

Expanding the Scope of Nanobiocatalysis and Nanosensing: Applications of Nanomaterial Constructs

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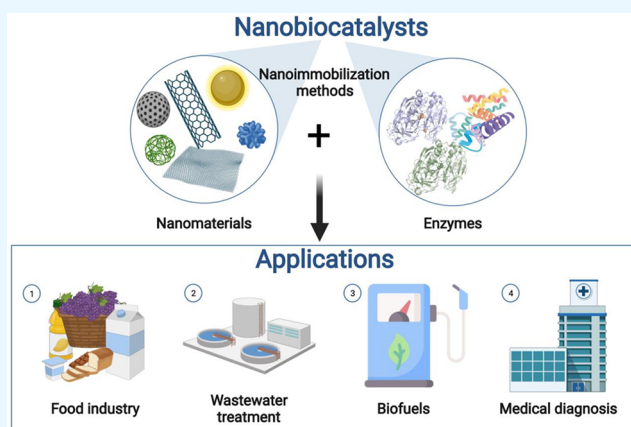
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ABSTRACT: The synergistic interaction between advanced biotechnology and nanotechnology has allowed the development of innovative nanomaterials. Those nanomaterials can conveniently act as supports for enzymes to be employed as nanobiocatalysts and nanosensing constructs. These systems generate a great capacity to improve the biocatalytic potential of enzymes by improving their stability, efficiency, and product yield, as well as facilitating their purification and reuse for various bioprocessing operating cycles. The different specific physicochemical characteristics and the supramolecular nature of the nanocarriers obtained from different economical and abundant sources have allowed the continuous development of functional nanostructures for different industries such as food and agriculture. The remarkable biotechnological potential of nanobiocatalysts and nanosensors has generated applied research and use in different areas such as biofuels, medical diagnosis, medical therapies, environmental bioremediation, and the food industry. The objective of this work is to present the different manufacturing strategies of nanomaterials with various advantages in biocatalysis and nanosensing of various compounds in the industry, providing great benefits to society and the environment.



1. INTRODUCTION

Environmental pollution has reached a tipping point in our biosphere, jumping from stage 2 to stage 3 of the Anthropocene epoch, where human activities have been predicted to affect the structure and functioning of the Earth System.¹ The major concerns are carbon dioxide emissions, greenhouse gas emissions, and water pollution, which are usually concentrated in urban areas as a centralized source of these contaminants. In contrast, soil and water from rural areas are mainly contaminated by chemical agricultural products. In addition, resource exploitation is responsible for burst environmental crises (e.g., hydrocarbon spills, mineral extraction, and waste management in different contexts and some remote locations). As a recent example, the long-term studies in air pollution comparing several cities reflect hot spots of air pollution.² A similar study on water pollution and its correlation to high-density populations was performed.³ In the case of soil and water pollution from rural areas, the contaminants are different and mostly related to pesticides and animal waste. As a consequence of high pollution, non-

accessible regions for humans have been polluted. The Arctic waters have reached alarming levels of contamination, and the Arctic Basin Ecosystem rivers have heavy metals, radionuclides, and oil hydrocarbons.⁴ Such studies give an overview of the pollution and sources, some of them directly identified with complex infrastructure and highly trained personnel. However, it is evident that information availability can catalyze awareness and action. The information on pollution can be available in a practical manner through novel sensing technology. The development of sensors, biosensors, and nanosensors is a research field that has bloomed with the availability of micro and nanofabrication technologies. In addition, nanobiocatalysis

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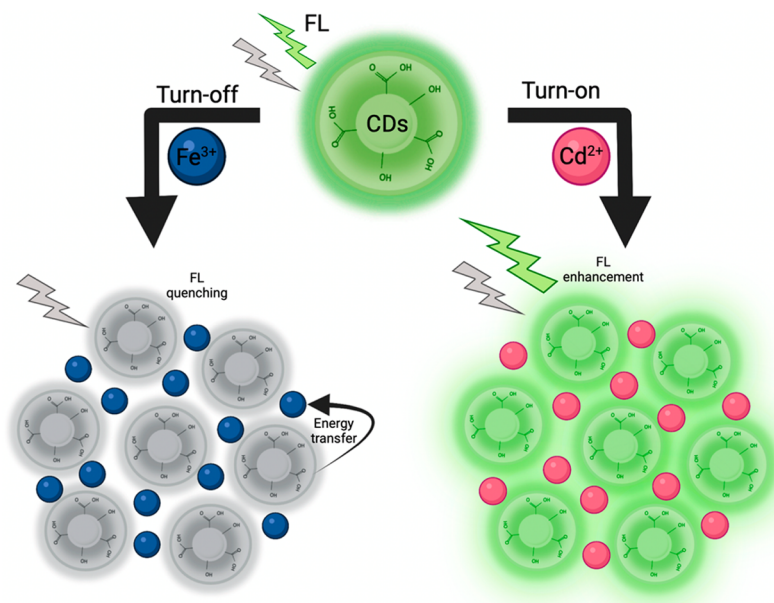


Figure 1. Schematic representation of fluorescence response for the detection of metal ions. Abbreviations: CDs (carbon dots), FL (fluorescence). Reprinted from ref 24. Copyright 2021 Elsevier B.V. License Number: 5356730106426.

has the potential to be applied for the degradation of complex pollutants with great advantages, such as specificity, efficiency, durability, applicability, and performance among others.

The present work discusses the recent advances in the applied research of new nanomaterials developed for nanobiocatalysis and nanosensing in the areas of food, environment, biomedicine, and biofuels, to improve the current biotechnological processes and provide economic and environmental benefits.

