches

The medical paradigm of the 21st century is changing; it is no longer sufficient to just "cure the patient," it is also a necessity for this healing process to be carried out "without harming the environment". Traditional nanotechnology methods often use toxic reducing chemicals like sodium borohydride or hydrazine, physical processes requiring high energy (laser ablation, high temperature), and organic solvents harmful to the environment in nanoparticle production. This situation causes both the accumulation of toxic residues on the surface of produced nanomaterials (which lowers biocompatibility) and the formation of serious amounts of hazardous chemical waste. In the context of the "Environment and Health" theme discussed in this book, nanomedicine's escape from this paradox is possible through the adoption of "Green Nanotechnology" principles [24]. Green synthesis or biogenic synthesis aims to use nature's own factories (plants, bacteria, fungi) in the production of nanomaterials, minimize energy consumption, and reduce toxic waste production to zero. This approach is not only an environmental sensitivity but also the most rational way to obtain safer (biocompatible) products in clinical applications.

Nanoparticle Production with Plant Extracts

Using plants in nanoparticle production, also known as Phyton-synthesis, offers significant advantages over microbial methods because it eliminates the need for aseptic laboratory conditions, complex cell culture maintenance, and rigorous biosafety measures. In this process, often referred to as the "One-pot" synthesis method, the extract of a plant leaf, root, or fruit is simply mixed with a metal salt solution (e.g., silver nitrate), allowing nanoparticle formation to occur naturally at room temperature (Figure 5) [14].

Figure 5. Schematic of plant-mediated green synthesis: Extraction, precursor mixing, bioreduction, and formation of phytochemical-capped nanoparticles (Created by the author)



The underlying mechanism of this process involves simultaneous Reduction and Capping. As detailed by Radulescu et al. (2023), plant extracts are inherently rich in phytochemicals such as polyphenols, flavonoids, terpenoids, alkaloids, and sugars, which undertake two critical roles simultaneously [14]. First, they act as reducing agents, reducing metal ions (M^+) to their metallic form (M^0). For instance, phenolic groups in the plant donate electrons to convert silver ions (Ag^+) into metallic silver (Ag^0). Second, these same molecules function as capping or stabilizing agents. They prevent aggregation by wrapping around the surface of the formed nano-sized nuclei. This natural coating ensures the particle size is kept under control and prevents precipitation over time, effectively eliminating the need for toxic stabilizers like CTAB used in chemical synthesis. Ultimately, the resulting nanoparticle carries a "bio-corona" of plant-specific healing molecules, which enhances its biological activity through a synergistic effect.

In terms of specific applications, the most commonly studied green synthesis product is Silver Nanoparticles (AgNPs). A prime example is the work by Alwhibi et al. (2021), who synthesized AgNPs using *Aloe vera* gel [13]. Their study demonstrated that bioactive components within the *Aloe vera* extract rapidly reduced silver ions, resulting in 50–100 nm sized spherical particles with strong antimicrobial properties. These particles offer potential as eco-friendly dressing materials for infected wounds by combining the ionic effect of silver with the wound-healing properties of *Aloe vera*. Similarly, Gold Nanoparticles (AuNPs) can be synthesized using tea leaves, turmeric (curcumin), or grape seed extracts. Plant-derived AuNPs are generally perceived as less toxic by cells compared to chemically produced counterparts and can be safely utilized as photothermal treatment agents in cancer therapy [21].

The adoption of green synthesis offers distinct advantages over traditional methods. Economically, it allows for the utilization of renewable plant wastes, such as banana or orange peels, instead of expensive chemicals and energy-intensive devices. From a production standpoint, the process is highly scalable and can be easily adapted to large reactors for industrial-scale manufacturing. Finally, regarding biocompatibility, the absence of toxic residues on the particle surface significantly lowers the risk of immunological reactions in *in vivo* applications, making these materials safer for clinical use.

Biodegradable and Eco-Friendly Nanomaterials

The environmental concerns of nanomedicine is the potential "nano-waste" problem, characterized by residues remaining in the body or mixing with wastewater after treatment. Inorganic materials like gold, silver, or carbon nanotubes do not naturally degrade (non-biodegradable), and their long-term bioaccumulation can lead to chronic toxicity and disruption of ecological balance. Consequently, the primary goal of sustainable nanomedicine is to develop biodegradable systems that naturally decompose into harmless components after completing their therapeutic duty [24].

The material most suitable for addressing this environmental imperative is undoubtedly Chitosan, representing a transformation from waste to cure. Chitosan is derived from the shells of crustaceans (shrimp, crab), a byproduct that constitutes a significant waste challenge for the food industry. Swain and Biswal (2023) highlight chitosan as a "super material" in the biomedical field [10]. Physiologically, when chitosan nanoparticles are administered, they are enzymatically broken down into non-toxic glucosamine and N-acetylglucosamine units by tissue lysozymes. These byproducts can be utilized by the body for cartilage synthesis or excreted via the metabolic Krebs cycle. From an environmental perspective, chitosan-based nanomaterials are rapidly mineralized by soil bacteria upon disposal, thereby preventing pollution.

Beyond chitosan, plant polysaccharides like Starch and Cellulose are also fundamental building blocks of green nanomedicine. As stated by Hasanin et al. (2023), starch-based nanocapsules or biosensors are derived from sustainable sources, unlike petroleum-based plastics, and possess full biodegradability [25]. For instance, porous nano-carriers produced from corn starch convert into glucose after drug release, serving as an energy source for the body. Similarly, protein-based systems such as viral nanoparticles (VNPs) and albumin carriers are degraded into amino acids by protease enzymes. This approach aligns perfectly with the "Zero Waste" principle in medicine.

To ensure true sustainability, the environmental impact of nanomedical products must be evaluated not merely at the production stage but through a Life Cycle Assessment (LCA) with a "Cradle-to-Grave" perspective—encompassing the entire process from raw material acquisition to waste management. Green synthesis methods are currently the most successful area of this analysis, significantly reducing energy consumption and carbon footprint.

Looking forward, legal regulations by agencies like the FDA and EMA are expected to focus not only on drug efficacy but also on the environmental footprint of production and the ultimate fate of the material in nature. In this context, "Hybrid Green Nanoparticles," synthesized with plant extracts and reinforced with biodegradable polymers, offer a holistic solution that protects both human health and the ecosystem.

Nanomedicine In the Clinic, Regulations, And Future

When scientific literature is scanned, hundreds of thousands of articles on the potential of nanomedicine are encountered. However, compared to this huge accumulation of knowledge, the number of nanomedical products that have taken their place on pharmacy shelves or entered routine use in hospitals is surprisingly low. This inefficiency in the process of transferring academic research (bench) to the patient bed (bedside) is termed the "Valley of Death" in the literature. Between a nanotherapy agent destroying cancerous cells in a petri dish in the laboratory and working as a safe and effective drug in the human body, there are huge biological, technological, and legal chasms that need to be overcome. In this final section, bottlenecks in the transition process of nanomedicine from laboratory to clinic, standards brought by regulatory institutions like FDA (US Food and Drug Administration) and EMA (European Medicines Agency), and the transformative role Artificial Intelligence (AI) technologies play in overcoming these difficulties will be examined.

Challenges in Transition from Laboratory to Clinic (FDA Processes)

The clinical translation of nanomedical products is significantly more complex than that of traditional small-molecule drugs like Aspirin. According to the comprehensive analysis by

Younis et al. (2022), these difficulties can be grouped under three main headings: Production and Quality Control (CMC) problems, insufficiency of preclinical models, and regulatory uncertainties [4].

The first major hurdle is Scale-Up and Production Consistency. In academic laboratories, nanotherapy agents are generally synthesized on a milligram scale in precisely controlled small reactors. However, clinical use necessitates kilogram-scale production. When the scale is increased, physicochemical properties such as size distribution, surface charge, and drug loading capacity generally undergo changes. Younis et al. (2022) emphasize that the "batch-to-batch reproducibility" problem is the biggest obstacle in FDA approval processes [4]. Engineering a complex nanostructure—for instance, a liposome coated with antibodies and filled with drugs—with exactly identical features in every production batch is extremely difficult. Even a 5% deviation in size can dramatically alter the drug's distribution in the body, blood circulation time, and toxicity. Consequently, the lack of facilities capable of producing at Good Manufacturing Practices (GMP) standards, combined with inadequate quality control methods, causes many promising nanodrugs to be eliminated before reaching Phase 1 clinical trials.

Another critical challenge involves Preclinical Models and the "EPR Paradox". The vast majority of nanomedicine research is conducted on mouse models, specifically xenograft models where human tumors are implanted into mice to monitor nanoparticle accumulation. Tumors grow very rapidly in mice, and the EPR effect (Enhanced Permeability and Retention), the mechanism of which was detailed earlier, works perfectly in these models. The weak lymphatic systems and highly permeable vessel structures of mice allow nanoparticles to accumulate in the tumor at a rate of 10–20%. However, human tumors are biologically distinct from those in mice;

they grow slower, possess a denser connective tissue (stroma), and exhibit vascular permeabilities that show great variability from patient to patient. Consequently, the passive targeting strategy that provides high success in mice generally fails to yield the expected efficiency in human clinical trials, with tumor accumulation sometimes falling below 1%. In the literature, this discrepancy is termed the "EPR Paradox". To increase translation success, Younis et al. (2022) state that it is essential to utilize "Organ-on-a-chip" systems or 3D tumor spheroids that better mimic human physiology, replacing misleading mouse models [4].

Finally, Legal Regulations and "Nanosimilars" present significant obstacles. Regulatory bodies like the FDA and EMA have long struggled with whether to classify nanomedical products as "drugs" or "medical devices". Currently, nanodrugs are generally evaluated under the "complex generics" or "combination products" class, yet a universal regulatory framework for nanomaterials remains not fully established. This issue is particularly debated regarding the production of generic versions, known as "Nanosimilars," of nanodrugs whose patent terms have expired (e.g., Doxil®). For classical drugs, demonstrating that the chemical formula of the generic product is identical (bioequivalence) is sufficient. However, for nanodrugs, even if the chemical formula is identical, the slightest difference in production technique—such as mixing speed or temperature—can alter the particle's 3D structure and, consequently, its biological effect. Therefore, the FDA demands not only chemical analysis but also much more comprehensive and costly clinical comparison tests from nanosimilar manufacturers [4].

Integration of Artificial Intelligence and Nanomedicine

The complexity and data intensity encountered by nanomedicine has begun to exceed the processing capacity of human intelligence. At this point, Artificial Intelligence (AI) and Machine

Learning (ML) step in. Das and J (2023) define the merging of AI and nanotechnology as the "Future Convergence of Medicine" [26]. This integration provides a transition from the trial-and-error (Edisonian) approach to rational design.

