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Review

A Comprehensive Review on the Use of Metal–Organic Frameworks (MOFs) Coupled with Enzymes as Biosensors

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Abstract: Several studies have shown the development of electrochemical biosensors based on enzymes immobilized in metal–organic frameworks (MOFs). Although enzymes have unique properties, such as efficiency, selectivity, and environmental sustainability, when immobilized, these properties are improved, presenting significant potential for several biotechnological applications. Using MOFs as matrices for enzyme immobilization has been considered a promising strategy due to their many advantages compared to other supporting materials, such as larger surface areas, higher porosity rates, and better stability. Biosensors are analytical tools that use a bioactive element and a transducer for the detection/quantification of biochemical substances in the most varied applications and areas, in particular, food, agriculture, pharmaceutical, and medical. This review will present novel insights on the construction of biosensors with materials based on MOFs. Herein, we have been highlighted the use of MOF for biosensing for biomedical, food safety, and environmental monitoring areas. Additionally, different methods by which immobilizations are performed in MOFs and their main advantages and disadvantages are presented.

Keywords: biosensors; MOFs; enzyme immobilization

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1. Introduction

In recent decades, biosensors that employ enzymes as their main sensing element have been used in various applications in the biomedical, food safety, and environmental monitoring areas [1–3]. However, although demonstrating high sensitivity and specificity to several analytes, as well as catalytic activity superior to that of artificial catalysts, enzymes, being biological structures, possess low thermal, chemical, and mechanical stability. Additionally, they may lose their activity during analytical protocols [4–6]. In this sense, one strategy to circumvent these limitations and provide operational improvements to these biocatalysts is their immobilization [1,4–6]. Recently, the use of metal–organic frameworks (MOFs) as immobilization matrices to this end has shown very encouraging results in the coupling of enzymes to biosensors [1,4–10].

MOFs are a unique class of materials due to their large surface area, porous crystalline structure, high porosity, and high flexibility [11]. These attributes give these materials remarkable physical and chemical properties [12]. They consist of metallic compounds that are interconnected by organic linkers arranged within a crystalline polymeric structure [12,13]. In addition, MOFs have large free volumes within their structure, pores

of uniform size, and remarkable surface area. This renders MOFs easily adaptable to a wide range of applications, such as the separation and storage of gases, drug delivery, and sensor detection [11–17]. As they are also malleable structures, there are a variety of morphologies and topologies in which MOFs can be synthesized, granting the ability to specifically design such materials for targeted applications [18]. In this sense, the relative ease of modification of MOFs suggests that they can be a promising alternative for enzyme immobilization protocols and, along with their potential for detection applications, they can also be a potent material for enzymatic biosensors [5,6,11,15]. According to the literature, MOFs can be used as enzyme immobilization matrices in the manufacture of biosensors [19].

This review summarizes the advances in, and the peculiarities of, the use of MOFs as supports for enzyme immobilization, and their subsequent incorporation into biosensors. Methods by which immobilizations are performed in MOFs are discussed, and some of their practical applications are presented, especially in the fields of biomedicine, food safety, and environmental monitoring.

2. Metal–Organic Frameworks

MOFs are porous crystalline compounds with elastic properties and peculiar geometry. They consist of organic bonds and inorganic metals arranged in a coordinated manner, as illustrated in Figure 1 [19–22]. They are also known as Metal–Organic Polyhedra (MOP), Porous Metal–Organic Frameworks (PMOF), Porous Coordination Polymers (PCP), Iso-Reticular Metal–Organic Frameworks (IRMOF), Coordination Polymers (CP), Microporous Metal–Organic Frameworks (MMOF) and Zeolitic Imidazole Frameworks (ZIF) [23–25]. This type of material can be obtained via different routes of synthesis, such as solvothermal, electrochemical, microwave-assisted, or hydrothermal synthesis [26–31]. Furthermore, MOFs show many notable and highly beneficial advantages for processes involving energy and gas storage, drug delivery, adsorption, catalysis, bioimaging and biosensing, molecule separation, and even cancer therapy [32–36]. This is owing to the possibility of designing these structures for many particular applications, as their chemical arrangement is easy to manipulate. This allows for their employment in a wide array of different industries, from medicine to engineering [37–39].

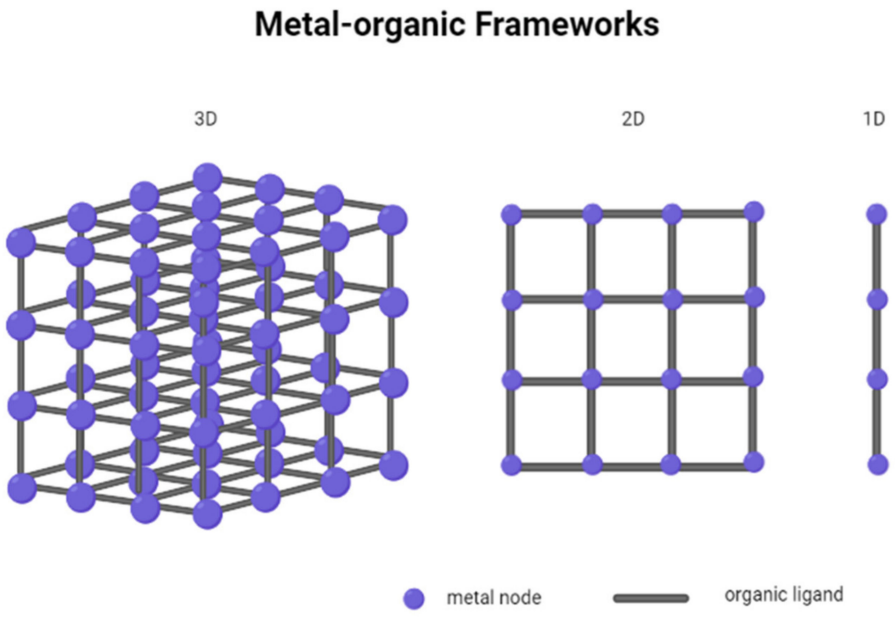

Figure 1. Structures of compound coordinated metal ions and organic binder arrangements shown in up to three dimensions.

Studies on the structures of MOFs began with Werner, who proposed an arrangement for coordinated substances via his model, which involved joining central metal ions with

binding molecules. The arrangement of these Werner-type coordinate complexes generates a supramolar architecture that evidence long chains, which are called coordinate polymers; these hybrid materials show organic ligands that uniformly connected the metal atoms in the structure [23,40,41]. In this way, numerous functional regions in the binders form long structures and configure polymers of varying molecule ratios.

For the construction of porous and rigid MOFs, it is necessary to consider that large organic binders cause MOF pores to extend, enabling a reduction in the accessible pore size and the interpenetration of the structure. The selection of exchangeable molecules and size adjustment is essential, as MOF pores must be filled with important molecules in order to synthesize materials. In this context, the control of structure topology is defined by an adequate choice of connectors and binders [23,42,43].

