magnetochemistry

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Review

Magnetic Particle Bioconjugates: A Versatile Sensor Approach

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Abstract: Nanomaterial biosensors have revolutionized the entire scientific, technology, biomedical, materials science, and engineering fields. Among all nanomaterials, magnetic nanoparticles, microparticles, and beads are unique in offering facile conjugation of biorecognition probes for selective capturing of any desired analytes from complex real sample matrices (e.g., biofluids such as whole blood, serum, urine and saliva, tissues, food, and environmental samples). In addition, rapid separation of the particle-captured analytes by the simple use of a magnet for subsequent detection on a sensor unit makes the magnetic particle sensor approach very attractive. The easy magnetic isolation feature of target analytes is not possible with other inorganic particles, both metallic (e.g., gold) and non-metallic (e.g., silica), which require difficult centrifugation and separation steps. Magnetic particle biosensors have thus enabled ultra-low detection with ultra-high sensitivity that has traditionally been achieved only by radioactive assays and other tedious optical sources. Moreover, when traditional approaches failed to selectively detect low-concentration analytes in complex matrices (e.g., colorimetric, electrochemistry, and optical methods), magnetic particle-incorporated sensing strategies enabled sample concentration into a defined microvolume of large surface area particles for a straightforward detection. The objective of this article is to highlight the ever-growing applications of magnetic materials for the detection of analytes present in various real sample matrices. The central idea of this paper was to show the versatility and advantages of using magnetic particles for a variety of sample matrices and analyte types and the adaptability of different transducers with the magnetic particle approaches.

Keywords: magnetic particles; sensor; biomarkers; cells/cancer cells; food analytes; pathogens; pharmaceuticals; real sample matrices; optical; electrochemical; surface sensitive methods

1. Introduction

Most chemical and biological detection labels are limited to one transducer type or, sometimes, a few at best. In contrast, nanomaterials are not limited to a particular type of transducer, and they can be employed to a wide range of transducers. Moreover, nanomaterials can be used as labels for signal amplification and detection in sensors and assays. Because of these astonishing properties, nanomaterial sensors can be used with various detection methods (e.g., sensors based on optical, electrical, electrochemical, mass, mechanical, luminescent, and other physical properties). Thus, the unusual versatility of nanomaterial sensors supersedes traditional approaches and enables the analysis of complex sample matrices [1,2]. The magnetic separability of nanomaterials allows selective capturing of desired target analytes from complex real sample matrices through the analyte-specific probes. The bioconjugation is made feasible through viable chemical functionalization of magnetic

materials to link desired molecular probes for analyte detection in sensors. Chemical and bio sensors constitute one common theme of involving magnetic particle applications [1,3–9], and other equally important areas include biomedical imaging [10–17], food science [18–20], drug delivery [21–23], disease treatment [24,25], nanomedicine [26], diagnostics [27–32], catalysis [33–40], separation and purification [41,42], health [43], and environmental applications [44–47]. Thus, a plethora of studies have been reviewed for the unusually broad research fields in which magnetic materials play crucial roles. In addition to several characteristics such as optical, electrochemical, and catalytic properties of magnetic particles, their biocompatibility and tunable chemical functionalities and geometries (i.e., size and shape) pave the way for their in vivo applications. A literature search by the authors conveys that the research progress, number of publications, and reviews on magnetic particles and their applications in a vast range of topics have gained never-ceasing attention. This article specifically focused on magnetic particle (both nano and micro) and magnetic bead-based biosensors for the detection of biomarkers (for the most part) and other classes of analytes.

Xianyu et al. [4] recently reviewed the advances in magnetic particle-based biosensors for point-of-care testing and mechanisms of assaying biomarkers. They additionally outlined the milestones that limit the realization of real-world applications of certain magnetic materials. They emphasized the need to synthesize high-quality magnetic particles with control over their size distribution and magnetization and the need of portable and miniaturized magnetic signal readout systems. Farka et al. [48] recently published a very informative and comprehensive review of nanomaterials, including magnetic materials for immunochemical biosensors and assays. They discussed several types of transducers (e.g., optical, electrochemical, surface-sensitive methods, and transistors) and covered a range of target analytes including proteins, small molecules, cancer cells, toxic substances, and pathogens.

With regard to the specific needs of successfully utilizing magnetic materials for ultra-low analyte detection with high sensitivity, several strategies are being explored. Magnetic preconcentration of desired analytes, (basically, capturing low concentrations of target analytes from real samples onto a large surface area of magnetic particles; as a result, the analyte molecules are concentrated in small geometric areas to enable sensitive detection) to minimize the effect of interference from coexisting irrelevant molecules in sample matrices, has been explored. In addition, the use of an external magnetic field to selectively attract desired target analytes attached to magnetic conjugates onto the sensor surface is another strategy. Furthermore, sensitive detection and imaging of magnetically tagged analytes (or their complexes with biorecognition molecules) in solutions have also been explored in sensors [48]. Another review discussed the transduction mechanisms and applications of complementary metal-oxide-semiconductor biosensor designs based on magnetic and other particles for in vitro diagnosis [49].

In a typical heterogeneous biosensor design, the analyte molecules in the magnetic conjugates diffuse to the sensor surface to generate signals. In contrast, magnetic particle sensors in which the analytes are detected in the whole solution volume of the sample as a homogeneous sensing approach have also been developed [50]. Sample preparation steps are shown to be reduced in the homogeneous sensor assay, and the combined diffusion of analyte molecules and capture probes is shown to reduce the total assay time compared with a heterogeneous assay. In this article, we will mainly focus on the heterogeneous sensor systems that are shown to offer high sensitivity, reduced nonspecific or false positive signals, ultra-low detection limits, and tunability to attain a wide dynamic range of detection.

In addition to the synthesis and sensor application of iron oxide-based magnetic particles, considerable focus has been also placed on making hybrid magnetic materials (e.g., core/shell, bimetallic, and alloys) and composites with other materials (e.g., polymers, graphene, chitosan, and carbon nanostructures) to obtain a multifactorial advantage from a single end material [51–56]. We also present here several examples on core/shell and nanocomposite magnetic materials. This article is not a comprehensive review of magnetic nanoparticles or biosensors.

2. Rationale for the Selection of Transducer

On deciding the type of sensor signal transducers, major factors, such as the molecular properties of the analytes, detection limits required, and the design of suitable biorecognition process for selective detection, are considered. For a redox-active analyte or reagents that can offer redox-active products, electrochemical methods are suitable and offer sensitive detection (e.g., amperometric, potentiometric, and impedance sensors) (Table 1). When the analyte concentration is large enough (e.g., micromolar to millimolar range) and can be selectively visualized by the naked eye by a color reaction, the colorimetric detection is advantageous. For ultra-low detection limits, fluorescence, luminescence, and surface-sensitive optical methods (e.g., surface-enhanced Raman scattering and surface plasmon resonance) have been developed using magnetic nanomaterials (Table 2). Thus, each transducer has its significance depending on the target analyte nature and the associated extractable molecular properties in the sensor design.