One of the most transformative applications of this convergence is In Silico Design and Nano-Informatics. In the traditional method, researchers would synthesize a nanoparticle, test it in cellular models, and if it failed, alter parameters to synthesize it again. This iterative process takes years and leads to a significant waste of resources. AI algorithms, on the other hand, can predict in a computer environment (in silico) which polymer will provide the best compatibility with a specific drug or which surface coating will minimize blood protein adsorption (protein corona) by scanning massive databases known as Nano-informatics. For example, Das & J (2023) convey that deep learning algorithms can predict whether a nanoparticle will accumulate in the liver or the tumor with over 90% accuracy by analyzing its size, charge, and hydrophobicity data [26]. In this way, thousands of candidates are eliminated virtually before being synthesized in the laboratory, and only formulations with the highest probability of success are advanced to production.

Furthermore, AI facilitates Patient Stratification and Personalized Nanomedicine, addressing a major cause of clinical trial failure: testing the drug in the "wrong patient group." Tumor biology and vascular structure exhibit significant heterogeneity among patients; while the EPR effect is robust in some, it is weak in others. AI can determine in advance which patient will respond to nanotherapy by analyzing genetic data, histopathological images, and radiological scans. Das & J (2023) term this approach "Artificial Intelligence Supported Precision Medicine" [26]. For instance, an AI algorithm analyzing vessel density in a patient's MRI images can provide a critical warning, such as "Nanodrug cannot penetrate the tumor in this patient, apply another treatment" [26]. This predictive capability prevents unnecessary drug administration and significantly increases the success rate of clinical trials.

Conclusion and Outlook

Nanomedicine, discussed in this chapter of the book "Nanotechnological Approaches in Energy, Environment and Health," has ceased to be a science fiction fantasy and transformed into one of the most powerful weapons in humanity's struggle for survival, as evidenced by the rapid development of COVID-19 mRNA vaccines. In light of the topics examined throughout the chapter, fundamental predictions regarding the future of nanomedicine suggest a transformative trajectory characterized by the removal of interdisciplinary boundaries. Future nanomedicine will evolve into an ecosystem where material scientists, biologists, physicians, and data engineers (AI experts) collaborate closely, making it mandatory to blend biophysical rules [8] with clinical realities [4] and digital intelligence [26].

In accordance with the main theme of this book, the field is expected to shift towards "Green" and sustainable solutions. Nanomedicine will not only cure humans but will also transform into an environmentally sensitive industry by adopting "Green Synthesis" methods in production processes, where biodegradable materials like chitosan and starch will serve as solutions to the growing medical waste problem. Furthermore, the standard of care will likely transition from treating diseases after symptoms appear to a "Theranostic" and preventive approach, utilizing nanodiagnostic sensors such as quantum sensors and wearable technologies to detect and destroy pathologies at a very early stage. Looking further ahead, the development of smart and autonomous systems may lead to the first clinical trials of nanorobots (micro-swimmers) capable of circulating inside the body, producing their own energy via nanogenerators, and making autonomous decisions—such as measuring glucose to secrete insulin or identifying cancer cells to release therapeutic agents.

Consequently, nanotechnology represents the engineering of medicine at the molecular level. Although the biological barriers, production difficulties, and legal obstacles encountered are significant, the promise of "a longer and healthier life" offered by this technology is worth every effort. The smallest scale of science—nano—will undoubtedly continue to be the solution to humanity's biggest problems, ranging from cancer and pandemics to genetic diseases.

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NANOTECHNOLOGY AND DENTISTRY/BIOMATERIALS

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Introduction

Nanotechnology represents a scientific and technological discipline that focuses on structures and particles at the nanometer scale. It aims to examine and deliberately manipulate the physical, chemical, and biological properties of materials when they are engineered at this extremely small dimension. According to the United States National Nanotechnology Initiative, nanotechnology involves controlling and processing matter with at least one dimension ranging between 1 and 100 nanometers (nm). A nanometer-equivalent to one billionth of a meter (10^{-9} m)-is typically used to describe dimensions approaching the atomic scale [1].

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Nanotechnology is a broad, multidisciplinary field that brings together principles from physics, chemistry, biology, engineering, and information technologies, with its conceptual roots extending back to late-19th-century research on colloidal science. The term *nanotechnology* was first introduced into the scientific literature by Prof. K. Eric Drexler in 1977. Functioning at the atomic and molecular scale, this technology provides a wide spectrum of applications, including biotechnology, nanorobotics, and the preservation of oral health. Harnessing the unique behaviors of materials at the nanoscale enables the development of novel substances with enhanced and superior properties. Despite operating at extremely small dimensions, nanotechnology holds remarkable potential for both scientific investigations and industrial innovations, shaping significant expectations for future technological advancement [2].

R.A. Freitas Jr. introduced the concept of *nano-dentistry* into the literature in 2000. In his visionary work, Freitas proposed advanced future applications such as the integration of nanorobots in orthodontic procedures, the regeneration of dental tissues, the development of novel nanomaterials, and the use of microrobotic systems in tooth-cleaning products. Although many of these ideas were perceived as largely speculative or even science-fiction at the time, contemporary developments demonstrate that several of these concepts are gradually becoming attainable. Indeed, numerous nanotechnology-based innovations are now being defined within the field of dentistry and are used for both clinical and research purposes [3].

Applications of Nanotechnology in Dentistry

Nano-dentistry encompasses innovative diagnostic, therapeutic, and preventive strategies for oral diseases through the use of nanoscale materials and nanotechnological approaches.

Within this field, nanosized materials, biotechnological products, tissue engineering constructs, and dental nanorobots are anticipated to support various clinical procedures. Future dental nanorobots are envisioned to possess mobility systems capable of navigating within tissues by responding to environmental stimuli, as well as simplified onboard processors. Communication between these devices and external instruments is expected to occur via acoustic signaling.

Although nano-dentistry remains an emerging discipline, these technologies hold the potential to make many processes-currently addressed through conventional methods-more efficient, comfortable, and precisely targeted. The possible applications of nanotechnology in dentistry span a wide spectrum, including the use of nanoscale restorative and therapeutic materials, advancements in local anesthesia, management of dentin hypersensitivity, facilitation of orthodontic tooth movement, enhancement of dental tissue repair, improvements in implant surface technologies, and innovations in the diagnosis and treatment of oral cancers [4].

Restorative Dentistry and Nanotechnology

The advancement of nanotechnology has significantly enriched restorative dentistry by introducing innovative and more effective strategies designed to enhance material performance. Nanocomposites are advanced restorative materials produced by incorporating nanoscale particles into polymer-, metal-, or ceramic-based matrices. The uniform dispersion of non-agglomerated nanoparticles within resin systems markedly improves the mechanical and surface properties of dental composites. As a result of ongoing efforts to minimize issues common in conventional composites-such as polymerization shrinkage, insufficient surface strength, brittleness, and aesthetic limitations-nanofiller technologies have rapidly evolved. Owing to their superior mechanical durability and anticariogenic potential, nanocomposites provide more stable and long-lasting restorations than traditional composites and have thus become increasingly favored in clinical practice [5, 6].

Nanocomposites may be classified as either nanofilled or nanohybrid materials. Nanofilled composites consist of nanosized particles (nanomers; 5–75 nm) combined with agglomerated nano-sized particles measuring approximately 1.3 μm; these agglomerated structures are referred to as nanoclusters. To enable silane penetration into the internal voids of the clusters, the porous agglomerates are lightly calcined and then infiltrated with a diluted silane coupling agent. Subsequently, a second, undiluted silane coupling agent is mixed with the nanoclusters, after which these structures are incorporated into the resin matrix. In contrast, nanohybrid composites combine nanometer-scale particles (20–60 nm) with more conventional filler technology, incorporating micron-sized fillers ranging from 0.1 to 2.5 μm [7].

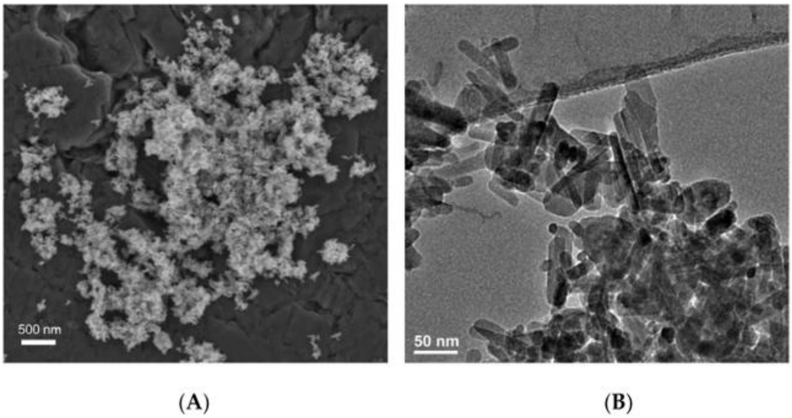
Nanocomposites significantly reduce polymerization shrinkage by decreasing the amount of resin within the matrix, as shrinkage can vary depending on the chemical composition and manufacturing characteristics of the composite. In addition, nanocomposite restorative materials incorporating silver nanoparticles (AgNPs) have been reported to exhibit notable antibacterial properties [8].

Nanocomposites also offer superior esthetic properties. Nanofilled composites exhibit high translucency because the size of the nanoparticles is smaller than the wavelength of visible light (0.4–0.8 μm). As a result, light is not absorbed but passes through the material without significant scattering. Additionally, nanoclusters gradually break down into primary particles over time, and because the surface defects created during this process remain smaller than the wavelength of light, the material is able to maintain its gloss and polishability for extended periods. Since nanoclusters are removed by fracturing or chipping rather than being pulled out intact, the surface remains smooth and glossy. Smaller filler particle sizes also increase polymerization depth and the degree of conversion; when viscosity is properly controlled, nanocomposites demonstrate excellent handling and application characteristics. The spherical morphology of the particles provides rounded edges that facilitate uniform stress distribution, a phenomenon referred to as the “roller-bearing effect” [9].

The growing interest in nanotechnology has brought nano-hydroxyapatite (n-HA), which contains crystalline structures measuring approximately 50–1000 nm, to the forefront as an important biomaterial in dentistry. Owing to its strong binding affinity for proteins, dental plaque, and bacterial debris, n-HA offers notable advantages—particularly in toothpaste formulations. This capability arises from its nanoscale particle structure, which provides an extensive surface area. Additionally, n-HA particles fill microscopic defects and porosities on the enamel surface, exerting a reparative effect; this remineralization potential becomes more pronounced as particle size decreases (Figure 1) [10].

The size of the filler particles is considered a critical variable in determining the performance of composite materials. Nanometer-scale particles, owing to their high surface-to-volume ratio and ability to disperse uniformly, positively influence the mechanical strength and overall behavior of biocomposites [11]. However, certain structural limitations associated with macro- or micro-sized hydroxyapatite (HA) particles may prevent composite resins from achieving the desired level of durability. Consequently, current research focuses on synthesizing nano-sized HA particles with controlled morphology in order to enhance the mechanical resilience of composite materials [12].

