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# Molecularly imprinted polymers for the detection of volatile biomarkers

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A B S T R A C T

In the field of cancer detection, the development of affordable, quick, and user-friendly sensors capable of detecting various cancer biomarkers, including those for lung cancer (LC), holds utmost significance. Sensors are expected to play a crucial role in the early-stage diagnosis of various diseases. Among the range of options, sensors emerge as particularly appealing for the diagnosis of various diseases, owing to their cost-effectiveness, simplicity, and promising analytical performance. There is growing interest in the application of molecularly imprinted polymers (MIPs) as promising recognition elements in gas sensors. MIPs, as a leading technology for sensing analytes where no suitable bioreceptor exists, are commonly used in artificial sensing that can be applied in key fields like early disease diagnostics, based on the detection of volatile biomarkers. There is an extensive demand for early, non-invasive detection of various diseases and for the self-monitoring of health conditions. Detection of biomarkers in point-of-care mode remains challenging and is limited by various factors. Hence, breath analysis has received enormous attention in healthcare due to its relatively low cost, non-invasive sampling method, and rapid detection capabilities. The latest developments in MIP-based sensors and their utility in disease diagnosis through the detection of volatile biomarkers are comprehensively and critically evaluated in this review. Furthermore, the challenges and perspectives of MIP-based sensors are elaborated upon, with a view towards introduction to the market and successful commercialization.

## 1. Introduction

A high number of deaths caused by multifactorial diseases (cancers, respiratory system diseases, cardiovascular disorders, infections, *etc*.) results mainly from late diagnosis, which effectively limits treatment and significantly increases the cost of medical care [1,2]. The identification of biomarkers, especially in exhaled breath, has the potential for clinical application in many diseases, such as those affecting the lungs, digestive system, oncological, and systemic diseases [3]. The gold standard in the field of biomarkers identification is still a combination of gas chromatography with mass spectrometry (GC-MS) where the limit of detection (LOD) oscillates at ppb/ppt level [4]. The other methods engulf proton transfer reaction mass spectrometry (PTR-MS) [5], selected ion stream tube mass spectrometry (SIFT-MS) [6], laser spectroscopy [7], ion mobility spectrometry (IMS) [8] and electronic noses (ENs) [9]. Much attention is also devoted to the possibility of breath analysis regarding diseases by specially trained dogs, but these methods are hard to standardized [10,11]. Moreover, the analysis of raw extracts can be challenging due to the inability to inject these directly into chromatographic columns, even with the MS selective detection capabilities. Large molecules can hinder the ionization process, leading to potential inaccuracies in quantification compared to other detection systems. Due to other inconveniences, like cumbersome and expensive equipment, labor-intensive preparation steps and trained personnel, connected with the mentioned classic techniques of VOCs analysis, the current trend is oriented to the development of the biosensors as smart and non-invasive analytical diagnostic tools [12]. The successful application of biosensors diagnostic tools requires (*i*) ultrasensitive transducers, (*ii*) changeable biorecognition elements, (*iii*) integration, (*iv*) miniaturization, (*v*) automation of sample preparation and amplification steps, (*vi*) need of low sample and reagent volume, and *(vii)* lower costs.

Molecularly imprinted polymers (MIPs), commonly named as 'plastic' or 'artificial antibodies' contained predefined cavities with specific

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shape and composition of functional groups that directly correspond to the composition of the target group [13,14]. It is difficult to determine the first MIP-based sensor developed for biomarker detection, but one of the earliest and most notable examples are the MIP-based sensor developed by Piletsky [15] and coworkers (Fig. 1B). Since then, the field of MIP-based sensors has rapidly grown, with numerous applications in fields such as environmental monitoring, food safety, and medical diagnostics [16]. The essential feature of MIP-based (bio)sensors is their ability to be compared and integrated with current systems, enhancing their recognition capabilities [17]. MIPs adaptability allows for their application across various point-of-care testing scenarios and detection of biomarkers in different body fluids, including saliva [18], serum [19], sweat [20], *etc.* [21,22]. Moreover, there is a continuously growing trend aimed at utilization of MIPs in sensors for breath analysis, including gas sensors [23–27].

The constantly increasing number of articles on MIP-based sensors and MIP-based sensors for biomarkers detection confirm the growing interest and niche in their development (Fig. 1A).

The pathways of MIPs development in the view of future sensors application for volatile biomarker analysis have been presented. In contrast to the previous reviews [28–33], we highlight what advancements have been achieved to increase the metrological parameters of MIP-based sensors devoted to the detection of VOCs, including volatiles classified as biomarkers. There is a pressing need to develop reusable, cost-effective, easy to manufacture, stable, and highly selective sensors based on MIPs. Critical analysis of previous achievements has allowed for the identification of possible routes for development, which should facilitate the realization of precise volatile biomarkers detection in clinical samples.

## 2. Challenges in diseases diagnosis and classic approaches for volatile biomarkers detection

The diagnosis of diseases presents several challenges, and the detection of volatile biomarkers has gained an important role in this process. Many diseases have multifactorial causes and diverse manifestations, making molecular diagnosis complex, especially in the early stages of some diseases [34–36]. Classical biomarker detection technologies, such as blood analysis, imaging, biopsy, genetic testing and immunohistochemistry are not adequate when the analyte is a volatile biomarker. Besides, most of diagnostic techniques for volatile biomarkers are expensive and time-consuming, limiting access to accurate diagnoses in underserved populations worldwide [37]. Different types of biological samples can be used to investigate the presence of disease indicators, biomarkers, and their collection can be invasive, such as blood and tissue samples, or non-invasive like urine, saliva, feces, or breath. Invasive sampling is inevitably associated with an element of discomfort and pain, which can lead to patient evasiveness. Limited sample medium and collection frequency, and usually a higher cost should be highlighted as drawbacks of this approach. Even though