Molecular Recognition Probes

Antibodies and aptamers for proteins and small molecules, complementary nucleotides for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) hybridization, enzymes for specific substrates by either direct or indirect catalytic conversions, receptors for ligands, and non-enzymatic molecular probes (e.g., molecularly imprinted polymers) for analytes are commonly used approaches in magnetic biosensors. For example, a magnetic force-aided electrochemical sensor was developed using sandwich biorecognitions from an aptamer and antibody combination for the detection of thrombin in serum samples [57]. Similarly, a magnetic field-induced self-assembly of Fe_3O_4(magnetite)@polyaniline nanoparticles incorporated with a molecularly imprinted polymer biorecognition element-delivered electrochemical sensing of creatinine in human plasma and urine samples [58]. Electrochemical glucose biosensing by glucose oxidase, on an electrode consisting of gold nanoparticles/bovine serum albumin/Fe_3O_4 nanocomposite [59], is an example for enzymatic biorecognition event (Figure 1-I–III).

An antibody biorecognition probe immobilized on a magnetic ($CoFe_2O_4$) metal–organic framework (MOF)@Au tetrapods (AuTPs) surface, with toluidine blue as the surface-enhanced Raman spectroscopy (SERS) tag, was used for detection of N-terminal pro-brain natriuretic peptides [54]. This strategy offered a large dynamic range with ultra-low detection limits. Effective magnetic bead-based separation and highly selective aptamer recognition of G-quadruplex formation of the anterior gradient homolog 2 (AGR2) protein, cancer biomarker, offered picomolar detection limits. This system also utilized gold nanoparticles. The detection was based on UV–vis spectrometry [60]. Another antibody-conjugated magnetic-bead sensor detected chloramphenicol antibiotic based on a competitive surface-enhanced Raman scattering method [61] (Figure 2-I,II).

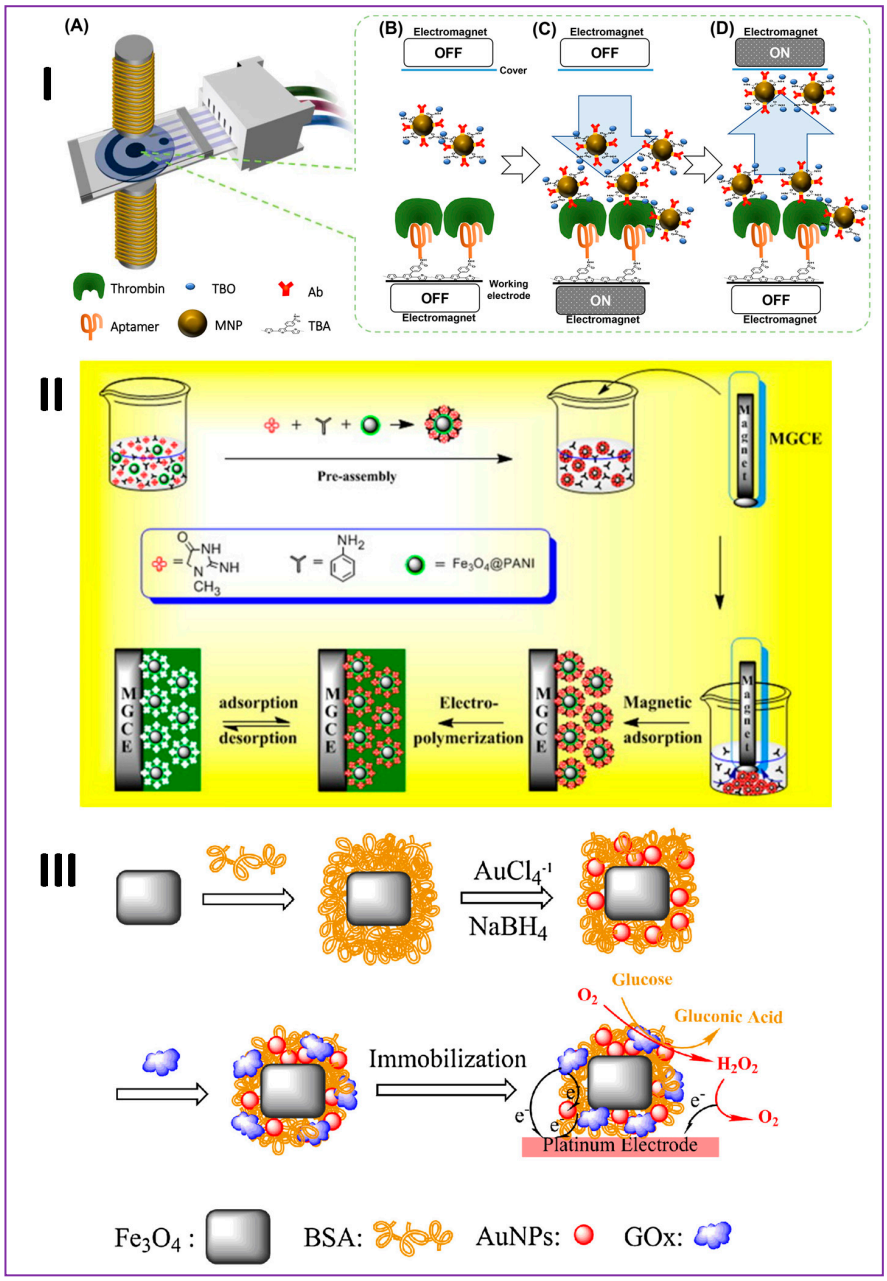

Figure 1. (**I**) (**A**) Sensing system composed of an electrochemical sensor, a pair of electromagnets, and a sample chamber. (**B**–**D**) The process of magnetic force-assisted electrochemical sandwich assays (MESA) is illustrated: (**B**) the sample loading step to mix the sample solution and the magnetic nanoparticle (MNP) bioconjugates with antibody and toluidine blue O (MNP@Ab-TBO); (**C**) the reaction step to form sandwich complexes on the electrode surface; and (**D**) the removal step to remove unbound MNP@Ab-TBO from the electrode surface. Reproduced with permission from Reference [57]. Copyright 2018 Elsevier. (**II**) Schematic representation of the preparation of the molecularly imprinted electrochemical sensor (MIES) for detection of creatinine. Reproduced with permission from Reference [58]. Copyright 2014 Elsevier. (**III**) Schematic illustration of the preparation of a GOx/AuNPs/BSA/Fe_3O_4/Pt electrode. Reproduced with permission from Reference [59]. Copyright 2016 Elsevier. Abbreviations: TBA - 2,2′:5′,5″-terthiophene-3′-p-benzoic acid; MGCE - magnetic glassy carbon electrode; Fe_3O_4@PANI - magnetite@polyaniline; BSA - bovine serum albumin; AuNPs - gold nanoparticles; GOx - glucose oxidase.