Figure 1—(A) Scanning electron microscope (SEM) image of n-HA; (B) Transmission electron microscope (TEM) image of n-HA



Pediatric Dentistry and Nanotechnology

The advantages offered by nanomaterials in restorative dentistry provide valuable opportunities not only for adult patients but also for the management of dental problems in children. Considering the early onset of carious lesions, biofilm-associated infections, and developmental defects affecting enamel and dentin structures, the demand for more effective, safe, and biocompatible materials in pediatric populations has been steadily increasing. In this context, nanoparticles with strong antimicrobial properties-particularly AgNPs-hold notable potential for pediatric dental practice.

AgNPs, owing to their distinctive physical, chemical, and biological properties, have emerged as one of the most widely utilized nanoparticle types in the field of nanotechnology today [13].

Among inorganic nanoparticles, AgNPs stand out, and numerous studies have demonstrated their efficacy against a wide spectrum of microorganisms, including Gram-positive and Gram-negative bacteria, fungi, viruses, and even antibiotic-resistant strains [14]. Although the antimicrobial mechanisms of AgNPs are still being elucidated, existing literature indicates that AgNPs inhibit microbial growth through multiple modes of action [15].

At the core of these antimicrobial actions lies the controlled release of silver ions (Ag^+). Once liberated, Ag^+ ions initially bind to the bacterial plasma membrane, disrupting membrane integrity and causing leakage of intracellular components. They have also been reported to denature ribosomal structures, thereby inhibiting protein synthesis. When internalized, Ag^+ ions can inactivate respiratory enzymes, effectively halting ATP production. Furthermore, by interrupting the electron transport chain, silver ions promote the formation of reactive oxygen species, which subsequently damage proteins and DNA. These molecular disruptions impair cellular replication and ultimately lead to microbial cell death [16].

Parallel to advancements in nanotechnology, numerous studies have investigated the antimicrobial activity of AgNP-based agents against cariogenic microorganisms such as *Streptococcus mutans* (S. mutans), as well as their potential to inhibit dental biofilm formation. These findings indicate that such materials may serve as effective anticariogenic agents [17, 18]. For this reason, numerous *in vitro* and *in vivo* studies have been conducted to evaluate the effectiveness of AgNPs in preventing and arresting early carious lesions.

In a comparative investigation evaluating the remineralization potential of different agents on sound primary incisors, sodium fluoride (NaF), nano-hydroxyapatite (n-HA) serum, and nano silver fluoride (NSF) were examined following 72 hours of demineralization and a subsequent 10-day pH-cycling protocol. Among all groups, NSF produced the highest surface microhardness values (222.90 ± 28.79), followed by NaF (192.48 ± 30.96), n-HA (172.65 ± 21.68), and the control group (114.11 ± 20.30), with statistically significant differences observed between the groups ($p < 0.05$). Atomic force microscopy images further confirmed the formation of protective surface layers in all treatment groups [19].

In pediatric patients, the rapid progression of early childhood caries (ECC), combined with limited oral hygiene habits and challenges in behavior management, has made non-restorative caries treatment an important clinical strategy. Among the available approaches, one of the most widely utilized is silver diamine fluoride (SDF). Composed of silver ions, fluoride, and ammonia, SDF has gained broad acceptance due to its ability both to arrest caries progression and to prevent the development of new lesions [20]. Silver ions act by binding to bacterial cell membranes, leading to protein denaturation and disruption of DNA replication, while fluoride ions promote the formation of fluorapatite, rendering enamel more resistant to acidic challenges. Ammonia, on the other hand, enhances the stability of the solution and extends its shelf life by maintaining an alkaline environment [20, 21].

The most prominent drawback of SDF is the permanent black discoloration that develops on the treated carious surface, which is of particular concern in the anterior esthetic zone. In addition, patients may experience a transient metallic taste during application, and mild gingival irritation has also been reported [22]. These limitations have led to the development of a nanotechnology-based alternative known as nano-silver fluoride (NSF). In this formulation, AgNPs, fluoride, and chitosan act synergistically to provide potent antibacterial and remineralizing effects. While AgNPs penetrate deeper layers of the biofilm and eliminate bacteria through oxidative stress and controlled ion release, the fluoride component strengthens enamel by promoting fluorapatite formation. Chitosan functions both as a stabilizing agent and an additional antimicrobial component, thereby enhancing the overall efficacy of the formulation. Unlike SDF, NSF does not cause black staining of carious surfaces, exhibits an extended shelf life, and remains effective with only a single annual application-features that offer considerable advantages for community-based preventive programs [21].

A randomized controlled clinical trial conducted among children from low-income communities evaluated the effectiveness of NSF by comparing it with physiological saline used in the control group. In the NSF group, 78% of active caries lesions were arrested within the first week, whereas no arrest was observed in the control group. By the fifth month, the proportion of arrested lesions reached 72.91% in the NSF group compared with 34% in the control group. At the 12-month follow-up, caries arrest was maintained in 65.21% of teeth treated with NSF, while only 20.88% of teeth in the control group demonstrated halted progression [23]. In a similar investigation involving 130 carious primary teeth, the participants were divided into two groups, and those receiving NSF demonstrated markedly higher rates of caries arrest throughout the follow-up period. In the NSF group, 81% of lesions were arrested by day 7, 72.7% by the fifth month, and 66.7% by the twelfth month ($p < 0.05$), whereas the control group consistently exhibited significantly lower arrest rates across all time points [24]. Furthermore, it has been reported that an NSF solution with a concentration of 600 ppm demonstrates greater effectiveness in arresting caries progression compared with the 400-ppm formulation [25].

In a clinical study evaluating the effect of AgNP-containing fissure sealants on demineralization, 80 sound permanent molars were examined. At six months, the microleakage rate was 33.6% in the nanoparticle-containing group and 30.6% in the conventional group, with no statistically significant difference between them. However, fluorescence loss was found to be three times higher in the nanoparticle group ($p < 0.05$). This finding suggests that AgNPs may substantially reduce demineralization and enhance remineralization [26].

In addition to antimicrobial strategies, an essential component of caries management in pediatric dentistry is the biological reinforcement of enamel and dentin structures. In this context, nano-hydroxyapatite (n-HA), which mimics the natural process of tooth mineralization, has emerged in recent years as a safe and effective remineralizing agent. This remineralization potential is particularly significant in primary teeth, as their enamel exhibits a lower mineral content and is therefore reported to be more susceptible to various environmental and chemical challenges [27].

In this context, the repair capacity of agents containing n-HA and NaF after erosive challenges has been investigated, and it has been demonstrated that n-HA application produces a pronounced improvement on the enamel surface. Specifically, n-HA has been shown to reorganize the crystal structure and effectively inhibit further demineralization [28]. The strong adhesion of n-HA to the tooth surface and its ability to promote calcium–phosphate release contribute to the recrystallization of enamel, while simultaneously providing a protective barrier that masks microscopic surface irregularities through the formation of a uniform layer [19, 29]. These findings indicate that n-HA represents an effective option for preserving and repairing the enamel of primary teeth. Its strong affinity for the tooth surface, combined with its ability to promote calcium-phosphate release, supports the recrystallization of enamel and contributes to the formation of a uniform protective layer capable of masking microscopic surface irregularities. Overall, the evidence demonstrates that n-HA can play a clinically meaningful role in maintaining the structural integrity of primary enamel and enhancing its resistance to demineralization [28].

Consistent with these findings, the remineralization potential of n-HA has also been supported by comparative studies conducted on artificial enamel lesions. Investigations evaluating the remineralizing effects of toothpastes containing n-HA, fluoride (F), and combinations of n-HAP+F have shown that n-HA provides superior remineralization compared with the other formulations [30]. A large number of studies have demonstrated that n-HA increases enamel surface hardness, slows demineralization, and significantly promotes the remineralization of early enamel lesions. Overall, the evidence indicates that the nanoscale structure and high surface area of n-HA facilitate dense apatite deposition on the enamel surface, thereby producing a more pronounced remineralization effect compared with other agents [31]. Analyses have shown that n-HA fills the microporosities with a uniform and continuous apatite layer, whereas fluoride tends to produce a thinner, more irregular, and incompletely sealed surface [32].

The literature largely indicates that the combination of n-HA and fluoride does not consistently produce a synergistic effect, a finding often attributed to the reduced binding capacity of fluoride when it interacts with n-HA. Overall, current evidence suggests that n-HA promotes denser mineral deposition in early enamel lesions and reconstructs the enamel surface with a more uniform apatite layer compared with fluoride, whereas fluoride tends to generate a thinner, more irregular remineralized surface [33]. Although a few studies have reported differing outcomes, the majority of the literature indicates that n-HA stands out as an effective mineral-based agent for the management of early enamel lesions [34]. These findings indicate that, beyond its remineralization capacity, n-HA also holds substantial potential for use in the development of advanced restorative materials**.**

Various investigations have explored the incorporation of n-HA as a potential additive to enhance the properties of materials currently used in pediatric dentistry. In a study by Moshaverinia et al., the effects of incorporating N-vinylpyrrolidone-containing acids, n-HA, and fluorapatite into conventional glass ionomer cements were examined. Glass ionomer cements are regarded as unique materials due to their biocompatibility, fluoride-releasing anticariogenic properties, and ability to chemically adhere to different dental tissues. The study focused on evaluating potential additives for the widely used Fuji II GC glass ionomer cement and investigated whether these components could improve its mechanical performance [35, 36].

The incorporation of synthetic n-HA and fluorapatite has been shown to enhance several mechanical properties of Fuji II glass ionomer cement, including compressive, tensile, and flexural strength, as well as bond strength to dentin. For this reason, these bioceramics are considered promising additives that may be integrated into glass ionomer cements used as restorative materials [36].

Overall, nanotechnology offers substantial advantages in pediatric dentistry by enhancing both antimicrobial activity and tissue remineralization. AgNPs stand out in the management of ECC due to their strong antibacterial effects and their ability to arrest caries progression, while n-HA emerges as an effective remineralizing agent because of its biomimetic capacity to rebuild enamel and dentin structures and its high biocompatibility in children. Moreover, the ability of n-HA to improve the mechanical properties of restorative materials demonstrates that nanotechnology contributes not only to therapeutic approaches but also strategically to modern dental material science. Current evidence indicates that nanotechnological agents have the potential to become standard components of both preventive and restorative procedures in pediatric dentistry in the future.

Endodontics and Nanotechnology

The advantages offered by nanotechnology in pediatric dentistry have also paved the way for significant developments in other dental disciplines, including endodontics. Owing to the complex anatomy of the root canal system and the persistence of resilient biofilms, more effective disinfection strategies are required in endodontic treatment. In this context, nanotechnological approaches provide innovative solutions that complement existing irrigation and disinfection protocols, thereby presenting a promising potential within contemporary endodontic practice.

Endodontic treatment is fundamentally based on the proper preparation of the root canal followed by its hermetic obturation.

