



# Recent molecularly imprinted polymers applications in bioanalysis

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## Abstract

Molecular imprinted polymers (MIPs) as extraordinary compounds with unique features have presented a wide range of applications and benefits to researchers. In particular when used as a sorbent in sample preparation methods for the analysis of biological samples and complex matrices. Its application in the extraction of medicinal species has attracted much attention and a growing interest. This review focus on articles and research that deals with the application of MIPs in the analysis of components such as biomarkers, drugs, hormones, blockers and inhibitors, especially in biological matrices. The studies based on MIP applications in bioanalysis and the deployment of MIPs in high-throughput settings and optimization of extraction methods are presented. A review of more than 200 articles and research works clearly shows that the superiority of MIP techniques lies in high accuracy, reproducibility, sensitivity, speed and cost effectiveness which make them suitable for clinical usage. Furthermore, this review present MIP-based extraction techniques and MIP-biosensors which are categorized on their classes based on common properties of target components. Extraction methods, studied sample matrices, target analytes, analytical techniques and their results for each study are described. Investigations indicate satisfactory results using MIP-based bioanalysis. According to the increasing number of studies on method development over the last decade, the use of MIPs in bioanalysis is growing and will further expand the scope of MIP applications for less studied samples and analytes.

**Keywords** Molecular imprinted polymers · Bioanalysis · Extraction techniques · Biological samples

## Abbreviations

MI-IPN	Molecular imprinted interpenetrating polymer network	E1	Estrone
MMST	Monolithic MIP sol–gel packed tips	α-E2	17α-Estradiol
INAT	Inside-needle adsorption trap	E3	Estriol
		β-E2	17β-Estradiol
		EE2	17β-Ethinylestradiol
		DES	Diethylstilbestrol
		COU	Coumestrol
		ENT	Enterolactone
		BPA	Bisphenol A
		BPS	Bisphenol S
		GEN	Genistein
		OP	4-N-Octylphenol
		NP	4-N-Nonylphenol
		E2	Estradiol
		RAM	Restricted access material
		EC	Electrochemically controlled
		NMSX	Needle trap utilizing a molecularly imprinted sol–gel xerogel
		MISM	Molecularly imprinted sol–gel membrane
		RAFT	Reversible addition-fragmentation chain transfer

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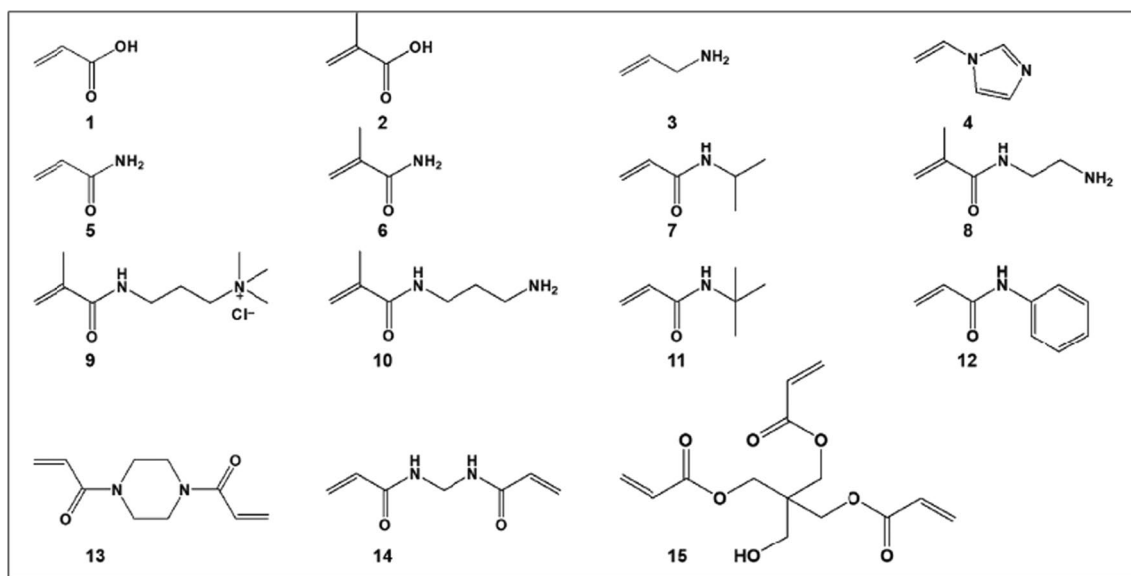
tt-MA	Trans,trans-muconic acid	3-PPA	3-Phenylpropylacrylate
DLLME	Dispersive liquid–liquid microextraction	TCAs	Tricyclic antidepressants
ZIC-HILIC	Zwitterionic hydrophilic interaction liquid chromatography	TF-MIP	Thin film molecularly imprinted polymer
EC	Electrochemically controlled	MC/GO	Magnetic chitosan/graphene oxide
IMS	Ion mobility spectrometry	ERSF-Hyp	The structural analogue derivative of Hyp with 6- <i>N</i> -ethyl-rhodamine 6G- <i>N</i> -hydroxysuccinimidyl formate
MIP	Magnetic ion imprinted polymer		
FAAS	Flame atomic absorption spectrophotometer		
EAAS	Electrothermal atomic absorption spectrometry		
PT-DMIP	Pipette-tip based dummy molecularly imprinted polymer		
MMISPE	Magnetic molecularly imprinted solid phase extraction		
MIPF	Molecular imprinted polymer fiber		
MNSs	Magnetic ion-imprinted polymer nanospheres		
MSPE	Magnetic solid phase extraction		
DI-ESI	Direct infusion electrospray ionization		
HPA	4-Hydroxyphenylacetic acid		
PHE	Phenylacetic acid		
NBA	3-Nitrobenzoic acid		
NFE	2-Nitrophenol		
PSM	Polysulfone membrane		
3-MSHM	Three-phase molecularly imprinted sol–gel based hollow fiber liquid-phase microextraction		
MMSTs	Monolithic molecularly imprinted polymer sol–gel packed tips		
DMIP	Dummy molecularly imprinted polymer		
DMMIP	Dummy magnetic molecularly imprinted polymer		
12-Plex- TCIL- MDSPE	12-Plex tags chemical isotope labeling combined with magnetic dispersive solid-phase extraction		
EBC	Exhaled breath condensate		
DLLME	Dispersive liquid–liquid microextraction		
MMIdSPME	Magnetic molecularly imprinted dispersive solid phase micro extraction		
CE-DAD	Capillary electrophoresis with diode array detector		

## Introduction

Molecular imprinted polymers (MIPs) have been in focus due to their special properties in many fields during the last decade. Many optimizations and developments of MIP techniques have been achieved for a range of goals. The most common applications of MIPs are detecting and quantifying of special targets in the field of chemistry. Due to the importance of analyzing drugs, biomarkers and other analytes in biological samples, scientists have developed MIP-based techniques to make analysis procedures more selective, sensitive, rapid and cost-effective. These efforts will allow MIP-based extraction techniques to be used as common approaches for clinical usage.

According to BelBruno (2019), for the first time the phrase “imprinted polymer” has been reported by Andersson et al. (1984). However, Wulff (2013) has claimed that the molecularly imprinted synthetic polymers were discovered in 1972 in his laboratory and his first article related to imprinted polymers is published in 1985 (Wulff et al. 1985). For more details, Wulff, in his early researches, has applied imprinted polymers in catalytic reactions (Liu and Wulff 2004; Wulff et al. 2006; Wulff and Knorr 2001; Wulff and Liu 2012) like K. Shea as well, who has reported on rather unique biological applications, like a plastic antibody inserted into living mice (BelBruno 2019). By the way, the presence of numerous MIP approaches and the obvious attention paid to these techniques is the consequence of these early researchers’ evaluations.

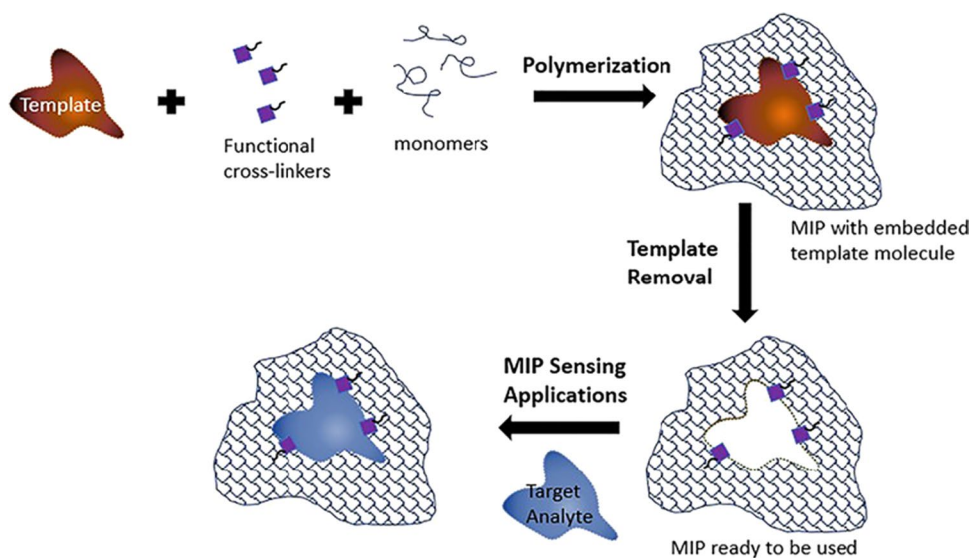
Several methods are recommended for the preparation of MIPs, some of which include synthesis, phase inversion and soft lithography or surface stamping methods. The synthesis methods are the most popular technique among researchers. In such methods, functional monomers interact with target molecules for developing a network of covalently or non-covalently complexes. Pyrrole, methacrylic acid (MAA), aniline, methyl methacrylate (MMA) and acrylamide are some of the most common functional monomers (Fig. 1) (BelBruno 2019; Xu et al. 2020). Briefly, in a synthesis method, the component process mainly includes a porogen solvent, a cross linker, a



**Fig. 1** Commonly used functional monomers. **1** acrylic acid; **2** methacrylic acid; **3** allylamine; **4** 1-vinyl imidazole; **5** acrylamide; **6** methacrylamide; **7** *N*-isopropylacrylamide; **8** aminoethylacrylamide; **9** (3-acrylamidopropyl) trimethyl ammonium chloride; **10** *N*-(3-aminopropyl) methacrylamide; **11** *N*-tert-butyl acrylamide; **12** *N*-phe-

nylacrylamide. Chemical structures of crosslinking monomers; **13** piperazine diacrylamide; **14** *N,N'*-methylene bis(acrylamide); **15** pentaerythritol triacrylate (Xu et al. 2020). Permission License Number: 5264270992160

**Fig. 2** Schematic process of MIPs synthesis method (Ang and Low 2019)



functional monomer, an initiator and a template as shown in Fig. 2.

Each component in a synthesis process plays significant roles in which changing and improving one of items will lead to optimized MIPs as a result. For instance, choosing a good template for a special analyte is very determinative in sensitivity and selectivity of the extraction process,

or finding the best way for removing templates and analytes (washing and eluting) in the last step is extremely important because an unsuccessful removal may affect the final results (BelBruno 2019). Polymerization is the first crucial level in MIP formation which monomers, initiators, cross-linkers and even every polymerization method impact on results. Hence, polymerization methodologies

and the optimal components for each analyte in different matrices must be investigated in order to obtain acceptable modifications (Souza et al. 2016; Asiabi et al. 2016; McKitterick et al. 2020a; Pajewska-Szmyt et al. 2020; Sartore et al. 2020; Gama and Bottoli 2017). Nanomaterials as sorbents are extensively applied in various extraction methods. Based on extensive researches, various nanomaterials are introduced and utilized in many extraction techniques. Among all nanomaterial sorbents, MIP nanoparticles have gained much attention of researches to have prosperous usage in significant extraction techniques (Ahmadi et al. 2017). Some examples of utilizing these sorbents are presented in this review. Finally, synthesized polymers may have a good selectivity on target molecules in the reason of binding supplementary sites with template in shape, size and also in the position of the functional groups (He et al. 2007; Djozan et al. 2011, 2012; Song et al. 2014; Sellergren et al. 1988; Rachkov and Minoura 2000). MIP nanoparticles have been thoroughly reviewed by Fresco-Cala et al. (2020).

In addition to the many benefits of MIP sorbents and the different established synthesis techniques, the production of such polymers confronts other difficulties; there is no general procedure for synthesis of MIPs and it is difficult to achieve a stable molecular shape memory of a polymer matrix. (Bossi et al. 2007). These issues have recently led to using computational modeling to achieve higher performance by optimization of MIP's structures with different computational methods such as molecular dynamics calculations, density functional theory, etc. which provide an opportunity to screen thousands of combinations (Gollowitzer and Ljubić 2011; Mazouz et al. 2020; Silva et al. 2021a; Rajpal and Mizaikoff 2022).

As a summary, MIP synthesis is a procedure in which a special functional monomer self-assembles by surrounding a chosen template and the process will continue by polymerization techniques (bulk, surface imprinting, precipitation, suspension and emulsion polymerizations) in a porogen solvent. The last step of the process is removing the template, resulting in the manifestation of a cavity complementary in chemical characteristic and shape to the structure (Gama and Bottoli 2017).

MIP techniques are significantly developed and used in many fields, such as food analysis, analytical chemistry, therapeutics, drug delivery, sensors, immunoassays, biomedical diagnosis and environmental studies (Otero-Pazos et al. 2014; Kou et al. 2020; Yang et al. 2014; He et al. 2021, 2020; Ciechanowska et al. 2020; Song et al. 2018; Bonatti et al. 2021; Gornik et al. 2021; Cennamo et al. 2018; Muhammad et al. 2017). For instance, efforts on finding the best method for detecting SARS-CoV-2 are very salient and applying MIP techniques is being considered. Nunzio Cennamo et al. (2021) reported about the sensitive on-site

detection of SARS-CoV-2 by plasmonic optical fibers and molecularly imprinted polymers and Raziq et al. (2021) explained the development of a portable MIP-based electrochemical sensor for detection of SARS-CoV-2 antigen. Furthermore, Fresco-Cala et al. (2021) reported the development and preparation of magnetic molecularly imprinted polymers by using epitope approach and SARS-CoV-2 peptide as a template. In this study, we concentrate on the use of MIPs in analytical chemistry, specifically their use in the extraction/microextraction of specific targets from biological samples as a key step in sample preparation techniques.

Biological samples are complicated mixtures with exclusive and diverse compositions for each person and species. Advanced strategies of sample preparation for each matrix and analyte aid to elimination of extra components from a sample to come over disorders of matrices and leading to elevated selectivity and recovery (Georgi and Boos 2006). Each matrix has its own challenges. For instance; (a) Blood is a composition of diverse blood cells sling within the plasma (b) Plasma consists glucose, proteins, hormones, minerals, and blood cells as well. (c) Serum is the fluid and solute component of blood without fibrinogens. (d) Urine is composed of water (95%), urea, creatinine, proteins, pigmented products of blood breakdown and also inorganic salts such as sodium, phosphate, sulfate, and ammonia, (e) Human breast milk is composed of certain amount of fat, proteins, lactose and minerals and (f) Saliva includes about 99% of water portion, had compounds secreted within the salivary glands. Saliva also consists of numerous electrolytes such as bicarbonate, sodium, magnesium, phosphate, potassium and calcium (Inoue et al. 2006; Fernández-Peralbo and Luque de Castro 2012; Rosenthal 1948; Kohler 2014). Due to the high complexity of biological samples, some important factors must be considered during a bioanalysis process to be sure about the validation of results such as stability, spiking, nonspecific binding and using internal standards. Extra attention on the sample stability during the collection, storage, shipping, and processing are also important. Despite spiking into biological matrices, the "Nonspecific Binding" also should be noticed in some biofluids like urine and cerebrospinal fluid as other important factor to reflect the whole complexity of study samples. Nonspecific binding can be resolved by decreasing the concentration of analytes and leading to more accurate results. To improve the accuracy of biological sample results, Internal Standards (IS) are very effective. Choosing the best Internal Standard, on the other hand, is a challenging task, because it must have physicochemical properties similar to a specific analyte. The two common types of ISs are *Structural analog* and *stable isotope-labeled internal standards* which the second one, is more effective and highly recommended (Yadav and Shrivastav 2011; Viswanathan et al. 2007; Wang et al. 2020).