Properties of Metal–Organic Frameworks

MOFs have an extensive surface area and a high porosity rate. Such characteristics allow for the molding of their structure into many different configurations, according to the intended purpose [44–46]. Pores can have sizes ranging from the micrometer scales to mesoscales [32,47,48]. In coordination polymers, such as the MOF-200, about 90% of their volume consists of pore voids, causing these porous materials to present lower crystal density [23,49,50]. These properties are fundamental for gas storage and separation processes, for example, and naturally, are considered singularities that makes MOFs stand out from other more conventional porous substances.

Furthermore, MOFs can flex their structure to maintain good stability, rendering them resistant to changes in pressure, chemical media, and temperature [51–54]. They also show the capacity to accommodate gases and liquids by reversibly adjusting its structure to expand or shrink without breaking bonds owing to their characteristic dynamics. Pore volume changes can be of several angstroms, reinforcing their flexibility also to guest molecules, giving them the beneficial property of carrying out reactions within the pore complex [55–57]. This type of 'multi-stable phase' works as a response to the environment and is only activated through external stimuli, such as the entry of guest molecules, which changes the pressure, magnetic field, or light in the vicinity of the pore [58–61]. Regarding this property, the MOF that best exemplifies the flexor capacity of these materials is the MIL-53, which has a structure similar to a wine rack [62–64].

As shown in Figure 2, the reversible, flexible, tunable, and responsive mechanisms of MOFs correspond to 'breathing' movements, when their structures expand and contract, and also deforming in the process. 'Swelling' happens when the monomer increases in size to accommodate the molecule within its space, without changing its shape; finally, a 'linker rotation' occurs when linkers change their angle while making a rotation movement without breaking their bonds, also to accommodate molecules [24,65–68].

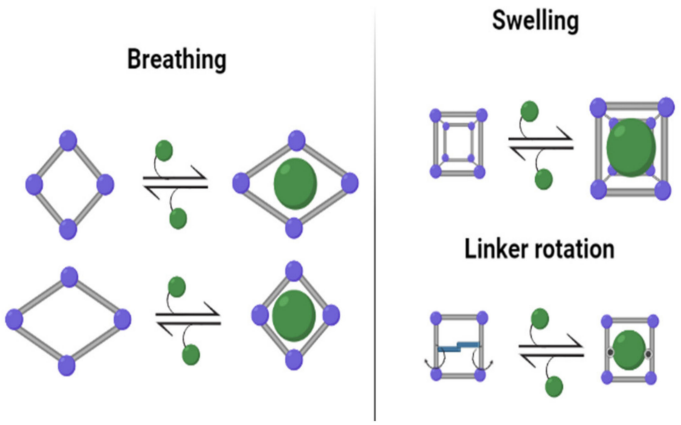

Figure 2. Mechanisms arising from the flexor capacity of MOFs. The green spheres represent the 'guest' molecules.

3. Preparation/Characterization of Enzyme–MOF Biosensors

Enzymatic immobilization in MOFs is achieved by the formation of bonds between the enzyme and their interactions with the material [7,69,70]. Most synthesized enzyme–MOF compounds are based on the mechanisms of co-inclusion, covalent bonding, trapping, or physical adsorption. Table 1 illustrates the most common immobilization strategies and their main advantages and disadvantages.

Table 1. Different methods of enzymatic immobilization on MOFs and their main advantages and disadvantages.

Synthesis of Metal–Organic Frameworks (MOFs) for Enzyme Immobilization		
Immobilization Strategies	**Main Advantage**	**Main Disadvantage**
Co-precipitation	More enzymes can be added to the MOF structure [71–73].	As synthesis and immobilization occur concomitantly, enzyme clusters may form, reducing the immobilization yield [74–77].
Covalent linkage	High binding strength usually involves several enzyme residues, providing outstanding structural rigidity [78,79].	Partial inactivation or reduction of catalytic activity may occur due to conformational changes in the enzyme structure [80,81].
Entrapment	Reduces enzyme exposure to unnatural environments [82,83].	Difficulty in controlling pore size facilitates enzyme desorption; this also causes problems of mass transfer limitations and diffusion of substrates in the pores [84,85].
Surface attachment	Reduces changes in the enzyme's active site [79].	Ease of desorption due to weak interactions between enzyme and support [81].

3.1. Co-Precipitation

Co-precipitation is a recent approach designed to encapsulate macro enzymes in the MOF structure. During co-precipitation, nucleation, MOF generation and expansion, and enzymatic immobilization occur simultaneously [71–73]. The main advantage of this process is that a higher number of enzymes can be added to the surface of MOFs [74]. Figure 3 depicts a synthesis process occurring by co-precipitation.

MOFs have high surface areas and adjustable pore sizes. Thus, there is a better distribution of enzymes in MOFs during synthesis [75]. Based on this, authors such as Wang et al. (2017) incorporated Chloroperoxidase in ZIF-8 to MOFs and modified an electrode using this material. The authors employed the multienzyme system in a glucose detection protocol [76]. Zhang et al. (2017), in turn, used this methodology for synthesizing enzyme–MOFs for CO_2 capture [77].

3.2. Covalent Linkage

Covalent bonding is considered one of the strongest chemical interactions between enzymes and supports [86–96]. This immobilization process involves several enzyme residues. The multipoint covalent bond immobilizes the enzyme, thus reducing its flexibility. This stiffens the enzyme, mitigating the structural rearrangements and denaturation caused by external agents such as heat, temperature, and organic solvents [79].

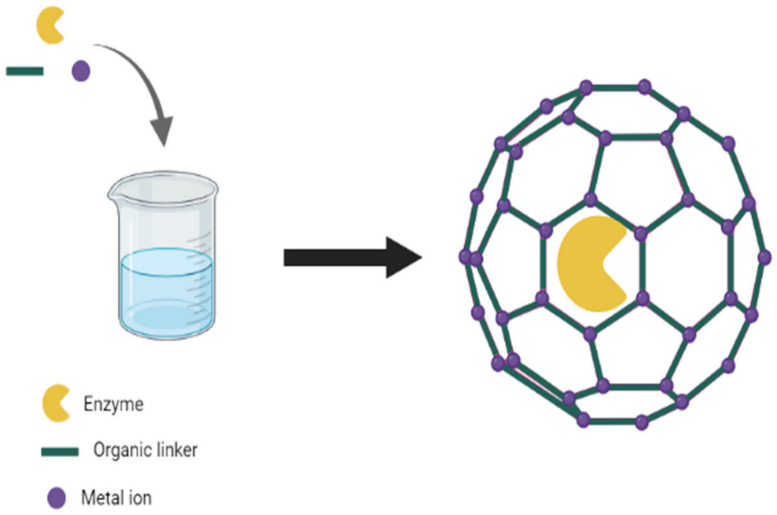

Figure 3. Schematic representation of the co-precipitation method.

This immobilization process commonly starts with a chemical modification of the MOFs. During this step, reactive groups are used, such as epoxy, glyoxyl, or amino groups. These groups react with the enzyme interface [97]. Amino groups are widely used especially due to their capacity of bonding with carboxylic groups [78]. Figure 4 shows the schematic representation of this type of immobilization method.