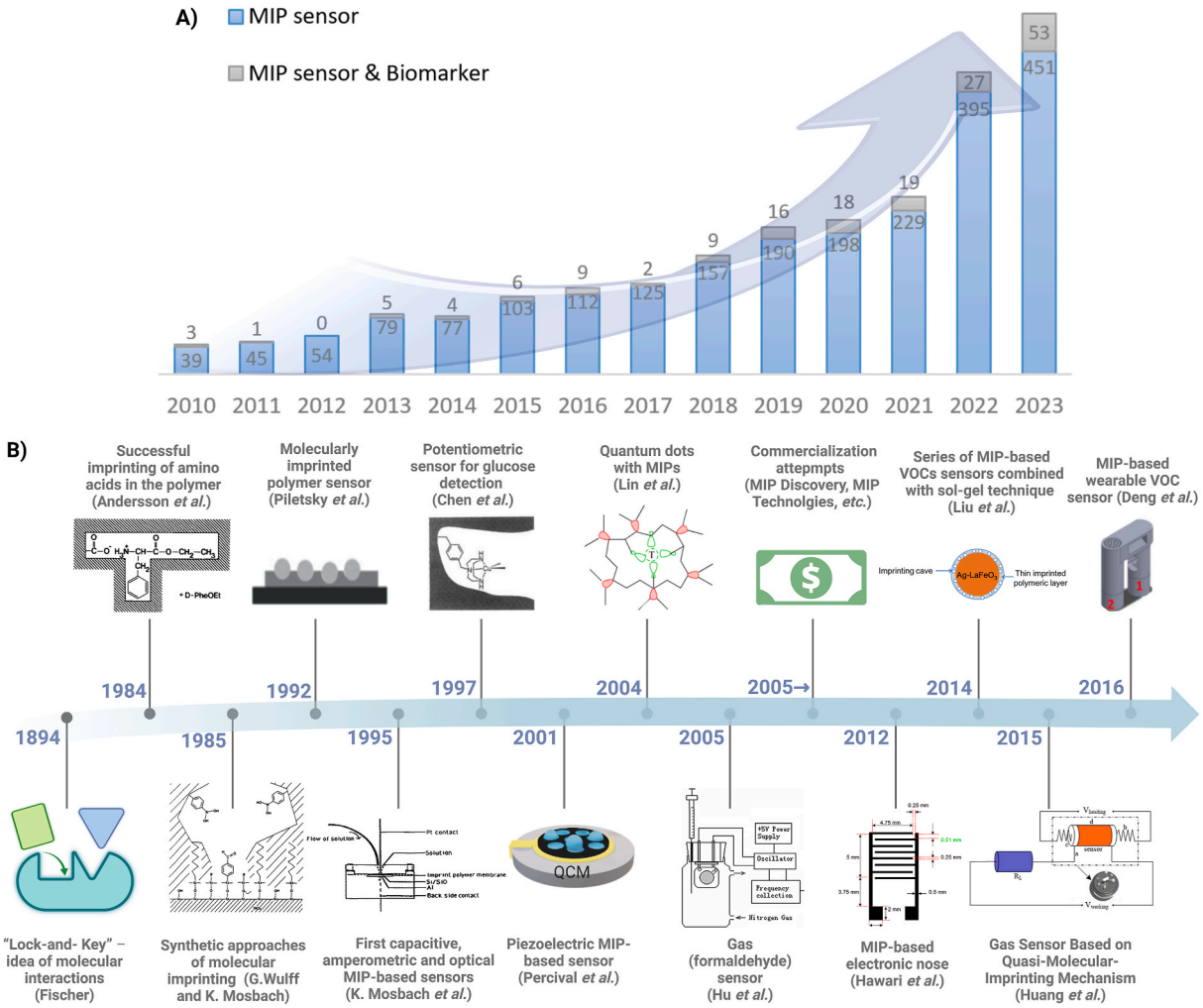


**Fig. 1.** (A) The number of scientific articles published since 2010, concerning sensors based on MIPs and their applications in biomarkers detection. (according to PubMed database). (B) Milestones in MIP-based sensors developments.

non-invasive collection overcomes most of these problems, samples such as urine, stool, and sputum do not exhibit an endless supply and uptake might be compromised due to patients' embarrassment and/or discomfort [38,39].

Invasive sampling is inevitably associated with an element of discomfort, which can lead to patient evasiveness, a limited sample medium and collection frequency, and usually a higher cost. Even though non-invasive collection overcomes most of these problems, samples such as urine, stool, and sputum do not exhibit an endless supply and uptake might be compromised due to patients' embarrassment and/or discomfort [38,39]. In this context, the relatively rapid equilibrium in the lungs between substances dissolved in the blood and alveolar gases offers the opportunity to detect these biomarkers in the gas phase in the forms of exhaled breath (EB) in direct way or indirectly, *e.g.* Tedlar®, Nalophan bags or sorption tubes [40]. Emissions of VOCs from organisms can have endogenous or exogenous origin [41]. Exogenous sources include compounds introduced from the external environment, such as those generated after consuming food or as a result of smoking cigarettes. On the other hand, endogenous VOCs refer to a class of compounds that may be present in the blood, released into the environment by the lungs, and/or produced by symbiotic bacteria [42]. When referring to VOCs, mainly quantified from patient's breath [43–48], skin, urine, and saliva [49]. VOCs can be detected: (*i*) directly from the headspace (*i.e.* the mixture of VOCs trapped above the abnormal cells in a sealed vessel); or (*ii*) in exhaled breath, blood or other body fluids with properly designed MIP-based sensors (Fig. 2).

The detection of chemical compounds in EB presents an opportunity to determine the physiological state, diagnose diseases, or assess environmental exposure [38]. Approved breath tests include the search for ethanol (law enforcement), $^{13}CO_2$ (*Helicobacter pylori* infection), nitric oxide (asthma), hydrogen (carbohydrate metabolism), carbon monoxide (neonatal jaundice), and branched hydrocarbons (heart transplant rejection) [40,51], except that numerus studies have demonstrated the biomarkers in EB for diagnosing and monitoring several health conditions [38,39,52]. Discovery and identification of reliable disease-specific VOCs at adequate levels are dependent on repeatable, accurate analysis of trace-level gaseous analytes. Early, fast and reliable diagnosis of patients' conditions, including respiratory system diseases, as well as the on-time launch of suitable treatment are critical factors influencing public health and the efficiency of clinical trials [53]. Human breath usually contains a rich mixture of VOCs presenting distinct VOC fingerprints that can be affected by diseases. The variations in exhaled VOC profiles can be leveraged to detect and diagnose diseases. However, any diagnostic application utilizing EB must address the potential influence of interferences. Assessing the efficacy of a breath biomarker requires understanding the impact of possible interferences on the composition of EB. Smoking, a well-known factor affecting breath composition, has been extensively studied in previous research [54]. Various activities can lead to elevated levels of exogenous compounds in EB, such as occupational exposures to certain environments, the use of consumer products (such as makeup, soaps, household cleaners, and pesticides), or even showering with tap water containing halogens. Previous and current exposure to environmental air has also been identified as a factor affecting the composition of exhaled air when used for diagnostic purposes. The recent study demonstrates the considerable impact of smoking, age, gender, BMI, and different medications on the composition of exhaled breath. It's noteworthy that the effect of medications can be seen as a combination of two factors: the underlying medical condition and the pharmaceutical compounds themselves. No notable correlations were observed between exhaled breath content and factors such as total cholesterol, triglycerides, LDL and HDL levels, contraceptive medications, neutrophils, basophils, monocytes, and total white blood cells [55].