Efforts in developing bioanalytical methods for clinical samples are making good progress. In this regard, recent

research on MIP-based extraction techniques and MIP-based biosensors have presented satisfactory results due to their high selectivity, sensitivity and accuracy. In this paper, we have reviewed the most common MIP applications in bioanalysis and recent advances of MIP utility in extraction/microextraction techniques and biosensor methods. The analysis of many important compounds such as inhibitors, biomarkers, anesthetic drugs, antimicrobial substances and etc., in several biofluids are widely presented, covering published papers over the last decade.

## MIP in bioanalysis

With regards to the development of extraction techniques, several kinds of sorbents have been investigated. Some of classic sorbents are chemically bonded silica with different functional groups, metal organic frameworks, metallic and metal oxide nanoparticles, carbon nanotubes and also fiber coating materials, each of which has been optimized for special analyte or analytes in special samples. Recently, MIP sorbents have attracted much more considerations due to their high selectivity, flexibility and capability of extracting various analytes from complicated matrices like biological samples (Hashemi et al. 2018).

Furthermore, biosensors are a kind of analytical techniques which are widely used in bioanalysis as a simple, real-time and effective approach. These high-selective techniques usually contain three key factors: the transducer, the signal processing system and the bio-receptor (Abid et al. 2021). Recently, MIP-based biosensors are developed for many types of analytes and samples. In this review, we have focused more on MIP-based extraction techniques and briefly on MIP-based biosensors.

## MIP-based sample preparation techniques

Sample preparation, as a main step of bioanalysis approaches, has always been a challenge for analyzing analytes in various samples. Many routine methods of sample

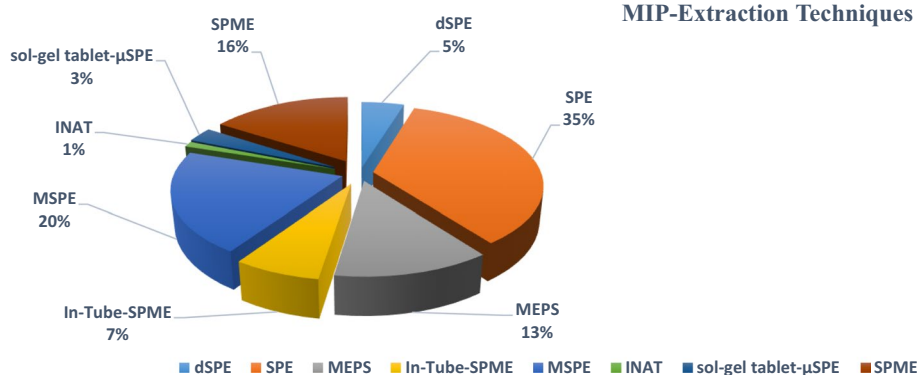
preparation are extraction, chromatographic sample purification, clean-up and enrichment, precipitation, etc. (Yang et al. 1998) The most common extraction techniques in analytical chemistry are solid-phase extraction, liquid–liquid extraction and membrane-based solid-phase extraction.

Researchers have always been attempting to develop extraction methods for various samples such as environmental, biological, foods and agricultural samples due to their unique complicated matrices. Biological samples have received the most attention due to their intricate matrices, which have always posed significant obstacles in preconcentration and extraction of unique analytes among other macromolecules and cells. Fortunately, researchers have devised a variety of approaches for dealing with complicated samples as well as selectively extracting special analytes with satisfactory results. Here the focus is more on MIP-based extraction techniques especially in biological matrices. MIPs (molecularly imprinted polymers) are known as selective separation materials. One of the benefits of such sorbents is the possibility to make polymers that are tailored to a certain target. The crucial stage is the polymerization of crosslinking and functional monomers in the attendance of a template or imprint sorts (Ashri and Abdel-Rehim 2011). There are several extraction/microextraction techniques that have been developed, including SPME, SPE, IT-SPME, MEPS, SBSE, Non-fiber SPME, and DSPME. The broad applicability and development of these techniques are thoroughly covered in our previous review paper (Daryanavard et al. 2021). Some of the developed MIP-based extraction approaches are widely covered in the following sections. The application rate of these techniques is shown in Fig. 3.

## MIP-SPE

The capacity of solid-phase extraction (SPE) to extract analytes from a variety of matrices makes it a popular method for sample preparation. Its simplicity of use, capacity to handle large loads, ability to provide acceptable recoveries, consumption of relatively little amounts of organic solvents, automation, and availability of a broad variety of

**Fig. 3** MIP-based Extraction Techniques used in bioanalysis





stationary phases have all contributed to its widespread use in laboratories (Shi et al. 2011). There are many SPE materials, common ones are silica-based, carbon-based, and clay-based resins. A similarity between SPE and liquid–liquid extraction is the distribution of analyte between two phases, but in SPE there is a solid phase which attracts a special analyte selectively. As mentioned above, the basic concept of SPE is the transportation of analyte from liquid to solid phase based on higher affinity for the solid phase than for the sample matrix (Ramos and Picó 2012). Accordingly, it has been used as a routine technique in sample preparation for both liquid and solid samples (Shi et al. 2011; Hennion 1999).

MIP-based solid phase extraction is known as a developed SPE with more extraction efficiency and selectivity. MIP-SPE has a great capability of preconcentration of analytes and efficacious removal of interfering factors from sample matrices (Shi et al. 2011; Pichon 2007; Pichon and Chapuis-Hugon 2008; Michailof et al. 2008). Offline and online-MIP-based SPE are the two common basic modes. Conditioning cartridge, loading of sample, washing of any interferences and elution of the analyte is the common process for both modes. Through the optimization of each process stage, the efficiency of this method can be impressive (Yi et al. 2013; Hussain 2015; Ncube et al. 2019; Haginaka 2009; Maranata et al. 2021).

MIP-SPE has been widely used as preconcentration method for selective analysis of special targets in biological samples including tissue, urine, bile, plasma and also from animal tissue. One of its applications was in the study by Mabrouk et al. (2020) to use a chitosan-based molecular imprinted polymer technique for the spectrophotometric determination of ketorolac in human plasma. In addition, MIP-SPE has also been used to extract components in other kind of samples, such as food, environmental samples and plants (Chapuis et al. 2003; Caro et al. 2006) and different kinds of water samples (Lian and Wang 2018; Sun et al. 2018; Kadhivel et al. 2019; Li et al. 2019).

#### MIP-MEPS

MEPS or *microextraction by packed sorbent* is a developed method of solid-phase-extraction by packing sorbent bed into a liquid-handling syringe which causes great improvements in analyte extraction (Moein et al. 2015a). Most of existing SPE techniques could be applied by MEPS while scaling down of sample volumes and reagents. In other words, MEPS is the miniaturization of conventional SPE (Daryanavard et al. 2013). Since the first MEPS report was released in 2004, it has been regarded as a desirable option

and successful sample preparation method that is suitable for fulfilling analytical and bioanalytical purposes (Abdel-Rehim 2004). The major difference between SPE and MEPS is solution flow direction which in SPE is up to down but in MEPS is in both directions (up and down) which naturally leads to a difference in the optimization of elution and washing steps (Abdel-Rehim 2010). MEPS is a revolutionary technology in that it has allowed for the combination of extraction, clean-up and preconcentration in a single device. The device consists of a barrel insert and needle, which contains the packed MEPS bed (Moein et al. 2015a). Being fully automated, having short analysis time, using small sample volumes, convenient analyte enrichment and being both simple and inexpensive are the advantages of MEPS that has made it distinctive and superior compared to other methods (Abdel-Rehim and Abdel-Rehim 2013). Like SPE, MEPS can be used manually offline and also online by connecting it directly to an HPLC or GC autosampler (Moein et al. 2015a).

MIP-MEPS is a recent advancement of MEPS technology by application of MIP sorbents to optimize the selectivity and efficiency in various samples such as plasma, urine and waters (Daryanavard et al. 2013; Prieto et al. 2011a, b). In 2019, Meng and Wang (2019) presented their findings on levofloxacin detection in human plasma using MEPS technique in conjunction with ultra-high-performance liquid chromatography. Deep eutectic solvents (DESs) were employed as pure porogen in this study to create DES-MIPs. Please refer to our in-depth study for additional information about MEPS (Moein et al. 2015a).

#### MIP-SPME

For the first time, SPME was presented by Pawliszyn and Lord in the early 1990s (Arthur and Pawliszyn 1990). A thin polymer film coating on a fiber to extract analytes from various matrix samples is used in this kind of extraction technique. This approach has undergone several improvements, yielding in outstanding results that make it widely applicable for integrating extraction, sampling, sample preparation and preconcentration into a single step. This approach, like the others discussed in this study, is highly simple, quick, inexpensive, solvent-free, easily automated, and it has been used to analyze direct aqueous samples by remarkable selectivity and sensitivity. SPME efficiency can be influenced by a number of variables, including the kind of stationary phase and its thickness, sample volume, temperature and fiber exposure (Sarafraz-Yazdi and Razavi 2015).

MIPs have been successfully employed as a selective and sensitive stationary (sorbent) phase in a variety of studies in

recent years. In our previous studies (El-Beqqali et al. 2017; El-Beqqali and Abdel-Rehim 2016), we described a novel SPME development known as MIP-sol-gel tablet-SPME for determining methadone and amphetamine in human plasma. The MIP-sol-gel was created as a thin layer over polyethylene material in the shape of a tablet. According to the results, each tablet may be used twenty times with a short extraction time (10 min).

The polymeric tablet is a new microextraction approach based on a polyethylene tablet coated with a thin layer of molecularly imprinted polymer or graphene oxide for extraction, enrichment and analysis of analytes from a variety of matrices such as biological, environmental and food samples, according to the extended explanation in our previous overview. In these approaches, the surface of polyethylene is altered with sol-gel imprinted polymers or a graphene oxide/polyethylene glycol combination. Finally, the analytes separated from the tablet surface can be eluted and injected into the analytical equipment for measurement (Abdel-Rehim et al. 2020).

As a result, MIP-SPME solves several SPME concerns, such as the expense of commercial fibers, instability (chemical or thermal), and difficulties in fiber synthesis. MIP fibers are well-known for their ease of preparation and low cost while preserving stiffness and selectivity toward a given analyte (Sarafraz-Yazdi and Razavi 2015).

## MMISPE

For the first time, monomer polymerization in liquid perfluoro chlorine was achieved in 1998 with the application of magnet iron oxide, an MMIP (magnetic molecularly imprinted polymer) with a mean diameter of 13  $\mu\text{m}$  (Ansell and Mosbach 1998). Among nanoparticles as sorbents, the superparamagnetic iron oxide nanoparticles (SPIONs) in bioanalysis have recently received much more attention. This sophisticated sorbent can be used for (a) diagnostics, (b) separations, and (c) treatments such as hyperthermia, drug delivery and magnetofection. Magnetic nanoparticles' sizes (MNPs) are related to the chosen synthesis method. For example, precipitation from microemulsions, surfactant or polymer solutions can readily form nanoparticles with diameters < 100 nm with giving superparamagnetic properties (Lee et al. 2010). Hung-Yin Lin et al. (Daryanavard et al. 2013) demonstrated the use of MIP-based nanoparticles to separate and sense lysozyme, urea and albumin-creatinine from urine sample. Magnetic separation technique is a batch-scale process based on functionalized magnetic materials (Lin et al. 2012). Due to the high biocompatibility, vast

surface area, ease of manipulations, and ease of functionalization of magnetic separation techniques, these could be ideal for extraction of biological macromolecules. In a nutshell, the magnetic separation process involves combining magnetic materials with target analytes, which bind to the magnetic particles during a period of incubation. Finally, without filtering or centrifugation, all magnetic complexes will be isolated from the sample by another magnetic field (Toh et al. 2012; Li et al. 2011; Kubo and Otsuka 2016).

Magnetic molecularly imprinted solid-phase extraction (MMISPE), a newly developed magnetic extraction method, is gaining favor among researchers due to its benefits such as simplicity, convenience, fast and effective binding to target analytes, magnetically susceptible characteristics, and shorter pretreatment time. Its use in the extraction and pre-concentration of target components in a variety of matrices, including food, biological and environmental samples, backs up these assertions (Zhang et al. 2011; Li et al. 2017). One of the applications of MMISPE, was in the study of McKitterick et al. (2020a). They developed a technique for selective clean-up of Protein biomarker measurement. They created NLLGLIEAK-targeting MMIPs as well as a method for extracting tryptic peptides from serum which are both selective and rapid. Four distinct MMIPs were synthesized in this work and MMISPE method for extracting low quantities of tryptic peptides from human serum was devised and improved.

## MIP-ITSPME

Eisert and Pawliszyn presented In-tube Solid Phase Microextraction (ITSPME) in 1997 as a simple operational approach for sample preparation in the laboratory (Eisert and Pawliszyn 1997). This method is an improvement on the previously stated conventional fiber SPME. The goal of this approach was to address issues such as limited sorption capacity, fragility and bleeding from fiber thick-film coatings. The goal was also to automate the SPME-HPLC process, allowing continuous extraction, desorption, and injection using a conventional autosampler. ITSPME is an online SPME by HPLC, GC or LC-MS with using open-tubular capillary column (Kataoka et al. 2009).

The utilization of monolithic MIPs on SPME is apparent due to their straightforward preparation and improved selectivity. ITSPMEs are methods that have benefited from MIPs to achieve special advantages (Ponce-Rodríguez et al. 2020). MIP-based ITSPME is used in many kinds of matrices and samples of purpose developing the method and also extracting special analytes by using different analytical methods (Souza et al. 2016; Chaves and Costa Queiroz 2013; Zhang

et al. 2009; Djozan et al. 2009, 2010; Rajabi Khorrami and Narounezhad 2011). Marchioni et al. (2020) described the determination of cannabinoids and  $\Delta^9$ -tetrahydrocannabinol in plasma by “dummy MIP-in-tube solid-phase microextraction”. In this study, an in-situ polymerization in a fused silica capillary yielded a new dummy molecularly imprinted monolithic capillary (MIP monolith) for in-tube SPME, with hydrogenated cannabidiol acting as the dummy template.

### Miscellaneous

Stir bar sorptive extraction (SBSE) is a solvent-less microextraction technique presented by Baltussen et al. (1999). Nowadays, the common commercial coating for SBSE is available for non-polar compounds but because of notable deficiencies of this method such as lower selectivity and low extraction efficiency, application of MIPs as a coating for SBSE has enabled the analysis of various analytes and the application in many complex samples, such as the analysis of sulfonamides from animal feeds (Cui et al. 2021), extraction of carbendazim and thiabendazole from orange samples (Díaz-Álvarez et al. 2019) as well as analysis of environmental estrogens in plastic and water samples (Xu et al. 2014).