This process involves chemo-mechanical preparation, which includes abundant irrigation and effective canal shaping. Although root canal instruments enlarge the main canal and remove most of its contents, a smear layer inevitably forms during mechanical instrumentation. This layer facilitates the adherence of microorganisms and organic–inorganic debris to canal walls, thereby compromising both effective disinfection and the ability to achieve a tight seal during obturation. Consequently, chemical irrigation plays a critical role in eliminating the smear layer and reducing the microbial load within the root canal system. The importance of disinfection protocols arises from the complex anatomy of the root canal system, which includes lateral canals, isthmuses, anastomoses, and dentinal tubules that cannot be fully reached by instruments. This anatomical intricacy renders mechanical cleaning alone insufficient and necessitates the use of chemical agents to ensure thorough decontamination [37, 38].

In recent years, the integration of nanotechnology into endodontic irrigation and disinfection protocols has emerged as a noteworthy innovation aimed at enhancing the effectiveness of these procedures. Nano-sized particles, owing to their large surface area, superior penetration capacity, and strong antimicrobial properties, are able to infiltrate dentinal tubules more deeply and act within microscopic regions that conventional irrigants cannot reach. As a result, they offer a promising adjunctive approach for improving decontamination within the complex anatomy of the root canal system [37].

The adaptation of nanotechnology to endodontic materials has enabled the development of more effective and innovative solutions for many challenges encountered in the field. Akbarianrad et al. highlighted the importance of nanotechnology particularly in the enhancement of filling materials, irrigation agents, and photodynamic therapy components, reporting that nanoscale additives improve the antibacterial properties of endodontic sealers and increase their resistance to microleakage [39]. Raura *et al.* examined the potential use of different NPs such as graphene, silver, and hydroxyapatite in endodontics, demonstrating that these particles significantly enhance the functionality of root canal sealers, obturation materials, and intracanal medicaments. Their ability to eliminate biofilms more effectively and improve the bonding performance of existing materials is regarded as a notable advancement in the field [40]. Chogle et al. proposed that modifying rotary NiTi files with nano-scale particles could enhance their mechanical performance, and furthermore, that nanosystems may play a significant role in regenerative endodontics by improving scaffold structures and growth factor–delivery platforms [41]. Verma et al. reported that the use of NP-based dental materials enhances root canal disinfection, improves the effectiveness of three-dimensional obturation, and positively influences tissue repair and regenerative processes. However, they emphasized that clinical evidence regarding the long-term performance of these nanomodified biomaterials is still limited, highlighting the need for more comprehensive studies in this field [42].

The integration of nanotechnology into endodontic disinfection has introduced significant advancements that enhance the effectiveness of current treatment protocols. Studies by Kishen and Shrestha [43], as well as Alfirdous et al. [44], clearly illustrate the progress made in this field. The use of antibacterial nanoparticles is regarded as a powerful strategy for eliminating biofilms residing within the root canal system. These nanoparticles not only enhance disinfection capacity but also improve the performance of materials developed to achieve superior sealing of the canal space during treatment [43].

In their comprehensive evaluation of modern approaches to endodontic disinfection, recent studies have highlighted how nanotechnology-based strategies significantly enhance the effectiveness of antimicrobial photodynamic therapy. The use of polymeric NPs and nanoemulsion-form photosensitizers has been shown to improve penetration into dentinal tubules and facilitate more efficient light transmission, thereby overcoming several limitations of conventional treatment modalities. Collectively, these findings indicate that nanotechnology-assisted methods offer a more targeted and potent antimicrobial action within the root canal system, reinforcing their growing relevance in advanced endodontic disinfection protocols [43, 44].

Recent evidence has increasingly highlighted the effectiveness of NP-based agents against *Enterococcus faecalis*, one of the microorganisms most frequently implicated in persistent endodontic infections. A 2021 systematic review reported that NPs, owing to their large surface area and nanoscale dimensions, interact more efficiently with the bacterial cell wall, thereby facilitating the disruption of biofilm architecture and intensifying cellular damage [45]. The same review also evaluated the performance of silver and iron oxide NPs, as well as their combined use with conventional irrigants such as sodium hypochlorite and chlorhexidine. When NP-containing disinfectants were applied, significant reductions were observed in both microbial load and biofilm biomass. Collectively, these findings demonstrate that NP-based antimicrobial agents possess substantial potential as alternative or adjunctive strategies to conventional irrigants for combating resistant bacterial strains in complex endodontic environments. [45, 46].

Oral and Maxillofacial Surgery and Nanotechnology

Similar to its applications in endodontics, nanotechnology also contributes to the development of innovative approaches in oral and maxillofacial surgery by enhancing treatment efficacy, improving biocompatibility, and accelerating tissue healing.

The widespread acceptance of graft materials used in the reconstruction of joint and bone defects in orthopedic surgery is largely attributed to their accessibility and their high rates of clinical success [47]. Various types of grafts-from gold-standard autologous bone to allografts-are used in the reconstruction of osseous defects [10, 48]. Despite the availability of multiple grafting options, autologous bone grafts continue to be regarded as the gold standard due to their superior clinical success, inherent biocompatibility, and osteogenic potential. However, the use of autologous grafts carries several notable disadvantages, including high cost, the need for a second surgical site-which increases pain and the risk of complications-and donor site morbidity [49].

Allografts-particularly fresh-frozen and demineralized freeze-dried forms-tend to undergo rapid resorption, which limits their effectiveness in the treatment of large bone defects. For this reason, xenograft materials have increasingly been preferred in recent years as an alternative to autogenous bone grafts, with numerous studies reporting favorable outcomes. In parallel with these developments, various synthetic graft materials have also been produced for the reconstruction of bone defects, particularly in the craniofacial region. Most of these synthetic materials are designed based on hydroxyapatite (HA) or other calcium phosphate components, owing to their close resemblance to natural bone mineralization [50, 51].

Synthetic HA-similar to other calcium phosphate-based salts-contributes to the healing of large segmental defects through osteoconduction, facilitating osteoblast deposition onto the collagen matrix. Previous studies have demonstrated that the chemical composition and crystalline architecture of synthetic HA closely resemble those of natural HA. Consequently, HA-based materials are considered osteoconductive, biocompatible biomaterials that can be easily sterilized and safely used in clinical practice [52, 53].

Ceramic-free, biologically active HA has also been reported to offer several advantages in the field of dentistry. Owing to its bacteriostatic properties, this material can contribute to the reduction or elimination of pathogenic microorganisms, while simultaneously supporting the differentiation and proliferation of human osteoblasts. In this context, its conversion to fluorapatite is considered an important biological process, as it further enhances the stability and functional integration of mineralized tissues [54]. Fluorapatite, in turn, is considered a complementary therapeutic option for the prevention of peri-implant infections [55].

Modern dental implantology is fundamentally based on the process of osseointegration, in which the implant surface establishes a direct and stable interface with the surrounding bone tissue. Throughout this process, biocompatible materials such as titanium achieve intimate contact with bone, ensuring long-term stability. Following implant placement, osseointegration progresses until completion, after which the abutment and prosthetic restoration are positioned to finalize the treatment sequence [56].

To enhance the long-term success of dental implants, it has been proposed that titanium surfaces be modified with calcium phosphate–based coatings. These coatings can be applied using various techniques, including sol–gel processing, hydrothermal treatment, electrophoretic deposition, biomimetic coating, and ion beam–assisted deposition. Their effectiveness is typically evaluated through cytotoxicity testing, removal-torque measurements, biocompatibility assessments, and in vivo histomorphometric analyses [57].

Among these materials, n-HA stands out due to its ability to accelerate bone formation, increase the percentage of bone–implant contact, and enhance osteoblast adhesion on implant surfaces. The structural composition of the implant, its surface morphology, and the size and shape of the particles used in the coating play a decisive role in regulating osteoblast activity. In addition, n-HA coatings exhibit inhibitory effects against both Gram-positive and Gram-negative bacteria and help modulate monocyte–macrophage activity, thereby contributing to a reduction in the early inflammatory response [58, 59].

Extraction socket–related alveolar bone resorption is a major factor that can complicate subsequent implant placement. Although autologous grafts are considered the gold standard, disadvantages such as donor-site morbidity limit their routine use. For this reason, alloplastic graft materials containing n-HA have emerged as a promising alternative. Their high porosity enhances angiogenesis, accelerates bone regeneration, and allows the implant placement timeline to be shortened. In such grafts, the healing period is typically around four months [60, 61].

In addition, n-HA is widely utilized as an effective material for the management of bone defects that occur following surgical interventions or traumatic injuries. Although macro-sized HA particles have long been employed in clinical practice, the injectable n-HA formulation is regarded as a more modern and innovative alternative [62].

Wound healing is a predominantly intraoral concern in oral and maxillofacial surgery and implant dentistry, arising in association with incisions, extractions, or trauma. The healing process is a gradual and tightly regulated sequence of events that depends on the disruption of the epithelial membrane and the involvement of the underlying connective tissue structures. Cytokines, growth factors, and various mediators collectively contribute to the progression and successful closure of the wound [63].

The contribution of AgNPs to wound healing is attributed to their ability to penetrate the thick peptidoglycan layer of Gram-positive bacteria as well as the thinner, lipopolysaccharide-containing structure of Gram-negative bacteria. The greater the exposure of tissues to these particles, the more actively they participate in the inflammatory, proliferative, and tissue-remodeling phases of the healing process [64]. Tian et al. also reported that AgNPs support wound healing by modulating the activity of inflammatory mediators, thereby reducing inflammation and promoting tissue repair [65].

The pharmaceutical industry has progressively developed silver-based wound dressings tailored to wound type, infection severity, and clinical conditions. Although these products have been reported to be effective and safe, they are not specifically designed for use in oral surgery [66]. In a rat study, Sugiharti et al. demonstrated that the incorporation of AgNPs into periodontal dressing materials significantly accelerated tissue healing [67].

AgNPs are also utilized in implant surface modifications to prevent biofilm formation, as dental implants remain at continuous risk of bacterial colonization and infection throughout their time in the oral environment [63]. Endosseous implant surface modifications enhance osseointegration and long-term stability by increasing surface area and wettability [68].

The incorporation of AgNPs into titanium implants is typically achieved by immersing the implant body in silver nitrate ($AgNO_3$) solutions of varying concentrations [69]. Evidence from recent investigations demonstrates that AgNPs exhibit strong antibacterial activity against *Pseudomonas aeruginosa*. These studies also indicate that AgNPs can adsorb onto titanium surfaces, forming antibacterial aggregates that enhance the material's resistance to microbial colonization [70].

Evidence from recent research indicates that AgNP-modified titania nanotubes on titanium implants exhibit strong antibacterial activity against *Staphylococcus aureus* and maintain this protective effect for up to 30 days [69].

Overall, nanotechnology has emerged as a significant area of innovation within oral and maxillofacial surgery, offering substantial improvements in both bone regeneration and implant success. Advanced materials such as n-HA and AgNPs provide enhanced biocompatibility, potent antibacterial effects, and accelerated tissue healing, making them more effective and reliable alternatives compared with traditional treatment approaches. Current evidence supports the clinical potential of these nanotechnology-based strategies, and it is anticipated that their applications will continue to expand as future studies provide more comprehensive data.