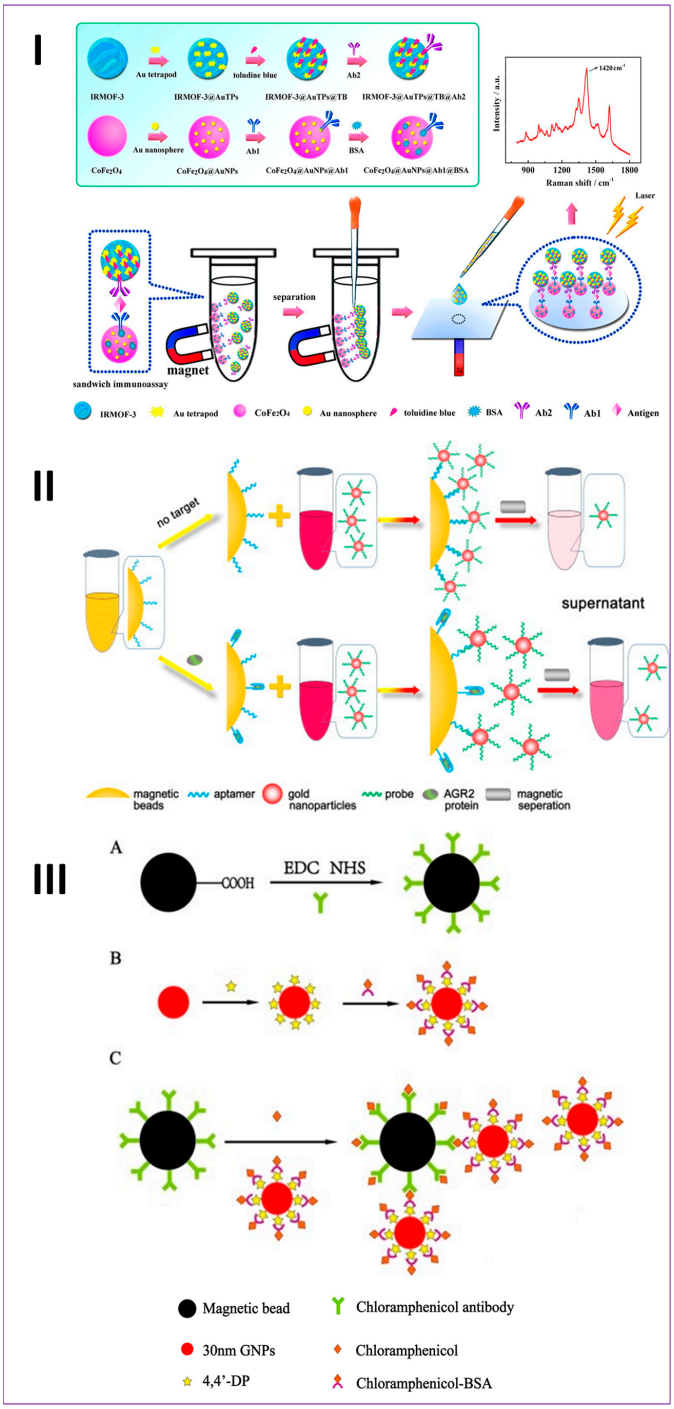

Figure 2. (**I**) Schematic representation of the surface-enhanced Raman spectroscopy (SERS)-based sandwich immunosensor for the detection of N-terminal pro-brain natriuretic peptides (NT-proBNPs). Reproduced with permission from Reference [54]. (**II**) Schematic representation of anterior gradient homolog 2 (AGR2) protein detection procedure. Reproduced with permission from Reference [60]. Copyright 2015 Elsevier. (**III**) (**A**) Preparation of MNPs modified with chloramphenicol antibody. (**B**) Preparation of SERS tags. (**C**) SERS-based magnetic immunosensor for chloramphenicol. Reproduced with permission from Reference [61]. Copyright 2016 Elsevier. Abbreviations: IRMOF- amino-functionalized metal–organic framework; AuTPs - gold tetrapods; AuNPs - gold nanoparticles; TB - toluidine blue; GNPs - gold nanoparticles; 4,4′-DP - 4,4′-dipyridyl; EDC - 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; NHS - N-Hydroxysuccinimide.

Magnetic particle sensors for detection of various classes of analytes in a variety of complex sample matrices. In the subsequent sections, we extend our discussion to selective classes of analytes and various sample matrices, biorecognition materials, and transducers that best addressed the sensor purpose and analytical performance.

3. Biomarkers

Biomarkers indicate normal versus abnormal conditions based on the levels of their concentrations in organs, tissues, and circulating body fluids. Hence, sensors that allow selective and required sensitive detection of the biomarkers are significant in diagnosis and treatment. We present here a few examples of biomarker sensors based on magnetic materials which use various transducers. Recently, Gooding et al. [62] devised a novel microRNA detection probe consisting of a DNA sequence attached to gold-coated magnetic nanoparticles. By electrically reconfiguring the nanoparticle probe, they achieved electrochemical (square wave voltammetry) detection of microRNA in whole blood samples over a wide concentration range from attomolar to nanomolar. Such ultrasensitive magnetic nanoparticle tools are significant for clinical diagnostics.

Similarly, magnetic nanoparticle-based voltammetric and electrochemical mass sensors recently enabled the detection of ultra-low clinically relevant picomolar serum insulin concentrations (Figure 3A(a,b),B) [63,64]. In the electrochemical mass sensor, magnetic isolation of insulin from a serum sample reduced the interference from the sample matrix and non-specific background signals which was quantitatively estimated by comparing the background signals for magnetically treated serum control response with that of a solution-based bulk serum control response (Figure 3A-b) [63]. Furthermore, enriching the surface –COOH groups of pyrenyl-carbon nanostructures by combined covalent and non-covalent carboxylation improved the sensitivity of serum insulin immunosensing compared to only a carboxylated nanotube-based sensor (Figure 3C) [65]. Another quartz crystal microbalance (QCM) mass sensor method has been reported for detection of thrombin (in diluted serum or fibrinogen-precipitated plasma samples) by a magnetic microbead polymeric material and detection on an aptamer-immobilized QCM crystal based on oscillation frequency decrease [66]. Translating the quantitative knowledge derived from a single-sample QCM analysis sensor into a relatively better throughput surface plasmon imaging gold array enabled magnetic nanoparticle captured serum insulin (50% serum in buffer) detection at picomolar concentrations (Figure 3D) [67]. Advancements in microfluidic designs enabled on-line protein capturing by magnetic beads and ultrasensitive electrochemical detection of interleukin cancer biomarkers (IL-6 and IL-8) in undiluted calf serum [68]. In addition to electrochemical detection, surface plasmon spectroscopy that offers detection with binding insights [69] has been successfully developed with a polyamidoamine (PAMAM)-magnetic nanoparticle quantum dot modification on a gold array for a dual imaging-based detection of blood insulin and glycated hemoglobin (20 time diluted whole blood samples in buffer) (Figure 3E) [70]. Subsequently, fluorescence imaging of the sensor array allowed an independent validation of the method. Table 1 presents various magnetic nanoparticles based electrochemical sensors for the detection of a wide range of analytes. Cyclic, square-wave, and differential voltammetry, and amperometric techniques have been widely used as electrochemical transducers. Moreover, the analytes ranged from small molecules such as glucose, bisphenol A, and ciprofloxacin antibiotics to various protein biomarkers, pesticides, and illicit drugs. The analyte recognition elements include enzymes, aptamers, antibodies, and molecularly imprinted polymers. The wide variety of sample matrices covered were blood, serum, plasma, urine, milk, juice, meat samples, and water (Table 1).