The dispersive solid phase microextraction (DSPME) method is the result of improving non-fiber SPME method in order to overcome the limitations of traditional SPME. Instead of depositing sorbents on the fiber core, these are poured directly into the sample solution and dispersed, respectively, which leads to an increase in contact surfaces between sorbents and samples and causes a higher efficiency in extraction of analytes and a reduction of the procedures time (Tsai et al. 2009). Even though DSPME has many advantages such as being simple, fast, and inexpensive, as well as being applicable to concentrate, clean up and to extract variety of components in real samples, etc., it has many significant restrictions including the difficulty of sorbent separation from the sample solution, method automation limitations, and restrictions in its usage for in vivo analysis (Ghorbani et al. 2019). The MIP-DSPME technique is utilized to extract analytes with more efficiency and selectivity in many real samples (Asfaram et al. 2018; Wu et al. 2017; Cheng et al. 2017; Bazmandegan-Shamili et al. 2016). Besides the MIP method, there are many other assistant techniques which have been used to modify the extraction efficiency of this method; using special analyte absorber components with suitable functional groups or cavities, using magnetic components such as Magnetic iron oxide, using Vortex-assisted DSPME and ultrasonic-assisted DSPME techniques (Ghorbani et al. 2019).

### MIP applications in bioanalysis

For the examination of biological samples, sampling, sample preparation and the storage of samples are critical. Plasma, blood, and urine are significantly more complex matrices including salts, proteins, bases, acids and other chemical components with chemistries comparable to analytes of interest, making target extraction from biological matrices challenging. These compounds would cause matrix effect which can dramatically influence analysis performance for both identification and quantification of an analyte. These may lead to false negative or positive results. Hence, the application of a clean-up step before analysis is essential to minimize the matrix effects especially for biologically active compounds in biological materials. Hence, it is impossible to inject drugs and metabolites in biological matrices directly into the analytical equipments before sample cleanup. The first and most important stage in the bioanalytical process is sample cleanup or sample preparation. Many significant factors should be considered while evaluating analytes in biological matrices, including; (1) Examination of the stability of analyte in blood and plasma. (2) The safe storage of samples in appropriate conditions, (3) Using suitable containers because unsuitable containers may cause medications to be lost or contaminated. Due to adsorption to the silica silanols, extremely polar compound glass tubes, for example, are not appropriate. (4) Reproducible sample preparation technique with excellent recovery. MIP methods may be the best choice for sample preparation since they are stable under a broad variety of circumstances and provide for flexibility in determining the optimal experimental conditions for sample cleanup (Ashri and Abdel-Rehim 2011; Zhou et al. 2017).

Measurement of biological components such as drugs, biomarkers, hormones and also pesticides is of utmost importance for medicine and environmental health. Hence, common methods development or inventing new methods in order to achieving high accuracy, reproducibility, simplicity and cost effectiveness are in the progress. MIP techniques have an extraordinary potential to be used as a clinical method for analysis of specific components. Below, we present some cases of their application in bioanalysis.

### Inhibitors

Metabolic inhibitors and receptor antagonists are essential tools in molecular life sciences. Because enzymes carry out their tasks with fidelity, from aiding central route metabolism to driving signal transmission, catalysis is at the heart of most cellular activities. Simplification the study of



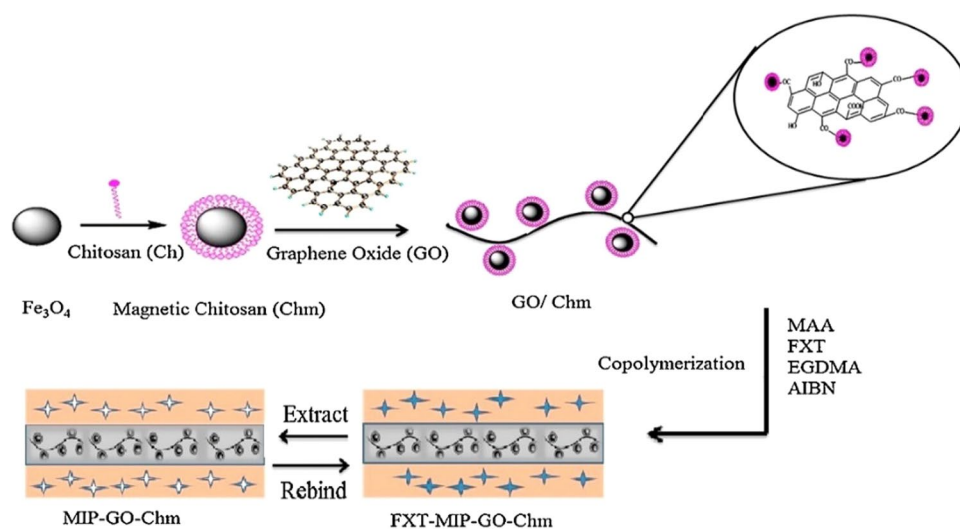
complex cellular processes using inhibitors and antagonists is extremely attractive, and this might be accomplished by inhibiting specific enzymes and/or receptor-mediated signaling. As a result of using inhibitors, a process will be connected to an inhibitor-sensitive enzyme or an antagonist-sensitive receptor, which provides an efficient method of limiting the influence of competitive pathways, which may otherwise conceal mechanistic properties of a reaction or experimental approach (Purich 2017). Various advancements for discovering a high selective extraction technique for a range of inhibitors such as venlafaxines, sitagliptin, fluoxetine, and others are thoroughly examined by scientists. As mentioned below, using techniques such as MISPE/UHPLC-MS/MS, magnetic adsorbents on MIP-SPE, MISPE coupled with ZIC-HILIC and MC/GO on MIP-SPE are highly appropriate for bioanalysis of inhibitors in plasma, urine and serum.

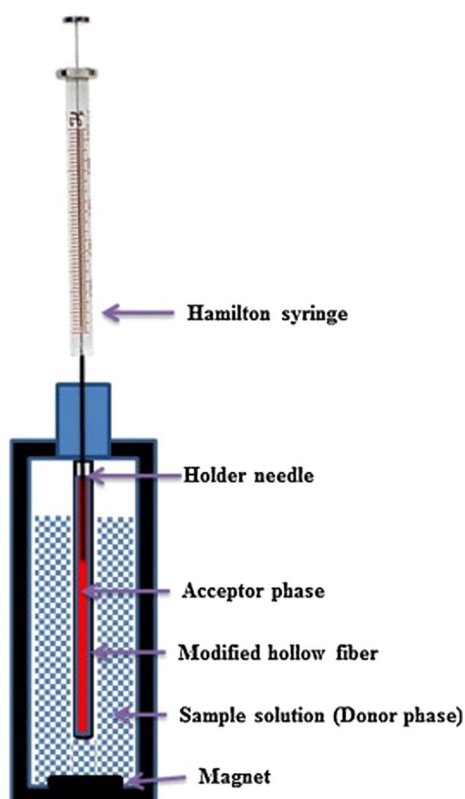
Venlafaxine (VEN) and its active metabolite, O-desmethylvenlafaxine (ODV), are selective inhibitors of serotonin-norepinephrine reuptake (SNRIs). VEN is generally used for adults to treat severe depression, generalized anxiety, phobias, and social anxiety disorders. VEN overdose, on the other hand, can induce symptoms such as hypertension, serotonin toxicity, seizures, or cardiac conduction disorders, necessitating therapeutic monitoring of this medication. VEN undergoes substantial metabolism to one main active O-desmethyl metabolite and two minor metabolites, which are subsequently combined to create O-desmethylvenlafaxine (ODV), N10 desmethylvenlafaxine (NDV), and N,O-didesmethylvenlafaxine (NDV) (Miranda et al. 2016). Analysis of VEN, ODV, and NDV in plasma samples by molecularly imprinted solid phase extraction coupled via

UHPLC-MS/MS (MISPE/UHPLC-MS/MS) is performed by Miranda et al. (2016). Ethylene glycol dimethacrylate, metacrylic acid, 2,2-azobisisobutyronitrile, toluene and VEN were used as crosslinker, monomer, initiator, porogen solvent and template, respectively. A linear concentration interval was obtained as a result of MISPE/UHPLC-MS/MS approach ranging from 3 to 700 ng mL<sup>-1</sup> of VEN, from 5 to 700 ng mL<sup>-1</sup> of ODV, and from 3 to 500 ng mL<sup>-1</sup> of NDV, with a correlation coefficient greater than 0.995. The method's accuracy displayed relative standard error values (RSE%) ranging from -11.8 to 16.01%. Analyzing of VEN in other biological samples such as serum and urine, is reported by using MIP-SPE as a selective extraction method and spectrofluorometric determination by Madrakian et al. (2015) which presented a VEN-imprinted polymer layer that was coated onto the surface of magnetite nanoparticles. The produced magnetic adsorbent dispersed well in water medium and could be readily magnetically isolated from the medium after loading with the adsorbate. The loaded VEN was readily desorbed with methanol and HCl and measured spectrofluorometrically at 598 nm in the linear concentration range of 2–400 ng mL<sup>-1</sup>.

Recently a new water-compatible molecularly imprinted solid-phase extraction (MISPE) technique coupled with zwitterionic hydrophilic interaction liquid chromatography (ZIC-HILIC) for selective extraction and detection of sitagliptin in urine and serum is developed by Rao et al. (2011). Sitagliptin is an orally active, strong, and specific inhibitor of dipeptidyl peptidase IV (DPP-IV) which is used to treat type 2 diabetes. It also leads to the growth of insulin-producing  $\beta$ -cells in pancreatic islets and improves glycemic control. The bulk of sitagliptin is eliminated in urine unchanged. As

**Fig. 4** Schematic illustration for preparation processes of MIP-GO/Chm (Barati et al. 2017).  
Permission License Number: 5264280668643





**Fig. 5** Schematic MSHM system (Moein et al. 2015b). Permission License Number: 5264280946580

a result, developing analytical techniques capable of detecting sitagliptin at low biologically active concentrations is critical not just to comprehend its pharmacological mechanism but also for remedial medication monitoring.

Fluoxetine (FXT), another kind of inhibitors, is the most commonly used as a selective serotonin re-uptake inhibitor (SSRI) antidepressant medication in the world. It has

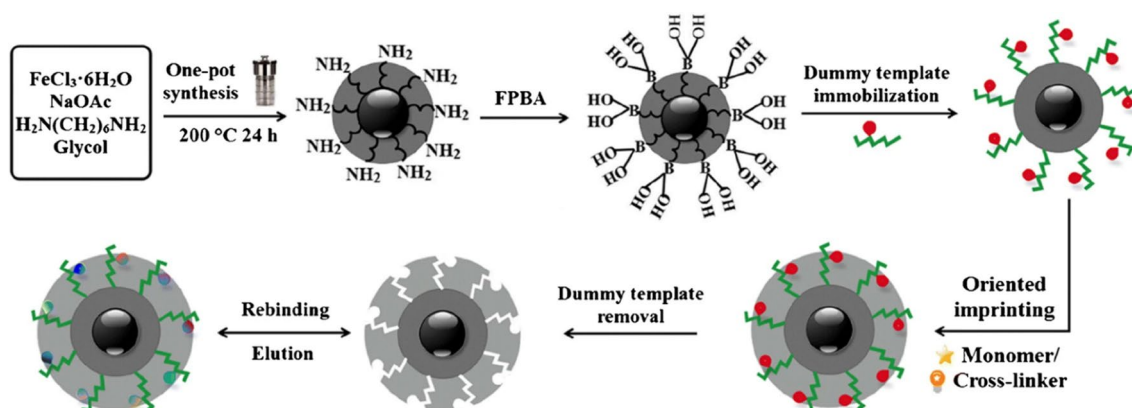
a lengthy elimination half-life of one to several days, and approximately 11% of the dosage is excreted as unmodified fluoxetine. As a result of the excessive use of this drug, there is a risk of its residue spreading in natural waterways. For accurate examination the amount of this inhibitor in biofluids and waters, as illustrated in Fig. 4, Barati et al. (2017) synthesized and characterized MIPs on magnetic chitosan/graphene oxide (MC/GO) for selective isolation and preconcentration of fluoxetine from environmental and biological samples (Figs. 5, 6 and 7).

The aforementioned researches' findings demonstrated that MIP sorbents may be utilized to successfully assess a variety of inhibitors with excellent accuracy and selectivity.

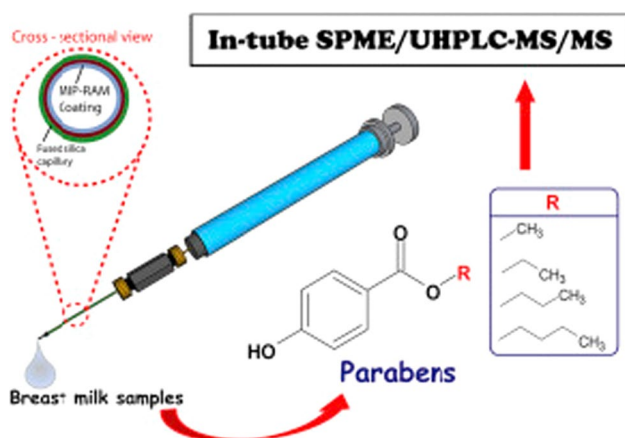
### Natural compounds

The major phytocannabinoids found in *cannabis sativa* are cannabidiol (CBD) and  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC). While  $\Delta^9$ -THC is the major psychoactive component, CBD has been studied for its potential to treat a variety of diseases including Depression, Parkinson, Multiple Sclerosis, Huntington, Epilepsy, Hypoxia–ischemia lesion, Anxiety, Pain and Alzheimer. Cannabidiol has been linked to neuroprotective qualities implicated in neurodegenerative disorders. Such qualities minimize anxiety, nightmares, and the prevalence of violent behavior. As a result, CBD may enhance the psychiatric degree of Parkinson's disease patients, who do not have psychiatric comorbidities. CBD heating in some acidic solutions leads in certain acids catalyzing cyclization inside the CBD molecule, yielding  $\Delta^9$ -THC under experimental circumstances. However, the oral conversion of CBD to  $\Delta^9$ -THC in human beings does not seem to occur (Marchioni et al. 2020).

Many developments for the purpose of cannabinoids determination in body and biofluids are reported such as MIP-in-tube-SPME/UHPLC-MS/MS technique for detecting



**Fig. 6** The preparation procedure for dummy magnetic molecularly imprinted polymers (DMIPs) (Hu et al. 2020). Permission License Number: 5264290710111



**Fig. 7** In-tube SPME device containing the fused silica capillary coated with RAM-MIP sorbents (Souza et al. 2016). Permission License Number: 5264290969592

CBD and  $\Delta^9$ -THC in plasma (Marchioni et al. 2020) which could be reused over fifty times without affecting extraction efficiency significantly and also the development of MIP-MEPS for a successful extraction of 11-hydroxy- $\Delta^9$  tetrahydrocannabinol,  $\Delta^9$ -tetrahydrocannabinol and 11-nor- $\Delta^9$ -tetrahydrocannabinol-9-carboxylic acid by liquid chromatography and tandem mass spectrometry (Sartore et al. 2020).

## Biomarkers

Biomarkers are characteristics which can be extracted and analyzed as an indicator of biological responses to an exposure or intervention, including therapeutic interventions. Diverse applications such as risk estimates, disease screening and detection, diagnosis, prognostic estimates, therapeutic benefit predictions and disease monitoring have been introduced. Cancer-based proteins, gene mutations, deletions, rearrangements and additional copy numbers of the genes are the most popular biomarkers (Ou et al. 2021). Many researchers have made efforts to improve MIP-based bioanalysis methods for biomarkers (such as bilirubin (BR), L-tyrosine (Tyr), sarcosine, globotriaosylsphingosine (lyso-Gb3), glucosylsphingosine (GlcS), galactosylsphingosine (GalS), L-Hydroxyproline (Hyp) and Mandelic acid (MA). Some of which are presented in this section) which are summarized in the following.