The analysis of VOCs present in breath is becoming increasingly attractive as a non-invasive tool for disease monitoring. This is mainly due to its easy accessibility compared to serum or urine samples. Breath analysis offers additional advantages, such as user-friendliness and point-of-care operation, making it a promising strategy for non-invasive health management [56]. As the profile of expired gas is directly influenced by metabolism, the gases exhaled can provide disease biomarkers

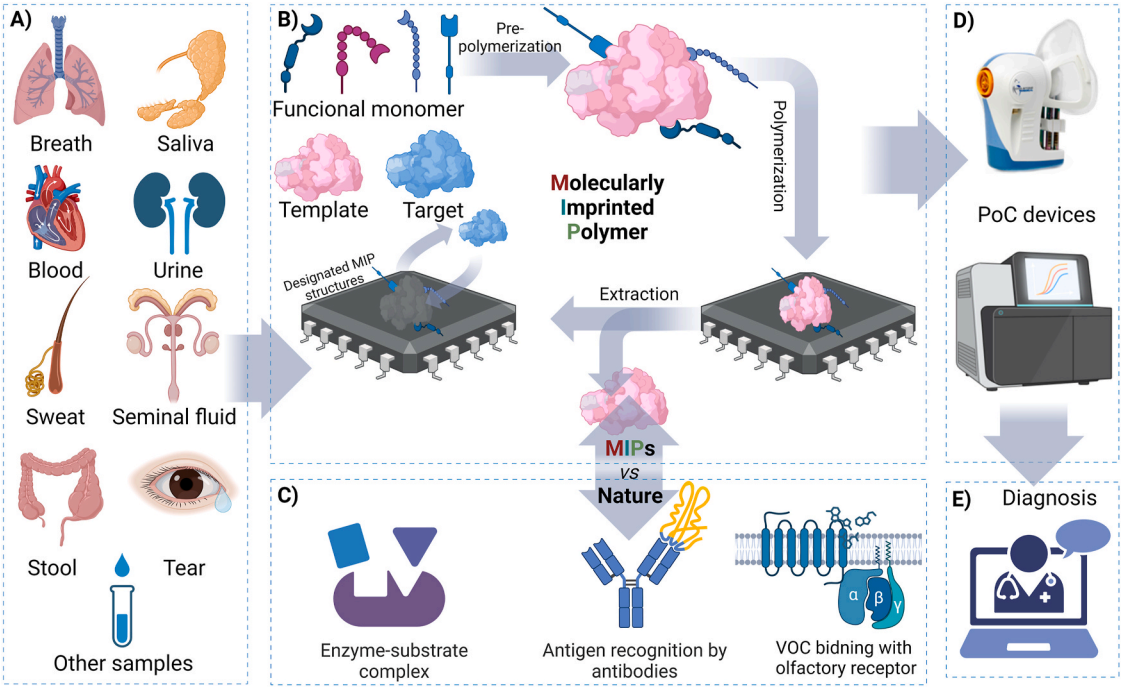


**Fig. 2.** Schematic for preparing point-of-care devices based on MIP sensors for biomarkers detection. A) Main sources of disease-related biomarkers in human body. They can be used in diagnosing pathologies, monitoring progress of disease or injury, identifying targets for intervention, and assessing risk of pathology [50]. B) Construction of a molecular imprinting system featuring biorecognition sites. C) Comparison of MIPs to examples exist in biological systems. D) A variety of PoC devices for biomarkers detection. E) Obtaining the results that enable a preliminary diagnosis. Created with biorender.com.

**Table 1**
Major biomarkers in EB and their related health conditions.

| VOCs | Disease | References |
|---|---|---|
| Acetone | Diabetes mellitus, heart failure | [57,58] |
| Acetaldehyde | LC, alcoholism | [59,60] |
| Ammonia | Kidney disease, *Helicobacter pylori* infections, liver disease, hepatic encephalopathy | [61–64] |
| Ethanol | Non-alcoholic liver disease, obesity, diabetes mellitus | [58,65] |
| Hexanal | LC | [60] |
| Hydrogen peroxide | Asthma, chronic obstructive pulmonary disease | [66] |
| Hydrogen sulfide | Asthma, allergic rhinitis, pulmonary disease | [67,68] |
| Isoprene | End-stage renal failure, advanced fibrosis in chronic liver disease | [69,70] |
| Isopropanol | Diabetes mellitus | [71] |
| Methane | Chronic constipation, obesity, irritable bowel syndrome | [72–74] |
| Nitric oxide | Asthma, chronic obstructive pulmonary disease | [67,75] |
| Nonanal | LC | [60] |

(Table 1).

Breath contains a complex mixture of VOCs, including metabolic processes, environmental exposures, and diet, which may vary in an inter- and intra-individual manner [76]. Factors such as age, sex, genetics, and lifestyle choices contribute to differences in baseline volatile biomarker levels, making it difficult to establish universal diagnostic thresholds among populations. Stratifying patients based on factors such as disease stage, comorbidities, and genetic predispositions can improve the specificity of volatile biomarker-based diagnostics.

Sample collection standardization, selectivity and sensitivity of low-concentration VOCs are also crucial to accurately identify and quantify volatile biomarkers [77,78]. Integrating data from multiple omics levels, such as genomics, proteomics, and metabolomics, can enhance the specificity and sensitivity of VOCs identification. Biomarkers present in EB, after thorough circulation through the lung-blood system, offer a comparatively precise representation of lung diseases and metabolic disorders. Poli et al. specified a combination of 13 VOCs to accurately categorize individuals into distinct groups, including LC patients, chronic obstructive pulmonary disease (COPD) patients, asymptomatic smokers, and healthy subjects. It is noteworthy that certain pulmonary diseases, particularly COPD or emphysema, can significantly increase the risk of developing LC. This association arises due to shared risk factors such as smoking [79]. Alcohols, aldehydes and ketones are most commonly detected compounds as biomarkers of LC [80]. Over time, a multitude of markers associated with LC have been extensively studied, identified, and utilized. Nevertheless, the diverse and intricate biological behavior of tumors poses a challenge in identifying a single marker that possesses both high sensitivity and specificity. As a result, combining different markers becomes an alternative strategy to enhance the clinical efficacy of LC diagnosis [81]. The discovery of VOC markers related to LC is summarized in Table 2.

Moreover, the accuracy of breath-based diagnostics can be influenced by confounding factors such as air pollution or dietary habits [90]. Addressing this challenge requires the integration of information across various biological and pathological levels to eliminate confounding factors, enabling a more comprehensive understanding of disease-related changes [91].

In this context, machine learning algorithms have emerged as pivotal tools for pattern recognition, facilitating the identification of subtle changes in volatile biomarker profiles that may signify specific diseases [47,92–94].

The continuous monitoring of disease-specific biomarkers necessitates the development of robust technologies that can deliver accurate and reliable results over an extended period [95]. These devices should empower patients to conduct regular breath analysis conveniently at home, thereby offering valuable data for effective disease management and facilitating early intervention [96]. The emphasis on creating technologies that are not only technologically advanced but also user-friendly and capable of sustained performance underscores the potential for transformative advancements in personalized healthcare through continuous biomarker monitoring.

