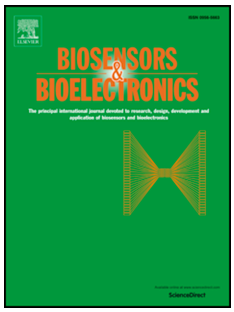

Biosensing of microcystins in water samples; recent advances

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Biosensing of Microcystins in water samples; recent advances

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Abstract

Safety and quality of water are significant matters for agriculture, animals and human health. Microcystins, as secondary metabolite of *cyanobacteria* (blue–green algae) and cyclic heptapeptide cyanotoxin, are one of the main marine toxins in continental aquatic ecosystems. More than 100 microcystins have been identified, of which MC-LR is the most important type due to its high toxicity and common detection in the environment. Climate change is an impressive factor with effects on cyanobacterial blooms as source of microcystins. The presence of this cyanotoxin in freshwater, drinking water, water reservoir supplies and food (vegetable, fish and shellfish) has created a common phenomenon in eutrophic freshwater ecosystems worldwide. International public health organizations have categorized microcystins as a kind of neurotoxin and carcinogen. There are several conventional methods for detection of microcystins. The limitations of traditional methods have encouraged the development of innovative methods for detection of microcystins. In recent years, the developed sensor techniques, with advantages, such as accuracy, reproducibility, portability and low cost, have attracted considerable attention. This review compares the well-known of biosensor types for detection of microcystins with a summary of their analytical performance.

Keywords: Water contamination; Microcystin; cyanotoxin; Biosensor; Human health; food, Marine toxin

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1. Introduction

Water is the most important natural resource for living organisms since life is not possible without it (Velichkova et al., 2020). This indicates the necessity for precious monitoring and global management of water resources (Garrote, 2017; Pradinaud et al., 2019). Water contamination and water-borne diseases can lead to the universal scale damage (Pandey et al., 2014). Cyanobacterial harmful algal blooms (Cyano-HABs) are one of the most important origins of water contamination, providing signs like color, odor and production of extremely toxic compounds, which are known as cyanobacterial toxins (cyanotoxins) (Pelaez et al., 2010). The existence of cyanotoxins in drinking water is considered as a hazardous problem for human health, because they can gather in aquatic organisms and then be transferred to human through the food chain (Codd et al., 2017). Cyanotoxins are classified as hepatotoxins, neurotoxins, cytotoxins and dermatotoxins, based on their mode of action (Vankova et al., 2019; Vogiazi et al., 2019). Also, according to their chemical structure, the major types of cyanotoxins are alkaloids, cyclic peptides and lipopolysaccharides (Vankova et al., 2019).

Microcystins (MCs) are the most common cyclic heptapeptide cyanotoxins with high toxicity and broad distribution (Chen et al., 2016b; Humbert, 2009) which is known as serious human and animal health threatening (Codd, 2000). MCs are secondary metabolites of different species of freshwater *cyanobacteria* (formerly known as blue-green algae) such as *Anabaena*, *Microcystis*, *Nostoc* and *Plankothrix* (Bartram and Chorus, 1999; Bownik and Skowroński, 2007). This toxin is released in water when cells are lysed under stress or age and may be transferred to sea-foods. Hence, consuming of MCs-contaminated foods and swimming in water contaminated with MCs would cause some health problems like headaches, fever, diarrhea, abdominal pain, nausea and vomiting. MCs are composed of an unusual aromatic amino acid, ADDA (3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid), and two variable amino acids (Fig. 1A) (Pravda et al., 2002; Van Apeldoorn et al., 2007). The unique structure of MCs causes the great stability at warm and cold water and in different pH. More than 100 different variants of MCs have been identified (Chen et al., 2016b). Microcystin-leucine arginine (microcystin-LR; MC-LR) (Fig. 1B) is the most prevalent and toxic MC in saltwater and freshwater worldwide (Rastogi et al., 2014).

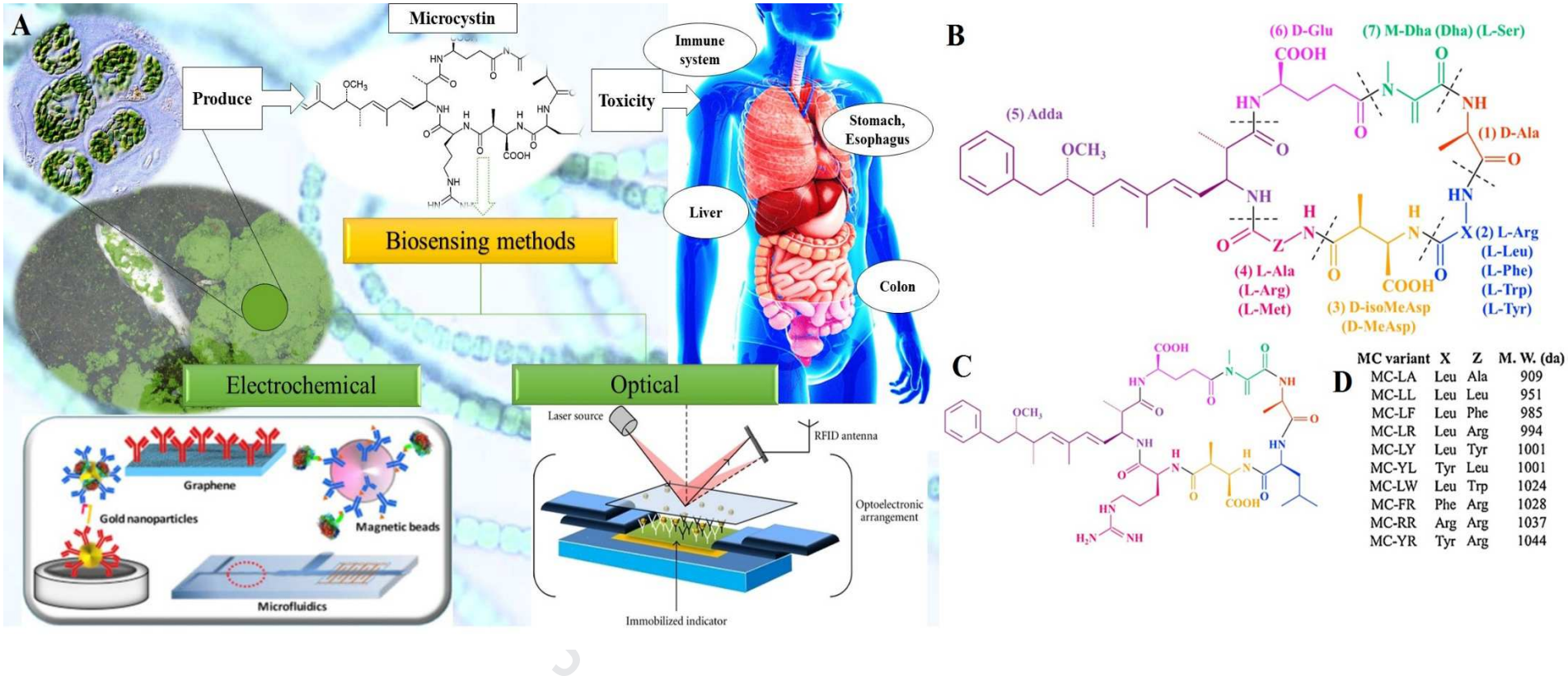

Fig. 1. (A) Cyanobacterial Bloom, Microcystin structure and their toxicity in human, Application of biosensors based methods for detection of microcystins. (B) Molecular weight and chemical structure of microcystins. General structure of the microcystins. Z and X in positions four and two are greatly variable L-amino acids that lead to determination of the suffix in the microcystins nomenclature. (C) Microcystin-LR (MC-LR) with the amino acid L (leucine) and R (arginine) in the variable positions X and Z, respectively. (D) Molecular weight of some frequent microcystins. Reprinted with permission from (Chen et al., 2016b).

MCs are specific and strong inhibitors of eukaryotic protein serine/threonine phosphatases 2A and 1 (PP2A and PP1), which have key roles in the regulation of apoptosis and organization of cytoskeleton (Chen et al., 2016b). Interaction of MCs with PP2A subunits results in cellular damage mainly through disruption in oxidative phosphorylation system and homeostasis of mitochondrial respiratory chain (Campos and Vasconcelos, 2010; McLellan and Manderville, 2017). There is also considerable evidence for MCs-induced oxidative stress in various organs such as the kidney, liver, intestine, brain and testis (Wang et al., 2010). MC-LR also leads to disturbance of the endoplasmic reticulum and mitochondrial pathways, inducement of apoptosis as well as upregulating proapoptotic genes (Zhou et al., 2015). MCs also demonstrate carcinogenic potential in many organs which is noticeable by upregulation of proto-oncogenes (Vichi et al., 2016). So, the growing concern about MCs in the aquatic ecosystems, especially in drinking water, shows an important aspect to the detection of MCs. Estimating the risk of MCs in water to human populations needs both experimental and epidemiological toxicological research. The maximum acceptable concentration of MC-LR recommended by World Health Organization (WHO) is 1 $\mu g\ L^{-1}$ in drinking water (Pham and Utsumi, 2018).