2. NANOMATERIAL CONSTRUCTS FOR NANOBIOCATALYSIS AND NANOSENSING

Nanotechnology has offered great opportunities for the biotechnological development of science and industry, achieving potential applications in areas such as medicine, environmental remediation, energy, aeronautics, space exploration, and electronics, among others.⁵ During the development of nanotechnology, synergistic effects have resulted from innovative interactions between different technologies; nanobiocatalysis and nanosensing are two typical examples.⁶ In this manner, nanomaterials—defined as materials with at least one dimension in the size range of 1 to 100 nm—have played a fundamental role in the development and progress of biocatalysis and sensing. According to the dimensionality, nanomaterials are classified into 0-D, 1-D, and 2-D nanostructures depending on the number of dimensions outside the nanoscale range.⁷ Interestingly, a wide diversity of nanomaterials can be derived since nanostructures can be composed of multiple functional materials such as carbon, metals, metal oxides, semiconductors, and polymers, among others.⁸

2.1. Carbon-Based Nanomaterials. Among the great diversity of nanostructured materials, carbon-based nanomaterials have been widely studied due to their exceptional and unique electrochemical properties and their availability to form 0-D, 1-D, 2-D, and 3-D nanostructures.⁸ For instance, carbon nanomaterials can be found as 0-D fullerenes and carbon dots,⁹ 1-D carbon nanotubes and carbon nanofibers,¹⁰ 2-D

graphene,¹¹ and 3-D graphite nanostructures.⁸ Carbon-based nanomaterials—as well as other nanomaterials—can be prepared through different synthesis methods, all of them belonging to the “top-down” or “bottom-up” approach, which are two opposite ways to approach the nanoscale. The “top-down” consists of reducing the size of bulk materials using physical or chemical forces such as occurs during pyrolysis, electrochemical synthesis, chemical oxidation, and arc discharge.¹² Size transformation of bulk materials into nanostructures is typically straightforward; however, the synthesis of nanomaterials with precise control of size and shape through these techniques remains a challenge.¹³ On the other hand, the “bottom-up” approach refers to constructive techniques that involve the assembling of molecules or atoms to form larger nanostructures.¹³ In comparison to “top-down”, this approach generates less/no waste materials, and the particle size of nanomaterials can be better controlled.¹⁴ Hydrothermal, microwave-assisted, coprecipitation, and sol-gel methods are common examples of this approach. For many researchers, carbon nanomaterials have been the preferred selection for sensing applications due to their charge transfer properties, large surface area, and easy surface functionalization.¹⁵

Among the vast array of carbon-based nanomaterials, carbon dots (CDs) are an ideal choice due to their fascinating properties such as fluorescence, biocompatibility, easy surface modification, and enzyme-mimicking capacities, among others.^{16,17} Since their discovery in 2004,¹⁸ studies regarding the understanding of CDs’ properties and their multiple applications have shown an increasing trend. CDs consist of a carbon spherical shaped nanoparticle smaller than 10 nm with a carbon core—either amorphous, crystalline, or a mix of both—and a surface typically rich in functional groups.¹⁶ In the literature can be found successful examples of the employment of CDs in many areas including biomedicine, energy storage, and environmental remediation;^{19–21} however, they have demonstrated outstanding performances in nanosensing, an application that has been widely explored in recent

times. CDs-based sensors have achieved a selective and sensitive detection of different molecules and pollutants including pharmaceutical compounds,¹⁹ amino acids,²² organic pollutants,²³ and heavy metals,²⁴ among others.

CDs' fluorescence properties are the main relevance for nanosensing applications since visible effects on their fluorescence are expected to be observed when being exposed to targets. In this manner, the presence of a specific molecule/pollutant leads to changes in the fluorescence intensity, either enhancement (turn-on) or quenching (turn-off) (Figure 1). Moreover, the enhancement of CDs' fluorescence properties and thus their performance as nanosensors has been recently explored by researchers using different strategies including surface passivation and element doping. As a representative example, CDs with a particle size in the range of 1–5 nm were prepared from *Mangifera indica* leaves through an eco-friendly method by Singh et al.²⁵ Their CDs showed excellent fluorescent properties and an excellent sensitivity to detect Fe²⁺ ions (detection limit of 0.62 ppm) based on photoluminescence quenching. In addition, CDs showed good performance on real samples and great stability over a long period.²⁵

Moreover, the enhancement of CDs' fluorescence properties and thus their performance as nanosensors has been recently explored by researchers using different strategies including element doping and surface passivation. The doping strategy consists of the addition of metallic elements or heteroatoms on the CDs to improve their properties and performance by the modifications in their electronic structure. Nitrogen, sulfur, phosphorus, and boron are frequently used to prepare doped-CDs as metal ion nanosensors.²⁶ Similarly, surface passivation processes can be added during the synthesis of CDs to improve their photoluminescence properties; this improvement is mainly associated with surface energy traps that become emissive. Passivation processes are commonly performed using polymers or organic molecules, in which polyethylene glycol (PEG) stands out due to its wide application for the passivation of CDs.²⁶

Other carbon-based nanomaterials have been used for the same purpose, including carbon nanotubes,^{26,27} carbon nanospheres,²⁸ graphitic carbon nitride,²⁹ and graphene;³⁰ those nanosensor constructs have been successfully applied to detect phenolic compounds, ethanol gas, endocrine-disrupting compounds, pharmaceutical compounds, and metal ions. Overall, carbon-based nanomaterials have shown great potential as nanosensors to detect a wide diversity of molecules, expanding their application in environmental monitoring, food security, and medical diagnosis.^{10,15,16,24}

Recently, carbon-based nanomaterials have also been used as supports to immobilize enzymes to produce nanobiocatalysts. This has led to great advancements in nanobiocatalysis, because of the synergistic interaction between biotechnology and nanotechnology. Many nanomaterials have been used as support matrices for the immobilization of enzymes. For instance, multiwalled carbon nanotubes (MWCNTs) and single-walled carbon nanotubes (SWCNTs) are considered excellent solid supports for the immobilization of enzymes due to their exceptional structural properties, in addition to their biocompatibility and mechanical, thermal, and electrical properties.^{31,32} The advantages of using carbon nanotubes (CNTs) as a support for enzymes have been reported by different research groups. An example is a study performed by Zhang and Cai,³³ who evaluated the immobilization of

horseradish peroxidase (HRP) for the degradation of phenol in wastewater. They compared the performance of the free HRP enzyme to HRP immobilized on carbon nanotubes functionalized with magnetic Fe₃O₄. Interestingly, optimal results were obtained with the immobilized enzyme; its catalytic activity was more stable within an ample range of pH values, temperature, and time. In addition, a reasonably good recycling capacity was observed (65% of the activity after six cycles) with an easy recovery/separation through the use of an external magnet.³³

Similarly, other enzymes have been immobilized on CNTs or CNTs-based composites. For example, laccase from *Trametes hirsute* was immobilized on MWCNTs combined with polyvinylidene fluoride (PVDF) for the efficient degradation of carbamazepine and diclofenac. The results demonstrated a significant improvement in the thermal stability and the operation by the immobilization of the enzyme on the carbon support; the immobilized enzyme presented a remarkable enzyme activity of 4.47 U/cm² and a removal efficiency of 95% within 4 h of reaction (for diclofenac).³⁴ CNTs have been used as excellent supports for a diverse variety of enzymes for different purposes including environmental remediation, water purification, energy production, biosensing, and the food industry.^{35,36} Like CNTs, graphene and its derivatives have been also widely employed as supports for enzymes to construct efficient nanobiocatalysts.^{37,38} In general, the potential of carbon-based nanomaterials for nanobiocatalysis is based on their advantages as an excellent support material for enzyme immobilization such as chemical/thermal stability, high affinity to enzymes, reusability, insolubility during the reactions, regeneration, and biocompatibility.³¹ Thus, carbon-based nanobiocatalysts would eventually enable more practical applications of enzymes in the food industry, bioremediation, fuel production, and medicine.