Prosthetic Dentistry and Nanotechnology

Nanotechnology-driven advancements are not limited to surgical and restorative procedures; they also provide significant benefits in prosthetic dentistry. This technology is increasingly implemented in clinical practice to enhance the physical, mechanical, biological, and functional properties of prosthetic materials. In particular, the incorporation of nanoparticles into polymethyl methacrylate (PMMA), composite resins, adhesives, dental cements, impression materials, maxillofacial prosthetic materials, and dental ceramics has led to substantial improvements in the durability, biocompatibility, and overall clinical performance of prosthetic restorations.

Nanotechnology enables the development of innovative materials with enhanced properties for use in prosthetic dentistry. Nanoparticles such as silicon dioxide (SiO_2), titanium dioxide (TiO_2), silver (Ag), and zirconium dioxide (ZrO_2) are incorporated into a wide range of dental materials including resin-based denture base resins, dental composites, impression materials, bonding cements, tissue conditioners, dental implants, dental ceramics, and maxillofacial prosthetic materials to improve their overall performance. The integration of these nanoparticles has been shown to enhance mechanical strength, surface characteristics, biocompatibility, and longevity, ultimately contributing to more durable and clinically reliable prosthetic restorations [71].

Although conventional heat-polymerized PMMA offers several advantages including biocompatibility and favorable esthetics it is generally regarded as mechanically weak [72]. To overcome these limitations, various nanoparticles such as ZrO_2, TiO_2, Al_2O_3, and SiO_2 have been incorporated into PMMA formulations. Among these, nano-ZrO_2 is particularly notable, as it enhances the dimensional stability and tensile strength of the material while also demonstrating the potential to reduce Candida adhesion on the surface [72, 73]. In addition, the incorporation of nano-ZrO_2 particles in different sizes and concentrations has been reported to enhance the flexural strength of repaired regions [74], and the addition of 5–15 nm ZrO_2 has been shown to significantly improve the mechanical properties of PMMA [75]. In addition, TiO_2, ZnO, and Ag nanoparticles represent an important option for the prevention of denture stomatitis due to their pronounced antimicrobial activity [71, 76]. However, it has been reported that SiO_2 nanoparticles provide lower flexural strength compared with TiO_2 and Al_2O_3 additives [77]. Carbon nanotubes have additionally been shown to reduce polymerization shrinkage in PMMA, thereby enhancing its impact strength [78].

Incorporating nanoparticles significantly enhances the mechanical performance of dental cements—particularly resin cements and glass ionomer cements—by improving fracture toughness, flexural strength, and compressive strength. Resin cements modified with AgNPs not only exhibit these mechanical advantages but also demonstrate long-lasting antibacterial activity. Additionally, ZnO and MgO nanoparticles have been reported to improve the mechanical strength of zinc polycarboxylate cements. Furthermore, the incorporation of n-HA/fluorapatite and TiO_2 into glass ionomer cements has been shown to markedly increase their tensile and flexural strength [76].

These findings demonstrate that nanotechnology-based surface modifications have the potential to enhance both the durability and the clinical performance of prosthetic restorations. In particular, HAp and other nanostructured coatings are anticipated to contribute significantly to the development of more predictable, biocompatible, and long-lasting restorations in modern prosthetic dentistry.

Conclusion

Nanotechnology is emerging as a rapidly evolving field with the capacity to fundamentally transform diagnostic and therapeutic approaches in dentistry. The unique characteristics of nanoscale materials such as high surface area, enhanced reactivity, superior biocompatibility, and targeted interactions with biological tissues contribute to improved efficacy and safety across a wide range of dental treatments. The evidence presented in this chapter clearly demonstrates that nanotechnology offers substantial advantages across multiple dental disciplines.

In restorative dentistry, nanocomposites and materials enriched with n-HA exhibit superior mechanical strength, enhanced esthetic properties, and improved biological compatibility when compared with conventional alternatives. In pediatric dentistry, AgNPs and n-HA play a pivotal role in preventing and arresting ECC while enabling biomimetic reconstruction of enamel. The high caries-arresting capacity of nano silver fluoride, combined with its esthetic benefits in pediatric applications, positions it as a promising candidate for future clinical standards.

Within the field of endodontics, nanoparticle-based irrigants, photosensitizers for antimicrobial photodynamic therapy, and nanostructured obturation materials contribute significantly to the elimination of complex biofilm communities and enhance overall root canal disinfection. In oral and maxillofacial surgery, the integration of n-HA and AgNPs accelerates bone regeneration, enhances the osseointegration of implant surfaces, and reduces postoperative infection risks. In prosthodontics, nanostructured coatings and nanoparticle-reinforced materials improve bond strength, mechanical stability, and the long-term clinical performance of restorations.

Collectively, these findings indicate that nanotechnology is not merely a complementary tool in dentistry but a strategic innovation with the potential to define future clinical protocols. Nevertheless, further comprehensive in vivo and clinical studies are required to establish long-term safety profiles, clinical success rates, and standardized application guidelines for nanomaterials. Based on current evidence, nanotechnology-based interventions are expected to become an integral component of both preventive and therapeutic dentistry, offering more effective, minimally invasive, and biologically compatible solutions that will shape the future of modern dental practice.

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NANOTOXICOLOGY, PUBLIC HEALTH, AND REGULATORY FRAMEWORK

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Introduction

Nanotechnology has revolutionized modern science and industry through its ability to manipulate materials at the atomic and molecular scales, typically within dimensions of 1–100 nanometers. At this scale, materials exhibit novel physicochemical properties that differ fundamentally from their bulk counterparts, such as increased surface reactivity, enhanced catalytic potential, quantum confinement, and unique optical or magnetic behavior [1,2]. These distinctive attributes have enabled the development of high-performance materials and biomedical systems that were previously unattainable with conventional technologies.

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The proliferation of engineered nanomaterials (ENMs) including metal oxides (exp. TiO_2, SiO_2), carbon-based structures (graphene, fullerene, carbon nanotubes), and polymeric nanoparticles has introduced innovative solutions for diagnostics, targeted drug delivery, environmental remediation, and food preservation. Yet, the same properties that make nanomaterials so effective such as high surface energy and nanoscale penetration also raise toxicological concerns, as they may interact unpredictably with cells, tissues, and biological macromolecules [3].

The emerging field of nanotoxicology was established to understand and predict these interactions. It extends beyond classical toxicology by incorporating physicochemical, molecular, and omics-based perspectives to assess dose–response relationships, biokinetics, and adverse outcome pathways (AOPs) specific to nanomaterials. Nanotoxicological findings are essential not only for occupational health and consumer protection but also for guiding regulatory policies, environmental safety, and ethical decision-making in nanotechnology applications [4,5].

From a public health perspective, the dual nature of nanotechnology its capacity to deliver both health benefits and potential risks necessitates a balanced, evidence-based approach. Nanomedicine and nano-enabled diagnostics have led to remarkable advances in disease prevention and therapy, while environmental exposure to nanoparticles through air, water, and food remains a concern. The challenge lies in maximizing the societal benefits of nanotechnology while minimizing harm through effective regulation, risk communication, and ethical governance.

Nanoparticles and Their Biological Interactions

Physicochemical Properties of Nanoparticles

Nanoparticles (NPs) are defined as materials with at least one dimension less than 100 nm. Their biological behavior is strongly influenced by physicochemical characteristics such as size, shape, surface charge (zeta potential), hydrophobicity, crystalline structure, and surface functionalization. These parameters determine how nanoparticles interact with biomolecules, cross biological barriers, and undergo degradation or persistence within living systems [6,7].

The surface area-to-volume ratio of nanoparticles significantly affects their reactivity and biological interface. Smaller particles present more reactive sites for protein adsorption, leading to the formation of a protein Corona a dynamic layer of biomolecules that defines the biological identity of the nanoparticle. This corona influences cellular uptake, biodistribution, and immune responses, thereby modulating toxicity outcomes [8].

Cellular Uptake and Biodistribution

Nanoparticles can enter cells through multiple mechanisms, including endocytosis (clathrin-dependent, caveolin-mediated, or macropinocytosis) and passive diffusion in some cases. Once internalized, they may localize in the cytoplasm, mitochondria, lysosomes, or even the nucleus, depending on their size and surface chemistry. After entering the systemic circulation, nanoparticles can cross physiological barriers such as the blood–brain barrier (BBB), placental barrier, and alveolar–capillary membrane, posing potential risks of neurotoxicity and developmental toxicity [9,10].

Biodistribution studies using radiolabeled or fluorescent nanoparticles have demonstrated their accumulation in organs such as the liver, spleen, lungs, and kidneys, which serve as primary sites for nanoparticle clearance. The reticuloendothelial system

(RES) plays a central role in nanoparticle sequestration and immune recognition. Prolonged accumulation, particularly of insoluble or non-biodegradable nanoparticles, may induce chronic inflammation and fibrotic changes [11].

Mechanisms of Nanotoxicity

The mechanisms underlying nanotoxicity are multifactorial and depend on both the intrinsic properties of nanoparticles (NPs) and the biological microenvironment they encounter. Once internalized, nanoparticles may interact with cellular organelles, disturb redox balance, alter signaling pathways, and induce structural or functional damage. The key mechanisms of nanotoxicity include oxidative stress, inflammation, genotoxicity, and organelle dysfunction, which often act in a synergistic manner to disrupt cellular homeostasis [5,12].

Oxidative Stress and Reactive Oxygen Species (ROS) Generation:

One of the most widely recognized pathways of nanotoxicity is the overproduction of reactive oxygen species (ROS). Due to their high surface area and catalytic potential, many metal and metal oxide nanoparticles (e.g., TiO_2, ZnO, Ag, CeO_2) can promote electron transfer reactions, generating ROS such as superoxide anions, hydroxyl radicals, and hydrogen peroxide. Excessive ROS causes lipid peroxidation, protein oxidation, mitochondrial damage, and DNA strand breaks, ultimately leading to apoptosis or necrosis [13,14].

Inflammatory and Immune Responses: Nanoparticles (NPs) interact with the immune system through multiple mechanisms, primarily involving recognition by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) on macrophages and dendritic cells.

This recognition triggers intracellular signaling cascades that lead to the activation of the complement system, inflammasome pathways (notably NLRP3), and the production of chemokines and cytokines including IL-8, IL-18, MCP-1, and TGF-β, resulting in acute or chronic inflammatory responses.

Upon exposure, protein corona formation at the NP surface alters their biological identity and modulates recognition by immune cells. Misfolded or denatured proteins within this corona can expose new epitopes, inducing complement activation and inflammatory mediator release. For instance, C1q and C3a/C5a-mediated complement activation may lead to pseudoallergic or hypersensitivity reactions, while inflammasome activation through the NLRP3–caspase-1 axis can induce pyroptosis and cytokine secretion, particularly IL-1β and IL-18.