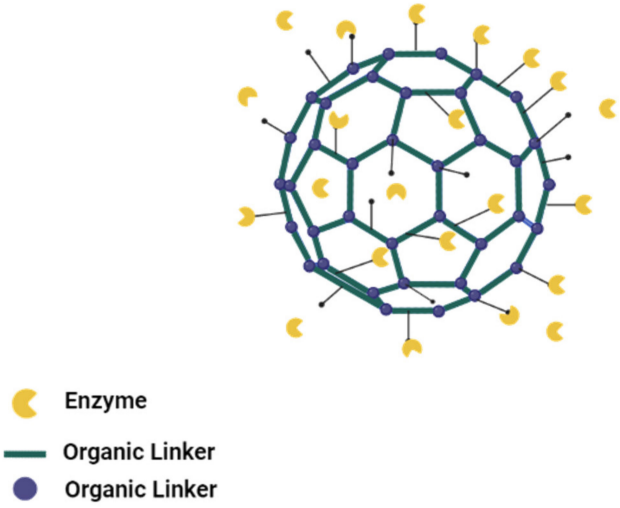

Figure 4. Schematic representation of the covalent linkage method.

Factors such as the density of reactive groups per unit area of the metal–organic material, the reactivity of functional groups of both the enzyme and the MOFs, and the complex protonation state directly influence the number of covalent bonds that are formed [81]. Thus, having to attain the correct parameters for immobilization renders this strategy challenging to implement.

3.3. Entrapment

Typically, MOFs have high porosity. Therefore, enzymes can be either physically adsorbed on the surface or trapped within the mesopores of these materials [82,83]. Enzyme entrapment in MOF mesopores increases enzyme stability under adverse environmental conditions. The resulting increased stability is a benefit of the structural protection provided by MOFs [84]. Li et al. (2016) observed that immobilizing organophosphorus acid

hydrolases (OPAA) on a metal–organic zirconium structure increased the enzymes' stability and long-term use [85].

It is worth pointing out, however, that one of the most significant difficulties reported in the literature with this technique refers to problems with enzyme diffusion in the pores of MOFs [82]. Figure 5 shows the schematic representation of enzyme entrapment in MOFs.

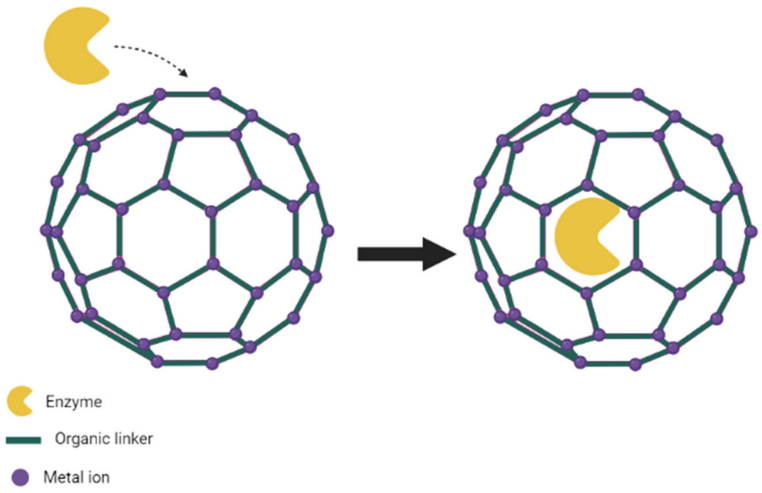

Figure 5. Schematic representation of enzyme entrapment in MOFs.

3.4. Surface Attachment

This strategy is based on the physical adsorption of the enzyme onto the material's surface through bonding (electrostatic interactions, Van der Waals forces, hydrogen bonds, and hydrophobic interactions) [98–100]. As the immobilization process is based on these interactions, conformational changes in the enzyme do not occur. This method also reduces changes in the active site, thus preserving the enzymatic activity [81].

The main advantages associated with this method are its easy implementation and low cost. However, enzymes immobilized onto MOFs via physical adsorption tend to show low operational stability. In addition, due to the disordered arrangement of the enzymes on the surface of the material, enzyme desorption may take place [101]. Figure 6, below, shows the schematic representation of this immobilization process.

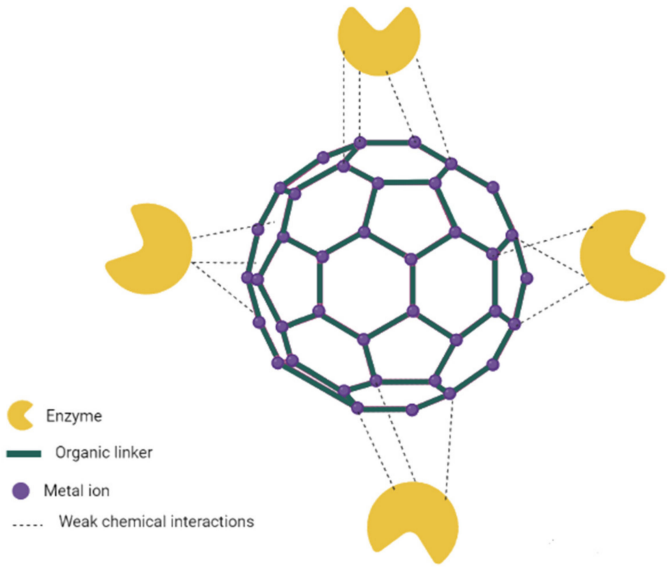

Figure 6. Schematic representation of the physical adsorption of enzymes in MOFs.

4. Application of Enzyme–MOF Biosensors

4.1. Biomedical Applications

4.1.1. Glucose Oxidase-Integrated MOFs as Biosensors

Glucose oxidase (Gox, EC 1.1.3.4) is an enzyme present in aerobic organisms, and its primary function is the oxidation of glucose to gluconic acid [102]. This oxidoreductase has also found applications as a glucose biosensor due to its high stability and specificity [68]. The immobilization of GOx onto zeolitic imidazolate 8 (ZIF-8), which is an organic-metallic framework [1], allows for better stability, increased catalytic activity in the degradation of commercial drugs, pH stability, greater tolerance to organic solvents, and greater reuse capacity when compared to the free enzyme [103]. Their use as biosensors allows for an ultrasensitive detection of glucose levels in human serum, in addition to good reproducibility in experiments, and a wide detection range (1–500 μM) (Figure 7). This technique has a minimum concentration sensitivity of less than 0.5 μM, well suited for clinical analyses [104].

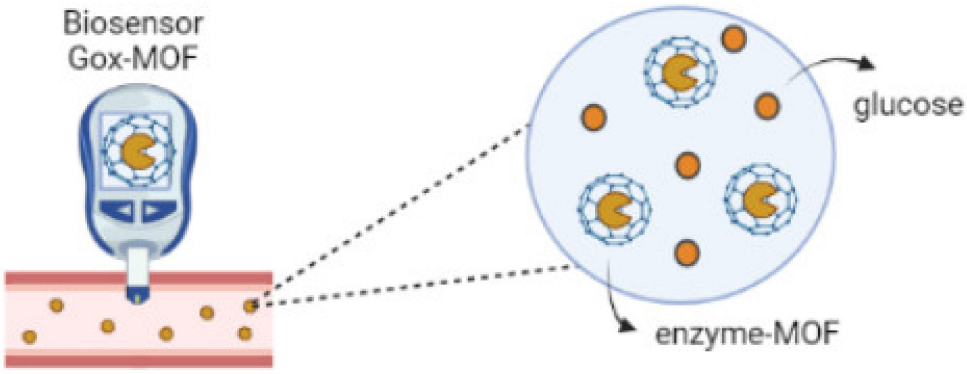

Figure 7. Enzyme–MOF biosensor for the ultra-sensitive detection of glucose levels in human serum, showing good reproducibility in experiments, wide detection range, and capacity of metabolization by the organism.