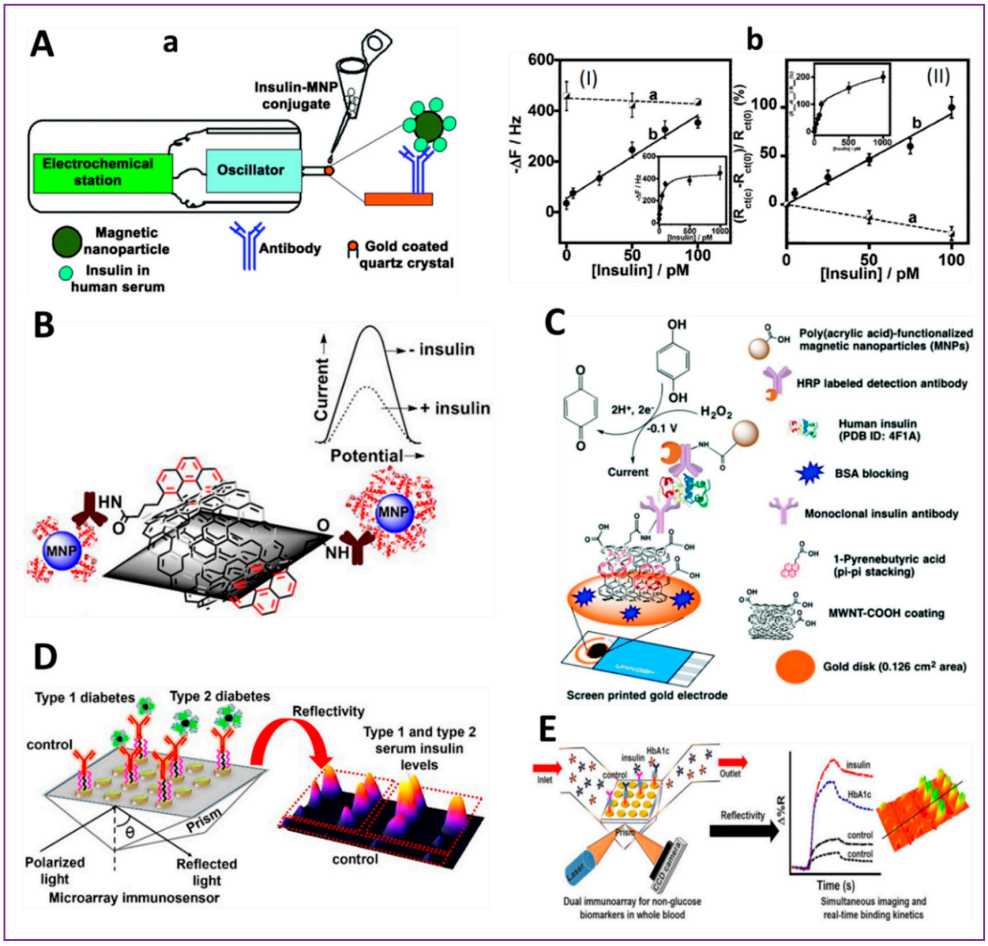

Figure 3. (**A**) An electrochemical mass sensor for clinically relevant detection of insulin in human serum conjugated to magnetic nanoparticles and captured onto antibody immobilized gold-coated quartz resonators was reported in this study: (**a**) Schematic of the electrochemical quartz crystal microbalance (eQCM) sensor and (**b**) sensor responses (QCM and Faradaic impedance) showing the significant reduction of non-specific signals for control serum due to the magnetic nanoparticle capturing of insulin and detection upon binding onto the surface antibody sensor, enabling picomolar detection limits. This is not possible by doing the assay from a solution form of the serum insulin sample due to the inability of ultra-low picomolar signals to overcome the large background signal response of the un-spiked serum solution control. Reproduced with permission from Reference [63]. Copyright 2014 Royal Society of Chemistry. (**B**) This report presented the first serum insulin voltammetric immunosensor for diagnosis of type-1 and type-2 diabetic disorders based on fasting serum insulin levels. The sensor was composed of multiwalled carbon nanotube-pyrenebutyric acid frameworks on edge plane pyrolytic graphite electrodes to which anti-insulin antibody was covalently attached. Magnetically captured insulin from 50% serum in buffer was detected upon binding onto the surface insulin-antibody sensor. Reproduced with permission from Reference [64]. Copyright 2015 American Chemical Society. (**C**) Schematic of a combined covalent and noncovalent carboxylation of carbon nanotubes for sensitivity enhancement of clinical immunosensors (demonstrated here with serum insulin). Reproduced with permission from Reference [65]. Copyright 2016 Royal Society of Chemistry. (**D**) Schematic of a magnetic optical microarray imager for diagnosing type of diabetes in clinical fasting blood serum samples based on picomolar insulin concentrations. Reproduced with permission from Reference [67]. Copyright 2016 American Chemical Society. (**E**) Schematic of a magnetite-quantum dot immunoarray for plasmon-coupled fluorescence imaging of blood insulin and glycated hemoglobin. Reproduced with permission from Reference [70]. Copyright 2017 American Chemical Society.

Table 1. Magnetic nanoparticle (MNP)-based electrochemical sensors for the detection of various analytes.