Persistent or non-biodegradable NPs, such as carbon nanotubes and metal oxides, may induce chronic low-grade inflammation, characterized by macrophage recruitment, oxidative stress, and tissue remodeling (fibrosis) in the lungs and liver. In contrast, surface-engineered or biocompatible coatings (e.g., PEG, albumin, or red blood cell membranes) can reduce immune recognition and limit inflammatory outcomes [15-16].

Genotoxicity and DNA Damage: Genotoxic effects of nanomaterials can occur through both primary and secondary mechanisms. Primary genotoxicity may result from the direct interaction of nanoparticles (NPs) with DNA or chromosomal structures, leading to strand breaks, chromosomal aberrations, and micronucleus formation. Alternatively, indirect mechanisms involve oxidative stress and the generation of reactive oxygen species (ROS), which cause base oxidation and DNA strand damage. The review by Kohl et al. (2020) emphasizes that nanoparticles with smaller sizes can more easily penetrate the nuclear membrane or enter the nucleus during mitosis, thereby enhancing the likelihood of DNA interaction. Furthermore, metal-based nanomaterials such as Ag, ZnO, and TiO_2 nanoparticles have been shown to induce oxidative DNA damage and chromosomal instability, with size, surface charge, and chemical composition playing key roles in their genotoxic potential [17].

Experimental findings further support these mechanisms. Zhang et al. (2022) reported that silver nanoclusters (AgNCs) of approximately 2 nm exhibited mutagenic activity in Salmonella typhimurium TA100 strains and induced oxidative stress in in vivo chicken embryo models. Their results demonstrated that smaller-sized AgNCs displayed higher mutagenic responses compared to larger TiO_2 nanoparticles, and these effects were correlated with particle size, aggregation behavior, and surface charge. The authors concluded that nanomaterial-induced mutagenicity and developmental toxicity are strongly influenced by physicochemical characteristics and environmental interactions of the nanoparticles [18].

Organelle Dysfunction and Cell Death Pathways: Nanoparticles (NPs) can induce profound disturbances in organelle homeostasis, leading to multiple cell death pathways including apoptosis, necrosis, and autophagy. Once internalized, NPs can accumulate in mitochondria, lysosomes, and the endoplasmic reticulum (ER), disrupting their normal functions and triggering stress responses that dictate cellular fate. Mitochondrial dysfunction is one of the earliest and most critical events, characterized by impaired oxidative phosphorylation, increased reactive oxygen species (ROS) generation, and collapse of the mitochondrial membrane potential. This oxidative stress leads to cytochrome c release and activation of intrinsic apoptotic pathways involving BAX, BAK, and caspase cascades. In parallel, ER stress induced by unfolded protein accumulation can activate the PERK–eIF2α–CHOP pathway, further promoting apoptosis or, when excessive, necrotic cell death. Lysosomal destabilization is another hallmark of NP-induced organelle dysfunction. The acidic environment of lysosomes can promote dissolution of certain metal-based NPs (e.g., ZnO, Ag, or Fe-based), leading to ionic release and damage to lysosomal membranes. This disruption results in the leakage of hydrolytic enzymes such as cathepsins into the cytoplasm, exacerbating oxidative damage and initiating apoptosis or necroptosis. Moreover, impaired lysosomal function interferes with autophagic flux, as autophagosomes fail to fuse efficiently with lysosomes, leading to accumulation of damaged organelles and proteins [19].

Collectively, these interlinked processes mitochondrial oxidative stress, ER stress, and lysosomal destabilization represent key mechanistic events connecting NP exposure to cellular demise. Such events are increasingly recognized as critical key events (KEs) within Adverse Outcome Pathways (AOPs) for nanomaterials, as highlighted by Halappanavar et al. (2021), who emphasized oxidative stress, inflammation, and cytotoxicity as upstream KEs contributing to tissue injury and adverse cellular outcomes [4].

Understanding these organelle-level perturbations is essential for elucidating nanotoxicity mechanisms and for designing safer nanomaterials with reduced cytotoxic potential.

Public Health Benefits and Risks

Potential Benefits to Public Health

Nanotechnology has demonstrated substantial potential to improve human health outcomes through advancements in diagnostics, therapeutics, drug delivery, and disease prevention. Nano-enabled medical devices and nanosensors facilitate early detection of infections, cancer, and metabolic disorders with high sensitivity and specificity [20,21]. Nanomedicine the medical application of nanotechnology allows for targeted delivery of therapeutic agents, reducing systemic toxicity while increasing treatment efficacy. For instance, liposomal and polymeric nanoparticles are now widely used to deliver anticancer drugs such as doxorubicin and paclitaxel directly to tumor tissues via the enhanced permeability and retention (EPR) effect [22,23]. Additionally, several studies have demonstrated that nanoparticles hold considerable promise as a viable alternative for the treatment of various infections, particularly those caused by multidrug-resistant (MDR) bacteria [24].

From a preventive medicine perspective, nanotechnology contributes to the development of vaccines, biosensors, and antimicrobial coatings. During the COVID-19 pandemic, lipid-based mRNA vaccine platforms illustrated how nano-formulations can revolutionize immunization by improving antigen stability and cellular uptake (25). Similarly, nanostructured coatings with silver, titanium dioxide, or zinc oxide nanoparticles have been integrated into hospital surfaces and medical devices to prevent microbial colonization and nosocomial infections [26,27].

In the context of food safety and nutrition, nanotechnology enables the encapsulation of vitamins, antioxidants, and probiotics to enhance bioavailability, and the development of smart packaging capable of detecting spoilage gases or pathogenic contamination. These innovations align with the One Health concept by bridging human health, food systems, and environmental sustainability [28].

Public Health Risks

Despite these benefits, the growing production and utilization of engineered nanomaterials have introduced new challenges for toxicology, occupational health, and environmental hygiene. Potential exposure routes include inhalation (industrial aerosols, urban nanoparticles), ingestion (food additives, packaging migration), dermal absorption (cosmetics, disinfectants), and parenteral administration (nanomedicines). Occupational exposure among workers in nanomaterial manufacturing or laboratory environments remains an under-investigated concern [26,29,30].

Several studies have demonstrated that chronic exposure to airborne ultrafine particles (UFPs) can cause pulmonary inflammation, oxidative stress, and cardiovascular dysfunction, mirroring the effects of ambient air pollution [31]. Similarly, ingestion of nano-sized additives such as TiO_2 (E171) or SiO_2 may alter gut microbiota composition and intestinal permeability, potentially leading to systemic inflammation [32]. Dermal exposure to silver nanoparticles from consumer products has also been associated with local irritation and systemic accumulation after prolonged use [33].

Epidemiological Evidence and Knowledge Gaps

Epidemiological evidence on the health effects of engineered nanomaterials (ENMs) remains sparse compared with the expanding toxicological literature. Most available data come from occupational settings in which workers manufacture or handle materials such as nano-TiO_2, carbon black, carbon nanotubes, metal oxides, and various nanometal particles. A systematic review of human studies up to 2018–2019 identified only a few dozen investigations, most of which were small cross-sectional studies with limited follow-up, inconsistent study design, and heterogeneous exposure metrics ranging from particle mass to number concentration or imprecisely defined “nanoparticle dust” [29].

Across studies, findings point to early biological effects rather than clear disease outcomes. Reported observations include markers of oxidative stress, low-grade inflammation, mild alterations in lung function, and occasional cardiovascular changes in exposed workers, but the available data are neither robust nor consistent enough to establish material-specific risk estimates or to link ENM exposure to chronic disease (Luo et al., 2022). A major obstacle is the absence of standardized nano-specific exposure metrics, such as particle number concentration, surface area dose, or measures of bioavailable fraction, all of which are essential for comparing results across studies and building dose–response relationships [29].

These gaps highlight the need for stronger integration of exposure science and epidemiology. Embedding nano-relevant metrics into occupational and environmental health surveillance would make human data more informative and improve alignment with mechanistic evidence from nanotoxicology. Larger, longitudinal studies with well-characterized exposures are particularly important as ENM use expands in industrial processes, diagnostics, therapeutics, and consumer products [34].

Taken together, the limited and heterogeneous nature of existing epidemiological evidence means that current findings neither confirm nor rule out substantial health risks for many engineered nanomaterials. In this context of scientific uncertainty, precautionary control of occupational and environmental exposures remains a sound public-health recommendation until stronger human evidence becomes available [29,35].

Regulatory Frameworks and Gaps in Legislation

Global Regulatory Landscape

Global governance of nanotechnology is still fragmented, with responsibilities distributed across existing chemical, pharmaceutical, food, and environmental authorities rather than dedicated nano-specific regulators [35,36]. International bodies such as the OECD's Working Party on Manufactured Nanomaterials, WHO's chemicals programmes, and ISO/TC 229 "Nanotechnologies" work to harmonize test methods, terminology, and risk-assessment guidance, and to promote grouping, read-across and life-cycle thinking (36, 37). However, there is still no globally agreed definition of "nanomaterial" or common exposure and hazard metrics, which remains a major barrier to coherent regulation [38].

Within this landscape, the European Union represents one of the most advanced regional approaches: nanomaterials are regulated through REACH and sectoral laws on food, cosmetics, biocides and medical devices, with explicit requirements for labelling, nanoform-specific assessment and detailed physico-chemical and toxicological data (39, 40). EFSA and EMA have issued guidance for nano in food/feed and nanomedicines, while the EU Observatory for Nanomaterials and the "Safe and Sustainable by Design" initiative embed nanosafety and sustainability early in R&D [36,40]. In practice, the EU treats nanomaterials as substances with specific forms and properties under existing law, but with additional obligations that place nanotoxicology and nano-specific exposure assessment at the core of regulatory decision-making [36,41].

In the United States, the Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) assess nano-formulations through existing chemical and drug safety laws, requiring manufacturers to submit data on composition, particle size, and toxicity prior to commercialization [42].

Turkey, as an EU-associated country, follows REACH-aligned guidelines and national legislation administered by the Ministry of Environment, Urbanization and Climate Change and the Turkish Standards Institution (TSE). Yet, a dedicated national registry for nanomaterials and fully harmonized nanospecific risk-assessment standards are still under development.

Risk-Assessment Approaches

Regulatory agencies increasingly apply a tiered risk-assessment framework to engineered nanomaterials (ENMs), structured around four core components. The first is material characterization, which evaluates properties such as size distribution, morphology, solubility, and agglomeration state, all of which influence how a nanomaterial behaves in biological systems. The second component is hazard identification through in-vitro and in-vivo assays. The third is exposure assessment, aimed at determining realistic levels of human and environmental contact. The fourth component is risk characterization, where dose–response data and uncertainty factors are integrated into a regulatory decision. This general tiered structure is widely reflected in nanosafety roadmaps and risk-governance analyses [37].