**Table 2**
Reported exhaled VOC markers for the early screening of LC.

| VOCs | Sample | Collection Method | Ref. |
|---|---|---|---|
| 1-Butanol and 3-hydroxy-2-butanone | Mixed expiratory samples | Tedlar® bags; SPME | [82] |
| Ethanol, acetone, butane, dimethyl sulfide, isoprene, propanal, 1-propanol, 2-pentanone, furan, o-xylene, ethylbenzene, pentanal, hexanal, nonane | Alveolar breath | Tedlar® bags; SPME | [83] |
| Butanal, ethyl acetate, 2-pentanone, ethylbenzene, 1-propanol, 2-propanol | Alveolar breath | Tedlar® bags; SPME | [84] |
| Pentanoic acid; hexanoic acid; phenol; methyl phenol; ethyl phenol; butanal; pentanal; hexanal; heptanal; octanal; nonanal; decanal | Mixed alveolar breath | Nalophan bag | [85] |
| Propanal, butanal, decanal, butanal, 2-butanone, ethylbenzene | Tidal breath | Gas bulbs; SPME | [86] |
| Hydrogen cyanide, methanol, acetonitrile, isoprene, 1-propanol | Alveolar breath | Analytic Barrier Bag | [87] |
| 1,4-Butanediol, 2-pentanamine, 4-methyl-, 2-propanamine, 3-butenamide, 4-penten-2-ol, acetamide, 2-cyanoalanine, n-methylglycine, octodrine | Alveolar breath | Carbotrap C and Carbopack C | [88] |
| Isopropanol, n-butanol, n-heptanol, n-hexanal, n-heptanal, n-decanal | End-tidal breath | Tedlar® bags; SPME | [89] |
| 2-hydroxyacetaldehyde, isoprene, pentanal, butyric acid, toluene, 2,5-dimethylfuran, cyclohexanone, hexanal, heptanal, acetophenone, propylcyclohexane, octanal, nonanal, decanal, and 2,2-dimethyldecane | Exhaled breath | Tedlar® bags | [60] |

Furthermore, the imperative for the widespread adoption of these technologies necessitates their design to be compact, user-friendly, and cost-effective. The development of affordable VOCs diagnosis technologies is pivotal for ensuring accessibility, particularly in underserved populations. Considerations of affordability, ease of use, and seamless integration into existing healthcare infrastructures are crucial factors in extending the benefits of these innovations to a broader demographic. The emphasis on creating solutions that are not only technologically advanced but also practical and economically viable underscores the commitment to democratizing access to cutting-edge diagnostic tools and improving overall healthcare equity.

In conclusion, the deployment of breath-based diagnostic technologies raises pertinent ethical considerations, particularly concerning privacy and consent, which demand careful attention and resolution. Addressing these ethical considerations becomes crucial in ensuring the responsible and respectful use of such technologies. Attaining regulatory approval, alongside addressing ethical aspects with health authorities, represents a pivotal milestone for the clinical adoption of breath-based diagnostic tools. This comprehensive approach is indispensable for fostering public trust, safeguarding individual privacy, and facilitating the ethical integration of innovative diagnostic technologies into healthcare practices.

## 3. Interfacing of MIPs onto the transducer substrate

For the comparison of different synthesis techniques, a distinction for template and porogen (solvent) imprinting can be made. Template

imprinting is the conventional method, which involves polymerization around the template. On the other hand, porogen imprinting involves imprinting in what would conventionally be considered an excess of template. An excellent review, prepared by Cowen and Cheffena was recently prepared [33]. A review was conducted to collect and assess the majority of findings that discuss porogen and template imprinting techniques used in MIP-based gas sensors. The incorporation of MIPs into transducers can be achieved through different methods, such as physical adsorption, covalent bonding, and electrostatic assembly [97]. Physical adsorption is a simple method for immobilizing MIPs onto the desired transducer. In this method, MIPs are adsorbed onto the surface of the transducer through non-specific interactions like van der Waals forces, hydrophobic interactions, or hydrogen bonding. The main advantage of this method is that it does not require any pre-treatment of the transducer surface and the MIPs can be easily removed or replaced. However, the binding strength between the MIPs and the transducer is weak, which may result in the loss of activity of the binding over time. Covalent bonding is a more stable and robust method for immobilizing MIPs to transducers. These methods require the covalent attachment of MIPs onto the transducer surface through chemical reactions such as amide formation, thiol-disulfide exchange, or thioester formation. Covalent bonding provides a strong and permanent attachment, enhancing the sensor design's stability and longevity [98]. The drawback of this method is that it requires a pre-treatment of the transducer surface to introduce functional groups, which cause alterations in the surface properties of the transducer. Another method is electrostatic assembly, a versatile method for the immobilization step [99]. This method adsorbed MIPs to the transducer surface *via* electrostatic interactions such as ionic bonding or dipole-dipole interactions. This method does not require pre-treatment of the transducer surface, and MIPs can be easily removed from the surface by changing the pH or ionic strength of the solution. When we look at the combination of MIPs with transducers in detail, we can classify the methods as *ex situ* and *in situ*. The immobilization of prefabricated MIPs or particles onto a transducer *via* physical adsorption can be achieved by spin-coating or drop-casting processes and considered as *ex situ* strategies [100].

In spin-coating, MIP prepolymer solution is deposited onto the transducer substrate and spun at high speeds to obtain a thin, uniform film layer. The thin film is cured, and the MIP layer is created onto a sensor substrate. Lieberzeit and coworkers [101] demonstrated a QCM sensor utilizing nanocomposites of polyurethane-based MIPs and Ag2S nanoparticles for aliphatic alcohol sensing. They proposed a spin coating method to obtain a thin MIP layer onto the gold transducer surface. QCM transducers were treated overnight with a 5–10 % solution of 1-butanethiol in n-heptane to create an alkanethiol layer on the surface. Coating experiments indicated that $Ag_2S$ nanoparticles are blended with MIP precursors and can lead to a thin film layer without problems. AFM did the characterization of the coated thin layer. The experimental results showed that they obtained three times higher response times than the average response time. More comparison studies of QCM sensors obtained from MIP and NIP (non-imprintedpolymer), as control groups. In 2019, Abdelghani et al. [102] proposed a SnO2 nanostructured electrochemical sensor using MIP to determine acetone and ammonia. They utilized the spin coating method under different conditions to acetone and ammonium hydroxide imprinted thin layer through hydrothermal synthesis. They obtained 500 nm thicker micro sheets developed from $SnO_2$ nanoparticles based on various synthesis conditions. They tested the sensing response of the sensor design, and the results exhibited a promising response for ammonia gas and acetone with sensitivity of 89 % and 77 %, respectively.