Over the past few years, several conventional strategies have been employed for the detection of MCs, including high-performance liquid chromatography (HPLC), the enzyme-linked immunosorbent assay (ELISA), thin layer chromatography (TLC), gas chromatography–mass spectrometry (GC-MS), liquid chromatography–mass spectrometry (LC-MS) and nuclear magnetic resonance (NMR). ELISA has been frequently applied for the determination of MCs in water, being it an on-site detection method. GC-MS can detect and quantify MCs based on complex procedures as compared with LC-MS, and thus the accuracy of GC-MS is lower than LC-MS. However, low sensitivity and specificity, being time-consuming, high-cost, requiring experienced operators and the difficulties in sample preparation are the drawbacks of these methods (Table 1). These limitations favor the development of portable, fast and sensitive devices such as biosensors or integrated analysis systems as appropriate alternatives to the classical approaches. Biosensor-based methods provide a great sensitivity and specificity and are fast, low-cost and reproducible with no need, in many cases, to difficult sample preparations as compared to conventional methods (Hassanpour et al., 2018a; Hassanpour et al., 2018b). Hence, the purpose of this review is to give an update of the literature regarding the use of biosensors for the determination of MCs.

Table 1. Summary of advantages and limitations of conventional methods for detection of microcystins

Method	Advantages	Limitations	Ref
HPLC [a]	Measure UV absorbance, ISO standard method, detection of individual variants	Requires standards, high-cost, no universal detector, difficult for novices	(Lawton et al., 1994)
ELISA [b]	Colorimetric, labor intensive, reproducible source, on-site detection, non-pretreatment	High-cost, sensitive cross reaction	(Metcalf and Codd, 2003)
TLC [c]	Easy operation	Requires standard, poor sensitivity	(Pelander et al., 2000)
NMR [d]	Structural information about cyanotoxins	Requires large amount of sample, requires sample extensive clean-up, expensive	(Harada et al., 1993)
GC–MS [e]	Determination in complex samples	Low sensitivity, tedious sample preparation	(Tanaka et al., 1993)
LC-MS [f]	Mass spectrometry, simultaneous separation and identification of similar compounds, sensitivity	Very expensive	(Robillot et al., 2000)

[a] high-performance liquid chromatography. [b] enzyme-linked immunosorbent assay. [C] thin layer chromatography. [d] nuclear magnetic resonance. [e] gas chromatography–mass spectrometry. [f] liquid chromatography–mass spectrometry.

2. Biosensors

2.1. Electrochemical biosensors

Electrochemical biosensors operate with transferring biochemical information through electrical signals in a real-time manner with a high selectivity. They have been used for the determination of various analytes. Redox reactions caused alteration in voltage, potential and current in the transducer system. Generally, the working electrode is modified with nanoparticles (NPs) to enhance the performance of biosensors (Hasanzadeh et al., 2018b; Ronkainen et al., 2010). The concentration of target analyte is directly examined by electrical response proportional. Recently, due to the need for quick quantitation in food supplies, environment contamination and human diseases, electrochemical biosensors have caught great attention. These types of biosensors have widespread application because of their interesting properties, containing well adaptability, great sensitivity and easy-to-use identity (Eivazzadeh-Keihan et al., 2018). Thus, they have excellent potential for future ultra-sensitive and fast detection applications. Electrochemical biosensors are categorized in three types, including amperometric-, potentiometric- and impedimetric-based biosensors (Hassanpour et al., 2019; Mokhtarzadeh et al., 2017).

2.1.1. Voltammetric Biosensors

Voltammetry is the most popular electrochemical method, because of its application in a variety of industrial processes and analytical chemistry and thus, it is the most common

method utilized in electrochemical sensors. A number of voltammetric methods have been used in electrochemical biosensors for determining of MCs, such as cyclic voltammetry (CV) (Kissinger and Heineman, 1983), differential pulse voltammetry (DPV), and square-wave voltammetry (SWV) (Kissinger and Ridgway, 1996). The main merit of voltammetric electrochemical biosensors concerns its very low noise. Therefore, this feature can lead to reproducible data with a great sensitivity and specificity. Also, it is a multi-detective method which could be employed for analyzing several targets with different potential peaks. Hence, in recent years, voltammetric techniques have been employed for the simultaneous determination of various analytes (Jahandari et al., 2019; Søpstad et al., 2019). Combination of high selectivity of specific antibody with high sensitivity of the electrochemical methods provides encouraging devices for MCs detection. Furthermore, comparison of conventional techniques with immunosensors evidences the extreme sensitivity of this technique. The limit of detection (LOD) and liner range (LR) of electrochemical methods based on the use of antibodies are better than other method for determining of MCs.

He et al. (2017) developed an ultra-sensitive and specific electrochemical immunosensor for determination of MCs in real water specimens. For this purpose, they created Fe_3O_4-polydopamine-graphene oxide (Fe_3O_4-PDA-GO) as a substrate for antibody immobilization onto the electrode surface. Moreover, the gold nanorods (AuNRs) were functionalized with secondary-antibody and circularization DNA (Ab_2–cirDNA) template as the signal label. Under optimum condition, the LOD of fabricated immunosensor was 0.007 mg L^{-1}. The main advantages of GO were high surface area and biocompatibility and high electrical conductivity. These benefits make this material as good substrate for immobilization of antibody.

Dopamine (DA) is a catecholamine, which is a transmitter in the nerve cells and, therefore, has very significant roles in the body and brain. Recently, polydopamine (PDA) was synthesized successfully as an outcome of non-covalent self-assembly and covalent polymerization. The unique stable substrate of PDA is related to residual catechol groups of PDA (Hong et al., 2011; Lee et al., 2007). Polypyrrole (PPy) is a heterocyclic organic conducting polymer, which is formed by the polymerization of pyrrole. The unique benefits of PPy include high conductivity, being low cost, easy preparation, and biocompatibility, which make this material as a specific polymer for being employed in the electronic devices as well as electrochemical sensors. PPy is often functionalized by anionic species (e.g., peptides, proteins, and polysaccharides), and negatively charged biological macromolecules

could be employed in order to get composite materials. PPy can be generated by chemical oxidative polymerization method (Ateh et al., 2006; Guimard et al., 2007). The main advantage of this material is its effect on conductivity enhancement, which draws researcher's attention. PDA and PPy, both are conductive polymers (CPs). Modification of electrodes surface with conductive polymers leads to increment in biosensors performance. Furthermore, the thickness and surface topography of CPs can easily be monitored through electrochemical polymerization conditions (e.g., electrode potential, current density, and electrolyte solutions) (Fan and Maier, 2006; Kim et al., 2018). Based on this advantages, Zhang et al. (2017a) employed gold nanoparticles (AuNPs) functional PPy microsphere (AuNPs/PPyMS) in the electrochemical immunosensor for enhancement of signal. They detected MCs with LOD 0.1 ng L^{-1} with a wide LR of 0.25 ng L^{-1} to 50 ng L^{-1}.

In 2016, a non-enzyme voltammetric immunosensor was developed by Zhang and co-workers for the determination of MCs (Zhang et al., 2016). Carbon nanofibers (CNFs) were engineered with carboxylic group electrodeposited onto the glassy carbon electrode (GCE) surface with the aid of polyethylene glycol (PEG) film. Then, first specific antibody (ab_1) was immobilized onto the modified electrode surface. Afterward, a second antibody, functionalized with AuNPs (ab_2-AuNPs), was conjugated to ab_1. The LOD of the designed immunosensor was 1.68 ng L^{-1} (Fig. 2). CNFs are one of the most important nanostructured members of carbon fibers. These materials have one-dimension (1D) structure with superior mechanical and chemical advantages over common types of carbon fibers owing to their specific small-size characteristics. The unique properties of carbon nanofibers including high specific area, flexibility and great mechanical strength, which may lead to multiple applications of them with great potential (Kim et al., 2013; Ruiz-Cornejo et al., 2018). Some attractive applications of CNFs concern their use in nano-electronics, nanolithography and as catalyst support (Zhou et al., 2014; Zou et al., 2014). Moreover, carbon nanofibers facilitate the electron transfer of electroactive analytes, which makes them as significant materials for electrochemical biosensors. For the first time, Marken and colleagues investigated the voltammetric behavior of CNFs composite modified electrodes (Marken et al., 2001).