However, traditional toxicological assays are often poorly suited for ENMs because they fail to capture nanoscale phenomena such as aggregation, dissolution kinetics, and protein-corona formation. Stone and colleagues (2017) demonstrated that these particle-specific transformations can change cellular uptake, distribution, and toxicity in ways that classical assays were never designed to measure, which can lead to inaccurate hazard estimates. In response, both the OECD and ISO Technical Committee 229 have strengthened nanomaterial-specific testing guidance by expanding physicochemical characterization requirements and incorporating mechanistic endpoints such as oxidative potential, surface reactivity, and omics-based readouts [34].

A major advance in modern nanotoxicology is the increasing alignment of regulatory assessment with Adverse Outcome Pathway (AOP) frameworks. AOPs link a molecular initiating event to sequential key biological events that culminate in an adverse outcome relevant for risk assessment. Halappanavar et al. (2020) highlighted the value of integrating omics technologies and high-content profiling into AOP development to better capture early biological perturbations and support predictive nanosafety models.(4) Jeong et al. (2018) provided a detailed mechanistic example by constructing an AOP for silver nanoparticles in Caenorhabditis elegans. Their work traced a pathway beginning with NADPH oxidase activation and reactive oxygen species formation, followed by PMK-1/p38 MAPK and HIF-1 activation, mitochondrial dysfunction, and DNA damage, ultimately leading to reproductive impairment. Their Bayesian-network analysis illustrated how AOPs can support multi-scale modelling and improve the mechanistic foundation of regulatory decision-making [43].

Together, these developments point toward a shift from conventional, hazard-centric testing toward mechanism-based, standardized, and integrative risk-assessment approaches. By combining improved characterization, validated mechanistic assays, AOP-guided modelling, and data-rich profiling strategies [4], regulatory bodies can better account for the complex behaviors of nanomaterials and advance safe-and-sustainable-by-design innovation.

Data Transparency, Labeling, and Traceability

Transparency in data reporting and consumer labeling is essential for regulatory compliance and ethical accountability. Under EU Regulation 1169/2011, all engineered nanomaterials used as food ingredients must be explicitly labeled, and the Cosmetics Regulation 1223/2009 imposes comparable requirements for nano-ingredients in personal-care products. Despite these measures, inconsistent labeling practices and the lack of harmonized nanomaterial definitions across jurisdictions continue to hinder effective enforcement [39,44].

Traceability presents an additional challenge. Once nanomaterials enter complex product matrices or environmental systems, tracking their transformations, degradation pathways, and potential release becomes technically difficult. Emerging digital tools, including blockchain-based product traceability and AI-enabled supply-chain analytics, may complement traditional regulatory instruments and improve life-cycle transparency [22].

Ethical, Legal, and Social Implications

Ethical governance of nanotechnology requires balancing technological innovation with precaution. Key concerns include informed consent in nano-enabled medical applications, privacy risks associated with nanoscale health-monitoring devices, adequate occupational protection, and intergenerational justice given the potential persistence of nanomaterials in ecosystems [45]. Public trust depends on open dialogue between scientists, regulators, industry, and civil society. Policies grounded in public participation, transparency, and responsible-innovation principles are essential for equitable deployment of emerging nanotechnologies, as emphasized in the responsible innovation framework proposed by Stilgoe and colleagues [46].

From a legal perspective, the absence of nano-specific legislation creates grey zones in liability and product-safety law. Questions regarding the burden of proof for safety data and the design of post-market surveillance systems remain unresolved in most jurisdictions [45]. These gaps underline the need for interdisciplinary cooperation between toxicologists, legal scholars, and policymakers to develop governance models that reflect the unique properties and uncertainties associated with engineered nanomaterials.

Standardization Challenges and Policy Directions

Standardization is vital for the comparability of safety data, yet global progress remains slow. ISO/TC 229 and CEN/TC 352 are currently developing terminology, measurement, and characterization standards, while OECD's *Nano Safety Testing Programme* focuses on cross-validation of toxicity assays. However, discrepancies between European, U.S., and Asian regulations complicate international trade and data exchange.

Future policy should prioritize:

- Establishing nano-specific exposure limits and classification systems;
- Implementing global nanosafety databases integrating physicochemical, toxicological, and epidemiological data;
- Promoting green nanotechnology and life-cycle assessment (LCA) approaches;
- Supporting capacity building in developing countries through education, technology transfer and international collaboration.

Only through harmonized, evidence-based, and transparent governance can promise of nanotechnology be realized while safeguarding ecological health [37,47,48].

Future Perspectives

The future of nanotoxicology lies in integrating systems biology, computational modeling, and artificial intelligence to better predict how nanoparticles interact with living systems. Conventional in vitro and in vivo assays are costly, slow, and limited in capturing chronic or low-dose effects. Emerging tools such as organ-on-a-chip systems, 3D bioprinting, and omics-based screening provide more mechanistic, high-throughput methods for assessing nanosafety [49,50].

Machine-learning approaches can now analyze large physicochemical and biological datasets to identify nanoparticle features associated with adverse responses. The Adverse Outcome Pathway (AOP) framework, strengthened by AI-assisted modeling and toxicogenomic data integration, offers a route toward predictive nanotoxicology with reduced reliance on animal testing [50].

Global collaboration will remain essential. Initiatives such as the EU NanoSafety Cluster, the OECD NanoData Hub, and the U.S. National Nanotechnology Initiative are working to harmonize nanosafety data, develop shared repositories, and establish common test guidelines. Environmental nanotoxicology will also become more prominent, as growing evidence shows that nanoplastics and metal oxide nanoparticles can disrupt microbial communities, impair photosynthesis, and bioaccumulate across food webs [51].

Finally, ethical foresight and responsible-innovation frameworks, including Responsible Research and Innovation (RRI), should guide the development of future nanotechnologies. Embedding ethical evaluation early in the design process can help prevent unintended harm and support equitable access to the benefits of nano-enabled innovation.

Conclusion

Nanotechnology sits at the intersection of scientific innovation and public responsibility. As nanomaterials reshape medicine, agriculture, energy, and environmental management, understanding their interactions with biological systems becomes increasingly important. Nanotoxicology provides the evidence base needed for risk assessment, regulation, and sustainable innovation.

While nanotechnology offers major benefits from precision therapeutics to cleaner manufacturing its uncontrolled use may pose risks to human health and ecosystems. The goal is not to restrict innovation but to guide it through evidence-based governance, ethical foresight, and international cooperation. Harmonized regulatory frameworks, global nanosafety databases, and advanced computational tools will help improve predictions of nanoparticle behavior and reduce uncertainty in risk assessments.

Integrating green chemistry principles, life cycle thinking, and holistic frameworks such as One Health and One Toxicology strengthens the foundation for responsible nanotechnology. One Health highlights the interconnectedness of human, animal, and environmental health, ensuring that nanosafety considerations extend beyond individual exposure scenarios to ecosystem-level impacts. One Toxicology emphasizes the need for unified principles across classical toxicology, mechanistic science, computational modeling, and exposure assessment, promoting consistency and coherence in evaluating risks across chemicals, pharmaceuticals, and nanomaterials.

Together, these approaches align nanotechnology with global sustainability goals, including the United Nations Sustainable

Development Goals on health, responsible production, and climate action. Ultimately, nanotoxicology must transition from a reactive discipline to a proactive, predictive science that enables safe-by-design materials. Achieving this vision will require close coordination among scientists, regulators, policymakers, and the public so that nanotechnology continues to advance human welfare while safeguarding ecological systems and planetary health.

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FUTURE PERSPECTIVES AND NANOTECHNOLOGY IN SMART SYSTEMS

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Rizvan İMAMOĞLU[2]

Introduction

Nanotechnology is a field that emerges through the manipulation of matter at the atomic and molecular scale, pushing the limits of science and engineering disciplines and offering revolutionary innovations at both theoretical and practical levels [1]. In recent years, the impacts of nanotechnology across many areas, including health, energy, the environment, and various industries, have made this discipline an important tool in the world of technology and innovation [2]. Thanks to the developing technology, the integration of nanotechnology with artificial intelligence and quantum technologies increases the performance of smart systems and produces innovative solutions that guide these systems [3].

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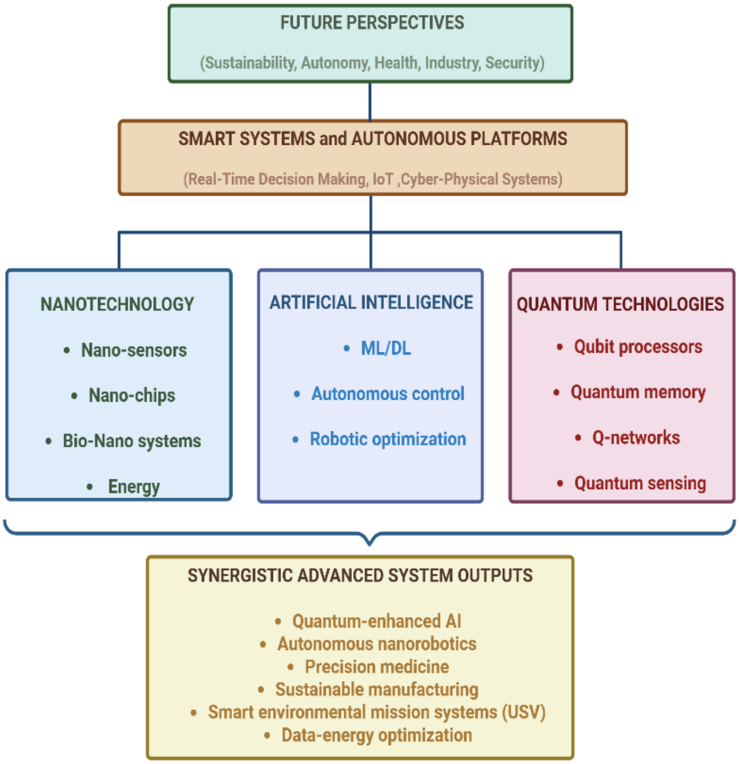
Figure 1. Demonstration of the evolution of intelligent systems through the synergy of nanotechnology, artificial intelligence, and quantum technologies



Source: This figure was drawn with Biorender.

It will play an important role in future studies and designs, in areas such as smart systems, automation, and data analysis, combined with technologies such as artificial intelligence and machine learning [4]. Nanotechnological applications enable these smart systems to better meet human needs while also contributing to achieving sustainability goals by increasing energy efficiency [5]. For example, nanotechnology offers innovative solutions in agricultural productivity and medical fields, owing to technologies such as biosensors and environmental monitoring that are currently in practice [6]. This situation enables smart systems to become more compatible with the human and natural environment.

In addition, future applications combining nanotechnology and artificial intelligence will achieve greater accuracy in decision-making and be effective in managing complex datasets [6]. For example, nanotechnological materials are used in artificial intelligence-supported maintenance systems, and system efficiency is increased through real-time decision-making in energy systems [7]. The development of nanotechnology and the innovations made possible in this field have occurred not only in laboratory environments but also on industrial scales [5].