As glucose is the primary energy source in cells, it also plays a vital role in the growth of tumors [105]. Thus, blocking the availability of this sugar in tumor cells can be a good alternative for treating tumors [101]. MOF-based biomimetic nanoreactors (TGZ @ eM) were developed and coupled to GOx, and the prodrug tirapazamine (TPZ) was encapsulated in the porous regions of MOFs [106]. Zhang and collaborators concluded that this MOF-based structure effectively carried GOx into the tumor, and the enzyme, through its catalytic activity, was able to consume the glucose and oxygen present in the malignant cells. This led to tumor hypoxia and the release of TPZ, activating the cells that induce apoptosis [106].

4.1.2. Detection of Hydrogen Peroxide Using MOF-Based Enzymes

Hydrogen peroxide is a metabolic product of obligate and facultative aerobic organisms [76]. It can be a byproduct of the conversion of fatty acids into energy or of the defense mechanisms of white blood cells in the immune system [107]. It is a harmful metabolite, and there is a need for its elimination, which occurs naturally in healthy organisms [108]. Its detection can be achieved through electrochemical biosensors associated with catalase (CAT) (E.C. 1.11.1.6), the enzyme that has the ability to break down hydrogen peroxide (Figure 8) [109]. Catalase immobilization in MOFs enables the mapping of the different concentrations of the oxidant in the body within a wide detection range, due to the high stability of the complex formed, and without compromising enzyme activity, which also facilitates electron transfers [74].

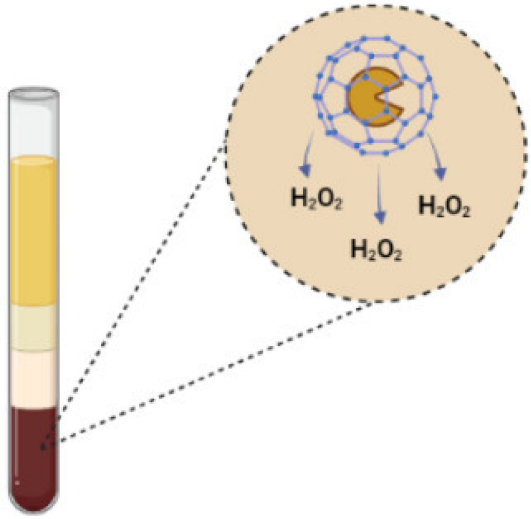

Figure 8. Hydrogen peroxide produced in white blood cells being detected by an enzyme–MOF biosensor produced using catalase, which is responsible for metabolizing this chemical compound in the body.

4.1.3. Enzymes Immobilized with MOFs for Drug Delivery as Immunosensors

Due to the high porosity of some MOFs being quite evident, researchers in the biomedical area have developed macromolecule encapsulation techniques to facilitate the delivery of therapeutic drugs in the body [110]. One of the problems related to this immobilization technique is the potential metabolization of these compounds, since this can lead to the release of the metals in the body, which in many cases, can be toxic [111]. Thus, the need for minimizing the toxic effects resulting from this release has led to research trials using endogenous metals and focusing on therapeutic effects [112].

A straightforward method for this would be the use of the biomolecule itself as a reagent, which binds to MOF, forming a porous capsule capable of housing the drug (Figure 9) [113]. It is essential to monitor the active site of the enzyme and the stability of the formed capsule, as these factors will directly affect the kinetics of drug release in the body. Release and delivery occur as a result of degradation of the MOFs and increases in pore diameter, which lead to the detachment of the drug from the complex [110].

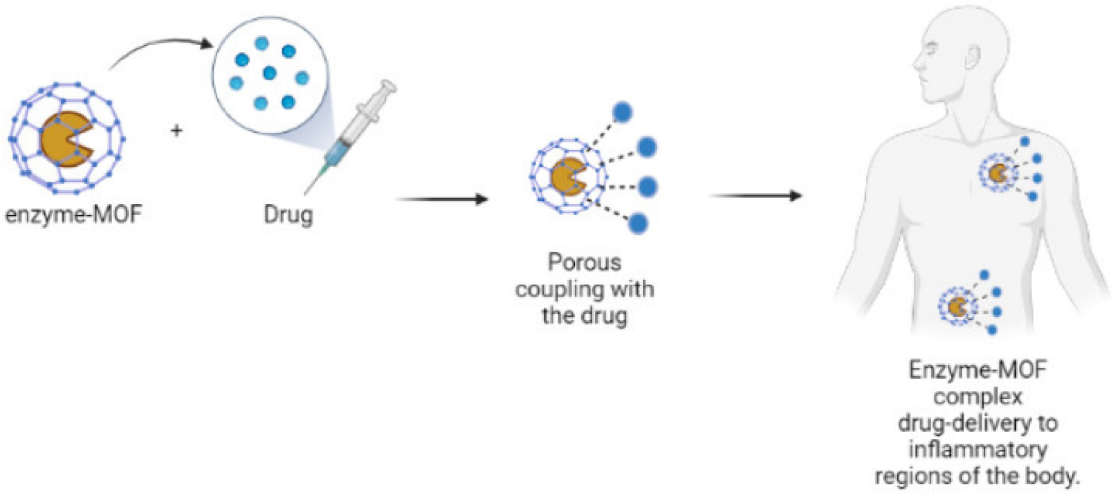

Figure 9. Enzyme–MOF composites carrying drugs in the pores of the immobilization support through the body, which can be a useful tool in the treatment of diseases in different parts of the body.

4.1.4. MOF-Based Electrochemical Biosensors for Detecting Cancer Biomarkers

Based on the work of Filik and Aslihan, the growth of several tumor lines can be evidenced by an abnormal production of proteins, overexpression of genes, and increased levels of primary metabolites known as biological markers. As diagnosis depends on identifying and analyzing these abnormal biological entities, MOF-based biosensors have been developed to measure apoptosis in in vivo systems [1]. Among these markers, special attention has been given to the protein tyrosine kinase-7 (PTK7), the lymphocyte activating gene-3 protein (LAG-3), the human growth factor receptor-2 (HER-2) epidermis, to several miRNAs (such as miRNA122, miRNA144, and miRNA21), as well as to various types of antigens, such as the prostate-specific antigen (PSA), the carbohydrate antigen 15-3 (CA 15-3), and the carcinoma antigen 125 (CA 125) [112,113]. These biomolecules are related to different types of cancers, and their mapping in the body allows for the detection of these diseases. To identify the overexpression of these molecules, techniques such as fluorescence, mass spectroscopy, colorimetry, and electrochemistry are commonly used [114,115]. MOF-based biosensors have been used as carriers to deliver biorecognition compounds or materials to cancerous tissues [116].