On the other hand, in the drop-casting method, a small droplet of MIPs solution was placed onto the surface of the transducer using a pipette or syringe. Then, the droplet is allowed to evaporate, leaving behind a thin film of polymer on the substrate. The thickness of the MIP film can be controlled by adjusting the volume and the concentration of the polymer solution. Janfaza et al. [103] introduced an artificial olfactory sensor for acetone detection. They utilized MIPs-coated microfluidic channels and metal oxide. MIP nanoparticles were dispersed in acetonitrile and drop-cast on the surface of microfluidic channels. The 2D feature extraction method analyzed the sensor response to determine different volatiles. In 2022, Mousazadeh et al. [104] developed a chemo-resistive sensor using hexanal imprinted polymers and gold nanoparticles. They utilized the drop-casting method to obtain a sensing layer onto the IDE. Different volumes of drop casting were examined for optimization, and the highest conductivity was received, with the volume of drop casting being 50 μl. The electrical response was observed when the hexanal gas entered the test chamber *via* a syringe. The results exhibited that this sensor design has great potential to detect the cancer biomarker in the biological matrices, including cell culture medium, serum, saliva, and urine. A recent example demonstrated a development of polyaniline (PANI) based MIP by a drop-casting method to obtain chemo-sensor to identify furaneol [105] (Fig. 3A). One of the reasons for selecting PANI was its high electrical conductivity. For the fabrication of the sensor, $Si/SiO_2$ films were used as a substrate, and IDE were patterned *via* a shadow mask method. MIP-PANI layers were fabricated on the obtained sensor substrate using the drop-casting method with 10 μL of prepolymer solution.

*Ex situ* strategies involve synthesizing and immobilizing the MIPs directly onto the transducer substrate in the sensing environment, which causes some disadvantages. One disadvantage is the low adherence of polymer and substrate, leading to incomplete coverage of the sensor surface. This can result in reduced sensitivity and selectivity. Another disadvantage of *ex situ* methods is that the properties of the resultant polymer film may be affected by the deposition methods and conditions, which leads to variations in the performance of the sensor batch to batch or under different environmental conditions. On the other hand, *in situ* methods enable the synthesis and immobilization of the MIPs directly onto the transducer substrate. One common *in situ* method is the *in situ* polymerization of the MIP on the sensor, either thermal or photo-induced polymerization. This involves adding a mixture of monomers, cross-linkers, and target molecules to the sensor surface in the presence of a polymerization initiator. Creating a crosslinked MIP layer on the sensor offers high selectivity and sensitivity. Hirayama et al. [106] demonstrated the thermal-induced polymerization of MIPs onto the QCM sensor to detect acetaldehyde After cleaning and preparing the QCM sensor, the acetaldehyde template containing the prepolymer solution was dropped onto the electrode surface. Polymerization was done under vacuum at 90 °C for 5h. The sensor's performance was evaluated by observing the frequency change following the template removal. Later, Jha et al. [107] proposed another MIP-coated QCM gas sensor that detects aldehydes in body odor. They followed the thermal-induced polymerization procedure to obtain a sensing MIP layer onto the QCM surface. Hexanal was used as the template molecule, and the polymer solution was dropped onto the surface of the transducer. Polymer-coated QCM were placed in an oven at 40 °C for 24 h. A gas chromatography-mass spectrometer (GC-MS) was used as reference method to characterize odor samples. The results showed that the MIP-based QCM sensor detected aldehydes selectively and with high sensitivity. The table below (Table 3) outlines the advantages and disadvantages of both *ex situ* and *in situ* strategies.

The electro-polymerization method is preferred to improve control of the deposited MIP layer. Debliguy et al. [108] demonstrated a chemical sensor for acetaldehyde detection. The MIP layer was electro-deposited onto the IDe in the presence of electroactive functional monomer pyrrole. The method involves using an electrical field to drive the polymerization of the MIP onto the transducer substrate and monitor acetaldehyde. Main disadvantage of electro-polymerization method is possible reduction in yield and lifetime of sensor. Therefore, the researchers introduce nanomaterials to improve the performance of the final system [101,109]. Alonso-Lomillo et al. [110] proposed a sensor system based on the electro-polymerization strategy on a glassy carbon electrode (GCE) to determine ethanethiol (Fig. 3B). After the GCE was


**Fig. 3.** Examples of MIP-based sensors for detection of volatile compounds. A) A concept of a MIP-PANI sensor for furaneol detection. Reproduced with permission from Ref. [105]. B) MIP-based sensor based on the electro-polymerization of pyrrole on a GCE, for the determination of ethanethiol. Reproduced with permission from Ref. [110]. C) Schematic diagram of the optical approach for determining IPA vapor utilizing a MIP layer on a glass slide with the image of the actual setup and a real-view of the sensor. Reproduced with permission from Ref. [27]. D) Scheme of MIP-based sensor fabrication for the detection of hexanal as cancer biomarker. Reproduced with permission from Ref. [104]. E) A Formaldehyde Sensor Based on Molecularly-Imprinted Polymer on a $TiO_2$ Nanotube Array. Reproduced with permission from Ref. [109]. F) Apparatus of MIP coated QCM sensor array with 9-Mhz AT-cut QCMs. Reprinted with permission from Ref. [150].

**Table 3**
Advantages and disadvantages of the ex situ and *in situ* strategies.

| Methods | | Advantages | Disadvantages |
|---|---|---|---|
| *Ex situ* | Spin-coating | - Better control over film thickness<br>- More uniformity<br>- Faster process | - Specialized equipment required<br>- Difficulties with high viscous solutions |
| | Drop-casting | - Simplicity<br>- Less equipment required | - Less uniformity<br>- Limited control over film thickness |
| *In situ* | Thermal polymerization | - More uniformity<br>- Can be easily scaled up for industrial production | - Limited control over polymerization process |
| | Photopolymerization | - More uniformity<br>- Compatibility with a wide range of monomers | - Limited penetration depth of light restricts the thickness of the polymer film<br>- Requires specific light sources |
| | Electro-polymerization | - Excellent control over polymerization for uniformity<br>- Can be performed under mild conditions | - Limited materials that electrochemically active<br>- Requires conductive substrates and suitable electrolytes. |

polished and cleaned, pyrrole was electro-deposited onto the electrode with ethanethiol as the template molecule. Later, the sensor's sensitivity performance was improved by incorporating gold nanoparticles (AuNPs). The final sensor design successfully detects the target volatile in spiked wine samples with a recovery range from 99 % to 107 %.