S. No.	Application	Transduction Method	Recognition Element	Analyte	Interface	Real Sample	Range	LOD	Reference
1	Medical	Voltammetry	Molecularly Imprinted Polymers (MIPs)	Hemoglobin	GCE[1]/Fe_3O_4@SiO_2/MMIP	Blood	0.005–0.1 mg mL^{-1}	0.001 mg mL^{-1}	[71]
2	Environmental	Differential Pulse Voltammetry (DPV)	MIP	Bisphenol A	SPCE[2]/AuNPs/ CBNPs[5]/Fe_3O_4/MMIP[3]	Mineral water	0.07–10 μM	8.8 nM	[72]
3	Medical	DPV	Chemical	Ciprofloxacin	CPE/Fe_3O_4/CMNPs	Serum, Urine	0.05–75 μM L^{-1}	0.01 μM L^{-1}	[73]
4	Food Clinical	DPV	MIP	*N*-Acyl-homoserine -lactones	MGCE[5]/Fe_3O_4@SiO_2-MIP		2.5×10^{-9}–1.0×10^{-7} mol L^{-1}	8×10^{-10} mol L^{-1}	[74]
5	Food	DPV	MIP	Kanamycin	CE[4]/MWCNTs/Fe_3O_4/PMMA	Milk, Chicken, Pig	1×10^{-10}–1.0×10^{-6} mol L^{-1}	2.3×10^{-11} mol L^{-1}	[75]
6	Food	Cyclic Voltammetry (CV)	Enzyme	Peroxide	Pt/MRGO[6]/chit/HRP	Orange juice	20–1000 μM 48.08 μA $\mu M^{-1} \cdot cm^{-2}$	2 μM	[76]
7	Security	DPV		Morphine	CPE/CHT[7]/Fe_3O_4	Serum, Urine	10–2000 nM	3 nM	[77]
8	Food	DPV		Quercetin and Tryptophan	CPE/Fe_3O_4@NiO core/shell nanoparticles	Human breast milk, cow milk, and honey	0.08–60 μM 0.1–120 μM	2.18 nM 14.23 nM	[78]
9	Medical	DPV	Antibody (Ab)	Prostate specific antigen (PSA)	Ab_2/MB[8]/ Au@Fe_3O_4@COF/GCE	Serum	0.0001–10 ng mL^{-1}	30 fg mL^{-1}	[79]
10	Medical	Amperometry	Enzyme	Glucose	GOx[14]/AuNPs/BSA/Fe_3O_4/PtE	-	0.25–7.0 mM	3.54 μM	[59]
11	Medical	DPV		Ractopamine	MSPE/RGO/Fe_3O_4	Pork meat	0.05–100 μM	13 nM	[80]
12	Medical	Amperometry	Aptamer-Antibody	Thrombin	pTBA/Apt/thrombin/ MNP@Ab-TBO[9]/SPCE	Serum	1–500 nM	0.49	[57]
13	Security	Square Wave Voltammetry (SWV)		Organo-phosphates	Fe_3O_4@ZrO_2/MGCE	-	7.60×10^{-8}–9.12×10^{-5} M	1.52×10^{-8} M	[81]
14	Medical	DPV	MIP	Creatinine	MGCE/Fe_3O_4@PANI[10] NPs/MIP	Plasma, Urine	0.02–1 μM L^{-1}	0.35 nM L^{-1}	[58]
15	Medical	DPV		Progesterone	Fe_3O_4@GQD[11]/ f–MWCNTs[12]/GCE	Serum	0.01–3.0 μM	2.18 nM	[82]
16	Medical	Amperometry		PSA, Prostate specific membrane antigen (PSMA) Cancer biomarker	Fe_3O_4@GO/Ab/PSMA		61 fg mL^{-1}–3.9 pg mL^{-1} 9.8 fg mL^{-1}–10 pg mL^{-1}	15 fg mL^{-1} 4.8 fg mL^{-1}	[83]
17	Medical	DPV		PSA, PSMA, IL6, Platelet factor 4 (PF4)	MNP/HRP[13]-Ab		0.05–2 pg mL^{-1}		[84]

GCE[1]: Glassy carbon electrode; SPCE[2]: screen-printed carbon electrode; MMIPs[3]: magnetic molecularly imprinted polymers; CE[4]: carbon electrode; CBNPs[4]: carbon black nanoparticles; MGCE[5]: magnetic glassy carbon electrode; MRGO[6]: magnetic reduced graphene oxide; CHT[7]: chitosan; MB[8]: methylene blue; TBO[9]: toluidine blue O; PANI[10]: polyaniline; GQD[11]: graphene quantum dots; MWCNTs[12]: multiwalled carbon nanotubes; HRP[13]: horseradish peroxidase; GOx: glucose oxidase.

A nanocomposite that consists of glucose oxidase with reduced graphene oxide and magnetic nanoparticles on a magnetic sticker attached to a screen-printed electrode was shown to offer micromolar glucose amperometric detection in simple aqueous solutions [55]. An antibody conjugation to a magnetic nitrogen-doped graphene-modified gold electrode was used for voltammetric detection of amyloid-beta peptide 1–42 (Aβ42), a biomarker of Alzheimer's disease, in solution [85]. However, the applicability of such sensors for practical sample matrices of biofluids would be more significant.

A recently reported magnetic-focus-lateral flow-colorimetric biosensor offered a million-fold improvement in sensitivity over the conventional lateral flow systems toward detection of the valosin-containing protein of relevance to cervical cancer [53] (Figure 4A(a,b)). The sensor applicability for protein mixtures extracted from the tissue of cervical cancer patients was successfully demonstrated. Spectral correlation interferometry, capable of picometer resolution of measured thickness changes of a layer of molecules or nanoparticles, was designed for sensitive detection of prostate-specific antigen by a magnetic nanoparticle-bioprobe amplification strategy [86] (Figure 4B). Another study utilized anodic stripping voltammetry for sensitive DNA detection on a magnetic porous pseudo-carbon paste electrode [87].

A magnetic bead-based colorimetric biosensor allowed for detection of two inflammatory salivary biomarkers, human neutrophil elastase and cathepsin-G, in solution and spiked saliva samples. The sensor utilized proteolytic activity-induced color changes with biomarker concentration. The sensor was validated with patients' saliva analysis [88]. Magnetic particles possess peroxidase-like enzymatic activity. This property has been extensively used in both electrochemical and optical sensors for analyte detection. An illustration would be the enzymatic colorimetric glucose sensors based on magnetic particles that exploited the peroxidase-like activity of these particles [89]. In this report, glucose oxidase was covalently attached to carboxylated magnetic beads (1 μm size) for spectrophotometric detection of glucose in solutions or that spiked in plasma samples using o-phenylenediamine dihydrochloride reagent.