The application and development of enzymes immobilized with MOFs are growing in relevance in the identification of tumor cells, and in addition to being easy to manufacture, they show excellent thermal and chemical stability [117]. Thus, the most promising biomedical application of these systems has been for the mapping of tumor cell biomarkers through colorimetric immunoassays [76]. This technique is efficient and enables cell cycle monitoring and cancer detection at an early stage, which has rendered it very promising in clinical screenings [118]. In addition to this, its high porosity allows for better stability in the anchoring of several bioactive elements, which can bind to the enzyme–MOF complex and be subsequently mapped by confocal microscopy. This can then lead to the identification of the affected tissue or even the path taken by the biomolecule inside the cell, allowing for the elucidation of the genesis of the tumor (Figure 10) [114].

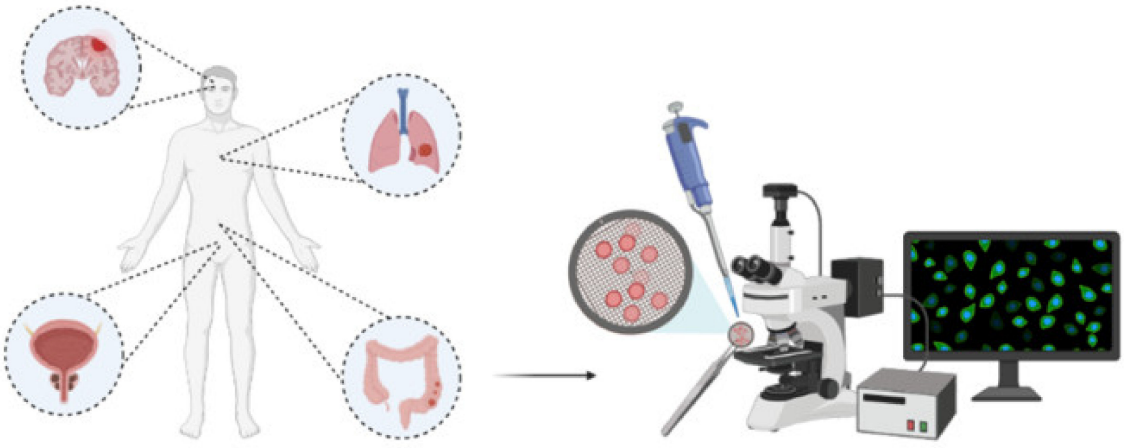

Figure 10. Confocal microscopy being used for the mapping of tissues experiencing tumor growth and for the monitoring of the path taken by the biomolecule inside the cell, which enables the detection of tumor genesis.

4.1.5. Detection of Other Analytes of Biomedical Interest

According to Mohammad et al., a simple method for developing MOF-based enzymatic biosensors is by producing a thin layer of immobilizers and applying the free enzymes to the surface of this material. These biosensors are widely used to identify several analytes produced in, or ingested by, living organisms [119]. The enzyme polyphenol oxidase (PPO) (EC. 1.14.18.1), for example, can be encapsulated with MOF and used as an electrochemical biosensor to map the oxidoreductase activity of this enzyme in phenols [117]. Cholesterol is another lipid-based biomolecule of relevance to biomedicine, as several cardiovascular

diseases are related to its consumption and accumulation in the body. Thus, mapping cholesterol can be done by immobilizing a cholesterol oxidase (CHOD) (EC 1.1.3.6) onto metal–organic frameworks, which can allow for an accurate detection and concentration measurement in blood vessels or in other tissues in the body [120].

Biomedical applications of enzyme–MOFs biosensors are a promising area to be explored, as these electrochemical sensors are an excellent alternative to the more conventional techniques. Furthermore, these devices can have numerous applications in many different areas by increasing the performance of process enzymes and optimizing industrial and laboratory processes (Figure 11). Again, a noteworthy benefit of these devices is the maintenance of the enzymatic activity, enabling its reuse and contributing to thermal and pH stability. An inherent downside, however, is the long times required for the manufacture of these devices, as a series of practical steps for synthesis, in vitro tests, and in vivo activity, are required before these systems can be considered safe to use as drug carriers, biomolecule detectors, sugar- and lipid-meters, and for other applications that involve direct human contact with the biosensor.

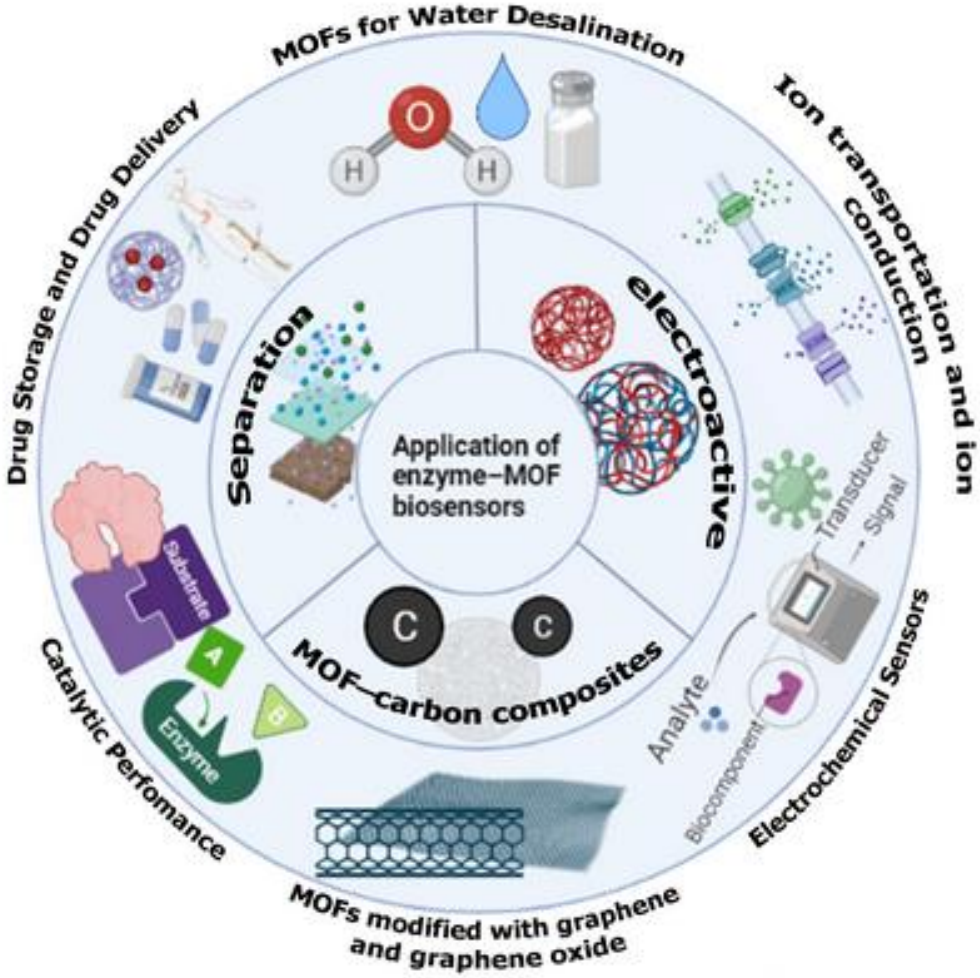

Figure 11. Applications of metal–organic frameworks in different chemical and biological areas of high interest.