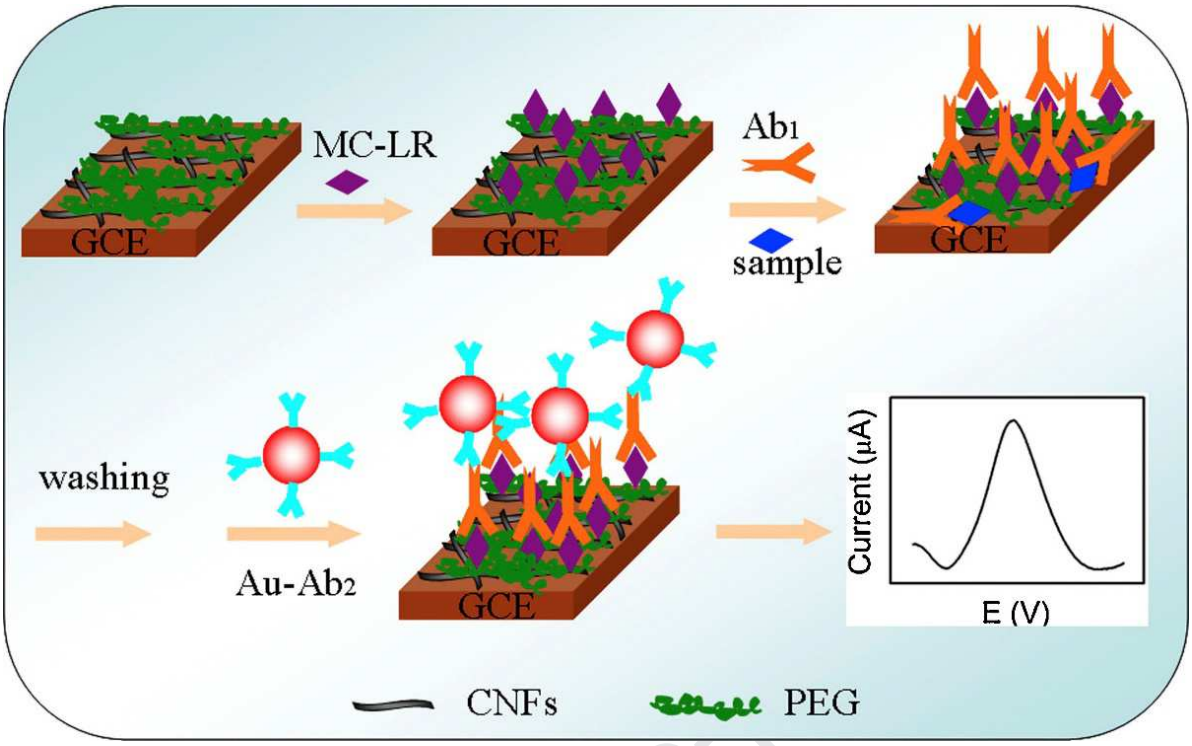

Fig. 2. Schematic representation of an electrochemical non-enzymatic immunosensor for the detection of MC-LR in polluted water sample based on carbon nanofibers (CNFs) as immobilization matrix and AuNPs as a label. Reprinted with permission from (Zhang et al., 2016).

Another recent research refers to electrodeposition of Fe_3O_4-AuNPs on the surface of screen-printed electrode for immobilization of antibody of microcystins (anti-MC-LR). The specific antibodies were linked to Fe_3O_4 by the adsorption between Fe_3O_4-AuNPs and antibody. The concentration of MCs was detected by direct competitive immunoassay between MCLR-horseradish peroxidase (HRP) and the target analyte. The immunosensor provided good sensitivity for MCs determination with detection limit of 0.38 μg L^{-1} (Zhang et al., 2013). Gold nanomaterials do not have good specificity towards targets. Therefore, these nanomaterials have been used in sensors together with antibody and aptamer for increasing sensitivity, efficiency and selectivity (Hasanzadeh et al., 2018a; Zeng et al., 2011). Although both AuNPs and silver nanoparticles (AgNPs) produced the same performances, AgNPs could be prepared with lower cost than AuNPs.

Aptamers are single-stranded DNA or RNA fragments that have 15-100 bases. Aptamers are generally selected by SELEX (systematic evolution of ligands by exponential enrichment) process (Mokhtarzadeh et al., 2016). High selectivity and sensitivity of aptamers are related to conjugation of aptamer with analyte. Aptamers have extremely wide detection range from small molecules to large microorganisms. To put it in nutshell, application of aptamers in

biosensors lead to fabrication of aptamer-based biosensors which termed aptasensors (Dollins et al., 2008; Ellington and Szostak, 1990). Eissa et al. (2014) developed a novel label-free electrochemical aptasensor based on graphene and aptamer for the detection of MCs from spiked tap water and fish extracts. For this purpose, aptamers (5′-GGC GCC AAA CAG GAC CAC CAT GAC AAT TAC CCA TAC CAC CTC ATT ATG CCC CAT CTC CGC3′) were immobilized on the surface of graphene-modified screen-printed carbon electrodes (SPCEs) by physical adsorption. SWV of $[Fe(CN)_6]^{4-/3-}$ was exploited to determine current modifications in front of MCs concentration. Peak current is indirectly/directly related to aptamer assembly and presence of MCs. The LOD and LR of developed aptasensor was from 1.9 pM to 0.1 pM and 10 nM in $[Fe(CN)_6]^{4-/3-}$, respectively.

The intrinsic limitations of protein enzymes such, sensitivity to temperature and pH create troubles for their use in electrochemical systems based on enzyme for detection of MCs. In this type of electrochemical biosensors, enzymes as HRP or alkaline phosphatase (ALP) were employed to generate the detection signal. The main advantage of these biosensors, in comparison with enzyme-free immunosensors, is that the detection conditions are not so rigorous and easily disturbed. Catanante et al. (2015) used recombinant protein phosphate type 1 (PP1α) and Cobalt-Phtalocyanine (CoPC) for building a novel electrochemical biosensor for the detection of MCs. The PP1α was entrapped in polyvinyl alcohol (azid unit) on CoPC modified screen-printed electrode (SPEs). Hence, the designed biosensor measured activity of the PP1α through assessing the oxidation peak current by DPV with a detection limit of 0.93 mg L^{-1} and a dynamic range from 0.93 to 40.32 µg L^{-1}. In the past decade, antibodies, recombinant proteins (as enzyme) and aptamers have been developed for detection of MCs. Methods based on antigen and antibody affinity interaction have high specificity. However, they have drawbacks, including poor selectivity and cross-reactivity with other analytes. Additionally, these systems are not stable at high temperatures. On the contrary, aptamers do not have these troubles. Table 2 summarizes the voltammetric-based biosensors for the detection of MCs.

Table. 2. Comparison of the characteristics of electrochemical-based biosensors designed for the detection of MC-LR

Detection method	Structure	Technique	Sample type	Linear range (LR)	LOD	Ref.
Voltammetry	Quantumdot/antibody	SWSV	water	0.227 to 50 µg L^{-1}	0.099 µg L^{-1}	(Yu et al., 2009)
	Enzymatic recycling	CV	Buffer	37.75 to 0.05 µg L^{-1}	0.05 µg L^{-1}	(Campàs et al.,

						2008)
	Double aptamer and terminal deoxynucleotidyl transferase	DPV	Serum and tap water	60 pM to 1000 nM	15 pM	(Abnous et al., 2019)
	Antigen/antibody/goat-anti-rabbit IgG-HRP	CV	Tap, reservoir and lake water	0.001 to 100 µg L^{-1}	0.00011 µg L^{-1}	(Guan et al., 2019)
	AuNPs/Au /graphene/aptamer	DPV	Sewage and Pond water	1.0 to 100 pM	0.8 pM	(Liu et al., 2019a)
	AuNP@MoS2/TiONB/aptamer	DPV	Buffer Tap, reservoir and river water	0.005 to 30 nM	0.002 nM	(Liu et al., 2019b)
	xGnP/AgNP-Nafion/antibody	SWV	Seawater	0.5 - 5000 ng mL^{-1}	0.017 ng mL^{-1}	(Zanato et al., 2017)
	Br-Py/AuNP-BSA/antibody	EIS	Spiked seawater samples	0.05 to 500.0 ng mL^{-1}	0.05 ng mL^{-1}	(Talamini et al., 2018)
Impedimetry	3D graphene-based	EIS	Drinking water	0.05 to 20 mg L^{-1}	0.05 mg L^{-1}	(Zhang et al., 2017b)
	rGO/antigen/BSA	ELS	Lake water	0.05 ng mL^{-1} to 75 µg mL^{-1}	0.02 ng mL^{-1}	(Zhang et al., 2019)
	Graphene film composite	ELS	Drinking and environmental water	0.005 to 10 µg L^{-1}	2.3 ng L^{-1}	(Zhang et al., 2018)
Amperometry	protein phosphatase 2A (PP2A)	CV	River water	37 to 188 µg L^{-1}	37 µg L^{-1}	(Campàs et al., 2007)
Chronoamperometry	MoS_2-PtPdNPs/aptamer	SWV	Buffer and lake water	0.01 to 50 ng mL^{-1} and 0.1 to 50 ng mL^{-1}	0.006 ng mL^{-1} and 0.045 ng mL^{-1}	(Wu et al., 2020)