Bilirubin (BR) is a bioactive molecule generated by the metabolism of hemoglobin. The serum BR level is an important liver function indicator and has recently been designated as a lung cancer biomarker by the American Association

for Cancer Research. Hence, developing a selective, easy, and robust technique for extracting and detecting BR from biological fluids is critical. For this reason, besides other new techniques in recent years, the technique; a needle trap using a molecularly imprinted sol-gel xerogel for on-line microextraction of bilirubin combined with liquid chromatography tandem mass spectroscopy (On-line- NMSX-MEPS/ LC-MS/MS) is introduced by Moein et al. (2014a) in 2014. Needles prepared in this technique could be used for roughly 100 extractions. The detection limit and the minimum quantity limit were found by utilizing plasma or urine samples, respectively, to be 1.6 and 5 nM in the range of 5–1000 nM standard calibration curves by extraction recovery of approximately 80%.

Hippuric acid (HA) is a molecule that has been identified as a lung cancer biomarker in both urine and plasma. Many attempts have been made in order to discover high-accuracy methods for analyzing this biomarker to be as clinical method. In this regard, two developed methods are reported by Moein et al. (2014b) and Mehran Javanbakht et al. (2015b) such as *MIP sol-gel polysulfone membrane-MEPS in the on-line connection with LC-MS/MS* and *three-phase molecularly imprinted sol-gel based hollow fiber membrane liquid-phase*, respectively, for extraction and microextraction of HA from plasma and urine samples. Several critical factors were carefully examined throughout the membrane preparation process to find the optimum extraction conditions for the first developed method including; determining the best template-to-precursor ratio, using variety of template (HA) and precursor concentrations, the influence of varying quantities of TFA as a catalyst in the sol-gel process and also the solution's "pass-time" for developing a thin layer of imprinted sol-gel on the membrane surface which was determined to be 5 times with a 10-min duration for immersing the polysulfone membrane in the imprinting sol-gel solution. These optimizations gradually resulted recoveries higher than 91% in the linear range of 1–1000 nM in both plasma and urine. The modification of a polysulfone hollow fiber membrane using an in situ molecularly imprinted sol-gel process (as a novel and one-step technique) was created and examined in the second developed method. In this regard, the inorganic precursor, 3-(propylmethacrylate) trimethoxysilane (3PMTMOS) was utilized to create molecularly imprinted sol-gel. According to the results, this method can be used for at least 50 extractions without significantly reducing extraction efficiency by achieving recoveries more than 89% in the linear range of 1–2000 nM in both urine and plasma samples (Moein et al. 2014b, 2015b).

L-Tyrosine (Tyr) is an amino acid that plays a key function in a variety of biomedical processes. It was recently

discovered to be effective as a lung cancer biomarker. Finding a dependable, robust, reproducible, and selective technique for separating Tyr from biological matrices is a significant issue. Therefore, for Tyr detection and extraction, many analytical equipment and sample clean-up techniques were devised. In this regard, in situ monolithic molecularly imprinted polymer sol-gel packed tips (MMSTs/LC-MS/MS) were developed and implemented for the extraction of the lung cancer biomarker L-tyrosine (Tyr) from human urine and plasma samples. Several extraction parameters were examined, including precondition, washing, and elution solutions, pH, and time. In addition, the extraction recovery (ER) and enrichment factor (EF) were investigated (Moein et al. 2014c). As a result, Tyr underwent total rebinding/elution at a pH of 6.0, which is close to its isoelectric point, providing a plausible explanation for the findings reported. The technique validation revealed good regression correlation coefficients ( $R^2 = 0.996$ ) for urine and plasma samples with concentration ranges of 5–1000 and 1–1000 nM, respectively. The results demonstrated that the created approach is more convenient, stable, durable, and repeatable than earlier equivalent methods.

As prostate cancer is one of the most common kinds of tumor illness in men, scientists are paying close attention to prostate-cancer indicators like sarcosine, especially its extraction and analysis in blood or urine samples (Moein et al. 2015c). Recently two methods for extraction and analysis of sarcosine including DMMIP-MTCIL-MDSPE/UHPLC-MS/MS and DMIP-MEPS/LC-MS/MS are introduced by Chen et al. (2021) and (Moein et al. 2015c) respectively. The DMMIP-MTCIL-MDSPE/UHPLC-MS/MS method for the determination of sarcosine in human urine by is developed by utilizing 12-Plex chemical isotope labeling (MTCIL360/361/362/363/364/365/366/375/376/378/379/381) and also MTCIL359 was created and utilized to label sarcosine standard as internal standard (IS) and MTCIL373-sarcosine was synthesized and applied as a new dummy template to prepare dummy magnetic molecularly imprinted polymers (DMMIPs). Results for this method from optimal condition provided linearity ( $R^2$  0.989–0.997), detection limits (0.02 nM), limits of quantitation (0.5 nM), accuracy (96.1–107.4%), precision (2.6–11.5%) and also validated matrix effect, labeling and extraction efficiency. The second method, DMIP-MEPS/LC-MS/MS, which known as dummy molecularly imprinted polymers in microextraction by packed sorbent with online liquid chromatography coupled to tandem mass spectrometry, is applied for bioanalysis of sarcosine in human urine and plasma matrices. Several parameters were evaluated and improved to get the highest efficiency and recovery for the online DMIP-MEPS process

including conditioning solvent (0.1 mL of water), washing solvent (mixed of water/HCl 0.1 M (80:20, 0.1 mL), eluting efficiency (ACN/water (80:20, 0.1 mL), loading time and absorption (10 loading cycles in 2 min) and sample-loading pH (pH = 7.0). These optimizations have resulted the LOD and LOQ 1.0 and 3.0 ng mL<sup>-1</sup> respectively in both plasma and urine and recoveries about 87 and 89% in plasma and urine, respectively, in the linear range of 3.0–10,000 ng mL<sup>-1</sup>.

Xian-En Zhao et al. informed an efficient technique for bioanalysis of various biomarkers. They effectively reported a new dummy magnetic molecularly imprinted polymers (DMMIP) material, using derivatization-based dummy template technology which designed and created for the magnetic dispersive solid phase extraction (MDSPE) procedure via application of a multiplexed stable isotope labeling derivatization (MSILD) strategy (MSILD-DMMIT-UHPLC-MS/MS). For instance, they presented a novel set of 9-plex chemical isotope-labeling reagents, levofloxacin-based mass tags (LMTs) called LMT359, 360, 361, 362, 363, 373, 375, 376, and 378, which initially developed and synthesized for the high-throughput labeling of globotriaosylsphingosine (lyso-Gb3) as a biomarker in plasma. As an internal standard, LMT359-labeled lyso-Gb3 was employed. This technique has the benefits of excellent sensitivity, selectivity (triple recognition), accuracy (recovery 93.5–108.8%), and throughput (8 samples in a single run) (Hu et al. 2020). By this technique in other report, an 8-Plex Amine-reactive Mass Difference Tags (M360/361/362/363/373/375/376/378-AMDTs) were developed and synthesized, and gradually utilized to label glucosylsphingosine (GlcS) and galactosylsphingosine (GalS) in separate 8 plasma samples (Chen et al. 2020). The above studied analytes, Globotriaosylsphingosine (lyso-Gb3), glucosylsphingosine (GlcS) and galactosylsphingosine (GalS) are reliable biomarkers of fabry, gaucher and krabbe diseases. By promoting this approach, the extraction of L-Hydroxyproline (Hyp), a potential indicator for early clinical diagnosis of liver fibrosis, is investigated (Zhu et al. 2020). In this study, 4-plex stable isotope labeling derivatization combined with dummy magnetic molecularly imprinted polymers (QSILD-DMMIPs) was synthesized. The new series of QSILD reagents are in the format of *d0/d1/d2/d3-6-N-methyl-rhodamine 6G-N-hydroxy-succinimidyl (d0/d1/d2/d3-MRSF)*. In the optimal condition, linearity (0.2–100 ng mL<sup>-1</sup>), LOD & LOQ (0.05 and 0.2 ng mL<sup>-1</sup>), precisions results (1.2–7.9%) and recoveries of Hyp (97.9–102.3%) are remarkable.

The International Agency for Research on Cancer (IARC) and the US Environmental Protection Agency (EPA) both classify benzene as a category I



carcinogen. Benzene is used in a variety of industries to create other compounds. As benzene can enter the body through the skin, biomonitoring should be regarded as an additional technique for determining the relative contributions from all exposure pathways when assessing a worker's total exposure. Trans,trans-Muconic acid (tt-MA) is a second biomarker that has been used as a biological exposure index (BEI) (Soleimani et al. 2017). This issue has been considered by scientists, who have proposed three techniques such as *MIP-SPE/HPLC-UV*, *MIP-DLLME/GC-MS* and *MIP-MEPS/HPLC-UV* for extracting and analyzing this biomarker. For comparison of these three methods, the linearity range ( $0.3\text{--}10\text{ mg L}^{-1}$ ,  $0.125\text{--}2\text{ }\mu\text{g mL}^{-1}$ ,  $0.015\text{--}2\text{ }\mu\text{g mL}^{-1}$ ),  $R^2$  (0.999, 0.997, 0.999), LOQ ( $0.3\text{ mg L}^{-1}$ ,  $0.109\text{ }\mu\text{g mL}^{-1}$ ,  $0.015\text{ }\mu\text{g mL}^{-1}$ ) and precisions ( $<3.7\%$ ,  $<6\%$ ,  $<6.6\%$ ) are achieved (Vieira et al. 2012; Soleimani et al. 2017; Mudiam et al. 2013).

2-aminothiazoline-4-carboxylic acid (ATCA) has piqued the interest of researchers as a possible biomarker of cyanide exposure because of its volatility and quick removal from biological media. ATCA has a good stability in biological samples for lengthy periods of time at freezing and ambient temperatures. ATCA is produced via the reaction with cysteine from cyanide and exists in equilibrium with its tautomeric form, 2-iminothiazolidine-4-carboxylic acid. For extraction and measurement of 2-iminothiazolidine-4-carboxylic acid in post-mortem whole blood, two methods such as MIP-dispersive solid phase extraction and MIP-hydrophilic interaction dispersive solid-phase extraction are developed by Giebułtowicz et al. (2019) and Luliński et al. (2015). The template that is used in both methods is ATCA.

Mandelic acid (MA) is a styrene and ethyl benzene (EB) metabolite. Styrene, a monomeric unit for polystyrene materials, is largely produced using EB. It is common in the environment, and many individuals are exposed to these compounds on a daily basis. The International Agency for Research on Cancer has categorized both styrene and EB as grade 2B carcinogens (possible carcinogens). The biomarker, mandelic acid (MA) is used as a target in various analytical methods. Soleimani et al. (2018) in 2018 suggested MIP-MEPS/ HPLC-UV as a sensitive, selective, inexpensive, fast and both environmentally friendly and user friendly method for determination of mandelic acid in urine samples. By the Six-point calibration curve, the linearity obtained between  $0.2$  and  $20\text{ }\mu\text{g mL}^{-1}$  ( $R^2 = 0.9994$ ) with recoveries higher than 88.8%. LOD and LOQ were 0.06 and  $0.2\text{ }\mu\text{g mL}^{-1}$  and the inter- and intra-day and precisions were in the range of 3.8–5.1% and 3.6–4.7%, respectively.

For more in-depth study, in our earlier review paper, a comprehensive evaluation of MIP synthesis methods and their use in the extraction and microextraction of cancer biomarkers is provided (Suzaei et al. 2022).

## Anesthetic drugs

The mechanisms of popular anesthesia represent one of the great unsolved troubles of classical neuropharmacology. The chemical, physical, and pharmacological characteristics of anesthetics vary greatly and because of the broad range of targets, it is clear that dealing with anesthetics pharmacologically is not the same as dealing with most other medicines used in pharmacology. There are several molecular targets of anesthetic action in the central nervous system, but many more are still to be identified. The identification of these novel targets may lead to the development of a new class of medicines that can be utilized to treat drug-resistant anesthetics (Bischoff et al. 2008).

Local anesthetics (LA) are weak bases with a lipophilic aromatic ring connected to a hydrophilic tertiary amine through an ester or amide bond. When administered to a nerve axon, LA produces a transient blockage of neuronal transmission. Cocaine was the first LA discovered by Albert Niemann in 1860, and many different types of LAs are now synthesized for clinical application (Perrin et al. 2020). Fentanyl (*N*-(1-phenethyl-4-piperidyl) propionanilide) is a powerful synthetic (man-made) narcotic analgesic that is widely applied in the operating room and intensive care unit for anesthesia and analgesia. It is used extensively during preoperative, induction, maintenance and postoperative surgeries for purposes of neuroleptic analgesia and sedation. Fentanyl has 50–100 times the potency of morphine. The blood concentration of these substances is below the limit of detection (LOD) of most analytical equipment. Because of the poor concentration of this analyte in plasma and urine, cleaning and sample preconcentration are required prior to instrumental analysis.

In this regard, studies on many anesthetic drugs such as fentanyl, lidocaine, ropivacaine, mepivacaine and bupivacaine extracting from biofluids are reported by Bagheri et al. (2013) and Daryanavard et al. (2013). Fentanyl was extracted from urine and plasma. The Sol-gel method was utilized in this work to successfully produce a molecularly imprinted xerogel (MIX) for fentanyl on the inner surface of a copper tube. The tube was first treated with self-assembly monolayers of 3-(mercaptopropyl) trimethoxysilane, and then [3-(2,3-epoxypropoxy)-propyl]-trimethoxysilane was used as a precursor for acidic imprinting of the template molecule (MIX-SPME/HPLC-UV) (Bagheri et al. 2013). In other report, microextraction by packed syringe (MEPS)



was coupled with LC–MS/MS especially for determination of local anesthetics such as lidocaine, ropivacaine, mepivacaine and bupivacaine (four local anesthetics drugs) in plasma and urine samples (Daryanavard et al. 2013). For the first method, the linearity was in the range of 5–5000  $\mu\text{g L}^{-1}$ , LOD and LOQ were found to be 3  $\mu\text{g L}^{-1}$  and 5  $\mu\text{g L}^{-1}$ , respectively, and the proposed technique was easily applied to urine and plasma samples spiked with the analyte, with relative recovery percentages of up to 85 percent for the spiked samples. For the second method, pentycaine was employed as a template, and results demonstrated linearity in the range of 5.0–2000 nM for all targets, with a correlation coefficient ( $R^2$ ) of 0.999 or higher. Recoveries for all analytes investigated varied from 60 to 80%. Similar to earlier methods that combined MIPs and MEPS techniques, they may be used for 100 extractions before being abandoned.

### Antimicrobial substances

According to a report by the London School of Economics, bacterial and parasitic diseases are the second biggest cause of mortality in the globe. Due to the advent of drug-resistant "superbugs," such as staphylococcus aureus (MRSA) methicillin-resistant, traditional antibiotics including penicillin and its derived products may become obsolete. Pharmaceutical companies and researchers are continuing to investigate novel and effective antibacterial compounds to address this challenge (Bycroft and Payne 2013). Recently, there has been a notable increase in the use of high-efficiency novel methods for bioanalysis of antimicrobial compounds using MIP techniques, such as MMISPE, MIPF-SPME, MIP-MSPE, MIP-SPE-boronate affinity based, MIP-SPE, MMIdSPME, MIP-SPME, and so on. These methods have been used to extract and analyze a variety of antimicrobial substances such as parabens, levofloxacin, chloramphenicol, florfenicol, thiamphenicol, fluoroquinolones, linezolid, gatifloxacin, tylosin, amoxicillin, ceftazidime, melatonin, cefatoxime, daptomycin, ciprofloxacin, fluconazole, clindamycin, gentamicin, linezolid, moxifloxacin and metronidazole in blood, plasma, urine and serum samples (Pajewska-Szmyt et al. 2020; Meng and Wang 2019; Wei et al. 2016; Mirzajani and Kardani 2016; Szultka et al. 2012; Xiao et al. 2013; Zeng et al. 2021; Parisa and Ameneh Porgham 2020). The procedures that have been employed for bioanalysis of parabens and levofloxacin are explained in the following paragraphs.