A survey on metal–organic structures for enzyme encapsulation and their applications is shown in Table 2.

Table 2. Summary of biomedical applications of enzyme–MOF composites reported in the literature in recent years.

No.	MOFs	Enzyme	Detection Ranges (mM)	LOD (μM)	Biomedical Applications	References
1	ZIF-8	Lactate/glucose oxidase	0.01–0.3	9.2	Tumor cell mapping and energy reduction in tumor cycle	[120]
2	QDs/CDs @ MOFs	Ascorbate oxidase	0.003–0.01	1.0	Improved ascorbic acid detection	[117,121]
3	OMUiO-66 (Ce)	Glutamate oxidase	0.125–8	1.2	Potential for screening for specific chiral amino acids in complex biological samples	[102,122]

Table 2. *Cont.*

No.	MOFs	Enzyme	Detection Ranges (mM)	LOD (μM)	Biomedical Applications	References
4	ZIF-90/Ce-MOF	Catalase	0.008–0.056	0.03	Sensitive detection and degradation of hydrogen peroxide	[123,124]
5	L-MOFs	Glucose oxidase	0.01–10	0.2	Insulin delivery	[125,126]
6	MOF-818 @ RGO/MWCNTs/GCE	Polyphenol oxidase	0.002–0.6	6.1	Mapping of oxidoreductase activity on phenols	[127]
7	PCN-333(Fe)	Alcohol Dehydrogenase	0.01–0.2	6.2	Catalysis of the conversion of toxic alcohols to aldehydes in cells	[128,129]
8	MIL-101(Cr)	Microperoxidase 8	0.001–2.22	3.0	Dual catalytic activity in the selective oxidation of organic molecules	[130–132]
9	ZIF-8	Urease	0–0.8	5.0	Sensitive urea detection	[133]
10	AgNC/Mo(II)-NS	Cholesterol oxidase	0.05–0.6	0.018	Detections and concentration measurements in blood vessels or body tissues	[134,135]
11	UiO-66	Lipase	0.001–0.2	0.35	Drug synthesis against venous thromboembolism	[136,137]
12	ZIF-8	Glucose oxidase	0.008–5	8.0	Electrochemical glucose detection	[76]
13	MIL-88B-NH_2(Cr)	Trypsin	0.05–1	3.0	Protein degradation by enzymatic hydrolysis	[5,138]
14	CYCU-4	Trypsin	0.001–0.2	0.5	Protein digestion	[84]
15	Tb-mesoMOF	Mb	0.01–5	5.0	Oxidation of ABTS and THB	[139]
16	ZIF-67	Glucose oxidase	0.002–1	0.66	Antimicrobial action	[140]

4.2. Environmental Applications

4.2.1. MOF-Based Biosensors for Detecting Environmental Pollutants

Catalytic biosensors are also widely used to detect environmental contaminants [141,142]. Marco and collaborators highlighted several biosensor devices using oxidase enzymes, such as peroxidase, laccase, and aldehyde dehydrogenase, aiming at their application as pollutant detectors. The most common techniques used to that end, qualitative and quantitative, are based on chromatographic principles [116,139]. However, the immobilization of enzymes with MOFs has shown to be very promising as an alternative to conventional analytical techniques, and they can be used to determine the presence of organophosphate compounds and various phenols, which are the primary environmental pollutants [143]. Synthesis by biosensors involves converting an optically inactive substrate into a compound with optical or electrochemical properties to enable the mapping and analysis of the device's enzymatic activity [84]. The detection of pollutants by these enzymes is not based on catalysis but on the substrate's inhibition of the enzymatic activity [141]. Although this detection technique is considered an excellent alternative for replacing more traditional methods that generate residues and waste, its employment is not always possible [144].

The enzyme must be commercially available, and factors such as purification, enzyme stability, and the need for co-dependent factors need to be taken into consideration [74].

In the literature, it is possible to find several environmental applications for metal–organic frameworks coupled with enzymes (MOF–enzymes), as shown in Table 3. However, the main focus of the present work is on the discussion of applications of MOF–enzyme composites as biosensors.

Table 3. Summary of environmental applications of enzyme–MOF composites described in the scientific literature.

No.	MOFs	Enzyme	Detection Ranges (mM)	LOD (μM)	Environmental Applications	References
1	MOF-199	Laccase	0.015–0.1	9.8	Removal of heavy metals from fluids and aquatic environments	[145,146]
2	UIO66-NH_2	Acetylcholinesterase	0–50	3.0	Organophosphorus pesticide detection	[147,148]
3	ZIF-8	Choline oxidase	0.01–0.8	7.8	Detection and removal of water pollutants	[149,150]
4	Ce (III)/UiO-66	Hydrolases	0.005–1	7.4	Adsorptive removal of organic dyes from aqueous solution	[151,152]
5	ZIF-90	Catalase	0–0.3	5.8	Effluent treatment for wastewaters	[153,154]
6	HKUST-1	Peroxidase	0.03–0.9	7.5	CO_2 adsorption	[5,155,156]
7	L-MOFs	Lipase	0.01–10	2.0	Luminescent sensors for environmental pollutants	[157,158]
8	QD-MOF	Oxidase	0.005–1	0.05	Degradation of organic dyes in industrial waters	[159,160]

4.2.2. Enzyme–MOF as Biosensors with Improved Electrochemical Performance for Pesticides

The use of insecticides and nematicides based on organophosphate compounds and carbamates is common in agriculture [161]. These compounds inhibit the action of the enzyme acetylcholinesterase (AChE), responsible for the hydrolysis of the neurotransmitter acetylcholine [162]. However, these pesticides can persist in the environment for long times and cause several environmental problems.

Dong and co-workers highlighted an efficient protocol for detecting this pollutant by using acetylcholinesterase biosensors. The immobilization of this hydrolase with a metal–organic structure allows for high stability without compromising the enzymatic activity, apart from allowing for the sensitive bioindication of pesticide levels in water bodies (Figure 12). The most common MOFs used for immobilization have a general M-MOF-NH_2 structure (M: Fe, La, and Zn) that can be efficiently coupled to the enzyme and allow the substrate to reach the active site of acetylcholinesterase, acting in its inhibition route. The detection range of these devices is comprehensive and linear, being very promising for identifying organophosphates in water, digested soil, and on the surface of bioaccumulated organic structures [163]. Compared to other MOFs, the general model used is easy to develop and well-suited as electrochemical detection materials. The AChE-M-MOF-NH_2 biosensor proves to be a sensitive pesticide detector and opens up a prospective alternative for the development of new electrochemical devices based on MOF enzymes, as they can be excellent options to spectrochemical and Sensormatic methods [164].