2.2. Hybrid Nanostructures. Nanostructures have been proved to have great potential in several applications in therapeutics, bioremediation, biosensing, diagnostic, quantification, and others. Hybrid nanostructures emerge as an effective platform for drug delivery, imaging agent, therapeutic, and medical biology applications. A hybrid nanostructure composed of lipid-nanoparticle complexes shows the inherited unique properties of both the inorganic nanoparticles and the lipid assemblies. The nanoparticles within the lipid assemblies largely dictate the attributes and functionalities of the hybrid complexes and are classified as such: liposomes with surface-bound nanoparticles, liposomes with bilayer embedded nanoparticles, liposomes with core-encapsulated nanoparticles, lipid assemblies with hydrophobic core-encapsulated nanoparticles, and lipid bilayer-coated nanoparticles. Those configurations allow encapsulating agents like enzymes, proteins, fluorescently labeled molecules, and others in a complex structure.^{39,40}

Meanwhile, manganese ferrite nanoparticles (MFNs), which can work as a Fenton catalyst, anchored to mesoporous silica nanoparticles (MFMSNs), can be loaded with the photosensitizer molecules like chlorin e6 (Ce6). MFNs have been exploited as an efficient catalyst for the decomposition of H₂O₂⁴¹ and the production of O₂ to relieve cancer hypoxia. Mesoporous silica nanoparticles (MSNs) can be functionalized with saline agents and exhibit great biocompatibility and high loading capacity due to their unique features such as tunable pore size, and they show excellent stability and biocompatibility and easy surface functionalization.^{42,43} Other hybrid

nanostructures are DNA–nanoparticle conjugates, that can integrate different types of DNA molecules and inorganic nanoparticles. This configuration provides unique properties of DNA such as addressability and recognition, which at the same time allow it to exploit the properties of the inorganic core.⁴⁴ Structures like nanoflare sensors exhibit negligible cytotoxicity, high stability, specificity, and good cellular uptake due to structural composition.⁴⁵ These structures are usually synthesized by the direct replacement method and the functional group grafting and subsequent conjugation method. The first method is applicable for NPs with weakly surface-bound ligands, allowing DNA to directly replace the original ligand via dative bonds. The second method is suitable for NPs covered by strong-bound surfactants, such as poly vinylpyrrolidone, trioctylphosphine oxide, and oleic acid, because they lack functional groups for conjugation or the surface-bound groups cannot be easily displaced by direct replacement or non-covalent attachments approaches.^{46,47}

2.3. Enzyme Immobilization on Nanomaterials.

Enzymes are natural biocatalysts that accelerate the rate of chemical reactions and contribute to a great variety of functions like photosynthesis and water splitting. These biocatalysts help a chemical reaction take place efficiently and rapidly, without being permanently modified or altering the chemical equilibrium between products and reactants.⁴⁸ Thus, natural enzymes have expanded their applications to the industry, being used in bioenergy; bioremediation; chemical transformation processes; and the production of fuel, pharmaceuticals, and food.⁴⁹ Frequently, those industrial applications depend on the ability of enzymes to maintain their structural stability during the reactions, which is a major challenge hindering their potential in the industry. A suitable approach to overcome this challenge involves the immobilization of enzymes on solid supports. In comparison to bulk materials, the use of nanomaterials as supports to immobilize enzymes presents multiple advantages including ease of surface functionalization and larger surface area, which leads to higher enzyme loading and increased exposure of the biocatalyst.⁵⁰

Immobilized methods are mainly relevant for nanobiocatalysts since they affect the performance of enzymes; typically, immobilized methods are classified as adsorption, cross-linking, covalent, and entrapped methods (Figure 2).³³ The adsorption method consists of taking advantage of the adsorption force (charge or physical adsorption) of the nanomaterial used as the support. Despite being a simple and direct immobilization methodology, unstable adsorptions

usually occur that make it difficult to retain enzymes on the support, which enables enzyme leaching.^{33,49} The covalent method refers to the covalent conjugation between the free enzyme and the active group of the support material; a long-lasting attachment is achieved, but the enzyme structure could be further altered, directly affecting enzyme activity.^{32,33} In contrast, the cross-linking method reduces the restriction of enzyme conformational space since immobilization is achieved by using a cross-linking agent that connects the support material with the free enzyme.³³ Finally, the entrapped method consists of the formation of the support material in the presence of the free enzyme, encapsulating the enzyme. Negligible structural changes of the enzyme and minimal loss of enzyme and support material can occur during this method, representing significant advantages over other immobilization methods. In addition, good operational stability is typically achieved; however, enzyme leaching can occur if the support material breaks down.⁵¹

3. APPLICATIONS IN NANOBIOCATALYSIS

Nanobiocatalysis has emerged as a synergistic interaction of nanotechnology and biotechnology. The different approaches to achieving effective immobilization of natural enzymes onto nanostructures have led to nanobiocatalysts with great potential in the food industry, wastewater treatment, biofuel production, and medical diagnosis, among others (Figure 3).