## 4. Various approaches for VOCs analysis

A wide diversity of sensor–system applications continue to be developed and applied to biomedical, clinical, and diagnostic (disease detection) applications. Among the key advantages of electronic instruments, designed to detect complex mixtures of VOC analytes in gaseous clinical samples, are the capabilities of achieving noninvasive early disease detection prior to symptom development. MIP-based sensors are undoubtedly one of the possibilities of using analytical techniques for the analysis of volatile biomarkers. However, compared to other commonly used techniques, they have a number of limitations. Compared to GC-TOF-MS, GC × GC-TOF-MS, PTR-MS or SIFT-MS, the use of MIP allows the detection of only one specific chemical compound, while in the case of methods using mass spectrometry it is possible to work in full-scan and multiple ion monitoring [111]. This feature gives MIP sensors an advantage over classic electronic noses, which are constructed from non-selective sensors [92,112]. The use of mass spectrometry ensures high resolution and the possibility to obtain multiple

**Table 4**
Comparison of technologies for VOCs analysis.

| Technology | Principle | Detection | Advantages | Disadvantages |
|---|---|---|---|---|
| Gas Chromatography (GC) | Separation of volatile compounds based on their different affinities for a stationary phase. | Flame Ionization Detector (FID), Mass Spectrometry (MS), or Thermal Conductivity Detector (TCD). | High sensitivity and specificity. | Requires sample pre-concentration, not well-suited for real-time monitoring, and may have limited capability for on-site analysis. |
| Mass Spectrometry (MS) | Ionization of volatile compounds followed by their separation based on mass-to-charge ratio. | Electron Impact (EI), Chemical Ionization (CI), or Selected Ion Monitoring (SIM). | High sensitivity and the ability to identify and quantify compounds. | Expensive instrumentation, complexity, and may require skilled operators. Some MS methods may have limited sensitivity for certain compounds. |
| Electronic Nose (E-Nose) | Mimicking the human olfactory system using an array of sensors. | Pattern recognition of sensor responses to volatile compounds. | Rapid analysis, non-invasive, and can be used for on-site monitoring. | Limited specificity for individual compounds, susceptibility to environmental interference, and may require frequent recalibration. |
| Fluorescence Spectroscopy | Measurement of the fluorescence emitted by certain biomarkers upon excitation with specific wavelengths of light. | Fluorescence emission signals. | High sensitivity and the ability to target specific compounds with fluorophores. | Limited to compounds with fluorescent properties, potential for interference from background fluorescence, and may require careful optimization of experimental conditions. |
| Optical sensors | Reaction of volatile compounds with specific reagents leading to a color change. | Visual inspection or spectrophotometry. | Simple, cost-effective, and suitable for on-site testing. | Limited specificity, potential for false positives, and may be affected by changes in environmental conditions. |
| Quartz Crystal Microbalance (QCM) | Detection based on piezoelectric effect and mass changes caused by adsorption of analytes. | Change in resonance frequency. | High sensitivity, broad analyte range, low energy consumption, effortless replacement, rapid and durable. | Limited to mass changes, increased susceptibility to environmental fluctuations, complex circuitry, potential interference among channels, necessity of additional maintenance and calibration. |
| Surface Acoustic Wave (SAW) Sensors | Detection of changes in surface acoustic wave velocity caused by the interaction with volatile compounds. | Change in resonance frequency. | Rapid response and sensitivity to mass changes. | Limited to changes in surface properties, potential for interference, and may require temperature control for stability. |
| Capillary Electrophoresis (CE) | Separation of volatile compounds based on their electrophoretic mobility in a capillary. | UV–Vis spectrophotometry or fluorescence. | High resolution and suitability for complex mixtures. | Limited to charged compounds, may have limited sensitivity for some analytes, and potential for sample matrix interference. |
| Raman Spectroscopy | Scattering of light by molecules, providing information about molecular vibrations. | Analysis of scattered light. | Non-destructive, minimal sample preparation, and molecular specificity. | Limited sensitivity for some compounds, fluorescence interference, and potential for sample heating. |
| Nuclear Magnetic Resonance (NMR) | Detection of signals from nuclei in a magnetic field, providing information about the molecular structure of compounds. | NMR spectra. | High resolution and structural information. | Expensive equipment, relatively low sensitivity compared to other techniques, and limited to certain compounds. |
| Photoacoustic Spectroscopy | Measurement of acoustic waves generated by the absorption of modulated light by volatile compounds. | Acoustic signals. | High sensitivity and specificity, especially for trace-level detection. | Complex instrumentation, limited to certain types of molecules, and potential for interference from background noise. |
| Microfabricated Gas Chromatography (μGC): | Miniaturized version of traditional GC for rapid and portable analysis. | Various detectors, including MS or thermal conductivity. | Portability and rapid analysis. | Limited to volatile and semi-volatile compounds, potential for column degradation, and may require skilled operation. |
| Nanostructured Materials-Based Sensors | Detection based on changes in the electrical, optical, or mechanical properties of nanostructured materials in the presence of volatile compounds. | Various readout methods depending on the type of nanostructure. | High sensitivity, miniaturization, and potential for sensor array development. | Potential for signal drift, limited selectivity, and susceptibility to environmental conditions. |
| Thermogravimetric Analysis (TGA) | Measures the change in mass of a sample as a function of temperature. | Weight loss associated with the release of volatile compounds. | Quantitative information about the volatile content. | Limited to volatile compounds that undergo significant weight loss, lack of specificity, and potential for interference. |
| Chemiluminescence Detection | Detection based on the light emission resulting from a chemical reaction involving volatile compounds. | Measurement of emitted light. | High sensitivity and potential for specific detection. | Limited to compounds that exhibit chemiluminescence, potential for interference, and may require optimization of reaction conditions. |

spectra within a short time. However, this instruments are expensive, complicated and stationary [113]. In the case of MIP sensors, the advantage is their small size and simple construction [23]. In terms of sample collection, direct analysis is possible, which is practically impossible in the case of chromatographic methods, where sample collection into bags or sorbents is usually used [114]. Methods based on mass spectrometry allow for obtaining very low LOD values (ppt), while MIP sensors, depending on the transducer used, can obtain higher values (ppb or single ppm).

Methods available for the analysis of gaseous analytes and their comparison a presented in Table 4.

Advances in sensor technologies, mass spectrometry, and gas chromatography have contributed to improving the precision and reliability of breath analysis for disease diagnosis (Table 4). Most studies analyzing VOCs are based on two main technologies, gas chromatography (GC) and mass spectrometry (MS), which are largely reviewed in the existing literature. We have focused on the more recent advancements in the field of sensing technologies.