4.2.3. Detoxification and Effluent Treatment Using MOF-Based Enzymes

A technique widely used in the treatment of wastes rich in organic matter is its subsequent dilution and the addition of enzymes capable of hydrolysis. This can be done along with the optimization of the treatment steps in this protocol, as it is an innovative and low-polluting alternative [165]. By coupling an enzyme to an MOF, the ability to monitor the biosensor behavior, route, and activity is gained [166]. Many suppressed materials have been developed with a focus on the environment, which enables the detection of specific substrates [167]. Since the enzyme is specific, we can selectively target the device to act on a specific chemical class of compounds [168].

Ahuja et al. highlighted some pollutants that can be detected using this technique. These include liquid solvents such as organochlorines, hexane, heptane, toluene, polyaromatics, industrial residues such as oils and naphthalenes, petroleum residues, metals, and radioactive effluents (Figure 13). The differential of this technique is that the detection range is wide enough to justify the replacement of more traditional and costly methods [169].

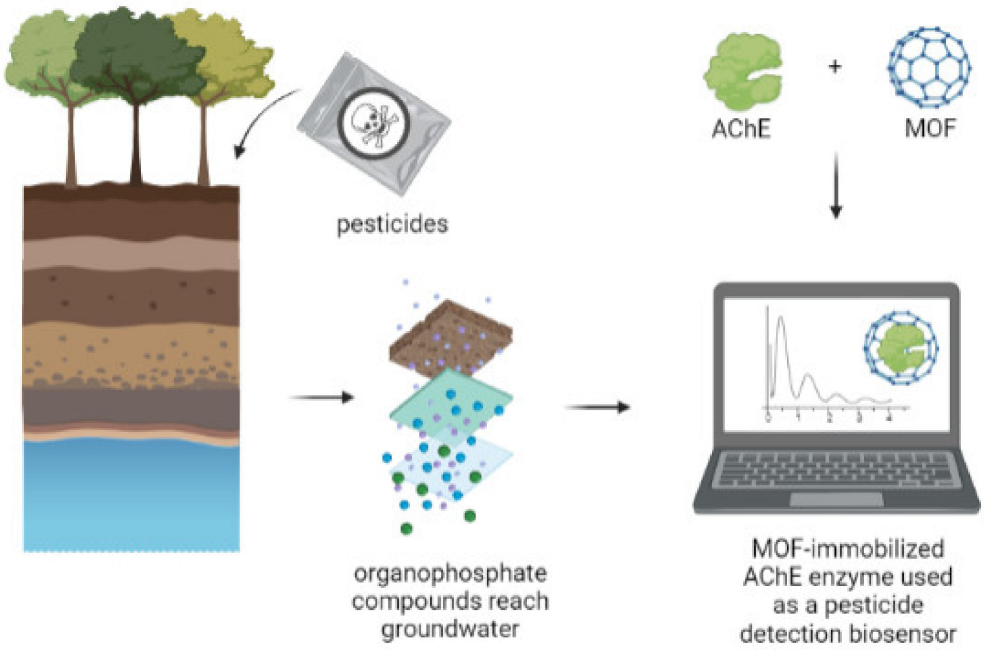

Figure 12. The identification protocol of organophosphate pesticides that is widely used in the agricultural industry. These pesticides are capable of permeating the soil and reaching groundwaters causing pollution; they can be detected with an AChE-MOF biosensor.

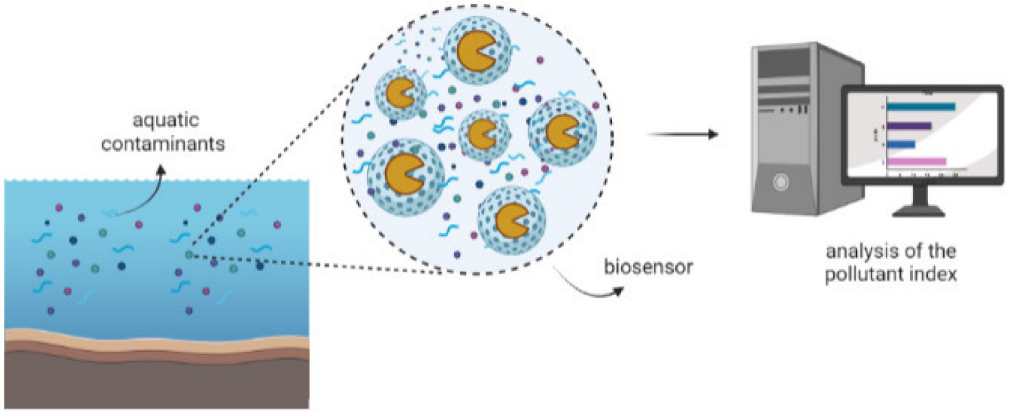

Figure 13. Pollutant detection protocol on the surface of metal–organic structures (MOFs) coupled with hydrolases, where contaminant particles attach to the material, detoxifying the wastewater.

It is essential to highlight that these enzymes play an essential role from an environmental point of view, and that with their application via immobilization onto a metal–organic structure, their use becomes increasingly promising. This is because they are employed in highly optimized processes and because they are also biodegradable, according to the parameters set in Green Chemistry [170].

4.3. Food Applications

In recent years, foodborne and food-related diseases have become a global concern due to the significant increase in the morbidity and mortality rates linked to food con-

sumption [171,172]. Bacterial pathogens, antibiotics, clandestine food additives, and heavy metal ions can lead to the contamination of food products at any stage of the food production chain [173]. Food contamination can have different causes, such as the misuse of veterinary drugs and pesticides, the production of phytotoxins and marine toxins by organisms, bacterial contamination, and the production of chemical compounds during processing stages. Due to the change in the population's eating habits, the globalization of food chains, and the mass growth of food establishments, food safety concerns have raised worldwide [174]. Food safety is an essential and critical issue in the modern food industry. Due to the imperative need for food safety monitoring, new methods of higher sensitivity, rapid detection, and greater portability must be developed to overcome the limitations and high costs linked with traditional methods.

Novel methods can improve the identification of food contaminants by mitigating the impact of potential outbreaks, helping in the combat of threats to human health, and improving the general population's well-being. In this scenario, enzymatic biosensors have been used as super-analytical devices to rapidly screen for hazardous chemicals and toxins aiming at ensuring food safety [175,176]. Enzyme–MOF complexes represent a promising class among biosensor materials due to their peculiar physicochemical characteristics such as ultra-high porosity, large surface area, and flexible structures. Lately, much research has been carried out using enzyme–MOFs in the manufacture of sensors for food safety detection, including luminescence, electrochemical and colorimetric sensors [174]. Due to the above properties, MOFs represent a niche in the field of new materials, allowing them to be specifically manipulated and adapted, which is highly advantageous and valuable in the realm of food safety. For enzyme–MOF biosensors, enzymatic immobilization techniques are highly significant due to the relative instability of the isolated enzyme and the difficulty in recovering them still in their active form [177].

Another essential element in food safety is food packaging. It is an integral component of the global food supply chain and protects foodstuffs from physical damage, chemical contamination, and microorganisms, helping to maintain food quality and safety during transport and storage. Paper-based food packaging can be produced with the help of novel technologies, such as enzyme–MOFs, via a group of functional materials possessing unique chemical and physical properties that are potentially promising in food safety due to its high surface area and porous structure [178]. Several organic binders have been developed and combined with various inorganic sites, leading to tens of thousands of MOFs with different compositions [173,179].