3.1. Food Industry. Enzymes are biocatalysts that play a very important role in the food industry for the research and development of food products. Enzymes are organic molecules that are considered “generally recognized as safe” (GRAS) that are applied on a large scale as ingredients or auxiliary agents in the processing of many foods.⁵² Biocatalyzed processes by enzymes are preferred to chemicals, since they have advantages derived from their biological nature, process safety, high yield rates, and low environmental impact.⁵³ The market value of food enzymes is estimated to exceed 3.6 billion US dollars by 2024, which justifies efforts in researching processes for obtaining, purifying, and stabilizing enzymes, which are the main concerns of industrial applications.⁵⁴ For an enzyme-mediated biotechnological process to be viable, it requires that these enzymes present high activity; high conversion rates; and stability at different temperatures, additives, and pH values. Recent advances in nanotechnology have made enzyme-mediated processes more profitable by providing stability, purification, and reuse facilities. In addition to the improvements in product performance, there have been cost reductions due to reuse and process improvements through nanosystems’ immobilization because it is inexpensive, highly available, and nontoxic.⁵⁵

Nanomaterials can load more enzymes due to the higher surface area/volume ratio, and nanobiocatalysts can be developed by nanoimmobilization methods tailored for each nanomaterial and biocatalyst.⁵⁶ Fish oil hydrolysis to produce omega-3 fatty acids is one of the applications in the food industry that has been extensively studied with lipases immobilized on magnetic nanoparticles. These nanobiocatalysts have shown a higher selectivity for docosahexaenoic acid (DHA) and a similar degree of selectivity for eicosapentaenoic acid (EPA) when compared with the free enzyme. An efficiency of up to 95% of biocatalysis was optimized for a nanobiocatalyst obtained by covalent bonding and revealed excellent operational stability, and up to 20 reuse cycles could be achieved with only a loss of 50% of the biocatalytic

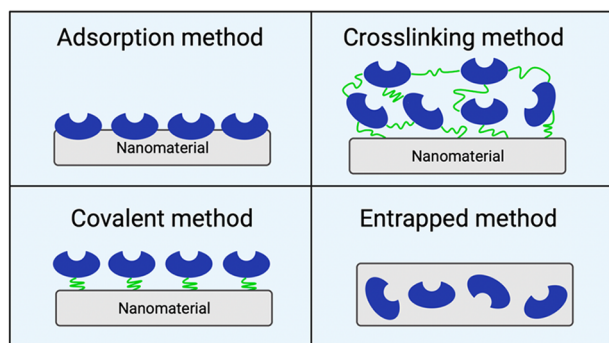


Figure 2. Immobilization methods employed for the development of nanobiocatalysts. Created with BioRender.com and extracted under premium membership.

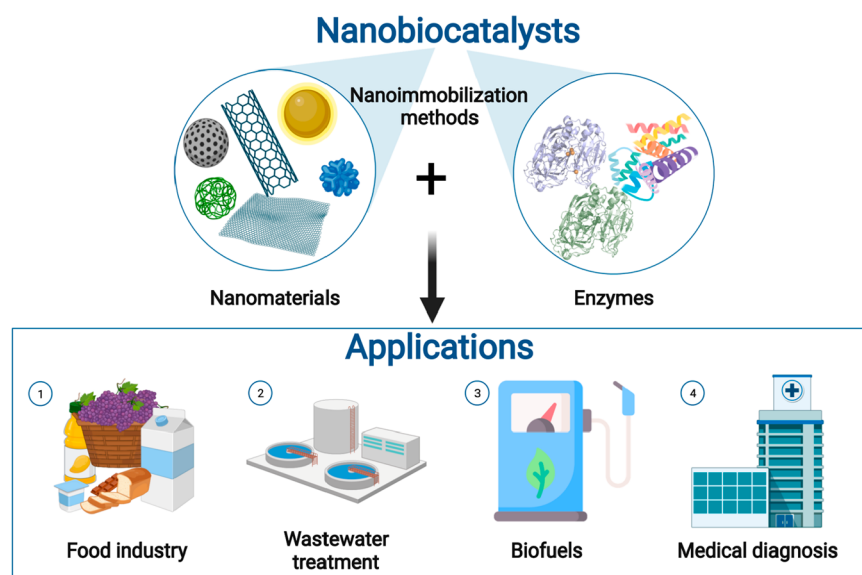


Figure 3. Components of nanobiocatalysts and their main applications: (1) food sector related applications, (2) wastewater treatment plants for decontamination and degradation of pollutants, (3) energy sector related applications, and (4) biomedical applications. Created with BioRender.com and extracted under premium membership.

potential; in addition, it presented a better thermochemical stability.^{54,57} Another study for the hydrolysis of fish oil immobilized lipases from *Thermomyces lanuginosus* for the preparation of robust nanobiocatalysts using a carbon nanotube carrier. The authors demonstrated that higher enzyme loading, up to 6 mg enzyme per g of support, up to 1.6-fold higher DHA enrichment, with 80% operational stability after 6 reuses, was achieved.⁵⁷

Amylases are hydrolytic enzymes that convert starch into different products such as reduced sugars, dextrans, and syrups, representing a wide variety of applications as biocatalysts in food, paper, textile, and detergent industries. Due to its multiple industrial applications, the need to immobilize amylases was also generated to improve their stability and reuse. Amylase immobilization with halloysite nanotubes followed by functionalization with 3-aminopropyl triethoxysilane resulted in improved enzyme stability and slightly increased enzyme activity when compared with free enzyme.⁵⁸ Defaei et al.⁵⁹ immobilized α -amylase on magnetic nanoparticles coated with silica and functionalized with naringin through ionic interactions. The authors reported biocatalytic improvements of the enzyme and excellent operational stability after more than 10 cycles of reuse. Moreover, in comparison to the free enzyme, the immobilized enzyme presented an improvement in storage stability of 60%.