Levofloxacin has a vast antibacterial action against both Gram-positive and Gram-negative bacteria. Infectious illnesses, such as community-acquired pneumonia and acute exacerbation of chronic bronchitis have widely been treated. This medication is one of the most widely used third-generation quinolones, with a very minimal risk of side effects (Meng and Wang 2019). Among all quantification methods

for levofloxacin determination in human plasma, Meng and Wang (2019) reported Deep eutectic solvents (DESs) based MIP-MEPS coupled with UHPLC with satisfactory results. As a porogen, deep eutectic solvents (DESs) were utilized to prepare water-compatible molecularly imprinted polymers (MIPs) using a pseudotemplate. The DESs are made up of charged species and have intraliquid structural characteristics. Choline chloride/ethylene glycol was used as the porogen in this work to produce DESs-MIPs. Levofloxacin's highest binding capacity on DESs-MIPs in methanol and water was clearly 0.077 and 0.216 mol g<sup>-1</sup>, respectively. The DESs-MIPs were used as adsorbing materials in microextraction by packed sorbent (MEPS), and the DESs-MIPs-MEPS settings were optimized, yielding the following observations; the linearity over 0.05–10  $\mu\text{g mL}^{-1}$  with coefficient of correlation equal to 0.9988, LOD and LOQ were 0.012 and 0.04  $\mu\text{g mL}^{-1}$ , respectively and the accuracy of the suggested approach ranged between 95.3% and 99.7% at three spiking levels, with interday and intraday relative standard deviations of 8.9 percent. In the investigation of pH, the pH of the loading sample was optimally between 6.0 and 8.0, which corresponded to the pH of human plasma.

Parabens are esters of p-hydroxybenzoic acid with different alkyl groups, including methyl-(MeP), ethyl-(EtP), propyl-(PrP), and butyl-(BuP) paraben. According to studies, they may have harmful effects on the human body, producing hormone abnormalities or skin allergies. Since parabens are widely used as additives in personal care items such as shampoos, bath gels, and body lotions, there is a need to discover the best method for analyzing parabens and monitoring their presence in the environment and, in particular, biological samples (Pajewska-Szmyt et al. 2020). Hence Souza et al. (2016) and Pajewska-Szmyt et al. (2020) separately reported two developed methods including *MIP-RAM-in-tube-SPME/UHPLC-MS/MS* and *MMIPs-HPLC-FLD* by, respectively. The method, *MIP-RAM-in-tube-SPME/UHPLC-MS/MS* is developed for detecting parabens in breast milk samples. This new molecularly imprinted polymer is modified with restricted access material (a hydrophilic external layer) (MIP-RAM) which is synthesized via polymerization in situ in an open fused silica capillary. MIP-RAM capillary, used as sorbent for in-tube SPME, established specific interactions with parabens present in milk samples. This technique produced linear ranges ranging from 10 (LLOQ) to 400 ng mL<sup>-1</sup> with coefficients of determination greater than 0.99. The last method, *MMIPs-HPLC-FLD* is also developed for isolation of parabens from breast milk. Magnetic molecularly imprinted polymers (MMIPs) are synthesized as a sorbent in solid phase extraction with 17 $\beta$ -estradiol as a template molecule in the production of imprinted polymers. After determination in optimum condition by HPLC-FLD, the LOD and LOQ were very low in the range of 1.1–2.7 ng mL<sup>-1</sup> and 3.6–8.1 ng mL<sup>-1</sup>, respectively.

## Anti-inflammatory drugs

Nonsteroidal anti-inflammatory medicines (NSAIDs) are a class of medications with varying structural and pharmacological characteristics but a common method of action. Despite their comparable toxicity profiles and mechanisms of action, they interact with the cyclooxygenase enzyme in somewhat different ways. Aryl alcanoic acids (indomethacin, diclofenac, sulindac, nabumetone), 2-arylpropionic acids (profens) and salicylates (aspirin) are the four types of NSAIDs (Al-kaf 2017). Many developed methods are used for a selective extraction of anti-inflammatory drugs including 3-D MI-IPN sorbent MEPS/HPLC–UV, On-line-EC-MIP-in-tube SPME/HPLC–UV, MIP-SPE/HPLC–DAD, EC-MIP-SPME/IMS and Chitosan-MIP-SPE/UV-Spec separately and respectively by Asgari et al. (2017), Asiabi et al. (2016), Martinez-Sena et al. (2016), Alizadeh et al. (2014) and Mabrouk et al. (2020).

The 3-D Molecular imprinted interpenetrating polymer network sorbent-MEPS method (3-D MI-IPN sorbent MEPS/HPLC–UV) developed in order to measuring and determining carbamazepine, dexamethasone and naproxen as anti-inflammatory drugs in urine samples. Carbamazepine, as the MIP template along with naproxen and dexamethasone were examined to prove the MI-IPN selectivity and efficiency by analyzing urine samples. Due to the presence of two-separated interlocked polymeric networks, suitable gaps inside the 3-D structure were formed to precisely assign the necessary template for a convenient MIP operation (Asgari et al. 2017). Selective extraction and determination of indomethacin as an anti-inflammatory drug in urine, blood and plasma is done by on-line-electrochemically controlled-MIP-in-tube-solid phase micro extraction (On-line-EC-MIP-in-tube SPME) combined with HPLC–UV method. Using an electrical potential can enhance extraction efficiency and allow for more straightforward modification of extraction system parameters such as clean-up, selectivity, efficiency and rate. A new molecularly imprinted polymer coated tube was created and used for indomethacin extraction to improve the selectivity and application of this technique (Asiabi et al. 2016). The method MIP-SPE/HPLC–DAD is utilized to analysis of ketoprofen, naproxen, diclofenac, and ibuprofen as anti-inflammatory targets. By above method in the linearity ranged 0.05–10 mg L<sup>-1</sup> in urine sample, recoveries ranges obtained 80–137%, 86–131%, 93–128% and 80–114% for ketoprofen, naproxen, ibuprofen and diclofenac, respectively (Martinez-Sena et al. 2016). Gradually methods EC-MIP-SPME/IMS and Chitosan-MIP-SPE/UV-Spec were used for microextraction of ibuprofen and ketorolac, respectively (Mabrouk et al. 2020; Alizadeh et al. 2014).

## Addictive drugs

Addiction is a chronic disease characterized by a three-stage cycle of bingeing/intoxication, withdrawal/negative affect, and preoccupation/anticipation. These levels respectively include neuroadaptations in brain circuits involved in incentive salience and addiction development, stress overload and reward deficit, and executive function (McGinn et al. 2021).

Methamphetamine (MAMP) and Amphetamine (AMP) are stimulants of the central nervous system that cause euphoria, hallucinations, enhanced alertness, and wakefulness. The drug's powerful reinforcing and addictive effects lead to drug addiction as well as tolerance to the drug's psychotropic effects, which leads to the usage of hazardous doses. Most nations classify 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) as an illegal drug due to the warnings of permanent harm to the central nervous system. Methadone, on the other hand, is primarily utilized as a synthetic opioid in the treatment of opiate addiction. It is critical for patients to have their plasma concentrations monitored in order to correctly adjust their daily dosage. MIPs researchers are actively developing a fast, selective, and low-cost method for extracting and identifying methadone in routine and clinical analyses of these medicines. Such developed methods for determination of addictive drugs are SPME-fiber-based MIP, MIP-INAT, MIP-MEPS and MIP-sol-gel tablet- $\mu$ SPE/LC–MS/MS. The two first methods are developed by Djozan et al. (2011, 2012) for detecting of MAMP from human saliva and determination of MAMP, AMP and ecstasy in human urine, respectively. The second method is based on a solvent-free and on the usage of a molecularly imprinted polymer (MIP) and an inside-needle adsorption trap (INAT).

Mohamed Abdel-Rehim et al. reported many papers to indicate their efforts on leading to a selective, rapid, inexpensive and fast approach appropriate for forensic and clinical bioanalysis of amphetamine and methadone in most common biofluids. Determination of methadone in human plasma (El-Beqqali and Abdel-Rehim 2016) and amphetamine in human urine (El-Beqqali et al. 2017) have been analyzed by MIP-sol-gel-tablet toward  $\mu$ SPE using liquid chromatography and tandem mass spectroscopy (MIP-sol-gel tablet- $\mu$ SPE/LC–MS/MS) in Mohamed Abdel-Rehim group. The MIP-sol-gel was produced as a thin layer on polyethylene material in tablet form in these investigations. The template was methadone-d9, and the precursor was 3-(propylmethacrylate)-trimethoxysilane. Each tablet may be utilized twenty times for the extraction and desorption durations of just 10 and 6 min, respectively.

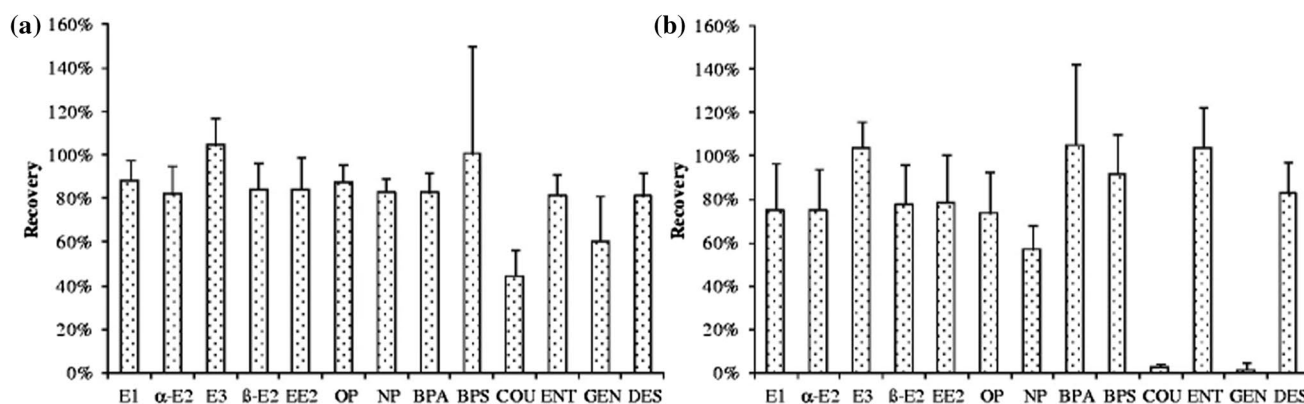
**Table 1** Validation parameters in serum and urine (Bousoumah et al. 2015)

Serum				Urine					
Linearity $R_2$	Intra-day precision RSD (%)		LOD $\mu\text{g L}^{-1}$	LOQ $\mu\text{g L}^{-1}$	Linearity $R_2$	Intra-day precision RSD (%)		LOD $\mu\text{g L}^{-1}$	LOQ $\mu\text{g L}^{-1}$
0.1–50 $\mu\text{g L}^{-1}$	1 <sup>a</sup> $\mu\text{g L}^{-1}$	5 $\mu\text{g L}^{-1}$			0.1–50 $\mu\text{g L}^{-1}$	1 <sup>b</sup> $\mu\text{g L}^{-1}$	5 $\mu\text{g L}^{-1}$		
	$n=5$	$n=3$				$n=5$	$n=3$		
E1	0.962	8.7	10.7	0.07	0.25	0.9953	4.7	28.6	0.06
$\alpha$ -E2	0.9858	5.8	15.4	0.08	0.3	0.9964	1.4	24.8	0.08
E3	nd	16.7	11.6	1	3.4	0.9889	15.7	11.9	0.54
$\beta$ -E2	0.9924	1.7	14.9	0.04	0.15	0.9989	2	23.4	0.06
EE2	0.999	5.9	17.4	0.06	0.2	0.9937	2.5	27.5	0.03
OP	nd	nd	9	0.04	0.15	nd	nd	25.6	0.04
NP	nd	nd	7.4	0.06	0.2	nd	nd	19.7	0.06
BPA	0.9893	4.8	10.9	0.01	0.04	0.9982	4.4	35.1	0.01
BPS	nd	33.3	49.2	0.09	0.3	nd	35.2	20	0.2
COU	nd	54	27.3	0.51	1.7	nd	nd	nd	nd
ENT	0.9986	10	11.9	0.16	0.55	0.9799	24.1	17.5	0.11
GEN	nd	59.4	34.3	0.7	2.4	nd	nd	nd	nd
DES	0.975	13.9	13.1	0.03	0.1	0.9966	3.6	16.2	0.03

nd not determined

<sup>a</sup>20  $\mu\text{g L}^{-1}$  for estrone,  $\beta$ -estradiol, estriol and enterolactone

<sup>b</sup>20  $\mu\text{g L}^{-1}$  for enterolactone and 50  $\mu\text{g L}^{-1}$  for estriol



**Fig. 8** Recovery profile for targeted estrogenic compounds in serum **a** and urine **b** at 5  $\mu\text{g mL}^{-1}$  (Bousoumah et al. 2015). Permission License Number: 5264300065359

## Hormones

Hormones are chemical messengers that transmit a signal from point *A* (secretion) to point *B* (organic action) inside a physiological system. The hormone is biosynthesized (and perhaps, but no longer always, stored) inside distinct cells associated with an anatomically defined endocrine gland. It flows via the bloodstream to one or more target cells, which are distinguished by the presence of a particular high affinity receptor (Norman et al. 2015). Application of molecularly imprinted polymers as sorbents for

extraction of hormones from various matrices has been widely investigated (Mpupa et al. 2021). Here, we summarize recent studies specifically extracted from biological samples.

Endocrine disrupting chemicals (EDCs) have piqued the interest of the scientific community. Endocrine disruptors are implicated in a broad variety of negative health consequences, including fertility disorders, cardiovascular disease, obesity, diabetes, and cancers. A unique concern is associated with the low-dose, long-term and combination effects of EDCs subsequently to early exposure in the

course of the perinatal period (fetus, pregnant women, new born). Estrogenic compounds are a particular source of concern among EDCs. Natural estrogens, synthetic estrogens, phytoestrogens, and several types of environmental contaminants are all included (Bousoumah et al. 2015). Attempts to discover and develop extraction methods for estrogenic compounds led to an increase in multi-residue methods that allow for the high throughput and minimal cost simultaneous determination of a broad variety of EDCs with decreased analytical time and cost, which is critical in order to characterize a large number of bioactive compounds. The MIP-SPE technique has been used to extract estrogenic endocrine disruptors from urine and serum with excellent results in both matrices, having recoveries above 70% for the majority of components; reported by Bousoumah et al. (2015). The linearity was determined at three levels of concentration ranging from 0.1 to 50  $\mu\text{g L}^{-1}$  by spiking urine and serum samples. LOD was in the range of 0.01–1  $\mu\text{g L}^{-1}$  for both matrices and the LOQ for urine and serum were 0.04–1.8  $\mu\text{g L}^{-1}$  and 0.04–3.4  $\mu\text{g L}^{-1}$ , respectively. Results are presented in Table 1 and Fig. 8 for all studied estrogenic compounds in this group (Bousoumah et al. 2015) in both serum and urine samples.

Oliveira et al. (2019a, 2019b) in 2019 reported two new methods in different papers for successfully determination of estrogens such as estriol (E3) and estrone (E1) from human urine by Restricted Access Mesoporous Molecularly Imprinted Polymer double coated with Hydrophilic Monomer and Bovine Serum Albumin (RA-MMIP-HM-BSA/HPLC–UV) method and ethinylestradiol (EE2) and estradiol (E2) from human urine by Restricted Access Material combined to Molecularly Imprinted Polymer for selective Magnetic Solid-Phase Extraction (RAM-MIP-MSPE/HPLC–UV) method. The first developed method was linear for each hormone in the concentration range of 100–1100  $\text{ng mL}^{-1}$ , with correlation coefficients of 0.9952 and 0.9954 for E3 and E1, respectively and the second improved technique produced linearity for each hormone across the concentration range of 80–1100  $\text{ng mL}^{-1}$ , with correlation coefficients of 0.9954 and 0.9971 for E2 and EE2, respectively.