2.1.2. Impedimetric biosensors

Electrochemical impedance spectroscopy (EIS) is a rapid, repeatable, and sensitive technique with several chemical and physical benefits. This method measures the concentration of analyte by catalyzed reactions of enzymes or the biomolecular recognition of specific binding proteins, lectins, receptors, nucleic acids, whole cells, antibodies or antibody-related substances (Amorim et al., 2009; Guan et al., 2004). In the last years, the specific properties of EIS have led to the development of impedimetric biosensors for the determination of MCs (Table 2). The comparison of voltammetric and impedimetric methods indicates that the voltammetric technique is more common and sensitive than impedimetric one. Capacitive biosensors are a new type of impedimetric methods which vary the dielectric feature of an electrode surface in order to increase protein adsorption and surface fouling (Berggren et al.,

2001). Recently, different types of capacitive biosensors have been developed for direct detection of MCs without the requirement of labeling or the use of an indicating reaction. For example, Lebogang et al. (2014a) designed a novel immunosensor based on tyramine, AuNPs and a monoclonal antibody (Adda-specific mAbs) for determination of MCs. Polytyramine was used as surface insulation and anchor for antibodies and was electrodeposited on the gold surface of the electrode. Moreover, AuNPs were bonded with polytyramine for enhancing surface area by amplifying the signal. Specific monoclonal antibodies were applied onto the modified surface. The LOD and LR of developed immunosensor were 2.1×10^{-14} M and from 1×10^{-13} M to 1×10^{-10} M, respectively. The main advantage of the fabricated immunosensor was its capability to determine other types of MCs. Hence, this immunosensor can broaden our understanding about concentration of MCs. This immunosensor is more sensitive than those prepared without application of AuNPs in their fabrication steps. On the other hand, this system has a lower stability than aptasensors. In another study based on AuNPs and mAbs conducted by the same group, firstly, the surface of gold electrode was modified with polytyramine. Then, the AuNPs were immobilized onto the modified electrode surface. Afterward, mAbs were immobilized onto the modified surface. They could detect MCs with a LOD of 0.00001 μg L^{-1} (Lebogang et al., 2014b). Dawan et al. (2011) showed the important rule of AgNPs in the development of immunosensor. They designed two types of ultra-sensitive immunosensors with/without AgNPs for the detection of MCs. In the immunosensor without AgNPs, the surface of the gold electrode was modified by thiourea, glutaraldehyde (for cross-linking) and antibody. The results showed that AgNPs enhanced the sensitivity of the immunosensor. The detection limits of developed immunosensors with/without AgNPs were 10 and 100 fM, respectively.

Over the last few years, the unique physicochemical and structural properties of dendrimer nanomaterials, such as high surface area and thermal stability, has led to their use in biosensing field (Kordasht et al., 2019; Xu et al., 2019). Dendrimer nanomaterials have been electrodeposited on the surface of electrodes for detection of microcystins. Bilibana et al. (2016) developed an electrochemical aptatoxisensor with high sensitivity and stability for MCs determination in tap water and distilled water based on cobalt (II) salicylaldiimine metallodendrimer (SDD–Co(II)) doped with AgNPs. AgNPs This system has a huge specific area and high ability to transfer photo-induced electrons at the surfaces of colloidal particles. Firstly, SDD–Co(II)-AgNPs were electrodeposited onto the GCE surface and then, specific thiolated aptamers of MCs were immobilized onto the modified GCE surface by functional

groups (their 5′ thiolated end). The complex of metals and dendrimeric structure arranges a molecular electronic communication on the surface of electrode in order to increase the sensitivity. The connection between MCs and aptamer on GCE|SDD–Co(II)-AgNPs led to form a complex that resulted in steric hindrance and electrostatic repulsion culminating in variation of the corresponding peak current of the electrochemical probe. The designed aptasensor provided a LOD and LR of 0.04 μg L^{-1} and 0.1 to 1.1μg L^{-1} for MCs detection by successive CV (Bilibana et al., 2016). He et al. (2019) developed a novel enzyme-based electrochemical immunosensor for the detection of MCs. For this purpose, surface of the microplate was modified with AuNPs-decorated-carbon nanotubes (AuNPs-CNTs) and antibody. Then, secondary antibody and initiator DNA strand were immobilized onto the surface of AgNPs/AuNRs by gold-thiolate bonds. The hybridization chain reaction (HCR) leads to the generation of copper nanoparticles (CuNPs) by appearance of long double-strands DNA (dsDNA) on AgNPs/AuNRs. This immunosensor detected MCs with a LR from 0.005 μg L^{-1} to 20 μg L^{-1} and a LOD of 2.8 ng L^{-1} (Fig. 3A).

Multi-walled carbon nanotubes (MWCNTs) are a subclass of CNTs commonly utilized as functionalization agents with surfactants, polymer, composites and biomolecules. (Scida et al., 2011; Sireesha et al., 2018). The MWCNTs have excellent electron conductivity, reproducibility, high surface area, linearity, easy modification with enormous materials and repeatability of measurements (Choi et al., 2008; Okpalugo et al., 2005). Han et al. (2013) employed CNTs in an impedimetric electrochemical biosensor for the determination of MC-LR in drinking water. The surface of electrode was modified with MWCNTs. Then, linking agents were conjugated with oxygenated surface groups on the MWCNTs. The attachment of linking agents led to conjugation of specific antibodies and toxin molecules. The sensing range of the developed biosensor was 0.05–20 μg L^{-1}. In another study, a simple and efficient impedance aptasensor for MC-LR detection in water samples (lake, river and tap water). The surface of gold electrode was modified with ssDNA-aptamer by covalent bond. Conjugation of MCs with aptamer caused impedance decreasing that showed a linear trend with the logarithm of the MC-LR concentration. This comprehensive aptasensor could detect MC-LR with a LOD of 1.8×10^{-11} mol L^{-1} and a dynamic range from 1.0×10^{-7} to 5.0×10^{-11} mol L^{-1}, respectively (Lin et al., 2013). Barreiros dos Santos and co-workers reported an impedance portable microfluidic immunosensor with three segment, specimen operation module and a determination module, using the electrochemical immunosensor for indirect detection of total MC-LR content (intracellular and extracellular) and free MC-LR toxin (extracellular). The

gold surface of ECCs (electrochemical-cell-chips) was modified with MC-LR by covalently bond. The performance of the MC-LR determination was made by analyzing the engineered surface. However, this MC-LR competitively inhibits the conjugation of anti-MC-LR antibodies to the MC-LR functionalization surface (Fig. 3B). This immunosensor provided a detection limit of 5.7×10^{-10} g L^{-1} with LR between 3.3×10^{-4} and 10^{-7} g L^{-1}. The main benefit of this biosensor was its portability together with its potential for determining both total MC-LR content and free MC-LR toxin (Barreiros dos Santos et al., 2019).