For the production of high-maltose syrups, a recent study reported the immobilization of α -amylase on graphene and magnetite nanoparticles through covalent bonds, which resulted in a nanobiocatalyst with a high enzyme load, 77.58 μ g of amylase per 1 μ g of support, a 20% increase in alkaline tolerance and reusability up to 11 cycles.⁵⁹ Many magnetic nanobiocatalytic systems with enzymes such as pectinases, hemicellulases, and cellulases are widely used in the food industry for the clarification of fruit juices.⁶⁰ Glutaraldehyde-activated magnetite magnetic biocatalysts using pectinases and cellulases were used to clarify grape juice, showing higher activity, thermal stability, and higher reusability, up to 8 cycles.^{60,61}

3.2. Environmental Remediation. The different strategies of nanobiocatalysts have great potential for the development and production of high-quality advanced nanomaterials. The increasing release of polluting agents to the environment due to anthropogenic activities such as mining, electroplating, and other industrial activities, has led to the search for alternative new technologies for the management and treatment of these residues.³¹ Nanobiocatalysis offers the biological capacity of an enzyme to remove specific pollutants in combination with a nanomaterial that synergistically integrates advanced biotechnology and nanotechnology to provide unique electronic, optical, magnetic, and external stimulate responsive properties that, during the treatment of organic contaminants, dyes, and others complex pollutants, had improved the capabilities showed by different enzymes when are proved by themselves compared with when are fixed over a nanocarrier.^{60,62} Immobilization of enzymes during biocatalysis avoids some typical barriers for the industrial application of enzymes at large-scale processes, since it allows the reusability and improves the stability of the enzymes during and after their use.⁶³

On the other hand, the increase of new emerging contaminants in wastewater is a major concern due to their potential effect on human health and the current challenges for their removal. Nanostructured materials provide advanced technologies to remove different water pollutants to improve the potentialities of the enzymes. An increase in the contact area is caused by the nanosize and shape, which reduces mass transfer limitation and increases the stabilization and reusability of the enzyme. In this manner, the operational cost decreases while novel nanocatalysts are created without compromising enzyme functionality for remediation.⁶⁴ The development and application of metallic, carbon-based and derivatives, polymer-based, silica-based, and magnetic nanostructured materials used as a host matrix for the immobilization of enzymes on nanobiocatalytic processes for wastewater remediation has been reported to increase the

Table 1. Description of the Most Used Nanobiocatalysts for the Removal of Pollutants in Wastewater

enzyme	nanomaterial	immobilization strategy	application	improvement due immobilization	reference
laccase	fumed silica	sorption assisted	oxidation of phenolic compounds	increase of enzymatic activity up to 1.64-fold free enzyme	66
laccase	fumed silica	sorption assisted	elimination of: hydroquinone bisphenol A diclofenac gemfibrozil benzophenone-2 benzophenone-4	higher activity retention over a wide pH range compared with free enzyme	67
laccase	zeolitic imidazole framework-8	covalently	acid blue 92:AB92 degradation	dye removal up to 90%	68
laccase	graphene oxide-zeolite nanocomposite	covalently	direct red 23 degradation	reusability over five cycles, high storage stability, and thermal stability	69
laccase	micronanobubbles (MNB)	NS ^a	degradation of: bisphenol A bisphenol B bisphenol C mixture of BPA, BPB, BPC	degradation 2.3–6.2 higher than only enzyme	70
laccase	Cu ₂ O nanowire-mesocrystal	covalently	degradation of 2,4-dichlorophenol	enzyme activity 10-fold higher than free enzyme	71
glucose oxidase horseradish peroxidase laccase	Fe ₂ O ₃ yolk-shell	covalently	decolorization of dyes' degradation of biophenol A	32-fold higher stability than the free enzyme	72
peroxidases polyphenol oxidase	magnetic-core	sorption assisted	phenol removal	enzymes retained 50% of their initial activity after 6 uses	73
horseradish peroxidase	GO-Fe ₃ O ₄ /Au@CA	sorption assisted	4-chlorophenols	removal of 98% 4-CP and retention of 95% of the initial activity after three cycles	74
lignin peroxidase	carbon nanotubes	sorption assisted	decolorization of dyes	increase of 18- and 27-fold of activity compared to the free enzyme	75
oxidase	Nafion/oil/Pt-nanoparticles	NS	oxidation of glucose, choline, lactate, and sucrose	oxidation rate enhancement by a factor of 10–30	76
cyanate hydratase	magnetic-multiwall carbon nanotubes	covalently	treatment of waters with cyanate, chromium, iron, lead, and copper	long-term storage stability	77
catalase	magnetic-multiwall carbon nanotubes	physical adsorption	treatment of wastewater	improvement of enzyme activity and stability	78
lipase	ionic liquids-modified carboxymethyl cellulose nanoparticles	covalently	industrial wastewater treatment	specific activity 1.43 higher than free enzyme	79
lipase	copper ferrite nanoparticles	covalently	industrial wastewater	high storage and temperature stability; reusability up to 80% after 10 cycles	80

^aNS = not specified.

removal efficiencies of dyes, phenols, pesticides, and other aromatic compounds.^{31,65}

Different research has been focused on the development of nanosupport materials that allows immobilization of enzymes without compromising the enzyme activity and the degradation potential while improving enzyme recovery and decreasing fixation cost.⁶⁶ Laccase immobilization for wastewater treatment has been one of the most studied nanobiocatalysts, showing great potential to remove multiple pollutants such as phenols, dyes, pharmaceuticals, and other aromatic compounds (Table 1).^{66–80} Nevertheless, in recent years, other enzymes such as glucose oxidase, horseradish peroxidase, and phenolic oxidase have gained interest. During their application, green nanomaterials have been used as supports for the oxidation of phenols and decolorization of dyes.^{72–74}

3.3. Biofuel Production. Environmental applications of nanobiocatalysis include the removal of organic compounds and dyes during wastewater treatments and soil remediation processes, as well as the improvement of biofuels' production.

Anaerobic digestion and fermentation are the most common processes used for obtaining biofuels and value-added products from biomass. Nevertheless, process efficiencies are mainly controlled by the biomass characterization than environmental and operational conditions, which can result in an inefficient production of the molecules of interest.⁶³ Nanobiocatalysis applied on solid wastes is focused on the degradation of the complex cell wall of different residues, facilitating the extraction of bioactive substances from natural sources. The use of enzymes such as cellulases, hemicellulases, and pectinases has been evaluated for their ability to hydrolyze biomass for biofuels' production.⁸¹ Nanobiocatalysis for biofuel production can be described in two main applications: (i) the production of biofuel by enzymatic technologies, which consume less energy and is more environmentally friendly than conventional alkaline catalyzed methods; and (ii) the hydrolysis of cellulose to generate sugars for bioethanol production by fermentation process.⁶⁰