## Blockers

Beta-blockers are a class of medications that are widely used to treat cardiovascular diseases such as irregular heartbeats, high blood pressure, and angina pectoris. The occurrence of  $\beta$ -blockers has raised significant worry about their potential chronic toxicity on aquatic species, emphasizing the importance of extensive research into their environmental distribution, destiny, and toxicity (Yi et al. 2020).

Atenolol (ATE) is a cardio-selective  $\beta$ -blocker that is used to treat high blood pressure for lengthy periods of time.

However, ATE, like propranolol, has the greatest potential for abuse as a performance-enhancing substance in a variety of sports. As a result, an effective and selective separation approach is required to detect and expose the quantity of ATE within the body. Determination of atenolol from biological samples is considered (Hasanah et al. 2019). Gorbani et al. (2017), reported a determination of atenolol from human urine by using ethylene glycol dimethacrylate, acrylic acid, dichloroethane and dibenzoyl peroxide as a cross-linker, functional monomer, porogen and initiator, respectively. In this study the molecular imprinted solid phase extraction (MI-SPE) was used as sample preparation method. The linearity of calibration curve was in the range of 0.10–2.0  $\mu\text{g mL}^{-1}$  for the developed method by recoveries of 74.5–75.3%. The LOD and LOQ values were 0.032 and 0.099  $\mu\text{g mL}^{-1}$ , respectively. Efforts on measuring ATE in blood serum are done and many methods have been developed for analyzing atenolol in plasma and urine samples using molecular imprinted solid phase extraction (MI-SPE) (Gorbani et al. 2017; Bodoki et al. 2018; Alizadeh 2014), as example; Hasanah et al. (2019) developed MIP-SPE method and application of UV–Vis spectrophotometry by recoveries of  $93.65 \pm 1.29\%$ .

Carvedilol, which known as 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl] amino]-2-propanol, is a medication authorized for the treatment of congestive heart failure having  $\beta$ - and  $\alpha$ 1-receptor blocking action (CHF). Carvedilol is effective at protein oxidation, suppressing lipid peroxidation and inhibiting the formation of reactive oxygen species due to its antioxidant activity. It is useful for patients with CHF because it protects the heart. Azodi-Deilami et al. (2014) reported a magnetic molecularly imprinted polymers (m-MIPs) by usage of a magnetic component ( $\text{Fe}_3\text{O}_4$ ) and carvedilol as a template molecule for in the solid-phase extraction (MISPE) technique combined with high-performance liquid chromatography (HPLC) for analysis of carvedilol from human blood and plasma samples. The calibration curve for this method was in the 2–350  $\mu\text{g L}^{-1}$  concentration range with the LOD and LOQ 0.13 and 0.45  $\mu\text{g L}^{-1}$ , respectively and recoveries between 85 and 93%.

Sotalol is a  $\beta$ -blocker that is used to treat rhythm abnormalities (cardiac arrhythmias) and is also used to treat hypertension in certain people. It is an antagonist at both  $\beta$ 1 and  $\beta$ 2 adrenoceptors. A new technique for extracting tiny amounts of sotalol from human urine samples was reported by Ansari and Karimi (2017). The development of molecularly imprinted solid-phase extraction (MIP-SPE/HPLC–UV) method resulted high recoveries (97–102%) and RSD (<5%) in the linearity of 0.05–100  $\mu\text{g mL}^{-1}$ . LOD and LOQ were 0.01 and 0.04  $\mu\text{g mL}^{-1}$ .

The development of a molecularly imprinted solid-phase extraction sorbent by Yılmaz and Basan (2015) resulted in



the selective extraction of telmisartan from human urine. Telmisartan is a kind of angiotensin II receptor antagonist that is used to treat heart failure and hypertension. Urinary excretion of telmisartan is in the range of 0.1–4%. Results presented good recovery values (76.1–79.1%) and precision values (0.11–1.6%) in the linearity of 0.04–1.40  $\mu\text{g mL}^{-1}$ .

### Multi-functional drugs

There are many components which have abilities to treat several disorders or may have this potential that we could put them here in multi-functional drugs category. The bio-analysis of multi-functional drugs has been in the consideration of scientists due to excessive usage of some of them and as common drugs in therapeutics. Techniques such as *MIP-in-tube SPME/LC-FD*, *HKUST-1-MOF-Fe<sub>3</sub>O<sub>4</sub>-GA-MIP/UV-Vis*, *MMWCNTs/HPLC-UV*, *water-compatible-MMISPE/HPLC-DAD*, *PT-DMIP/HPLC-UV*, *MIP-SPE/HPLC* and *PT-MIP-SPME/HPLC-UV* are developed in order to extract and analyzing interferon alpha 2a (Chaves et al. 2011), gallic acid (Asfaram et al. 2017), curcumin (Baharani et al. 2017), risperidone and 9-hydroxyrisperidone (Ji et al. 2018), prednisolone (Arabi et al. 2016), dextromethorphan (Moein et al. 2011) and enkephalind (Li and Li 2015) respectively in biofluids.

The method *MIP-in-tube SPME/LC-FD* is a fused silica capillary packed with restricted access materials (RAM, C18-BSA) as well as an immunosorbent (monoclonal anti-interferon alpha 2a). It is designed to detect interferon alpha 2a in plasma samples with the goal of therapeutic drug monitoring. In this reason, glycoprotein-imprinted biomaterials that preferentially bind to interferon alpha 2a molecules, were synthesized using a sol-gel method (Chaves et al. 2011). Interferon alpha 2a is a recombinant form of the natural protein and comprises 165 amino acids. A wide range of illnesses such melanoma, hepatitis B and C, leukemia and carcinomas of the renal cells have been under the treatment of these protein (Chaves and Costa Queiroz 2013).

In the interpretation of the second method, *HKUST-1-MOF-Fe<sub>3</sub>O<sub>4</sub>-GA-MIP/UV-Vis*, it was used for measuring gallic acid from urine, plasma and water samples by application of magnetite (Fe<sub>3</sub>O<sub>4</sub> nanoparticles (NPs)) HKUST-1 metal organic framework (MOF) composite as a support for surface imprinting of gallic acid imprinted polymer (HKUST-1-MOF-Fe<sub>3</sub>O<sub>4</sub>-GA-MIP) by using vinyltrimethoxysilane (VTMOS) as a cross-linker. This type of MIP was used for the rapid, selective, and sensitive ultrasound aided dispersive magnetic solid phase microextraction of gallic acid (GA) using the UV-Vis's detection technique (UA DMSPE-UV-Vis). Gallic acid (GA) known as bio-active phenolic acid, has a variety of applications including mutation-resistance, anti-inflammatory, anti-oxygen-free-radical's, strong anticancer efficacy toward prostate, breast,

and lung cancer, and a few commercial applications such as the manufacture of the antibiotic trimethoprim. On the other hand, GA is generated from the basic hydrolysis of tannic acid, which produces toxic effluents that pollute the environment. This large use placed greater emphasis on the researchers to design and develop new material and/or methods to be able to measure GA in an accurate and repeatable manner (Asfaram et al. 2017).

In the method, *water-compatible-MMISPE/HPLC-DAD*, which is utilized for extraction and measurement of 9-hydroxyrisperidone and risperidone from urine, the water-compatible magnetic molecularly imprinted polymer was used as a sorbent for solid phase extraction coupled with HPLC-DAD. Results display this method as an appropriate saturation magnetization for magnetic separation (< 30 s) with a high selectivity and high adsorption capacity (18 mg g<sup>-1</sup>). The achieved linearity for both 9-hydroxyrisperidone and risperidone was in the range 1–2000 ng mL<sup>-1</sup> with correlation coefficient  $\geq 0.991$ . The detection limit of 9-hydroxyrisperidone and risperidone were 0.24 ng mL<sup>-1</sup> and 0.21 ng mL<sup>-1</sup>, respectively and the recovery rates at three different spike levels varied from 94.6% to 102.4% (Ji et al. 2018).

The purification and analysis of prednisolone from urine by creating a new pipette-tip based on nano-sized dummy molecularly imprinted polymer (PT-DMIP) assisted by ultrasonication was reported by Mehrorang Ghaedi and co-workers. Prednisolone is a synthetic glucocorticoid that is widely used to treat acute rejection episodes in inflammatory diseases including colitis, arthritis, asthma, bronchitis and certain skin rashes. Furthermore, prednisolone is used in organ transplants to reduce the danger of organ injection. The PT-DMIP cartridge was created by filling the tip of the micropipette with a dummy molecularly imprinted polymer (Arabi et al. 2016). The pipette tip-based molecularly imprinted solid-phase microextraction monolith technique was used by Li and Li (2015) to determine enkephalins in human cerebrospinal fluid. In this work, a new molecularly imprinted polymer (MIP) monolith for highly selective extraction of enkephalins was synthesized and produced in a micropipette tip utilizing the epitope imprinting technique. Enkephalins were first recognized as a kind of endogenous opioid around the middle of the 1970s. The first two enkephalins discovered were Leu-enkephalin and Met-enkephalin, two pentapeptides that varied only at the C-terminus. Enkephalins' role in physiological and pathological procedures in the central nervous system (CNS) necessitates the advancement of specialized and ultrasensitive analytical techniques to assist clinical research.



## Heavy metals

Occupational toxicologists pay specific attention to determining heavy metals among other hazardous contaminants. Global worry exists as a result of fast industrial growth and the discharge of hazardous chemicals into the environment. Most businesses nowadays utilize heavy metals directly or indirectly, exposing a significant number of people to such elements, particularly heavy metals, through food, water, air, smoking and workplace. For instance, cadmium is mostly utilized in the battery, plating, welding, alloying sectors and semi-conductive. Cadmium is also a non-essential material element in the human body (Panjali et al. 2015). Hence, metal analysis techniques for human matrices have been developed and improved, resulting in excellent accuracy and recovery. Panjali et al. (2015) developed an ion imprinted polymer (IIP), based on coating of a polymer on a Fe<sub>3</sub>O<sub>4</sub> nanoparticle (NP) core, is used as a magnetic sorbent for the preconcentration and determination of the Cd(II) ion level in human urine samples. In optimal condition by applying flame atomic absorption spectrophotometer, recoveries were higher than 80 and lower than 100%. In other report, Fazelirad et al. (2019) explained preconcentration of Cu(II) in water, biological (hair) and agricultural samples by using nanoporous Cu(II) ion imprinted polymer method. The measurement procedure was completed by electrothermal atomic absorption spectrometry. The linearity of this method obtained 0.03–33 µg L<sup>-1</sup> by LOD of 0.0087 µg L<sup>-1</sup> and RSD 4.3%. Cui et al. (2013) also reported the determination of free Cu(II) in urine and serum samples by restricted accessed material-copper(II) ion imprinted polymer solid phase extraction combined with inductively coupled plasma-optical emission spectrometry. In optimized conditions, the adsorption capacity was 15.9 mg g<sup>-1</sup>. The linearity ranged from 1 to 100 µg L<sup>-1</sup> with LOD 0.17 µg L<sup>-1</sup>.

## Other target compounds

6-mercaptopurine (6-MP), that is extremely utilized as an immunosuppressive and anti-leukemic agent, has necessitated its selective detection in biofluids with its active metabolite 6-thioguanine (TG). Healing drug monitoring of 6-mercaptopurine and its metabolite 6-thioguanine is generally conducted to examine toxicity and effectiveness, particularly when the therapy is not reaching the intended therapeutic effects at the recommended dosages for treatment. As a result, several methods for determining 6-MP and its metabolites in biofluids to disclose their kinetics have been presented (Attallah et al. 2018). Attallah et al. (2018) reported their studies on Extraction and determination of 6-mercaptopurine and its active metabolite thioguanine in plasma, a novel bioanalysis technique (MMI-SPE/LC–MS/MS) has been synthesized as a magnetic molecularly imprinted

nanoparticles. The presented MMI-SPE in pH=5 and via 100 mg amount of Fe<sub>3</sub>O<sub>4</sub>@MIP NPs offered as the best technique in comparison to other documented approaches for achieving high extraction recoveries (85.94–103.03%).

Buprenorphine (Bup), a semisynthetic opioid, is commonly utilized for chronic pain treatment and opioid addiction maintenance therapy. The analgesic effect of Bup, which has a molecular structure comparable to morphine, is 20–25 times stronger than morphine. The therapeutic concentration in body fluids is quite low due to modest dosages in typical prescriptions and, on the other hand, the wide tissue dispersion produced by Bup's remarkably high lipophilicity (log*P* of 4.98). In this study for analysis of Bup in human urine, Habibi et al. (2018) reported a satisfactory result by applying magnetic molecularly imprinted polymer nanoparticles based dispersive micro solid-phase extraction method for extraction and high performance liquid chromatography connected with fluorescence detector for measuring (MMIPNP-d-µSPE/ HPLC-FL method). Recoveries of Bup were between 97.4 and 100.3%, in the linear dynamic range of 1–1000 ng mL<sup>-1</sup> (*R*<sup>2</sup>=0.9998).

Coenzyme Q10 (CoQ10) is a powerful endogenous antioxidant and an important cofactor in the mitochondrial respiratory chain. CoQ10 insufficiency is now linked to a variety of diseases, including neurodegenerative and mitochondrial disorders, making early diagnosis and remedy with CoQ10 supplementation critical for patient care. As a result, determining CoQ10 levels in various biofluids is an efficient process. Analysis of CoQ10 through MIP-SPE pretreatment approach is accomplished in urine and liver extract matrices (García Becerra et al. 2019; Contin et al. 2014). In order to measuring CoQ10 from liver extract (Contin et al. 2014), the coenzyme Q0 is used as a template and methacrylic acid, acetonitrile and ethylene glycol dimethacrylate as functional monomer, porogen and crosslinker, respectively. By using HPLC–UV for measurement step, the extraction recoveries were higher than 73.7% with good precision (3.6–8.3%). Analysis of CoQ10 from urine (García Becerra et al. 2019) is done by using HPLC–MS/MS. Results showed recoveries more than 90%.

The most major trace biogenic amine produced in the mammalian brain and peripheral nervous tissues is tyramine (2-(4-hydroxyphenyl) ethylamine). Trace biogenic amines are biologically related to the dopamine, norepinephrine, and serotonin neurotransmitter systems, and have been linked to a wide range of mood, emotion, attention, and cognition problems in humans. Tyramine is a product of tyrosine metabolism after the activation of tyrosine decarboxylase and functions as a biosynthetic intermediate precursor of octopamine. New tyramine receptors have recently been identified. This discovery sparked a flurry of research into the possibility that tyramine has its own neurotransmitter system. Tyramine is found in the mammalian brain at

extremely low levels, ranging from 0.1 to 100 ng g<sup>-1</sup> of tissue. After consuming tyramine-rich foods, the intracorporeal concentration of tyramine may rise. For the purpose of bioanalysis of tyramine, MIP-SPE/HPLC-FLD method is developed by Dorota Maciejewska et al. specially for analysis of tyramine from bovine serum albumin sample. A computational analysis was utilized in this work to estimate the affinity of the polymer matrix toward tyramine, and a preliminary experimental assessment for the target analyte was performed. The polymer's experimental analysis toward tyramine was then proceeded. In comparison, the imprinted, non-imprinted, and commercial C18 sorbents recovered 95 ± 2%, 14 ± 3%, and 1.9 ± 0.4% of tyramine from spiked bovine serum albumin samples, respectively, demonstrating significantly higher efficiency than previous techniques. The linearity of the calibration curve was in the range of 2.5–50 μmol.L<sup>-1</sup> ( $R^2 = 0.998$ ) under optimal conditions (Luliński et al. 2014).