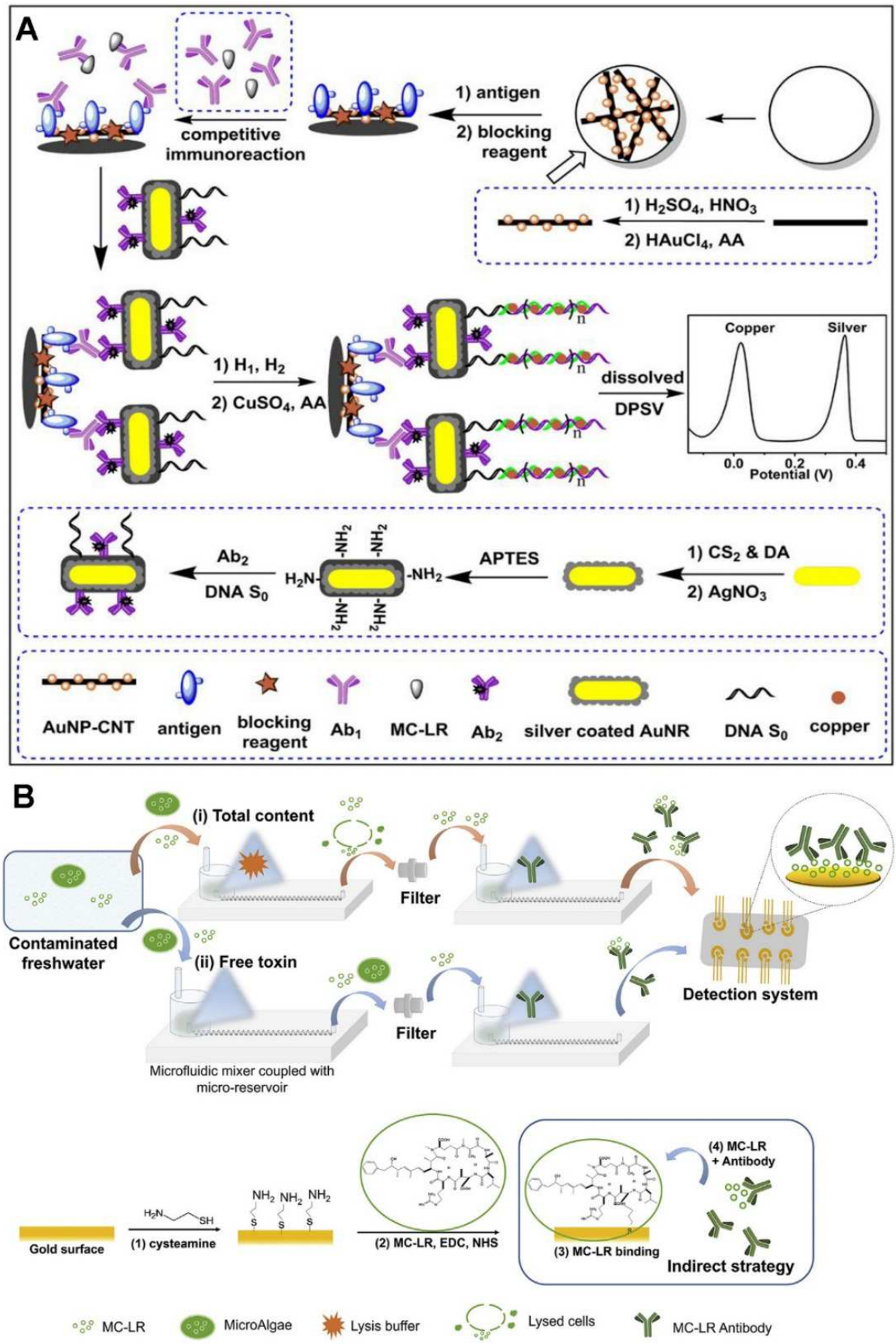

Fig. 3. (A) Schematic representation of an enzyme-based immunosensor for the detection of MCs. This strategy was made up of AuNPs-CNTs-ab_1-AgNPs/AuNRs-ab_2-DNA and presented a dual-signal immunoassay from the

electrochemical response of AgNPs and CuNPs. (B) A portable immunosensor based on EIS for the detection of total MC-LR content and free MC-LR toxin. Reprinted with permission from (He et al., 2019) and (Barreiros dos Santos et al., 2019).

2.1.3. Amperometric biosensors

Amperometric biosensors are self-contained integrated electrochemical devices that conduct the target analyte determination based on measuring the current at a fixed voltage. These biosensors have dynamic ranges, response times and sensitivities similar to those of potentiometric biosensors. The first amperometric biosensor was designed for detection of glucose (Lau and Slater, 2006). Different kinds of amperometric biosensors have been developed for MC-LR detection. Lebogang and colleagues designed a new sequential microflow-ELISA amperometric system based on a mAbs for the determination of MC-LR. Adda-specific mAbs were immobilized onto the CNBr-activated sepharose beads, then, the modified sepharose beads were located into a micro-immunocolumn. The modified surface was exploited to capture free MCs and microcystin-HRP as tracer. The detection process carries out electrochemically using ABTS (2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)) as electron transfer between the electrode and HRP. The peak current was indirectly related to the amount of bonding analyte with antibodies (Fig. 4) (Lebogang et al., 2017).

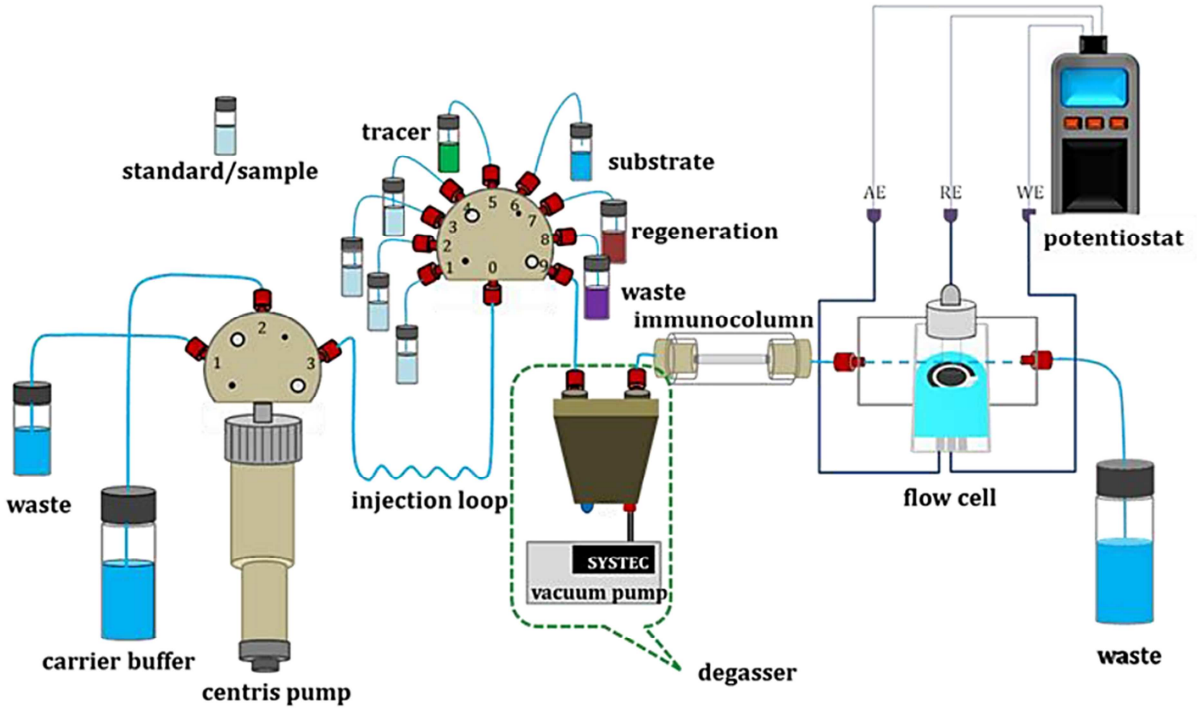

Fig. 4. Schematic representation of an automated sequential injection configuration of an amperometric immunosensor for the detection of MC-LR. Reprinted with permission from (Lebogang et al., 2017).

High specificity and sensitivity of polyclonal antibodies (PAbs) and MAbs make the aforementioned materials very useful for screening in both medical and non-medical applications. An amperometric immunosensors was developed based on the direct conjugation of MCs with MAbs and PAbs for determination of MC-LR in algae and their associated biofilms. Both antibodies were immobilized on microtiter wells and screen-printed graphite electrodes. In this method, electrochemical measurement was performed at -200 mV and exploited MPMS (5-methyl-phenazinium methyl sulfate) as mediator for HRP, the enzymatic label of the competitor for examination of microcystin. The obtained results showed that MAb-based biosensor provided an enhanced LOD. Furthermore, the reproducibility and reliability of PAb biosensor was better than that of MAbs. The sensing ranges were 10^{-1} to 10^{2} and 10^{-4} to 10^{2} µg L^{-1} for PAb and MAb, respectively (Campàs and Marty, 2007). In the last few years, nanomaterial-based electrochemical biosensors have been reported for the detection of MCs. Tong et al. (2011) designed a label-free amperometric immunosensor for MC-LR determination with LOD of 20 ng L^{-1}. The surface of gold electrode was decorated with L-cysteine-AuNPs, followed by immobilization of antibody. The analytical performances of designed amperometric-based biosensors for detection of MCs are summarized in Table 2.

2.2. Optical biosensors

During the last two decades, optical biosensors have gained improvements and become one of the precious and significant elements for activities like drug screening and biosensing. Therefore, these biosensors become as one of the most useful biosensor types (Hassanpour et al., 2018b). Some advantages of these biosensors include direct detection of numerous chemical and biological materials and label-free and real-time determinations. These advantages have made the optical biosensors alternatives to conventional analytical strategies (Hassanpour et al., 2018b; Saadati et al., 2019). Most of the applications of these biosensors concern healthcare and environmental control. Different varieties of optical biosensors including fluorescence, absorption, refraction, surface plasmon resonance (SPR), optical fiber and luminescence (Hassanpour et al., 2018a; Hassanpour et al., 2018b; Saadati et al., 2019).