The delay in obtaining prompt and precise PCR, ELISA or GC results underscored the necessity for novel noninvasive detection methods capable of delivering accurate outcomes in PoC scenarios, where rapid, high-volume, and reliable testing results are essential. In response to the limitations inherent in traditional molecular diagnostic approaches, a range of sensing devices has been investigated, with the electronic nose emerging as a particularly promising solution. Subsequently, a significant amount of new research emerged, focusing on the development of innovative noninvasive early detection methods for COVID-19. These methods utilize EN devices, employing a distinct detection approach based on alterations in the composition of VOC emissions present in human breath. These changes result from the effects of COVID-19 pathogenesis, which concurrently disrupt various specific metabolic pathways across different organ systems [115]. Recently, Li and colleagues have employed an array of electrical resistivity-based nanosensors for on-site diagnosis of COVID-19 infection through the analysis of exhaled patient breath [116]. The system demonstrated a commendable accuracy, correctly identifying 79 % of samples diagnosed *via* RT-PCR. Similarly, Wintjens and collaborators [117] have developed an electronic nose utilizing conductivity metal-oxide sensors for the diagnosis of COVID-19 from EB [117]. The acquired data were subsequently subjected to machine learning analysis for pattern recognition, yielding a sensitivity of 0.86 and a negative predictive value (NPV) of 0.96.

### 4.1. MIP-based optical sensors

Essential issue is the choice of the transducer, which depends on the type of measurement required and the properties of the target molecule. The sensing methods can be classified as optical, electrochemical, and mass-sensitive [118]. In case of optical sensors, MIPs can be combined with optical transducers such as fluorescence, absorbance, or surface plasmon resonance (SPR) sensors. These transducers can detect changes in the optical properties of the MIP layer upon binding to the target molecule. In 2022, Pathak et al. [27] reported an optical approach for determining isopropanol (IPA) vapor utilizing a MIP layer on a glass slide. They used a UV–Vis spectrophotometer and a quartz cuvette for the experiments, and the sensing performance was observed, as shown in Fig. 3C. They demonstrated the morphological differences between the MIP and control group by field emission scanning electron microscopy (FESEM) and AFM.

Most of the research adopted the SPR-based optical systems to fabricate MIP-based VOC sensors [119–121]. SPR-based VOC sensors work based on changes in the refractive index (RI) caused by catching VOC molecules. Au and Ag are the most common materials since their superior plasmonic properties and inert and stable features. In one example [121], AuNPs were used in an SPR-based sensor to detect terpene vapor. Au ion sputtering was used for the deposition of AuNPs on glass slides. Hayashi and coworkers also utilized AuNPs for the LSPR sensor array based on molecularly imprinted sol-gels [122]. The imprinted layer is designed to recognize typical organic acid odorants, propanoic acid (PA), hexanoic acid (HA), heptanoic acid (HPA), and octanoic acid (OA), from the human body. Their experimental results showed that the plasmon resonance peak and the RI highly depend on the MIP layer thickness. Optical-based VOC sensors provide fast response time, versatility, high sensitivity, and low contact measurement. However, the complicated process compared to other systems should be considered. Examples of MIP-based optical sensors for VOC analysis are presented in Table 5.

### 4.2. MIP-based electrochemical sensors

Electrochemical sensors that utilize MIPs have shown great potential for detecting VOCs due to their high selectivity and sensitivity. As with other materials, electrochemical sensors use standard measurement techniques: amperometry at fix potential, capacitive *via* current pulse method; cyclic voltammetry, double-pulse chronoamperometry, differential pulse voltammetry, electrochemical impedance spectroscopy, linear sweep voltammetry, potentiometric, square wave voltammetry or square wave anodic stripping voltammetric [125]. The detection mechanism typically involves the measurement of the electrochemical signal generated by the binding of the target molecule to the MIP film coated onto the electrode surface. To enhance the performance of electrochemical MIP sensors, various strategies are employed. The binding of gas analytes to the active sites within the MIPs leads to the swelling of the polymer matrix. This swelling effect causes the conductive materials, such as nanoparticles or conducting polymers, to move farther apart from each other, increasing sensor resistance. This change in resistance serves as a measurable signal indicative of the presence and concentration of the target volatile analyte. Sensors utilizing MIPs can immobilized on the surface of an existing electrode, e.g. gold screen-printed electrode, boron-doped diamond electrode, carbon paste electrode, glassy carbon electrode; graphite electrode or indium tin oxide. However, by using them, the selectivity of the sensor can be significantly increased. The difference can also be noticed in the operating parameters of the sensors - chemoresistive MIPs operate at room temperature, while other materials (modified semiconductors) usually operate at higher temperatures [126].

Incorporating nanomaterials, such as nanoparticles or nanowires, within the MIP layer can amplify the sensor's sensitivity and response. Nanomaterials can increase the surface area of the MIP layer. The high surface-to-volume ratio of nanoparticles or nanowires provides a larger area for interacting between the target volatile analyte and the imprinted sites within the MIP. This leads to a higher probability of binding events and consequently improves the sensor's sensitivity. Mousazadeh and coworkers [104] utilized gold nanoparticles (AuNPs) (Fig. 3D) to detect hexanal. They first synthesized the AuNPs and functionalized them with 11-mercaptoundecanoic acid, which has two functional groups, thiol, and carboxylic acid. While thiol groups covalently bind to the AuNPs, the carboxylic acid group interacts with the functional group of MIPs. MIP-AuNPs were used as the sensing layer on IDE. Due to their small size and unique electronic properties, AuNPs have excellent electrical conductivity. When incorporated into the MIP layer, they can promote efficient charge transfer between the analyte-bound MIP and the electrode, resulting in a more rapid sensor response.

The choice of nanomaterials depends on the specific requirements of the sensor and the target analyte. Commonly used nanomaterials include metal nanoparticles (*e.g.*, gold, silver), carbon-based nanomaterials (*e.g.*, carbon nanotubes, graphene), and metal oxide nanoparticles (*e.g.*, zinc oxide, titanium dioxide). Surface modifications, such as introducing functional groups or using conductive polymers, can improve the stability and selectivity of the MIP layer. In one example, Debliquy et al. [108] used polypyrrole (PPy) as a conductive layer onto

**Table 5**
MIP-based optical sensors for VOC analysis.

| Analyte | Sensor construction | Template molecule | Monomers for MIP preparation | Polymerization method | Detection method | Ref. |
|---|---|---|---|---|---|---|
| Isopropyl alcohol | MIP functionalized glass slides | Isopropyl alcohol | Ethylene glycol dimethacrylate, 2,2′-azobis-isobutyronitrile, methacrylic acid | Free radical polymerization, UV at 365 nm | Transmittance measurement at UV (150–270 nm) | [123] |
| Formaldehyde | MIP gold-coated optical fibers | Formaldehyde | Pyrrole | Electropolymerization | RI | [119] |
| α-Pinene | MIP Au nano-islands film on glass slides | α-Pinene | Methacylic acid, ethylene glycol dimethylacrylate, 2,2′-azobis (isobutyronitrile) | Free radical polymerization | RI | [120] |
| α-Pinene | MIP AuNPs on glass slides | α-Pinene | Methacylic acid, ethylene glycol dimethylacrylate, 2,2′-azobis (isobutyronitrile) | Free radical polymerization | RI and surface plasmon resonance | [121] |
| 2-Furaldehyde | MIP on plastic optical fiber platform | 2-Furaldehyde | Divynilbenzene, methacrylic acid, and 2,2′-azobis(isobutyronitrile) | Free radical polymerization | RI and surface plasmon resonance | [124] |