### MIP-based biosensors

Biosensors are a strong instrument that is frequently utilized in the examination of biological samples, and they provide several advantages. Biosensors are useful instruments for detecting different analytes, particularly viruses, in clinical diagnosis, food processing, and environmental monitoring. Biosensors are quick and effective tools for detecting illnesses in real time, both qualitatively and quantitatively. The most frequent biosensors used for viral detection are electrochemical and optical (e.g., Surface plasmon resonance (SPR), surface-enhanced Raman scattering (SERS)) and even the usefulness of biosensors on SARS-CoV-2 (the causative agent of COVID-19) has recently been studied (Abid et al. 2021; Zhu et al. 2021). The first biosensor created by Clark and Lyons (1962) to quantify glucose in biological matrices.

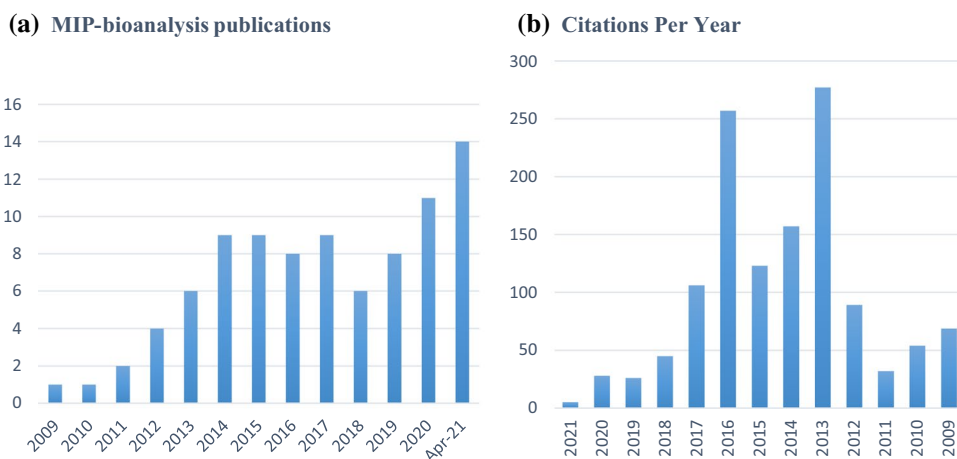
Biosensor development has recently been the most appealing research topic due to its ease of use, rapidity, low price, sensitivity, and selectivity in contributing to advancements in next-generation medications such as personalized therapy and ultrasensitive point-of-care detection of disease markers. Biosensors are categorized based on the mechanism of physicochemical transduction or the type of biorecognition element used. Biosensors are categorized as optical, electrochemical, piezoelectric, and thermal based on the transducer. Optical biosensors rely on a variety of optical methods, including fluorescence, absorption, luminescence, surface plasmon resonance (SPR), and others. Electrochemical biosensors have received the greatest attention because

of their low detection limit, selectivity, ease of fabrication and operation (Sawant 2017).

MIPs, as a type of sensor identification element, have several commercial applications and a great practical application value in the field of sensor analysis. Because electrochemical sensors offer the distinct benefits of high sensitivities, quick analytical rates, simple device operation, and simplicity of miniaturization, they are ideal for use in medical applications. As a result, molecularly imprinted electrochemical sensors that use MIPs as recognition elements have garnered broad interest and have become a global research hotspot. For instance, various types of magnetic molecularly imprinted electrochemical sensors (MIECS) have been widely developed which are divided into two categories; (1) MMIECS based on traditional electrodes (such as; electrochemical sensors coupled with magnetic molecularly imprinted solid-phase extraction, electrochemical sensors with MIP membranes prepared directly on electrodes modified with magnetic nanomaterials and electrochemical sensors with MMIPs modified on electrodes by drop-casting, spin coating, or filling) and (2) MMIECS based on magnetically controlled electrodes (such as; MMIECS based on self-made magnetically controlled electrodes or devices, MMIECS based on commercially available magnetically controlled electrodes and MMIECS achieving high-throughput detection using magnetically controlled electrodes) which each of them have been optimized for special analytes and matrices (Yang et al. 2020).

Recently, MIP-based biosensors are highly considered for determination drugs, biomarkers, hormones and etc. in human fluids. For instance, Gajda et al. (2020) determined aripiprazole antipsychotic drug by electropolymerization of new thiophene-carbazole functional and cross-linking monomers used in molecular imprinting polymer. MIP-aripiprazole film-coated electrodes were utilized as extended gates in this study for selective aripiprazole determination using the extended-gate field-effect transistor (EG-FET) chemosensor. In the optimum condition, the dynamic linearity obtained 30–300 pM with LOD of 22 fM. In another report, Abbasy et al. (2020) created a dependable bioanalytical technique based on prostate-specific antigen entrapment in the cavity of molecularly imprinted polymers. As an artificial receptor, electrically-conducting poly [Toluidine Blue] was used in this investigation. It was put together using molecular imprinting techniques and an electrochemical method. Using the DPV method, the bio-device also demonstrated linear response from 1 to 60 μg L<sup>-1</sup> and LLOQ of 1 μg L<sup>-1</sup>,

**Fig. 9** **a** Growth trend of publishing numbers on bioanalysis using MIP-extraction techniques; **b** Citations of discussed papers for each year extracted from their journals



allowing Prostate-Specific Antigen monitoring in clinical samples.

MIP sensors have been used in determination of pain medications. Diouf et al. (2021) described the use of MIP sensors to detect tramadol in spiked saliva and urine. Tramadol (TRA) is a weak opioid analgesic that is used to treat mild to moderately severe pain. However, TRA overdose adverse effects from moderate to death were frequently reported. An electrochemical sensor based on molecularly imprinted conductive polymer was initially improved in this study for non-invasive and quantitative detection, and a voltammetric electronic tongue (VE-Tongue) combined with chemometric techniques was utilized for qualitative analysis TRA. The obtained LOD was  $9.42 \mu\text{g mL}^{-1}$  in the linear range of  $0.01\text{--}100 \mu\text{g mL}^{-1}$  with a significant recovery more than 90%.

Tryptophan (Trp) is a subset of the 18 essential amino acid groups of human body, and it is a key precursor for the formation of neurotransmitters such as serotonin and niacin, as well as neurohormones such as melatonin. It is worth noting that they cannot be produced in the human body, and according to current studies an excess of Trp in the human body may lead to parkinson's and alzheimer's sicknesses. The measurement of Trp in the body prompted scientists to develop a suitable method in this regard. Jingting Luo et al. a satisfactory analysis of Trp in urine excellent recoveries ranging 97–104%. They optimized MIP pre-polymer solution coated on quartz crystal microbalance (QCM) electrode surface for a selective biosensing. The LOD was determined  $0.73 \text{ ng mL}^{-1}$  (Prabakaran et al. 2021).

In short, many kinds of MIP-based biosensor analysis developments have been reported for special targets such as paracetamol (acetaminophen) in plasma (Alanazi et al. 2021), glycoprotein in human serum sample (You et al. 2017), uric acid in serum and urine (Göçenoğlu Sarıkaya

et al. 2017), heart-fatty acid binding protein in human serum, human plasma, and bovine serum (Sanati et al. 2021),  $\beta$ -amyloid in serum (Pereira et al. 2020) and  $\alpha$  synuclein in human brain organoids (Lee et al. 2020) with high accuracy and recovery which may lead to clinical usage as fast and reproducible approaches. The use of MIPs in biological sensing has also been the subject of recent several review studies (Batista et al. 2021; Kadhem et al. 2021; Ramana-vicius et al. 2022) (Fig. 9).

## Conclusion and future perspectives

MIP techniques have shown high potential of bioanalysis as fast, selective and ultrasensitive in a range of great interest. Hence, the dose of biological components in body is an essential factor in physical and mental human health, monitoring and controlling of these components rate in body either due to the health maintaining and preventing diseases or for treatment purposes are seriously significant. So, the MIP applications in bioanalysis of many important components have been reviewed from literature covering the last decade. To achieve the considered goal of this study, the analyzed components in complex biofluids are categorized into different classes and the prepared Table 2 presents satisfactory results in recoveries, repeatability and wide linearity range with low LODs and LOQs. In addition, the applied MIP-based extraction techniques and MIP based biosensors have been summarized due to their ability of overcoming interfering species in biological samples and evaluating high selectivity and recoveries. Through all MIP-based extraction techniques, SPE, MSPE, SPME and MEPS are the most applied techniques respectively (Fig. 3). Despite The growing trend of papers entitled with MIP applications presented significant results, it is far from the expected rate state. The results of this study and review of published sources shows hormones and antimicrobial substances had

**Table 2** Recent application of MIP based extraction methods in biological analysis of inhibitors, biomarkers, antimicrobial substances, hormones, blockers, multi-functional compounds, natural compounds, heavy metals and kinds of drugs

Sample Matrix	Target	Template	Extraction method	Analytical techniques	(RSD) %	Recovery %	Linear range (ng mL <sup>-1</sup> )	References
<i>Biomarkers</i>								
1	Plasma	Glucosylsphingosine, Galactosylsphingosine	M387-AMDTs-GlcS 8-plex	UHPLC-MS/MS	2.3–11.4	96.1–107.2	0.009–369.31	Chen et al. (2020)
2	Serum	L-Hydroxyproline	ERSF-Hyp	LC-MS/MS	1.2–7.9	97.9–102.3	0.2–100	Zhu et al. (2020)
3	Blood	2-Aminothiazole-4-carboxylic acid	MIP-HI-d-SPE	LC-MS/MS	2–5	–	30–900	Griebutowicz et al. (2019)
4	Blood	2-Aminothiazole-4-carboxylic acid	MIP-dispersive SPE	HPLC	1.5–2.7	81–89	–	Lulifski et al. (2015)
5	Urine	Mandelic acid	MIP-MEPS	HPLC-UV	< 5.2	88.8	200–20,000	Soleimani et al. (2018)
6	Urine	Trans, trans-muconic acid	MIP-SPE	HPLC-UV	3.3–3.7	87–112	300–10,000	Vieira et al. (2012)
7	Urine	trans, trans-muconic acid	MIP-MEPS	HPLC-UV	3.4–6.6	> 89.8	15–2000	Soleimani et al. (2017)
8	Urine	8-hydroxy-2'-deoxyguanosine	MIP-In-Tube-SPME	HPLC/UV	1.1–6.8	84 ± 3%	2.83–1501.17	Zhang et al. (2009)
9	Serum	NLLGLEAK	MIP-MSPE	LC-MS/MS	–	–	–	McKitterick et al. (2020a)
10		Z-NLLGLEA-Nle-OH	MIP-RAFT-SPE					Rossetti et al. (2014)
11		Z-NLLGLEA[Nle]	On-line-MIP-SPE					Rossetti et al. (2017)
12	Plasma	Bilirubin	On-line-NMSX-MEPS	LC-MS/MS	1.2–7.0	80	2.92–584.66	Moein et al. (2014a)
13	Plasma	Hippuric acid	Online-MIP-PSM	LC-MS/MS	1.1–6.7	> 91	0.18–180	Moein et al. (2014b)
14	Plasma	Hippuric acid	3-MSHM	LC-MS/MS	1.2–4.5	> 89	0.18–360	Moein et al. (2015b)
15	Plasma	L-Tyrosine	MMSTs	LC-MS/MS	1.0–6.0	88–90	0.9–180	Moein et al. (2014c)
16	Plasma	Sarcosine	Online-DMIP-MEPS	LC-MS/MS	1.0–7.0	87	0.18–180	Moein et al. (2015c)
17	Urine	Sarcosine	DMMPs-12-Plex-TCIL-MDSPE	UHPLC-MS/MS	2.6–11.5	96.1–107.4	0.89–1781.86	Chen et al. (2021)
18	Serum	neuron-specific enolase	Z-NLLGLEA[Nle]	HPLC-MS/MS	–	100.8 ± 6.2%	7.5–375	McKitterick et al. (2020b)

Table 2 (continued)

Sample Matrix	Target	Template	Extraction method	Analytical techniques	(RSD) %	Recovery %	Linear range (ng mL <sup>-1</sup> )	References
19 Urine	4-hydroxyphenylacetic acids	4-hydroxyphenylacetic acid	MIP-SPE	UPLC-MS/MS	< 4.5	–	25–1000	Janczura et al. (2021)
		Phenylacetic acid						
		3-nitrobenzoic acid						
		2-nitrophenol						
<i>Antimicrobial substances</i>								
20 Plasma	Levofloxacin	Levofloxacin	DESS-MIP-MEPS	UHPLC	≤ 8.9	95.3–99.7	50–10,000	Meng and Wang (2019)
21 Breast Milk	Parabens	Benzylparaben	MIP-RAM-in tube-SPME	UHPLC-MS/MS	-1.0–19.0	55–80	10–400	Souza et al. (2016)
22 Breast Milk	Methylparabens	17β-Estradiol	MMISPE	LC-FLD	> 8	92–102	10.28–411.20 9.98–399.20 19.95–798.00 20.20–808.00 20.16–806.40	Pajewska-Szmyt et al. (2020)
	Ethylparaben							
	Propylparaben							
	Burylparaben							
	Benzylparaben							
23 Blood	Chloramphenicol	Chloramphenicol	MMISPE	HPLC-UV	2.7–7.9	83.3–99.1	0.25–25	Wei et al. (2016)
	Florfenicol	Florfenicol						
	Thiamphenicol							
24 Plasma Serum	Fluoroquinolones	Ciprofloxacin	MIPF-SPME	HPLC-UV	1.3–6.7	97.81–102	0.1–40	Mirzajani and Kardani (2016)
25 Plasma	Linezolid	Linezolid	MIPF-SPME	HPLC-MS	3.4–11.2	–	1000–20,000	Szultka et al. (2012)
26 Serum	Gatifloxacin	Gatifloxacin	MIP-MSPE	HPLC	3.3–4.9	79.1–85.3	800–450,000	Xiao et al. (2013)
27 Biological samples	Tylosin	Tylosin	MIP-SPE	HPLC-UV	–	75.6 ± 5.6%	–	Zeng et al. (2021)
			Boronate affinity based					
28 Urine Serum	Ceftazidime	Ceftazidime	MIP-SPE	HPLC-DAD	4.1	> 90	25–800	Parisa and Ameneh Porgham (2020)
29 Urine Plasma	Melatonin	Melatonin	MMIIdSPME	HPLC-UV	0.71–6.02	93.07–104.1	0.2–4200	Dil et al. (2021)



Table 2 (continued)