2.2.1. Fluorescence biosensors

Fluorescence optical biosensors are label-based devices, which use dyes, quantum dots (QDs) or fluorescence proteins as labels. These kinds of optical biosensors can be categorized into two groups regarding "*in vitro*" and "*in vivo*" determinations. In the "*in vitro*" measurements,

metabolic activity of microorganisms causes alterations in light emission due to the existence of exogenous fluorescent elements. However in the "*in vivo*" analysis, there is no need to add exogenous elements because some microorganisms have the ability to produce fluorescence in these measurements (Eivazzadeh-Keihan et al., 2017; Pashazadeh et al., 2017). Long and co-workers developed a unique immunoassay based on optic fiber for multiple mini and small analytes determination in which they immobilized two types of hapten conjugates such as NB-OVA and MC-LR-OVA (anti-nitrobenzene and anti-microcystin-LR monoclonal antibodies) on the same fiber optic. Trinitrotoluene (TNT) and MC-LR were detected specifically and simultaneously within 10 min of analysis time. The detection limits for TNT and MC-LR were 0.09 mg L^{-1} and 0.04 µg L^{-1}, respectively. Binding features, great regeneration performance and strength of sensor surface of the developed biosensor guarantee the accurate and cost-efficient measurements of mini analytes (Long et al., 2010). A sandwich-like immunoassay method based on anti-mouse IgG antibody labeled with QDs through employing reusable and portable opto-fluidic nanobiosensing platform was designed for ultrasensitive and quick determination of small molecules. This strategy had two steps, including pre-incubation of mixture of various concentrations of anti-small molecule antibody and small molecules, followed by the introduction of QDs immunoprobe into opto-fluidic cell. Two-step immunoassay technique, as compared with one-step methods, has the ability to increase sensitivity and fluorescence as well as enhancing performance of nanobiosensing (Fig. 5). Based on the suggested method, bisphenol-A (BPA) and MC-LR were analyzed with quickness, great sensitivity and simplicity. High concentration of small molecules in the specimen caused low conjugation of anti-small molecule antibody with antigen carrier protein which was immobilized on the surface of sensor. It also resulted in conjugation of QDs immunoprobes with anti-small molecule antibody, thus reduced the signal of fluorescence determined by nanobiosensor. Under optimum conditions, BPA and MC-LR were determined with detection limits of 0.04 and 0.003 µg L^{-1}, respectively (Zhou et al., 2016).

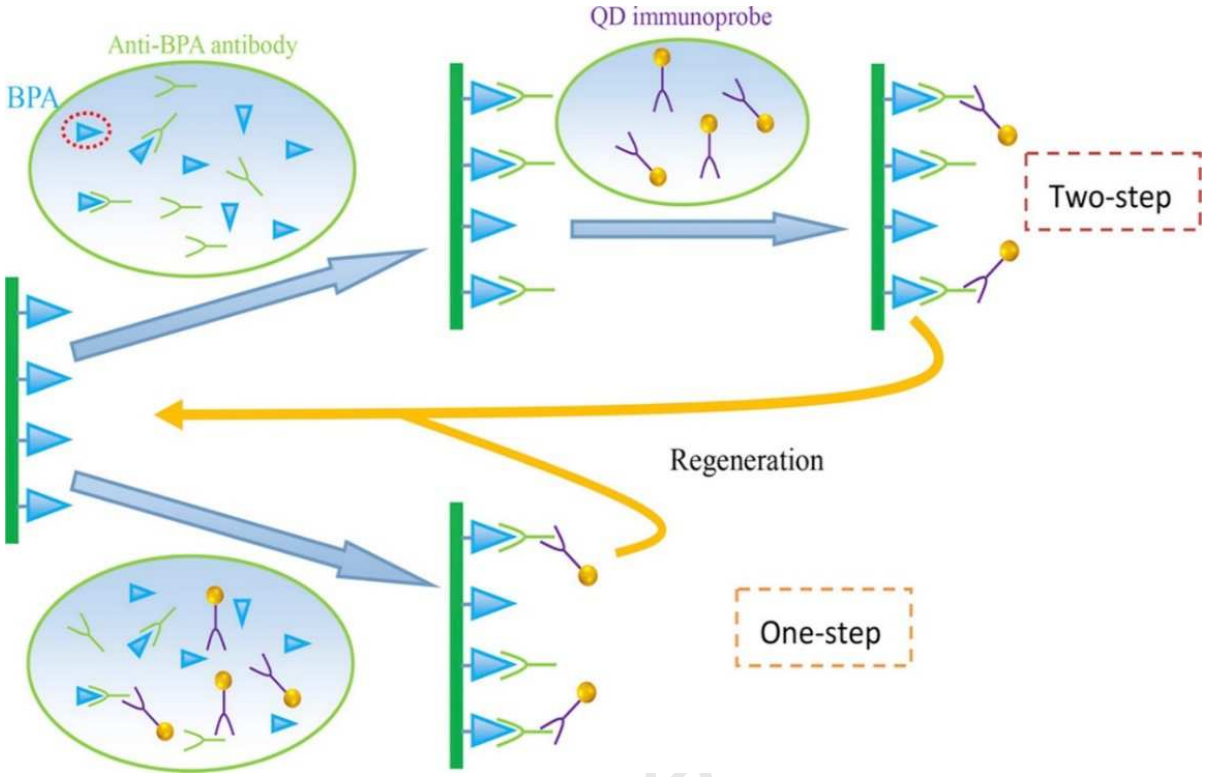

Fig. 5. Scheme of the sandwich-like immunoassay mechanism for determination of bisphenol-A and MC-LR using quantum dot immunoprobe based on the one-step and two-step immunoassay formats. Reprinted with permission from (Zhou et al., 2016).

Liu et al. (2018b) made laser-induced fluorescence based determination of multi analytes through linking of biomolecules to an integrated TriPleX™ waveguide chip surface on a glass substrate (FS, fused silica). The analytes determined with the waveguide biosensor were atrazine, 2,4-D, BPA and MC-LR which were sensitively detected with LOD of 0.2 µg L^{-1}, 1.18 µg L^{-1}, 0.06 µg $L^{-1}$and 0.22 µg L^{-1}, respectively. Recoveries of atrazine, 2,4-D, BPA and MC-LR in spiked water specimens varied from 84 % to 120 %, indicating the acceptable accuracy of the developed technology. In another study, a fluorescent immunosensor was designed based on integrated channel waveguide with the capability to determine maximum 32 contaminants simultaneously and quickly. They employed waveguide tapers for enhancing the efficacy of collection and excitation of fluorescent signals in the existence of fluorophore photo-bleaching in a bioassay with solid surface. It was the first application of this kind of waveguide immunosensor for determination of MC-LR in lake water. (3-Mercaptopropyl) trimethoxysilane/N-(4-maleimidobutyryloxy) succinimide (MTS/GMBS) used for activation of waveguide chip for immobilizing BSA-MC-LR conjugate. The recovery of target analyte in lake water samples varied between 84 % and 108 %, validating the potential of this

immunosensor for the determination of MC-LR in water (Liu et al., 2017). In a study made by Lv et al. (2017) a simple, sensitive and specific fluorescence aptasensor was developed for MC-LR determination. It was based on application of improved fluorescence through upconversion nanoparticles (UCNP). The system provided a great affinity towards single strand DNA (ss-DNA) of MoS_2 (named as FAUM). The proposed method specifically detected MC-LR within a LR between 0.01 and 50 ng mL^{-1} and a detection limit of 0.002 ng mL^{-1}. Reasonable feasibility and reliability in the detection of MC-LR was evidenced in the analysis of natural water samples.

McNamee and colleagues built a multiplex microarray sensor for the determination of five types of harmful cyanobacterial and algal toxins present in fresh-water, brackish, and marine environments, involving saxitoxin (STX) and analogues, MCs and analogues, cylindrospemopsin (CYN), okadaic acid (OA) and analogues and domoic acid (DA). The specificity, sensitivity and feasibility of designed method were evaluated. The LOD for 15 min detection were 0.40, 0.08, 0.05, 0.44, and 0.37 ng ml^{-1} for MC, CYN, STX, OA, and DA, respectively. The microarray showed easy-to-use, quick, and great sensitivity as well as advanced caution screening assay for supporting national controlling agencies (McNamee et al., 2014). Bickman and co-workers designed a portable and easy-to-use biosensor system (MBio) utilizing new planar waveguide optical sensor for simultaneous and fast determination of multiple cyanotoxins in freshwater. The first duplex MC/CYN assay cartridge employing combination of monoclonal antibodies conjugated with fluorophore as detector molecule, provided LOD for MC and CYN of 0.4 and 0.7 µg L^{-1}, respectively (Bickman et al., 2018). Liu et al. (2018a) built an optical biosensor for the determination of microcystin synthetase A (mcyA) gene. The mcyA-specific ssDNA probes were designed *in silico* and synthesized for covalent immobilization on the surface of optical fiber. The completion of target DNA modified fluorescently was done using Cy5-tagged dCTPs (deoxycytidine triphosphates) in PCR. PCR amplicons were captured on the surface of optical fiber through easy surface-based hybridization, followed by emission of fluorescent induced with evanescent wave field. Under optimal conditions, the LOD was 10 pM equal to 10^3 gene copies mL^{-1}. The assay provided satisfactory reproducibility and stability. Table 3 summarizes the examples of the fluorescence-based biosensing methods for detection of MCs.