Notably, these advantages of MOFs make them good candidates for the manufacture of biosensors with broad applications, especially in the food and environmental fields [180,181]. Consequently, biosensorization techniques based on MOFs present great potential in manufacturing robust analytical sensors aimed at detecting analytes in food engineering, environmental and industrial applications [182]. A simple and sensitive electrochemical sensor, for example, has been built to monitor lead in leafy vegetables at the scale of parts per trillion (ppt) [182]. For biosensors based on enzyme–MOFs, enzymatic immobilization techniques are highly significant due to the enzyme's relative instability and fragile nature, which makes them prone to denaturation under adverse conditions [167]. Sensing devices with MOFs-enzymes represent a valuable niche in materials, allowing them to be specifically built and adapted, which is highly significant in food engineering.

4.4. General Applications

Biosensors are devices that incorporate a biologically active element into an appropriate transduction element to detect, reversibly and selectively, the concentration or activity of chemical species in a given sample. A few elements are necessary for designing efficient biosensor systems, such as biorecognition molecules (aptamers, antibodies, or enzymes) that can specifically interact with targets [183,184]; signal transducers that can generate measurable signals in response to the interactions between biorecognition elements and analytes; and data management tools such as electronic systems [185,186]. Close and

specific interactions between biorecognition molecules and analytes produce detectable responses on the biosensor's surface.

Biologically active entities that can be used in the process include enzymes, antibodies, nucleic acids, organelles, and microorganisms [117,158]. Enzymatic biosensors have shown great potential applications in clinical diagnostics, the food industry, and environmental analyses. Therefore, the methods to produce effective biosensors have received great attention [187,188]. Due to their high specificity, enzymatic biocatalysts such as glucose oxidase, tyrosinase, and lycase can be used in bioanalytical chemistry, especially for biosensing applications [189]. The importance of enzymatic biocatalysts lies in their ability to catalyze reactions only with their corresponding substrates, rendering these devices highly capable of distinguishing specific analytes in complex matrices. A classic example is the glucose biosensor used in blood glucose test strips to monitor blood glucose levels in diabetic patients [190].

MOFs have a range of peculiar physical and chemical properties that make them very promising for various applications (Figure 14) [183,191–194]. Several innovative structures and materials based on MOFs and their derivatives have been developed, and are widely used (Figure 8) in areas such as biosensing [195], gas storage [194], drug distribution [196], catalysis [197], food engineering [198], adsorption, gas separation [199], among others [200]. MOFs have tunable pore sizes (ranging from several angstroms to about 10 nm), good adsorption capacity, large surface area, and high stability [201]. They are considered promising structures for the production of enzymatic biosensors due to favorable anchoring biorecognition molecules [123].

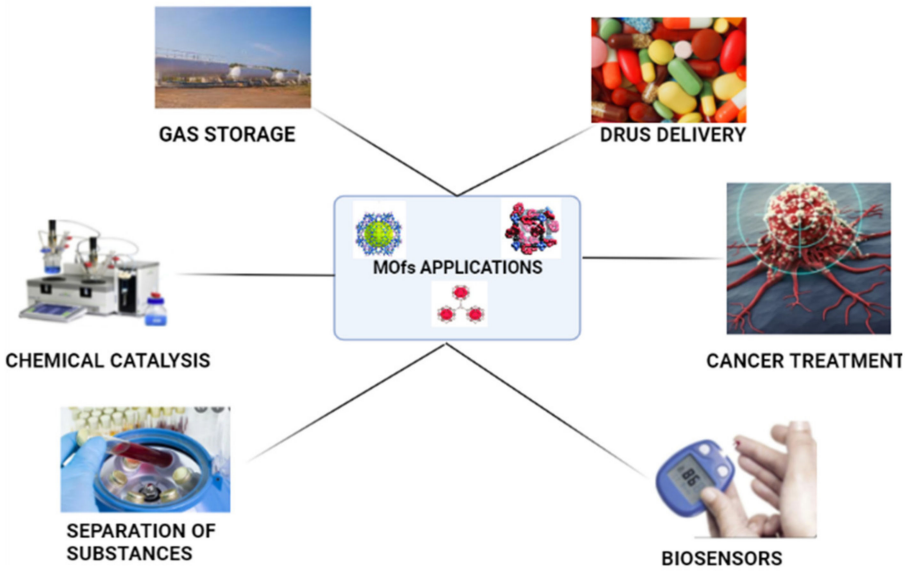

Figure 14. MOFs Schematic illustration showing the large number of MOFs applications.

In vitro biosensors are specific analytical instruments used in the prognosis and monitoring of urine, blood, tumor tissues containing enzymes, cancer markers, live cancer cells, small molecules, and proteins. The creation of ultra-sensitive and highly selective biosensors is of fundamental relevance in the early diagnosis of cancer and for monitoring the treatment process of cancer patients. Biosensors, and especially enzyme-based electrochemical biosensors, have become a viable, valuable, popular, and potentially portable tool for detecting a broad spectrum of analytes. Additionally, MOFs have been used as immobilizers to protect vulnerable biological macromolecules, including enzymes [202].

Enzyme–MOF complexes are widely applied in biocatalysis. Depending on the nature of the enzyme, these complexes can catalyze many reactions classes such as hydrolysis, oxidation-reduction, Michael addition, esterification, and transesterification [160].

The number of publications on biosensors produced with enzymes and MOFs has been notoriously increasing. This is due to MOFs showing great structural diversity, high porosity, large specific surface area, improved stability, biocompatibility, and structural controllability [203,204]. These characteristics demonstrate their great potential for biological applications involving enzymatic biomolecules [205,206]. MOFs are also considered promising candidates for immobilizing catalysts with large pores or channels, such as metallic complexes, nanoparticles, and enzymes [207].

5. Conclusions

A comprehensive review of metal–organic frameworks (MOFs) based on enzymatic biosensors was presented. The structures of coordinated metal ions compounds and arrangements of organic ligands of MOFs were also shown. Furthermore, the review introduced the different methods of enzymatic immobilization on MOFs, comparing their advantages and disadvantages. Some examples of MOFs-based biosensing applications were discussed.

MOFs can be synthesized and molded according to the specific application towards which they will be used. In addition, they possess highly interesting characteristics that enable their use as enzyme immobilization matrices for subsequent application in biosensors [18]. Among the characteristics of MOFs that make them a good alternative for enzyme immobilization, their large surface area and adjustable pore sizes can be highlighted [208,209]. In addition, such properties also grant biosensors with greater sensitivity for electrochemical detection [15].

However, despite the several advantages of MOFs in the manufacture of enzymatic biosensors, the transduction step still remains a challenge in the incorporation of these materials during electrochemical detection assays [15]. In this sense, despite the great potential of MOFs for use as solid support in the immobilization of enzymes and subsequent preparation of biosensors, this technology is still in its early stages of development, requiring further research aiming at its improvement. Despite this, metal–organic frameworks (MOFs) based on enzyme biosensors are promising and can be potentially applied in the most diverse technological fields delivering satisfactory results in the detection of a variety of analytes.

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