Immobilization of lipases by the covalent method using different nanomaterials as a host matrix is one of the most reported nanobiocatalyst used for biodiesel production.⁸² Zulfiqar et al.⁸³ obtained biodiesel that meets the physicochemical characteristics of international standards for biofuels, by the transesterification of *Jatropha curcas* seed oil using novel nanobiocatalyst lipase-PDA-TiO₂, reaching an optimum biodiesel yield of 92%.⁸³ Nanobiocatalysis using immobilized lipase for biodiesel production compared with the application of free lipase demonstrates multiple benefits, such as the increase of the enzyme activity up to 190%, high tolerance to methanol, storage stability, reuse for 10 cycles maintaining up to 84% of its initial activity, and a biodiesel yield of 88% compared with 69% obtained with a free enzyme.⁸⁴ Another application of lipases as a nanocatalyst is the improvement of biofuels' production from microalgae, where biodiesel production has reached a biodiesel conversion of 71%, showing a reusability of five cycles and maintaining up to 59% of the catalytic activity.⁸⁵

Enzyme-based biofuel cells are a technology with attractive attributes for energy conversion, which include renewable catalysts, fuel flexibility, and operation at room temperature. Unfortunately, their limitations remain and include short lifetimes, low power densities, and inefficient fuels' oxidations.⁸⁶ Nanostructure biocatalysts have emerged as an alternative to improve the power density of enzyme-based biofuel cells allowing the immobilization of enzymes in a large surface area using various nanostructures including mesoporous media, nanoparticles, nanofibers, and nanocomposites that lead to high concentration loads of enzymes. Is important to consider that both, enzyme stabilization and activation, together with high enzyme loadings in various nanostructures, will significantly improve enzyme-based biofuel cells, due to the apparent enzyme activity improvement by the relieved mass transfer limitations of substrates in nanostructures compared with macro-scale matrices for conventional enzyme immobilization.^{86,87}

The use of nanoparticles has been growing as an enzyme host, an achievement of 6.4 or 10 wt % has been reported thanks to the large surface area per unit mass of nanoparticles. On the other hand, some reports revealed that the mobility associated with the particle size and fluid viscosity could affect the intrinsic activity of the enzymes attached to the particles. Also, it is important to consider that the nanoparticles are frequently in dispersion in the reaction solution, which represents a challenge for recovery and reuse. Nonetheless, the use of magnetic nanoparticles could be a solution to this problem, making easier the recovery using a magnetic field. This approach can increase the stability since the immobilization shows a lower activity.⁸⁶

Mesoporous materials have been popularized for many applications thanks to controlled porosity and high surface areas. Hosting enzymes for immobilization is one of the widely studied applications for these materials.⁸⁸ One of the novelties of mesoporous media is their capability to suffer several modifications such as the enlargement of the pore size. It is important to notice that the stability of immobilized enzymes is dependent on factors like pore size and charge interaction. Some authors have reported that the pore size in the material should be similar to or larger than the enzyme size to achieve a successful enzyme immobilization; this also provides better stability on the immobilized enzymes; meanwhile, the charge has a key role in the enzyme stability in mesoporous materials.

In this manner, mesoporous materials with the same charge of enzymes, might repel themselves and provide instability in the enzyme immobilization.^{86,87}

The use of nanofibers or nanotubes has been shown to overcome the problems observed in nanoparticles by their dispersions in buffer solution and difficult recovery, and electrospin technologies have proven to be an easier method for nanofibers' preparations allowing us to use of a wide range of materials that keep the advantages of nanoparticle materials, providing a large surface area to attach enzymes. The use of electrospin technologies allows control of the size, composition, and arrays; because of the structure of nanoparticle materials, their separations can be conducted by highly porous substrates relieving the mass-transfer limitation.^{86,89–91}

3.4. Medical Diagnosis. A constant evaluation of biomarkers is key to surveilling human health and for the diagnosis of several diseases, including cancer. Currently, there is a myriad of detection techniques that require a long preparation time or are susceptible to interference by molecules mixed within samples. Multiple methodologies based on nanotechnology have been developed to increase the resolution of detection without compromising specificity and to minimize costs and time consumption. For example, a fluorescence resonance energy transfer (FRET)-based sensor for inorganic phosphate in urine samples has been developed with a limit of detection (LOD) of 3.8 $\mu\text{mol/L}$ for procedures of 10 samples that lasts 10 min.⁹² Here, the phosphate in a sample interacts with molecules of cetyltrimethylammonium bromide (CTAB) that are attached to Au nanoparticles (AuNP) and competes with terbium-ethylenediaminetetraacetic acid complex ([Tb-EDTA]-1), a luminescent probe. This competition provokes a change in fluorescence intensity that is proportional to the phosphate concentration. Similarly, fluorescence quenching has been used for glutathione sensing based on nanostructures of gold coupled with bovine serum albumin (BSA) and coated with graphene oxide and folic acid. The glutathione, an antioxidant molecule strongly related to several types of cancer, competes with the BSA which leads to the photobleaching of the nanostructure.⁹³

Similarly, functionalized nanostructures have been coupled with enzymes like horseradish peroxidase (HRP) to sense iodide levels in biological fluids;⁹⁴ with glucose oxidase (GOx) to detect HIV DNA biomarkers⁹⁵ and colorimetric determination of glucose levels;⁹⁶ with cholesterol oxidase (ChOx) for cholesterol concentration analysis;⁹⁷ or with alkaline phosphatase (ALP) for ATP determination.⁹⁸ Notably, there is a sensor for glucose that utilizes the catalytic energy derived from a combination of HRP and GOx as biofuel.⁹⁹ Although the enzymatic activity determines its implementation, the stability of nanostructures of polystyrene,⁹⁵ gold,^{94,96} graphene,⁹⁹ or manganese oxide⁹⁷ allows a reduction in sample manipulation, improves the reaction velocity, and promotes repeatability and reusability. Intrinsic properties of nanostructures have also been used for detection. Principally, optical properties, like those presented for quantum dots¹⁰⁰ or CsPbX₃ nanocrystals,¹⁰¹ were used to detect pH levels in mitochondria and reactive oxygen species, respectively. Coupling nanostructures with immunology have increased sensing capacity too. Nanosensors based on nanorods of zinc oxide (ZnO) functionalized with monoclonal antibodies for endocrine disruptors with femtomolar sensitivity³⁶ or antibodies attached to magnetic AuNP for detection of hepatotoxins.¹⁰²