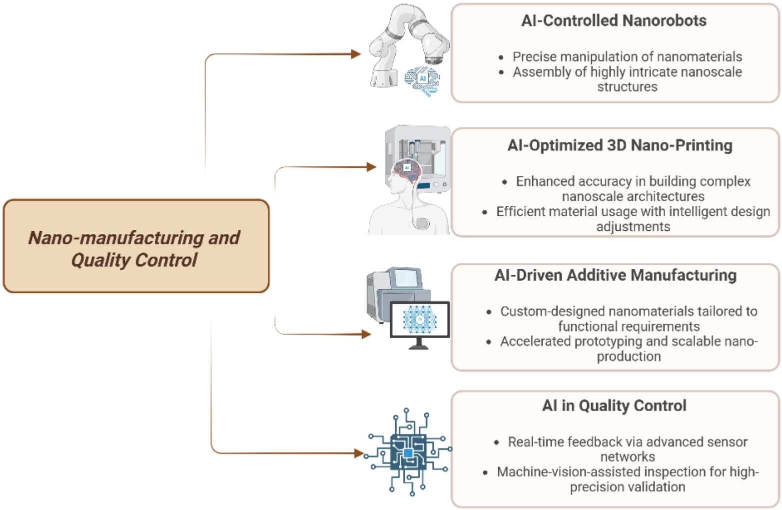
Quantum technologies, a significant field in recent times, have become even more important with the integration of nanotechnology and artificial intelligence. Quantum computing offers revolutionary capacity for processing large data sets and contributes to intelligent systems by enabling accurate and rapid innovations in problem-solving [8]. Quantum systems make possible the development of more powerful and effective sensing systems by leveraging the properties of nanotechnological materials. This enables better solutions in critical areas such as advanced healthcare, environmental sustainability, and data security [9].

Consequently, the integration of nanotechnology with smart systems is poised to lead to revolutionary changes in various sectors in the future. Among these future perspectives, developments in this field offer a wide range of impacts, both economic and social, paving the way for the development of innovative strategies. To achieve success, due importance must be given to multidisciplinary studies and collaborations; in particular, it is essential to consider ethical and social responsibility issues in the development of these integrated systems.

Artificial Intelligence Integration

Recently, the integration of nanotechnology and artificial intelligence (AI) has become a significant milestone in the development of intelligent systems [3]. This integration holds the potential to transform not only research and application but also industries. AI and machine learning are not only revolutionizing data analysis but also playing a significant role in optimizing nanotechnology applications. In many areas, such as education, healthcare, finance, manufacturing, and automation, the collaboration of these technologies is enabling innovative solutions and increased efficiency [10].

Figure 2. The illustration of artificial intelligence-assisted approaches in nanotechnology-based production



Source: This figure was drawn with Biorender.

Nanotechnology's fundamental properties make it suitable for high-precision applications. Nanoscale materials present complex structures that require analytical thinking. At this point, the introduction of AI facilitates the processing and interpretation of large amounts of data, thereby accelerating decision-making. AI algorithms analyze observed data to optimize nanotechnological processes and draw important conclusions, which in turn guide R&D phases [10, 11].

Particularly in healthcare, the combination of AI and nanotechnology is enabling the development of personalized treatment methods. AI plays a critical role in early disease diagnosis and treatment processes. For example, AI-powered systems can predict the distribution and interactions of nanoparticles, helping to maximize drug efficacy while minimizing side effects. These analyses allow doctors to make more informed decisions when treating complex diseases like cancer [12].

Another significant synergy between nanotechnology and AI is experienced in product development [4, 13]. Processing nanomaterials and their associated data with AI algorithms enables the rapid creation of new material designs and increases process efficiency. Characterization and classification of nanomaterials become faster and more accurate with the help of AI, thereby accelerating the innovation process [4].

Another important aspect of integrating AI with nanotechnology concerns data security and ethical issues. The use of AI systems raises concerns about data privacy and security. Therefore, establishing ethical norms and regulations is crucial during the development of these systems [13].

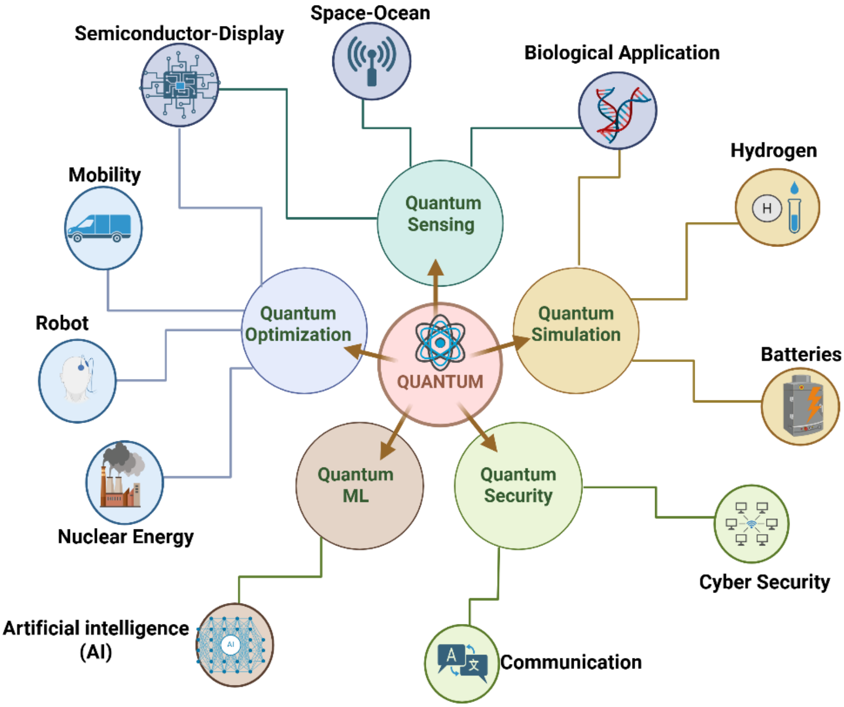
Ultimately, the integration of AI and nanotechnology will play a critical role in solving many of the challenges we face in the future. The combination of these two fields offers multifaceted innovations not only in health and science but also in a wide range of fields, including industry and environmental sustainability, and has the potential to transform human life. Going forward, interdisciplinary collaborations and ethical discussions will be essential to establish this integration on even stronger foundations.

Junction Points with Quantum Technologies

The integration between quantum technologies and nanotechnology opens new horizons for technological advancements, enabling revolutionary changes in various sectors. Quantum technologies, by leveraging the fundamental principles of quantum mechanics, offer new possibilities in information processing, communication, and measurement, while nanotechnology, through its use of diverse materials and structures, expands the applicability of these principles [9]. Quantum information processing is emerging as a field that processes information bits (qubits) via quantum states, and nanotechnology plays a significant role in the production and use of these qubits [8]. For example, semiconductor quantum dots and other nanoengineered structures offer highly efficient qubit sources that can be integrated into silicon-based systems. The nanotechnological properties of these structures facilitate the identification and application of quantum characteristics, enabling the development of more complex systems [7, 14].

The role of nanotechnology in quantum memory and quantum networks is also critical. Quantum memory is a key building block for storing and retrieving quantum information in real-time. The combination of nanomaterials and integrated photonic systems is contributing to the development of quantum memory systems with high density and phase-determining capabilities [15]. Quantum communication is based on the transmission of information via quantum bits, and techniques such as quantum key distribution ensure communication security [8]. Nanotechnology plays a crucial role in the miniaturization and efficiency of such communication systems. Integrated nanophotonic circuits are supported by the complex optical structures required to realize quantum communication [7]. Furthermore, precise control of quantum states allows for the development of new strategies to enhance security during communication. Nanotechnological structures increase the reliability of communication by enabling the faster generation and transfer of quantum keys [8, 14].

Figure 3. Demonstration of multidisciplinary application areas of quantum Technologies



Source: This figure was drawn with Biorender.

Nanotechnology significantly increases measurement precision by exploiting the advantages provided by quantum mechanical principles, and quantum sensors play a critical role in the realization of these systems [7]. In the future, the integration between nanotechnology and quantum technologies promises to open the door to many previously impossible applications [8, 14]. The ability to profoundly impact smart sensing, data analysis, and communication systems will yield tangible results from the combined efforts of these two fields. Thus, the impact of nanotechnological materials on quantum communication and information processing will pave the way for the development of integrated systems at an international level, enabling the implementation of more reliable, fast, and efficient systems [15].

Ultimately, this synergy between quantum technologies and nanotechnology has the potential to create transformative changes in societal and industrial spheres. Innovations in this field will not only transform human life but also play a critical role in shaping future scientific relationships and commercial applications.

Predictions for the Next 10-20 Years

Over the next 10-20 years, the integration of quantum technologies and nanotechnology will enable revolutionary changes in the creation of complex systems and in many areas of daily life. During this period, the coordination of quantum computing and artificial intelligence (AI) will enable major advances in a wide range of fields, from industrial applications to healthcare. Quantum computing enables the rapid solution of complex problems that classical computers struggle with, while AI algorithms provide speed, accuracy, and efficiency in analyzing and interpreting big data. In particular, quantum machine learning (QML) is expected to contribute to the creation of smarter systems with its innovative approach to data processing and analysis [4, 13].

Quantum communication stands out as a crucial building block for secure data transfer. Quantum key distribution (QKD) techniques will enhance communication security, providing strong protection against cyberattacks. Miniaturization of these quantum communication systems, combined with nanotechnology, will enable faster, more reliable, and more efficient data transfer, enabling revolutionary innovations in the commerce, finance, and healthcare sectors. Quantum memory systems and integrated nanophotonic structures will make international data exchange more efficient and pave the way for the creation of smart networks [9, 14].

In the biomedical field, the integration of quantum technologies and nanotechnology is expected to enable the development of more effective diagnostic and therapeutic methods [16]. Smart sensor systems and AI-enabled biomedical applications will make patient monitoring systems more accurate and foster personalized medicine. Furthermore, the use of nanotechnological structures will transform healthcare by revolutionizing the targeted delivery of biomolecules and drug delivery systems [16, 17].

In the energy sector, quantum technologies will increase energy efficiency and develop sustainable energy solutions. The use of nanotechnology materials in energy storage systems will increase the efficiency and durability of batteries, facilitating the integration of renewable energy sources. Furthermore, the combination of quantum devices and nanoengineering applications will enable more efficient management of systems such as smart grids, resulting in significant energy savings [18].

In conclusion, the interaction between quantum and nanotechnology will play a critical role in the transformation of social and industrial structures over the next 10-20 years. Innovations across sectors such as education, healthcare, energy, and communications will not only transform human life but also pave the way for new business opportunities and economic models. This technological evolution will also enhance humanity's ability to overcome future challenges. This transformation process will be more inclusive and effective if interdisciplinary collaborations and ethical discussions are given due consideration.

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