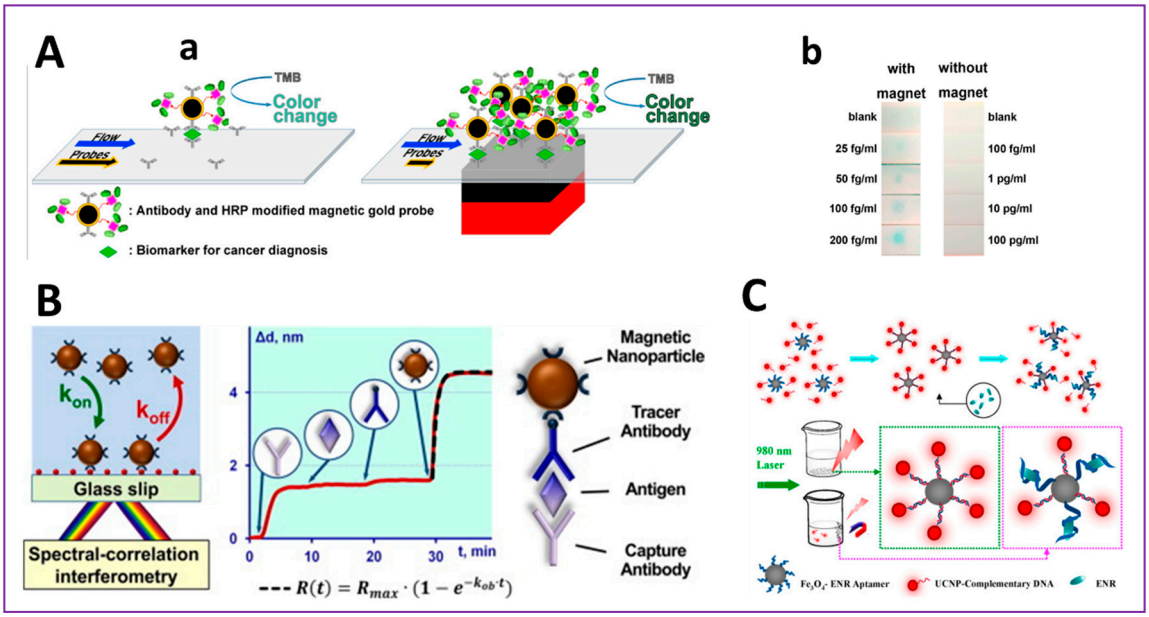

Figure 4. (**A**) (**a**) Schematic depicting the effect of magnetic focus lateral flow biosensor. Without the magnet, the magnetic probe-labeled targets move along with the sample flow on the lateral flow strip, resulting in a low capture efficiency (left). With magnet, the probe-labeled targets are focused at the signal generation zone due to the magnetic focus thus increasing the capture efficiency of labeled targets (right). (**b**) Comparison of the detection results with and without magnet. Reproduced with permission from Reference [53]. Copyright 2019 American Chemical Society. (**B**) Sandwich immunoassay for t-PSA: on the left—sensograms demonstrating all assay steps in absence of t-PSA (lower blue curve)

and in the presence of 1 µg/ml t-PSA (upper red curve); on the right—scheme of sandwich assay: 1—capture antibody, 2—antigen, 3—biotinylated tracer antibody, 4—magnetic nanoparticle coated by streptavidin. Reproduced with permission from Reference [86]. Copyright 2016 Elsevier. (**C**) Schematic diagram of upconversion nanoparticles (UCNPs) luminescence-based aptasensor for the selective detection of ENR. Reproduced with permission from Reference [90]. Copyright 2016 Elsevier. Abbreviations: TMB - Tetramethyl benzidine; HRP - Horseradish peroxidase; UCNPs - Upconversion nanoparticles; ENR – Enrofloxacin.

An enzymatic biosensor composed of poly(dopamine)-modified magnetic nanoparticles, covalently attached with a PAMAM dendrimer (ethylenediamine core polyamidoamine G-4; fourth-generation) and additionally incorporated with platinum nanoparticles, was used for amperometric detection of micromolar xanthine in fish samples [91]. Similarly, magnetic nanocomposite materials with carbon nanostructures (e.g., graphene and nanotubes) have been devised for sensitive electrochemical enzymatic glucose detection in spiked urine samples [92] and progesterone in human serum samples and pharmaceutical products [82] with good recoveries. Magnetic susceptibility measurements combined with a optomagnetic method was developed for detection of C-reactive protein in serum from the agglutination of magnetic nanoparticles conjugated with the protein antibody [93]. A chemiluminescent biosensor combining magnetic beads with platinum nanoparticles for thyroid-stimulating hormone detection in serum has been devised [94].

Protein A/G-functionalized 2 µm magnetic beads successfully isolated glutamic acid decarboxylase-65 autoantibody from 10% serum and enabled sensitive (picomolar) detection on the glutamic acid decarboxylase-65 immobilized carboxylated graphene surface [95] (Figure 5A(a,b)). In this report, the correlation of picomolar affinities between surface plasmon resonance and electrochemical immunosensors was demonstrated. Furthermore, multiplex biosensing of a panel of biomarkers allows reliable and rapid quantification of several analytes in complex clinical matrices. A new surface plasmon-imaging array based on core/shell Fe_3O_4@Au nanoparticles enabled combined detection of two interleukin proteins and two microRNAs in a diluted serum (Figure 5B) [96]. The gold shell can facilitate the enhancement of the plasmon signals and the magnetic core for easy separation and magnetic isolation of desired target analytes present in complex sample matrices. Moreover, the core/shell material exhibited higher plasmonic signals than the individual nanoparticle components of similar hydrodynamic sizes [96]. Such multifunctional magnetic materials and composites offer several distinct properties but centralized into a single component to enable designing ultra-sensitive sensors [59,97–101]. A multiplex sensor featuring magnetic nanoparticle–antibody conjugates for detection of ovarian cancer biomarkers, CA-125, β-2M, and ApoA1, has been reported [102]. Fluorescence spectroscopy and surface plasmon resonance analysis were utilized. Thus, emerging directions of magnetic particle biosensor designs [103] are pushing the limits of applications to increasingly complex real samples and multianalyte biosensing. One other example of a biocatalytic real-sample system is the design of magnetic nanoparticle-based liver microsomal biofilms (subcellular liver fractions containing drug-metabolizing cytochrome P450 enzymes with their reductase) for reduced-nicotinamide adenine dinucleotide phosphate (NADPH)-free direct electrochemical drug biosensing and stereoselective metabolite production [104] (Figure 5C).