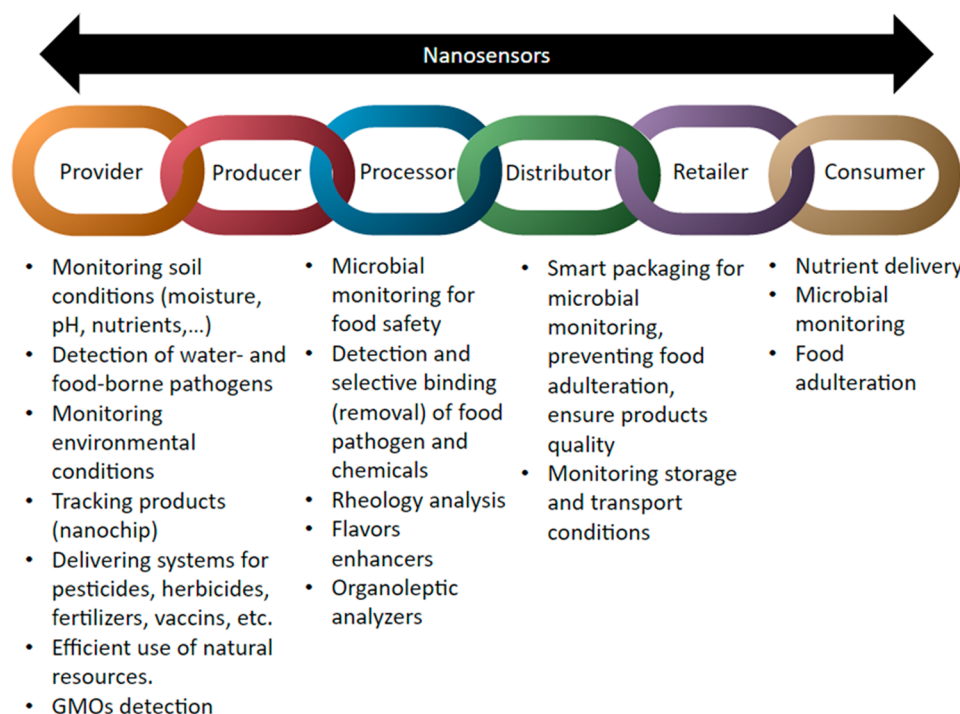


Figure 4. Application of nanosensors throughout the food supply chain.

4. APPLICATIONS IN NANOSENSING

Nanosensing platforms have been recently able to detect concentrations of chemical species and pollutants or even monitor physical parameters like temperature. In this manner, they can be employed in diverse areas such as to ensure food and water quality and for health purposes.

4.1. Food Industry. The increasing demand and the diversification of the global food industry require technological development to ensure food quality, safety, and traceability. There is a major shift toward the use of nanosensing in the food industry due to its advantages over other sensing technologies, including high sensitivity, specificity, reliability, and high-throughput analysis.¹⁰³ Nanosensors have been implemented across each step of the food supply chain (Figure 4). The extended use of sensors involving nanotechnology in agroindustry, food processing, distribution chain, and even at the consumer level has aimed to enhance food sustainability.

Microbial detection, including viruses, bacteria, fungi, and parasites, is crucial to control water- and food-borne pathogen outbreaks and ensure food security. Nanosensors are used in food microbiology to detect pathogens in food material, processing plants, final products, and across the distribution chain.¹⁰⁴ Pathogens can be detected through the presence of whole cells, nucleic acids, proteins, and metabolites (e.g., toxins, urea, glucose). Nanotubes, nanowires, nanoparticles, nanosheets, and porous nanostructures have been designed as nanostructured transducers for monitoring pathogens in food (Figure 5).¹⁰⁵ Such nanostructures are coupled to antibodies, antimicrobial peptides (AMPs), and nucleic acids to selectively bind with targets. These nanosensors have been developed to improve detection limits,^{106–108} allow simultaneous detection of pathogens,¹⁰⁹ differentiate Gram-positive and Gram-negative bacteria,¹⁰⁵ and detect multidrug resistant strains.¹¹⁰ Recently, nanosensors have been applied in packaging material to respond to environmental conditions during storage and

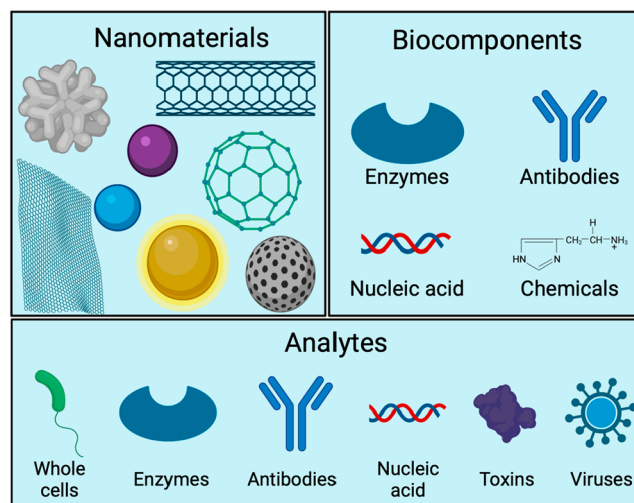


Figure 5. Common types of nanomaterials, biocomponents, and analytes in nanosensing. Created with BioRender.com and extracted under premium membership.

transport to monitor food degradation due to temperature, pH, and moisture changes. Nanosensors are also used to monitor the growth of pathogens, mycotoxins, and some chemicals such as antibiotics that can act as preservatives or antimicrobials to ensure food quality and safety (Table 2).¹⁰⁶

4.2. Environmental Remediation. Another potential application of nanosensing has focused on the development of sensors for environmental applications. Some of the advantages of these sensors are a decrease in fabrication cost, improved sensitivity and detection potential, and selectivity. The use of some high-cost materials during the construction of sensors is usually required and their substitution represents a great challenge. Nanosensors have successfully been fabricated, and their comparison with conventional sensors showed that