Table 3. Comparison of analytical performance for reported optical-based biosensors for the detection of Microcystins

Detection method	Strategy	Sample type	Linear range	LOD	Ref.
	Simultaneous detection of TNT and MC-LR by based on optic fiber	Drinking water	0 - 1000 µg L^{-1}	0.04 µg L^{-1}	(Long et al., 2010)
	Simultaneous detection of bisphenol-A and MC-LR by quantum dot immunoprobe	Tap and bottled water	0.01 – 10 µg L^{-1}	0.003 µg L^{-1}	(Zhou et al., 2016)
	Linking of biomolecules to an integrated TriPleX™ waveguide chip	Tap, lake and bottled water	0.53 - 11.28 µg L^{-1}	0.22 µg L^{-1}	(Liu et al., 2018b)
	Integrated channel waveguide	Lake water	0.36 - 2.50 µg L^{-1}	0.21 µg L^{-1}	(Liu et al., 2017).
Fluorescence-based biosensors	Upconversion nanoparticles (UCNP)-based aptasensors	Tap and lake water	0.01 and 50 ng mL^{-1}	0.002 ng mL^{-1}	(Lv et al., 2017)
	Multiplex microarray sensor	Buffer and seawater	Buffer: 0.48 - 3.78 ng ml^{-1} Seawater: 0.40 - 3.35 ng ml^{-1}	0.40 ng ml^{-1}	(McNamee et al., 2014)
	A portable biosensor for simultaneous determination of multiple cyanotoxins	Lake water	0.4 - 3.1 µg L^{-1}	0.4 µg L^{-1}	(Bickman et al., 2018)
	determination of microcystin synthetase A gene by using Cy5-tagged dCTPs PCR	Freshwater	0.05 to 5 nM	10 pM	(Liu et al., 2018a)
	SPR immunoassay based on monoclonal antibody	Drinking and pool water	0.69 - 4.24 ng mL^{-1}	Intracellular MCs: 0.05 ng mL^{-1} Extracellular MCs: 0.5 ng mL^{-1}	(Devlin et al., 2014)
SPR-based biosensors	Covalent coupling between cio-conjugation of MC-LR and BSA	Pool and tap water	1.56 - 25.00 ng mL^{-1}	0.55 ng mL^{-1}	(Chen et al., 2011).
	Immobilization of MC-LR to functionalized SPR chip with SAM	Drinking water	0.2 - 2.0 µg L^{-1}	~ 73 ng L^{-1}	(Herranz et al., 2010)
	Competitive inhibition SPR biosensor for detection of MCs in *Aphanizomenon flos-aquae* BGA	Drinking water	<0.5- 2.21 mg kg^{-1}	0.561 mg kg^{-1}	(Vinogradova et al., 2011)

2.2.2. Surface Plasmon Resonance biosensors

The technology of SPR has been employed since 1982. SPR biosensors have some advantages such as direct determination without addition of any label as well as online controlling of interaction affinity (Homola et al., 1999; Yao and Fu, 2014). Devlin and co-workers developed a SPR immunoassay through production of greatly sensitive mAbs for the detection of MCs. The produced antibody provided cross-reactivity of MC-RR 108 %, MC-

LR 100 %, MC- LW 71 %, MC-LA 69 %, MC-LF 68 %, MC-YR 68 %, as well as Nodularin 94 %. MC-LR was covalently bound to CM5-chip and with antibody applied in 4 minutes injection permitted to determine MCs in water under the WHO limit (1 µg L^{-1}). The method provided a good reproducibility and repeatability with recovery percentages in spiked samples varying from 74 - 123 % and below 10 % for variation coefficient of intra-assay and 15 % for inter-assay analyses. The method permitted to measure 0.05 ng mL^{-1} of intracellular MCs and 0.5 ng mL^{-1} of extracellular toxins. The comparison between LC-MS/MS and SPR for 6 *Microcystis aeruginosa* cultures provided a correlation coefficient $R^2 = 0.9989$ (Devlin et al., 2014). Chen et al. (2011) developed a SPR-based immunoassay for detection of MC-LR in surface water. A Spreeta-biosensor was adapted in the flow injection analysis (FIA) mode, using a biofilm immobilization done through covalent coupling between cio-conjugation of MC-LR and bovin serum albumin (BSA) and golden-surface. The results provided a LOD of 0.55 ng mL^{-1} with a dynamic range of 1.56 to 25.00 ng mL^{-1} and IC_{50} (half-maximal inhibitory concentration) of 5.6 ng mL^{-1}.The recovery results in water samples for MC-LR varied from 90 % till 112 %. Analysis of pool and tap water evidenced that pool water had 2.39 ng mL^{-1} of analyte whereas tap water did not have measurable amounts. In comparison with other techniques, SPR-based immunoassay is fast, label-free, cost-efficient as well as able to determine easily levels of the recommended MC-LR in drinking water by WHO.

Herranz and colleagues established a SPR-based biosensor for the determination of MCs in drinking water. SPR chip was functionalized with self-assembled monolayer (SAM), then covalent immobilization of MC-LR was made onto the functionalized SPR surface. The developed biosensor showed IC_{50} of 0.67 ± 0.09 µg L^{-1} with LOD of 73 ± 8 ng L^{-1} and LR between 0.2 and 2.0 µg L^{-1} for detection of MC-LR. Cross-reactivity to different MCs like MC-YR (94 %) and MC-RR (88 %) was measured. This SPR-based biosensor could perform 4 simultaneous detection in 60 minutes. The SPR chip was reusable for 40 analysis-regeneration cycles without significant loss of binding capacity. This biosensor was successfully applied for direct analysis of MC-LR in drinking water (Herranz et al., 2010). Vinogradova and co-workers built a SPR-based immunosensor for detection of MCs in *Aphanizomenon flos-aquae* blue-green algae (BGA) and *Spirulina* food supplements with LOD of 0.561 mg kg^{-1} and LR from <0.5 - 2.21 mg kg^{-1} (Vinogradova et al., 2011). The analytical performances of some SPR systems for detection of MCs are summarized in Table 3.

2.3. Mass biosensors

2.3.1. Piezoelectric biosensors

Over the last decade, mass-sensitive systems have been developed with the ability for determining extra attached mass to the biosensor, thus providing detectable alteration in resonance frequency which called piezoelectric biosensors (Hassanpour et al., 2018a; Hassanpour et al., 2018b). This type of analytical devices has been operated based on oscillations change due to a mass bound on a piezoelectric crystal surface for the measurement of concentration of target (Pohanka, 2018; Skládal, 2016). Although most biosensors need specific reagents and labeling for recording interactions affinity, the piezoelectric biosensors are able to recognize the targets with simple materials. For that reason, it is cheaper and faster to build piezoelectric sensors than other systems for detection of MC-LR. However, the sensitivity of piezoelectric biosensors is lower than that of other biosensors designed for detection of MC-LR (Montagut et al., 2011; Pramanik et al., 2013). The classical quartz crystal microbalance (QCM) contains a thin slice of AT-cut quartz crystal wafer sandwiched between two metal electrodes. An employed oscillating electric field induces an acoustic wave. Furthermore, the unique benefits of QCM such as minimal reagents, miniature size and rapid operation make this technique as a popular transducer in immunoassays (Kurosawa et al., 2004; Ngo et al., 2014).

Molecularly imprinted polymer (MIP) is an attractive tool with specific properties of stability, affordable cost and easy synthesis. In 2003, Chianella et al. (2003) developed a QCM biosensor based on artificial MIP receptor for the detection of MC-LR. They used the imprinted polymer for solid-phase extraction (SPE) and as a sensing element in a piezoelectric sensor. Thus, the piezoelectric crystal was decorated by a layer of MIP particle. The achieved LOD was 0.35 nM (≈ 35 µg L^{-1}) for MC-LR. Moreover, the response time was about 5 - 10 minutes which is very low in comparison to similar biosensors, and the sensitivity was higher than that of required by the WHO value of 1 µg L^{-1} for drinking water. Xia and co-workers reported a novel immunosensor based on nanodendritic surfactant for detection of MC-LR. They modified the surface of QCM with C18N3 (bis (amidoethyl-carbamoylethyl) octadecylamine) as dendritic surface for increasing immobilization of AuNPs-functionalized MC-LR antibodies on the primary antibodies. MCs caused conjugation anti-MC-LR-AuNPs with primary antibodies resulting in a large frequency shift. The LOD of this immunosensor was 100 ng mL^{-1}. Although the comparison of nanodendritic surfactant with commercial phospholipids, for modifying QCM interface, shows that nanodendritic

surfactant could decrease the cost of sensor manufacture, this immunosensor without two amplifications (nanodendritic surfactant and AuNPs) showed very poor sensitivity (Xia et al., 2011).