Sample Matrix	Target	Template	Extraction method	Analytical techniques	(RSD) %	Recovery %	Linear range (ng mL <sup>-1</sup> )	References
30 Blood	Amoxicillin, Cefatoxime Ciprofloxacin, Daptomycin Fluconazole, Gentamicin Clindamycin, Linezolid Metronidazole, Moxifloxacin	–	MIP-SPME	HPLC-MS/MS	0.58–5.01	96.08–101.87	1000–50,000	Szultka et al. (2013)
31 Plasma Urine	Meropenem	Meropenem	MIP-SPE	HPLC-PDA	2.8–5.6	83.6–100.6 87.2–96.6	120–800	Amlashi et al. (2019)
<i>Anesthetic Drugs</i>								
32 Urine Plasma	Fentanyl	Fentanyl	MIX-SPME	HPLC-UV	5.5–6.5	> 85	5–5000	Bagheri et al. (2013)
33 Urine	Lidocaine Ropivacaine Mepivacaine Bupivacaine	Pentycaine	MIP-MEPS	LC-MS/MS	< ± 14	60–80	1.17–468.67 1.37–548.8 1.23–492.70 1.44–576.86	Daryanavard et al. (2013)
<i>Hormones</i>								
34 Urine	Estrone (E1) Estriol (E3)	Estrone (E1)	RA-MMIP-HM-BSA	HPLC-UV	1.76 4.21	79.5 ± 7.1% 69.5 ± 1.5%	100–1100	Oliveira et al. (2019a)
35 Urine Serum	E1, α-E2, E3, B-E2, EE2, OP, NP, BPA, BPS, COU, ENT, GEN, DES	Phenolic template	MIP-SPE	LC-MS/MS		> 70 for a majority of compounds	100–50,000	Bousoumah et al. (2015)
36 Urine	EE2 E2	E2	RAM-MIP-MSPE	HPLC-UV	> 15	98.75 ± 4.02% 95.73 ± 0.24%	80–1100	Oliveira et al. (2019b)
37 Plasma	Catecholamines	3-Phenylpropylacrylate	MIP-dSPE	UHPLC-MS/MS	–	58–92	–	Podjava and Šilaks (2021)
38 Urine	Androsterone Stanolone Androstenedione Methyltestosterone	Testosterone	MIP-SPME	GC-MS	4.2–14.7	80.1–108.4	0.08–0.8	Qiu et al. (2010)
39 Urine Serum	Epinephrine Norepinephrine Dopamine	Epinephrine	MIPF-SPME	Capillary electrophoresis	6.0–11.1 3.3–14.4 4.7–11	86–96 85–94 85–103	1.83–109.92 1.69–101.51 1.53–91.91	Zhang et al. (2012)

Table 2 (continued)

Sample Matrix	Target	Template	Extraction method	Analytical techniques	(RSD) %	Recovery %	Linear range (ng mL <sup>-1</sup> )	References
40 Urine	Insulin	Insulin	MIP-SPE	HPLC-PDA	3.4-4.6	> 87	0.1-270	Moein et al. (2014d)
Plasma							0.07-250	
41 -	Erythropoietin-alfa	Erythropoietin-alfa	MIP	HPLC	0.03-0.06	87.45-113.96	10-100	El-Aal et al. (2021)
42 Urine	Progesterone	Progesterone	MIP	GC-FID	-	101.32 ± 4.5%	1.25-5000	Nezhadali et al. (2016)
Blood						88.25 ± 3.8%		
<i>Blockers</i>								
43 Urine	Atenolol	Atenolol	MIP-SPE	Spectrofluorometer	0.38-2.05	74.5-75.3	100-2000	Gorbani et al. (2017)
44 Serum	Atenolol	Atenolol	MIP-SPE	UV-Vis Spectrophotometry	0.38-2.05	74.5-5.3	100-2000	Hasanah et al. (2019)
45 Plasma	Atenolol	Atenolol	MSPE	CE-DAD	0.54-13.63	Around 70	5-1500	Silva et al. (2021b)
46 Serum	Carvedilol	Carvedilol	MIP-SPE	HPLC-UV	3.5	85-93	2-350	Azodi-Deilami et al. (2014)
47 Urine	Sotalol	Sotalol	MIP-SPE	HPLC-UV	1.85-4.84	97.4-102.5	50-100,000	Ansari and Karimi (2017)
48 Urine	Telmisartan	Telmisartan	MIP-SPE	Spectrofluorimeter	0.11-1.6	76.1-79.1	40-1400	Yilmaz and Basan (2015)
49 Bovine serum	Propranolol	Propranolol	MIP-dSPME	HPLC	2.3-3.7	85.2-97.4	0.03-25.93	Tu et al. (2021)
<i>Multi-functional compounds</i>								
50 Urine	Risperidone 9-Hydroxy-risperidone	Risperidone	Water compatible-MMISPE	HPLC-DAD	> 5.3	94.6-102.4	1-2000	Ji et al. (2018)
51 Urine	Gallic acid	Gallic acid	Ultra-assisted DMSPME	UV-Vis	> 3.5	98.13	8-6000	Asfaram et al. (2017)
Plasma								
52 Plasma	Curcumin trace	Curcumin	MMWCNTs	HPLC-UV	0.94-4.44	> 98	0.1-1200	Bahrani et al. (2017)
53 Plasma	Dextromethorphan	Dextromethorphan	MIP-SPE	HPLC	3.2-4.4	> 87	0.3-150	Moein et al. (2011)
54 Urine	Prednisolone	Betamethasone	PT-DMIP-SPE	HPLC-UV	2.2-8.8	89-96.1	0.22-220	Arabi et al. (2016)
55 Human cerebrospinal fluid	Met-Enkephalin	Tetrapeptide (Tyr-Gly-Gly-Phe)	Pipet tip-MIP-SPME	HPLC-UV	1.28-5.9	85.1-95.7	0.17-286.83	Li and Li (2015)
56 Plasma	Interferon alpha 2a	Interferon alpha 2a	MIP-in tube-SPME	HPLC-FD	3.0-9.2	-	0.11-277.8	Chaves and Costa Queiroz (2013)
57 EBC	Valproic acid	Valproic acid	MIP-SPE-DLLME	GC-MS	1.6-5.8	82 ± 5	0.06-250	Jouyban et al. (2021)
58 Plasma	Baicalein	Baicalein	MIP-SPE (SBA-15@MIP)	HPLC-UV	2.9	94.4	20-7990	He et al. (2015)
<i>Other</i>								
59 Urine	Buprenorphine	Buprenorphine	MMIPNP-d-μSPE	HPLC-FL	> 10	97.4-100.3	1-1000	Habibi et al. (2018)
60 Urine	Coenzyme Q10	-	MIP-SPE	HPLC-MS/MS	4.4-11.1	> 90	3-500	García Becerra et al. (2019)

Table 2 (continued)

Sample Matrix	Target	Template	Extraction method	Analytical techniques	(RSD) %	Recovery %	Linear range (ng mL <sup>-1</sup> )	References
61 Liver	Coenzyme Q10	Coenzyme Q0	MIP-SPE	HPLC-UV	3.6–8.3	70–89	7.5–150 µg g <sup>-1</sup>	Contin et al. (2014)
62 Plasma	Amiodarone	Amiodarone	MMIP-SPE	HPLC	–	97.33	–	Banan et al. (2022)
63 Plasma	Neurotensin, Neuromedin N	Pro-Tyr-Ile-Leu	Bulk MIP-SPE	HPLC-UV	3.7–4.6	91.38	17–16729	Lei et al. (2022)
			Molecularly imprinted monolithic-capillary microextraction			98.8		
64 Urine	Phenobarbital	–	MIP-SPME	HPLC-UV	–	–	20–100000	Rahimi and Bahar (2022)
65 Urine	Ribavirin	Ribavirin	MIP-SPE	HPLC-UV	< 5	93–102	500–80000	Zafarghandi et al. (2022)
66 Plasma	6-Mercaptopurine	6-Mercaptopurine	MMISPE	LC-MS/MS	0.68–7.99	85.94–103.03	–	Attallah et al. (2018)
67 Serum	Tyramine	Tyramine	MIP-SPE	HPLC-FLD	–	95 ± 2	342.95–6858.95	Lulinski et al. (2014)
			MIP-SPME fiber			–		
68 Urine	Abacavir	Abacavir	MIP-SPME fiber	LC/MS	3.7–9.7	–	0.05–1	Terzopoulou et al. (2016)
69 Plasma	Zolpidem	Zolpidem	MIP-SPE	HPLC-FLD	0.45–2.86	> 90	10–100	Alimohammadi and Pourmoslemi (2021)
70 Fetal bovine serum	Proteins	Bovine serum albumin	MIP based on magnetic graphene microspheres	–	–	–	–	Yang et al. (2021)
71 Urine	p-Aminosalicylic acid	p-Aminosalicylic acid	MMISPE	HPLC-UV	7.8–10.8	92 ± 8.3%	3–1000	Bagheri et al. (2016)
72 Plasma	Haloperidol	Haloperidol	MIP-SPE	HPLC-DAD	3.8–6.9	> 98	2–10,000	Ebrahimzadeh et al. (2013)
73 Plasma	Antazoline, Hydroxyantazoline	2-(4-imidazolyl) ethylamine dihydrochloride	magnetic-MIP-dSPE	LC-MS/MS	> 12	–	30–3000	Giebutowicz et al. (2021)
			Thin Film-MIP			–		
74 Plasma	Tricyclic antidepressants	benzyl (3-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)propyl)(methyl)carbamate	Thin Film-MIP	LC-MS/MS	> 15	–	1–500	Shahhoseini et al. (2021)
<i>Anti-inflammatory drugs</i>								
75 Urine	Indomethacin	indomethacin	MIP-EC-In-Tube-SPME	HPLC-UV	4.3–5.8	0.998	1–200	Asiabi et al. (2016)
						0.998		
Plasma					5.8–7.5	0.998	2–200	
Blood					7.1–8.4	0.996	4–200	

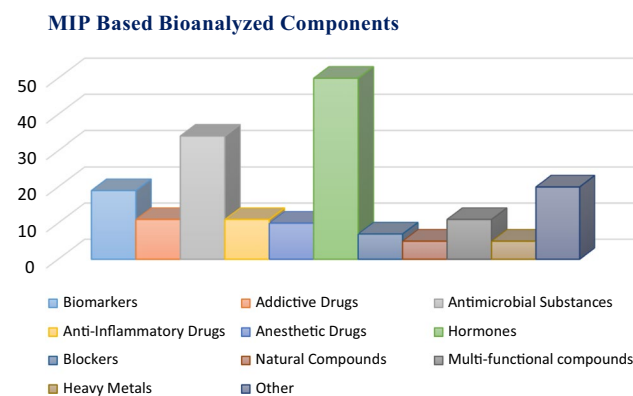
Table 2 (continued)

Sample Matrix	Target	Template	Extraction method	Analytical techniques	(RSD) %	Recovery %	Linear range (ng mL <sup>-1</sup> )	References
76 Plasma	Ketorolac	Ketorolac	Chitosan-MIP-SPE	UV-Spectrophotometer	7.30–12.86	> 80	2000–20000	Mabrouk et al. (2020)
77 Urine	Ketoprofen, Naproxen, Diclofenac, Ibuprofen	–	SupelMIP SPE-NSAIDs (Commercially available)	HPLC-DAD	> 20	80–131	50–10000	Martinez-Sena et al. (2016)
78 Serum	Ibuprofen	Ibuprofen	EC-MIP-SPME	IMS	> 6	89–128	5–100 and 100–1000	Alizadeh et al. (2014)
79 Serum	Carbamazepine	Carbamazepine	MIP-MSPE	HPLC-UV	1.4–2.0	About 95	50–12000	Alvani-Alamdari et al. (2019)
80 Urine	Carbamazepine,	Carbamazepine,	MIP-SBSE	HPLC-UV	2.1–3.3	91	200–12000	Asgari et al. (2017)
	Dexamethasone,	Dexamethasone,	3-D MI-IPN sorbent -MEPS	HPLC-UV	2.4–6.3	83	5–500	
	Naproxen	Naproxen			3.9–7.2	83	4.2–500	
<i>Addictive drugs</i>								
81 Urine	Methamphetamine	Methamphetamine	MIP-INAT	GC-FID	4.9–5.8	81–93	40–3000	Djozan et al. (2012)
	Amphetamine and Ecstasy				5.7–7.1	74–89	75–3000	
	Amphetamine	Amphetamine	MIP-sol-gel tablet- $\mu$ SPE	LC-MS/MS	6.9–8.7	69–86	125–2000	
82 Urine	Methadone	Methadone-d9	MIP-sol-gel tablet- $\mu$ SPE	LC-MS/MS	3.3–8.5	> 80	5–5000	El-Beqqali et al. (2017)
83 Plasma	Methamphetamine	Methamphetamine	MIP-SPME	GC-FID	4.0–8.0	> 80	5–5000	El-Beqqali and Abdel-Rehim (2016)
84 Salvia	Morphine	Morphine	MMISPE	UHPLC-DAD	< 5.5	7.8	50–3500	Djozan et al. (2011)
	Cocaine, Methamphetamine	Cocaine, Methamphetamine	MIP papers	DI-ESI-MS/MS	1.7–5.2	> 84.8	100–30000	
85 Urine	Cocaine, Methamphetamine	Cocaine, Methamphetamine	MIP papers	DI-ESI-MS/MS	< 5.9	84.3–98	1–100	Ebrahimi Rahmani et al. (2018)
86 Saliva	Cannabinoids (CBD)	hydrogenated cannabinoid	MIP-in tube-SPME	UHPLC-MS/MS	0.2–19.1	> 50	10–300	Díaz-Liñán et al. (2021)
87 Plasma	$\Delta$ 9-tetrahydrocannabinol and 11-hydroxy- $\Delta$ 9-tetrahydrocannabinol and 11-nor- $\Delta$ 9-tetrahydrocannabinol-9-carboxylic acid	Catechin-hydrate	MIP-MEPS	LC-MS/MS	–	3.45–17.8	25–250	Marchioni et al. (2020)
							25–250	Sartore et al. (2020)
							25–250	
<i>Natural compounds</i>								
88 Urine								

Table 2 (continued)

Sample Matrix	Target	Template	Extraction method	Analytical techniques	(RSD) %	Recovery %	Linear range (ng mL <sup>-1</sup> )	References
89 Urine	Cannabinoids	JWH007, JWH015 and JWH098	MIP- $\mu$ SPE	HPLC-MS/MS	> 8	> 75	50–2500	Sánchez-González et al. (2018)
<i>Heavy metals</i>								
90 Urine	Cd(II)	Cd(II)	MIP-SPE	FAAS	–	80 < x < 100	–	Panjali et al. (2015)
91 Hair	Cu(II)	Cu(II)	MIP-SPE	EAAS	4.3	96 $\pm$ 4.2%	0.03–33	Fazelirad et al. (2019)
92 Urine Serum	Cu(II)	Cu(II)	Restricted access-Cu(II) MIP-SPE	Plasma-optical emission spectrometry	2.2	90–108	1–100	Cui et al. (2013)
93 Hair	Pb <sup>2+</sup>	Pb <sup>2+</sup>	MIP-MNNS-SPE	FAAS	–	99.7–109	0.5–850	Kiani and Ghorbani (2017)
<i>Inhibitors</i>								
94 plasma	Venlafaxine, O-desmethylyvenlafaxine, N-des-methylvenlafaxine	venlafaxine	MISPE	UHPLC-MS/MS	–	99	3–700	Miranda et al. (2016)
95 Urine Serum	venlafaxine	venlafaxine	Magnetite MIP-SPE	HPLC	–	97–102.4	2.0–400	Madrakian et al. (2015)
96 Urine Serum	Sitagliptin	sitagliptin	MISPE	MISPE	–	> 98	100–1000	Rao et al. (2011)
97 Urine	Fluoxetine	Fluoxetine	MC/GO MIP-SPE	ZIC-HILIC Spectrophotometry	2.5	95.7–104	0.8–10	Barati et al. (2017)





**Fig. 10** Number of bio-analyzed compounds by MIP-extraction techniques in bio-matrices

the most attentions unlike natural components and heavy metals (Fig. 10). However, several challenges remain to be overcome to expand the variety range of components in bio-matrices. Going further, the more application of MIPs on bioanalysis of other important components such as pollutants (like mycotoxins, heavy metals, and pesticides), other kinds of drugs, biomarkers, inhibitors and hormones can be expected. Complete and expand studies in these areas will facilitate the development and optimization of approaches in trace analysis and clinical assessments.

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## Declarations

**Conflict of interest** The all authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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