Table 2. Examples of Nanostructured-Based Sensors for Detection of Food Contaminants

type of food contaminants	materials	detection techniques	applications	detection limit	reference
		Pathogens			
<i>Salmonella typhimurium</i>	Fe-MOF/PtNPs	microfluidic immunosensor	food sample	93 cfu/mL	111
<i>Escherichia coli</i>	MIL-53(Fe)/PEDOT	electrochemical	water	4 cfu/mL	112
	Ab/Cu ₃ (BTC) ₂ -PANI/ITO	electrochemical	water	2 cfu/mL	113
	Cu-MOF NP	colorimetric	milk	2 cfu/mL	114
<i>Staphylococcus aureus</i>	2D MOF	electrochemical	-	6 cfu/mL	115
	NH ₂ -MIL-53(Fe)	photoluminescence	cream pastry	85 cfu/mL	116
		Mycotoxins			
3-nitropropionic acid	[Zn ₂ (tcppb)(4,40 -bipy) ₂]	fluorescence	sugar cane	1.0 μM	117
	Eu-MOF (1)	r fluorescence	moldy sugar cane	12.6 μM	118
aflatoxin B1	UiO-66-NH ₂	fluorescence	corn, rice and milk	0.35 ng/mL	119
	Zr-LMOF/MF	fluorescence	water	1.6 mg/L	120
patulin	MIP/Au@Cu-MOF/N-GQDs/GCE	electrochemical	fruit juices	0.0007 ng/mL	121
		Antibiotics			
tetracycline	Eu-MOF (1)	fluorescence	water	3 nM	122
	Eu-MOF	fluorescence	milk and beef	22 and 21 μM	123
cephalexin	gCDc/AuNCs @ ZIF-8	r fluorescence	milk	0.04 ng/mL	124
metronidazole	MIL-53(Fe)@MIP	fluorescence	milk	53.4 nM	125
chloramphenicol	MIP/Zr-LMOF	fluorescence	milk and honey	0.11 and 0.13 μg/L	126
nitrofurans	Eu-MOFs	fluorescence	food	1.08 μM	127
	{[Cd ₃ (TDCPB) ₂ DMAC]·DMAC·4H ₂ O} _n	fluorescence	milk	105 μM	128

no significant difference has been found between the detection of some contaminants when nanosensors are used, in terms of concentration sensitivity and detection capacity.¹²⁹ Environmental applications of nanosensing are directed to the detection of different contaminants. Ethanol detection by a chemical sensor fabricated by employing CeO₂ nanoparticles, showed high sensitivity and detection even at low concentrations.¹³⁰ Furthermore, nanosensors can take advantage of nanobiocatalysis for the detection of a broad range of analytes improving the selectivity for the detection of some specific contaminants.¹³¹ In this sense, Patel et al.,⁷⁰ developed a nanosensor based on the nanobiocatalyst prepared using yolk-shell particle-based laccase that showed an improvement in the selectivity of 2,6-dimethoxyphenol.⁷²

Globally, agriculture is one of the primary industries and its development involves a high-water demand and discharges of pesticides, fertilizers, and other pollutants. Nanobiosensors can be applied to monitor parameters like temperature, humidity, and other soil components in order to reduce the usage of water and chemicals at specific times and locations.¹³² The development of nanobiosensors for the detection of organic pollutants and their application in agriculture includes the detection of acetamiprid, dinosulfon, phenols, and organophosphate pesticides, reaching high accuracies and sensibility.^{107,133–136} Lipid membrane nanosensors have provided a tool for the detection of insecticides, pesticides, hydrazines, toxins, and polyaromatic hydrocarbons, among other contaminants; they have been implemented in real samples and even at a pilot scale, showing excellent results. This new generation of biosensing has the potential for developing site-specific responses that ensure environmental protection.¹³⁷

4.3. Medical Diagnosis. Nanomaterials have emerged recently as multifunctional blocks for the development of next generation sensing technologies for a wide range of industrial sectors, including the medical field. Emerging nanoparticles-based sensors include electrochemical, electrochemiluminescent, colorimetric, fluorescent, chemiluminescent, surface plasmon resonance sensors, quartz crystal microbalance,

surface-enhanced Raman scattering, fluorescence resonance energy transfer, and metal-oxide gas, among other sensors. Most of these nanosensing technologies are based on nanoparticle detection.¹³⁸ Nanosensors are designed to detect target analytes and measure them through spectral, optical, chemical, electrical, electrochemical, magnetic, or mechanical signals.¹³⁹

Traditional diagnostic methods, including chemical markers and imaging methods, have been in constant development to increase the real-time measurements, lower the costs and time-consumption, and provide early-stage and disease prognosis as gold-standard tests.¹⁴⁰ Including a conversion between diagnostic and nanomaterials can improve the precision, treatment outcomes, early-stage disease detection, a personalized patient treatment plan, low concentration of metabolites, identification of biomarkers, sensitivity, and so on. Also, these detection markers have been identified in different types of human samples, such as liquid biopsies taken from blood, urine, sweat, saliva, and breath, where the aim is to determine an accurate diagnosis in a noninvasive type of sample.¹³⁹

5. CONCLUSIONS, CURRENT CHALLENGES, AND RECOMMENDATIONS

Recent developments in nanobiocatalysis and nanosensing have shown great potential in the food industry, medical diagnosis, and environmental remediation. In this Review, we summarized and discussed the employment of novel nanomaterials for the quantification of a range of substances on different media. Overall, they have demonstrated high effectiveness and specificity. On the other hand, a vast diversity of nanostructures has been applied as a support material for enzymes to form efficient nanobiocatalysts. In this regard, we have discussed the most recent advancements in nanobiocatalysis. Finally, current challenges regarding specificity, stability, and toxicity concerns for nanomaterials' leaching are presented. Thus, further research efforts should be directed to address such inconveniences. Despite the great benefits of nanosensors in the food industry, potential toxicity and

environmental effects are raising concerns. Therefore, studies must be standardized to determine the effect of nanoparticles on humans and the environment.¹⁰³ Selectivity, specificity, linearity of the response, reproducibility of signal response, quick response time, stability, and operating life are key requirements to successfully develop biosensors.¹⁰³

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ABBREVIATIONS

CDs	carbon dots
MWCNTs	multiwalled carbon nanotubes
SWCNTs	single-walled carbon nanotubes
CNTs	carbon nanotubes
HRP	horseradish peroxidase
MFNs	mesoporous silica nanoparticles
MFMSNs	manganese ferrite nanoparticles
GRAS	generally recognized as safe
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
FRET	fluorescence resonance energy transfer
LOD	limit of detection
CTAB	cetyltrimethylammonium bromide
AuNP	Au nanoparticles
Tb-EDTA]-1	terbium-ethylenediaminetetraacetic acid complex
BSA	bovine serum albumin
GOx	glucose oxidase
ChOx	cholesterol oxidase
ALP	alkaline phosphatase
ZnO	zinc oxide
AMPs	antimicrobial peptides

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