2.4. Other type of biosensors for the detection of microcystins

Apart of the aforementioned common types of biosensors, some alternative biosensors have been designed for the determination of MCs. Colorimetric techniques provide easy-operation, low-cost and portability. There are few researchers who used colorimetric techniques (Chen et al., 2016a; Seok et al., 2015). Hoa et al. (2018) designed a low-cost biosensor based on pH-resolved colorimetry for MCs determination. They combined two platforms (with/without Fe_3O_4) with two different DNA probes (1 and 2). Firstly, the surface of non Fe_3O_4 modified with DNA probe 1 and allochroic dyes (as indicator) included phenolphthalein (PP), malachite green carbinol base (MGCB), thymolphthalein (TP) and methyl violet (MV). Apart from that, the second platform included assistant of DNA probe 2 adsorbed on surface of GO/Fe_3O_4. In the aqueous media, DNA probe 1 and DNA probe 2 were bonded with aptamer for combining aptamer with two platforms. In the presence of MCs, the attachment of MCs with aptamer was led to the separation of aptamer and release of dyes. Furthermore, pH value was used to control the order of release of the dye from GO layer. Therefore, the concentration of the MCs was directly related to release of MV (as indicator).

Over the last few years, several researchers exploited discs for the detection of biomarkers (Li et al., 2008; Potyrailo et al., 2009). Morais et al. (2010) developed a novel optical multiplexed micro-immunoassays immobilized on the polycarbonate side of a digital versatile disk (DVD) for the determination of MCs. Specific mAbs was immobilized onto the surface of disk and each disk surface was designed with 48 arrays (Fig. 6). Micro immunoreaction was detected with a DVD drive in minutes. The detection limit and LR of designed biosensor were 1.04 μg L^{-1} and 0.12 to 2.0 μg L^{-1}, respectively. The main advantage of this method is the great biotype reactivity to MC-LA, MC-LY, MC-LW, MC-LF, MC-YR together with its stability for long duration (at least seven weeks without any alteration). The main advantage of the proposed system is the portability of the analytical set-up and the low-cost in comparison with other MCs biosensors.

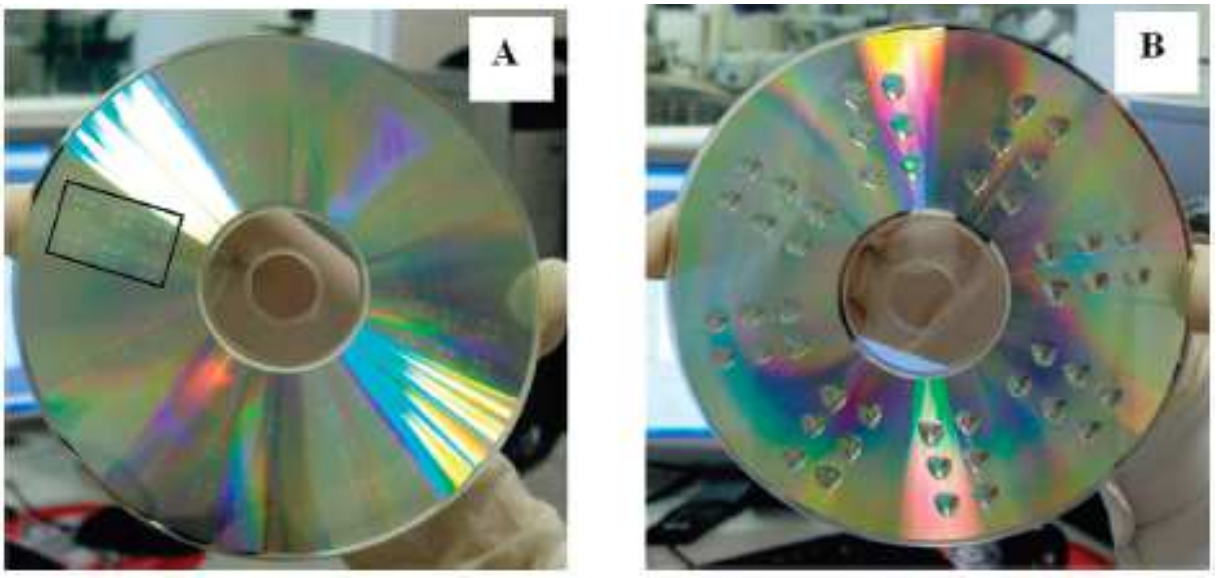

Fig. 6. A disk-based microsensor array for the detection of MCs. (A) The disk holds 8 sections of six arrays (48 arrays) of four blocks (2 × 2 spots) each including immobilized specific anti-MC-LR monoclonal antibody. In this method, conjugation of free MC-LR (sample) with immobilized antibody was evaluated in comparison with biotin as internal calibration and non-immunized mouse (MIgG) and rabbit sera (RIgG) as positive controls. (B) Image of a disk after eight minutes in vertical position. Reprinted with permission from (Morais et al., 2010).

Another type of portable biosensors have been carried out by using lateral flow format (Sangolkar et al., 2006; Spoof et al., 2001). However, there are some difficulties related to the accurate quantification of the analyte which strongly depends on the user appreciation. Devlin et al. (2013) introduced a novel portable biosensor based on evanescent wave/planar waveguide for avoiding drawback of lateral flow forma, based on the use of anti-MCs mAbs (5C4) immobilized on a cartridges. They used SnapEsi® LS sensor for detection of MCs with LOD of 1 ng mL^{-1} in 10 minutes. Cumbersome and high-cost microfluidics have been used in most of portable biosensors. Therefore, use of the cartridges was a significant advantage of this work which provided a rapid biosensor.

In this review, several electrochemical-, optical- and mass-based MCs biosensors responding with different manners have been described. Comparison of advantages and limitations of these biosensing methods for MCs detection are summarized in Table 4. The difference between platforms can be ascribed to several factors including the type of biosensors, type of sample, platform compositions, and measurement protocols.

Table 4: Comparison of advantages and limitations of various biosensing methods for MCs detection

Principle	Advantages	Limitations	Ref.
Optical biosensor	Real-time and quantitative Direct and label-free detection In colorimetric assay observed with the naked eye	Commonly expensive Low portability for fluorescence based biosensors Time consuming fabrication	(Jamali et al., 2014; Perumal and Hashim, 2014)
Electrochemical biosensor	Quantitative Reusable Low-volume sample/reagent requirement	Influenced by the working electrode material False positive results originated from electrolytes	(Jamali et al., 2014; Saei et al., 2013; Zuo et al., 2007)
Mass-based biosensors	Direct, label-free, interaction with analyte Real-time output, simplicity of use and cost-effectiveness No need to expensive or hazardous labels	Low sensitivity in comparison with other biosensor Depend on buffer composition, pH, and the ionic strength of sample long time needed to reestablish a stable baseline	(Marrazza, 2014)

3. Conclusion and future perspectives

The high toxic potential of MCs increases the necessity of monitoring the quality of water and existence of MC-LR-contaminated water. The analysis of MCs is usually done by a variety of traditional methods, but they have some negative points such as being high-cost, time-consuming, need of preparation of specimen, and trained technicians. Advancement of reliable and sensitive analytical techniques is crucial for the efficient detection of MC-LR levels. Hence, the emergence of biosensors as precious tools leads to urgent, rapid examination and as a solution for the mentioned problems. A variety of different biosensing methods explored up to now, electrochemical-, optical-, and piezoelectric-based biosensors have been continuously applied.

Owing to selectivity and high affinity of aptamers towards MCs, they are employed as recognition elements in biosensors. Great stability, ease of fabrication and reproducibility are some of good attributes of biosensors. Although, notable progresses have been made in advancement of biosensors during the recent years, there are some restrictions such as ionic strength and temperature, which may affect the biosensing performance. In addition, despite the successful *in vitro* procedures for the detection of MCs by means of biosensor platforms, there is still much effort need to develop applicable and easy-to-use MCs biosensors for *in situ* detection. Moreover, interference of designed MCs biosensors with other cyanotoxins remains a challenge to be solved, since numerous cyanotoxins present in most of water resources. The development of biosensors with multi-target detection ability and integration

of biosensing platforms with nanomaterials or microfluidics (microchip tools) are suggested as future platforms for simultaneous MCs detection.

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Highlights:

- Quality and safety of water has paramount importance for animals and human health
- Contamination of water with Microcystins causes serious health threatening problems
- Monitoring water quality is necessary due to the hepatotoxicity potential of MC-LR
- Sensitive analytical methods are vital for controlling of Microcystins levels
- Biosensors are emerged as precious and sensitive tools for Microcystins detection

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