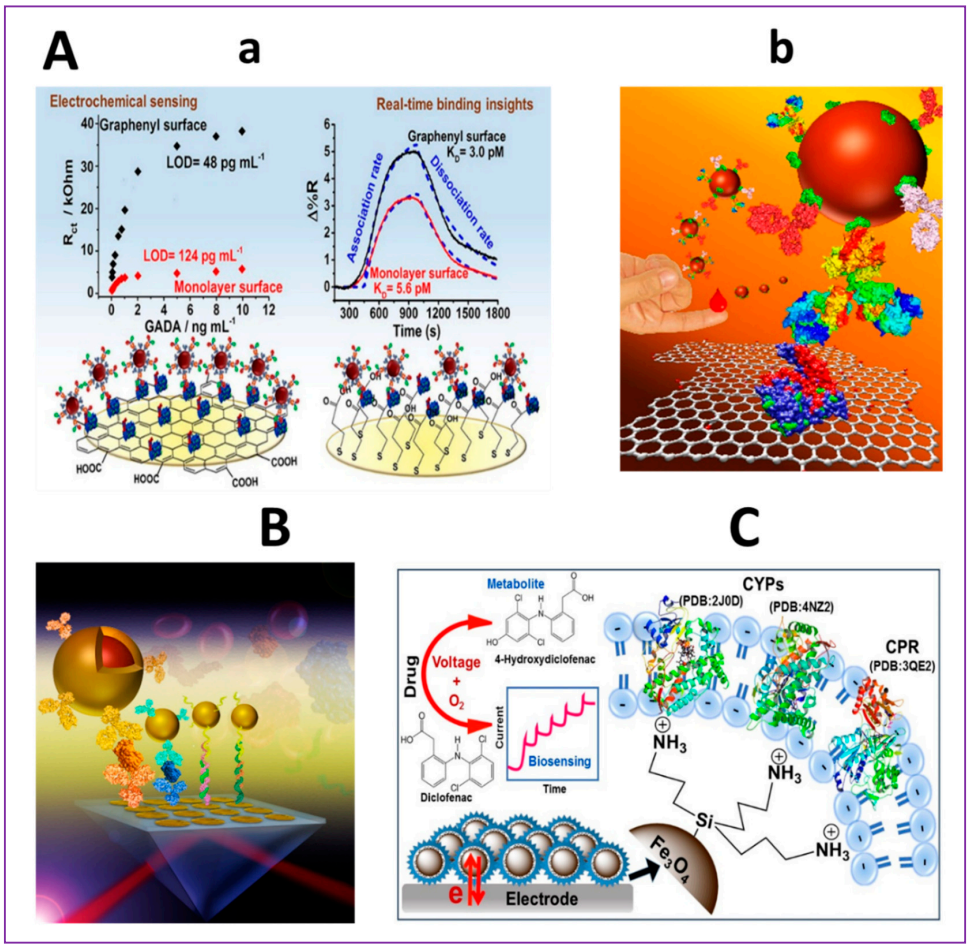

Figure 5. (**A**) (**a**) Electrochemical and surface plasmon correlation of serum autoantibody immunosensors with binding insights. In this report, a comparative account of carboxylated graphenyl and mercapto-monolayer surfaces was made for the detection of serum glutamic acid decarboxylase-65 autoantibody (GADA), a biomarker of type 1 diabetes and (**b**) schematic representation. Reproduced with permission from Reference [95]. Copyright 2018 American Chemical Society. (**B**) Schematic representation of a multiplexed surface plasmon imaging of serum biomolecules. In this report, Fe_3O_4@Au core/shell nanoparticles carrying analyte-specific second biorecognition element (the first one was immobilized on the sensor surface) were used for signal amplification purpose and presented with plasmonic simulation insights. Reproduced with permission from Reference [96]. Copyright 2019 Elsevier. (**C**) Schematic of a biocatalytic system constructed by electrostatically immobilizing drug-metabolizing human liver microsomes (HLMs, negatively charged due to the phospholipids) onto positively charged amine-functionalized magnetic nanoparticles (100 nm hydrodynamic diameter). This report presented electrochemical biosensing of cytochrome P450 (CYP)-specific drug candidates and electrocatalyzing drug conversion into metabolites with electron mediation in the biofilm by cytochrome P450-reductase (CPR). Reproduced with permission from Reference [104]. Copyright 2018 Elsevier.

Katz et al. [105] reported a novel magnetic field-activated binary deoxyribozyme sensor for fluorescent detection of a specific messenger RNA that is a cancer biomarker. The sensor functioned well when internalized in live MCF-7 breast cancer cells and activated by a magnetic field. The sensor utilized two types of magnetic bead bioconjugates that carried different components of a multicomponent deoxyribozyme sensor. The sensor function was activated only in the presence of a specific target messenger RNA and upon an applied magnetic field thus adding control over the selectivity [106]. Pang et al. [107] designed a DNA probe Fe_3O_4@Ag magnetic nanoparticle biosensor for capturing

microRNA from cancer cells and detection at ultra-low concentrations (0.3 fM). In this study, surface-enhanced Raman scattering with a duplex-specific nuclease signal amplification strategy was used. Application for point-of-care clinical diagnostics of microRNA has been envisioned. Discussed above are a range of illustrative examples of bioanalytes, and, in the subsequent sections, we highlight magnetic particle sensors developed for other analyte classes.

4. Food Analytes, Pathogens, and Pharmaceuticals

In addition to the important detection advantages of the magnetic particle sensor approaches for a range of diagnostically useful biomarkers and small molecules, the broader applicability for food, pathogens, and pharmaceuticals are illustrated in this section. Food and pharmaceuticals represent two essential components for sustaining life and health. Biosensors play important roles in the detection of foodborne pathogens and the development of valuable therapeutic molecules. Andreescu et al. [108], in the year 2015, published an excellent review of the design and development of nanoparticle-based (including magnetic) sensors for food safety assessment. They covered both colorimetric and electrochemical detection of chemical and biological contaminants (e.g., pesticides, heavy metals, bacterial pathogens, and natural toxins). Therefore, we provide some representative recent reports specifically on magnetic material sensors for food contaminants, pathogens, and pharmaceuticals.

An impedimetric electrochemical aptasensor allowed rapid and sensitive detection of *Escherichia coli* [109]. The sensor system contained biotinylated polyclonal antibodies bound strongly to streptavidin-modified magnetic nanoparticles for selective separation of target bacteria from the sample in a coaxial capillary designed with high-gradient magnetic fields. For measuring impedance signals with the bacteria concentration, urease-catalyzed hydrolysis of urea into ammonium ions and carbonate ions in the capillary was used. A disposable amperometric sensor based on core/shell Fe_3O_4@SiO_2 superparamagnetic nanoparticles conjugated with specific bioreceptors for selective detection and quantification of *Brettanomyces bruxellensis* (Brett) and total yeast content in wine has been developed (Figure 6) [110]. Maghemite nanoparticles (Fe_2O_3) have been identified to be an efficient and reliable material for removal of citrinin, a nephrotoxic mycotoxin, from food samples [111]. Table 2 presents various magnetic nanoparticles based optical sensors for detection of a wide range of analytes. Colorimetric, luminescence, surface plasmon resonance (SPR), and other surface-sensitive techniques are illustrated as representative transducers. Aptamers, peptides, antibodies, and MIPs are presented as recognition elements. The analytes ranged from proteins, hormones, peptides, miRNA, and bacteria to small molecules (Table 2).

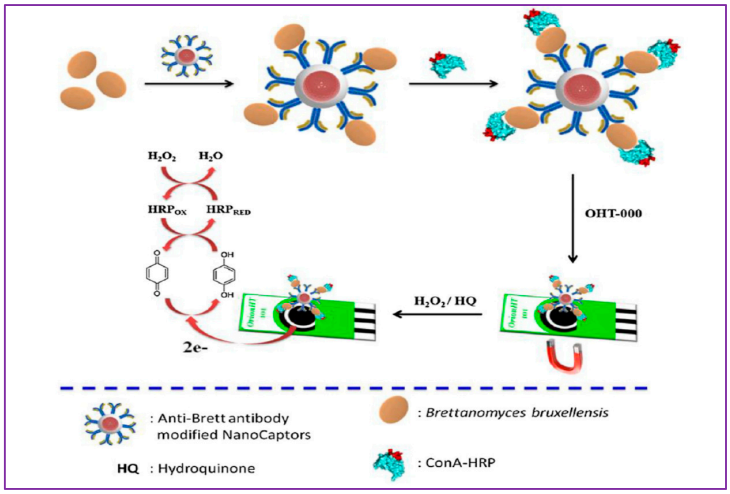

Figure 6. Schematic display of the steps involved in the preparation and performance of the biosensor for Brett (Ab-B sensor). Reproduced with permission from Reference [110]. Copyright 2019 Elsevier. Abbreviations: ConA - Concanavalin A.

Table 2. Magnetic nanoparticle (MNP)-based optical sensors for the detection of various analytes.

S.No.	Transduction Method	Recognition Element	Analyte	Assay	Range	LOD	Reference
1	Ultraviolet-Visible (UV-Vis)	Aptamer	Cancer biomarker AGR2[1]	Au NPs/DNA/MBs	10–1280 pM	6.6 pM	[60]
2	Surface Plasmon Resonance (SPR)	Aptamer	Thrombin	Fe_3O_4@Au NPs/Apt	0.1–100 nM	0.1 nM	[112]
3	Colorimetric	Ab	Listeria	MNB-MAb-Listeria-PAb-AuNP-urease	1.1×10^2–1.1×10^6 CFU mL^{-1}	102 CFU mL^{-1}	[113]
4	Colorimetric	Peptide	*E coli.*	MNP[2]/Peptide/AuNPs/SAM	30–300 CFU mL^{-1}	12 CFU mL^{-1}	[114]
5	Photonic crystal	Ab	soluble transferrin receptor	fAb-IONs[3]	0.01–0.2 µg mL^{-1}	-	[115]
6	Surface Enhanced Raman Spectroscopy (SERS)	Ab	chloramphenicol	AuNPs/MNPs/Ab	0–10 ng mL^{-1}	1 pg mL^{-1}	[61]
7	Chemiluminescence	MIP	Lysozyme	ILs[3]-Fe_3O_4@DA/GO[6]/β-CD[4]	1.0×10^{-9}–8.0×10^{-8} mg mL^{-1}	3.0×10^{-10} mg mL^{-1}	[116]
8	Chemiluminescence	Enzyme-Ab	Thyroid stimulant hormone	Pt NPs/HRP-Ab/magnetic beads	0.013–12 mU L^{-1}	0.005 mU L^{-1}	[94]
9	SERS		MiRNA let-7b (cancer cells)	Fe_3O_4@Ag NPs	0–1000 pM	0.3 fM	[107]
10	SERS	Ab	Ovarian cancer Multiplexed (CA-125, β2-M and ApoA1)	MNPs/Abs		0.26 U mL^{-1}, 0.55 ng mL^{-1}, and 7.7 ng mL^{-1}	[102]
11	SERS	Ab	N-Terminal pro-brain natriuretic peptide (heart failure)	$CoFe_2O_4$@AuNPs/MOFs	1 fg mL^{-1}–1 ng mL^{-1}	0.75 fg mL^{-1}	[54]
12	SERS		Carcinoembryonic antigen	MBA-labeled NiFe@Au NPs	0–1 ng mL^{-1}	0.1 pM	[56]
13	SERS			Fe_3O_4@Au Core/shell nanoparticles			[96]

AGR2[1]: anterior gradient homolog 2; MNP[2]: magnetic nanoparticles; IONs[3]: iron oxide nanoparticles; Ils[3]: ionic liquids; β-CD[4]: β-cyclodextrins[5]; GO[6]: graphene oxide.

Aptamer-functionalized magnetite (Fe_3O_4) conjugated upconversion nanoparticles were constructed to quantify trace enrofloxacin (a fluoroquinolone antibiotic) in fish samples; hybridization reaction-based luminescent intensity decreased when the analyte concentration was used as the signal transduction output [90] (Figure 4C). The "upconversion" terminology is related to the property of high-energy photon emission by a shorter wavelength excitation source of lower energy such as near-infrared photons. Other representative magnetic nanoparticle sensors for separation and/or detection include colorimetric tetracycline detection [117], chloramphenicol [61], lysozyme (an antimicrobial enzyme) [116], aflatoxins [118] (a review covering electrochemical, optical, and mass-sensitive biosensors), *Listeria monocytogenes* (a Gram-positive bacterium) [119], *Staphylococcus aureus* (a Gram-positive bacterium) [120], *Salmonella enteritidis* (a Gram-negative bacterium) [121], impedimetric hepatitis B virus DNA [122], and *Vibrio cholerae* DNA detection [123,124].

5. Environment

Environmental biosensors play significant roles in human safety and protecting the planet from devastations. Nanotechnology as a whole has contributed to the development of modern real-time environmental sensors (e.g., pollution monitoring, agriculture, renewable energy, water, and aviation) [47,125,126]. Herein, we illustrate literature reports on magnetic particle-based environmental biosensor system for organophosphorus pesticides, which are known to be toxic agricultural wastes despite their widespread use. Co-immobilization of carboxylic acid group-modified magnetic nanoparticles and acetylcholinesterase enzyme onto an electropolymerized surface of 4,7-di(furan-2-yl)benzo[c][1,2,5]-thiadiazole allowed sensitive micromolar detection of paraoxon and trichlorfon used as model organophosphates [127]. Amperometric current signals were used as the transduction method. Good reproducibility, long-term stability over 10 days, and applicability of the sensor for analysis in real tap water samples were demonstrated. Another acetylcholinesterase-magnetic particle electrochemical biosensor operated in flow injection analysis also delivered sensitive detection of organophosphate insecticides [128].

Summary/Prospects

The versatile nature of magnetic materials for applications with a range of transduction and biorecognition principles is detailed. Moreover, magnetic sensor designs for the detection of a broad range of analytes present in various complex real sample matrices of relevance to disease diagnosis, health, food, agriculture, energy, and environment are highlighted. Future directions in the field are aimed at synthesizing new multifunctional magnetic materials that offer simplicity and rapid detection platforms from the prior methods and quantitative insights into size and shape distributions as well as chemical and surface functionality aspects of magnetic materials. Moreover, efficient strategies for oriented and other modes of immobilization of bioprobes, their quantitative characterizations, activity, bioconjugation and catalytic efficiency, need of reproducibility, and long-term stability of sensor designs are being addressed. Emerging magnetic particle biosensor designs with multifunctional and multiplex features are discussed. Improvements on the scientific rigor of methodologies and approaches developed and standardization of protocols for reliable end applications are some of the currently emphasized benchmarks for successful magnetic particle sensor designs.

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