the IDE for acetaldehyde detection. The conductive materials incorporated within the MIP matrix experience an increase in the distance between them. This separation leads to a decrease in the interparticle or intermolecular interactions that facilitate electron transfer, resulting in a higher resistance across the sensor. The presence and concentration of the target volatile analyte can be determined by monitoring the changes in resistance, either through direct measurement or by tracking the electrical current flowing through the sensor. By comparing the metrological parameters of sensors based on MIPs with sensors using other materials, it can be concluded that, for instance, detection of hexanal with the use of MIP is competitive with other materials. Shantini et al. [127] developed a chitosan-based hexanal electrochemical sensor whose LOD was 20 ppm for a measurement linear range of 20–300 ppm. For this analyte, Huang et al. [128] developed a sensor based on nano-$SnO_2$, obtaining an LOD of 100 ppb, but at an operating temperature of 350 °C. The use of MIP by Mousazadeh et al. [104] allowed the determination of hexanal with an LOD of 1.1 ppm in the linear range of 2.5–300 ppm.

Examples of MIP-based optical sensors for VOC analysis are presented in Table 6.

### 4.3. MIP-based mass-sensitive sensors

Mass-sensitive sensors are used to detect and quantify the mass changes occurring due to various interactions, such as adsorption or desorption of analytes. When used in mass-sensitive sensors, MIPs can be coated onto a transducer surface, such as QCM and surface acoustic wave (SAW) device, or a microcantilever. These sensors are designed with a polymer matrix that has been "imprinted" with a specific molecule, which allows it to selectively bind to that molecule and produce a measurable signal. However, these sensors can sometimes suffer from poor sensing performance due to poor selectivity, sensitivity, or stability. One approach to improving the sensing performance of MIP-based piezoelectric VOC sensors is to introduce conductive nanomaterials as in electrochemical sensors. Tang et al. [109] exhibited an electro-polymerized MIP layer on a $TiO_2$-NT array to determine formaldehyde (Fig. 3E). The nanotube array was used to increase the porosity and the surface area. Incorporating nanomaterial leads to relatively high LOD and good response/recovery time.

Later, Chul Yang and coworkers [133] proposed a sensor design with imprinted polymer films of hierarchical pore structures. They utilized the lithographic imprinting method to fabricate imprinted pore-patterned thin film composed of poly(2(trifluoromethyl)acrylic

**Table 6**
MIP-based electrochemical sensors for VOC analysis.

| Analyte | Sensor | Template molecule | Monomers for MIP preparation | Polymerization method | Detection method | Ref. |
|---|---|---|---|---|---|---|
| Hexanal | MIP-AuNPs on IDE | Hexanal | Methacrylic acid, ethylene glycol dimethacrylate, 2,2′-azobis-isobutyronitrile | Free radical polymerization | Conductivity | [104] |
| Acetaldehyde | MIP on IDE | Acedaldehyde | Pyrrole | Electropolymerization | Conductivity | [108] |
| Methanol | MIP-graphite composite on gold screen -printed elenctrode | Methanol | Poly(vinyl alcohol), glutaraldehyde | Free radical polymerization | Cyclic voltammetry and differential pulse voltammetry measurements | [129] |
| Butylated hydroxytoluene | MIP-graphene-glassy carbon electrode | Butylated hydroxytoluene | Pyrrole | Electropolymerization | Resistance | [26] |
| Methanol | Nanoparticles MIP on multiwalled carbon nanotubes on screen printed electrodes | Methanol | Poly(vinyl alcohol), glutaraldehyde | Free radical polymerization | Cyclic voltammetry or differential pulse voltammetry | [130] |
| 4-ethylphenol | MIP on glassy carbon electrode | 4-ethylphenol | Pyrrole | Electropolymerization | Differential pulse voltammetry | [131] |
| Acetone | MIPs and AuNPs nanocomposite on interdigited elctrode | Acetone | Methacrylic acid, ethylene glycol dimethacrylate, 2,2′-azobis-isobutyronitrile | Free radical polymerization | Conductivity | [126] |
| Eugenol | Polyacrylonitrile molecularly imprinted polymer embedded on graphite electrode | Eugenol | Acrylonitryle, ethylene glycol dimethacrylate | Free radical polymerization | Voltammetry | [132] |
| Furaneol | MIP - polyaniline nanocomposite | Furaneol | Methacrylic acid, ethylene glycol dimethacrylate, benzoyl peroxide | Free radical polymerization | Voltammetry and conductivity | [105] |
| Nonanal | MIP – AuNPs nanocomposite on IDE | Nonanal | Methacrylic acid, ethylene glycol dimethacrylate | Precipitation polymerization method | Conductivity | [105] |

acid-co-ethylene glycol dimetachrylate-co-styrene) (poly (TFMAA--co-EGDMA-co-ST)). In 5 min, they obtained a hierarchical porous MIP-coated QCM sensor under UV irradiation. Their results showed promising performances, including the adsorption capacity and sensitivity of the MIP films toward formaldehyde.

Although QCM sensors are highly sensitive, their fragility and mechanical instability can be obstacles to their practical application. The quartz crystal is delicate and can easily break or become damaged during handling, transportation, or use. This fragility can limit the sensor's lifespan and make it difficult to use in harsh or rugged environments. Additionally, the mechanical instability of QCM sensors can cause drift in the baseline signal and reduce the accuracy and precision of the measurements. This instability can be caused by changes in temperature, humidity, or mechanical stress, which can affect the resonance frequency of the crystal.

The application of quartz crystal microbalance (QCM) in the realm of LC diagnosis has been exemplified in the work of Gashimova and colleagues [134]. They employed an electronic nose based on the QCM sensor to analyze skin samples from LC patients. The study demonstrated a sensitivity of 69 and specificity of 68 when compared to young healthy subjects, while against old healthy subjects, the sensitivity and specificity were reported as 74 and 66, respectively. Notably, this research also delved into the analysis of patient breath using gas chromatography in conjunction with mass spectrometry. The combined utilization of VOCs analysis technologies showcases a comprehensive and promising approach in the quest for enhanced diagnostic methodologies. Table 5 provides an overview of various sensors based on MIPs, designed for the detection of volatile compounds. In recent developments, the diagnosis of COVID-19 has extended beyond traditional methods to incorporate advanced techniques such as surface plasmon resonance spectroscopy and QCM. Nilsson and colleagues have contributed to this field by employing a SARS-CoV-2 S-antigen–antibody capture mechanism on a QCM platform [135]. In their study, a total of 119 human serum samples were subjected to analysis, revealing 48 positive samples among the 59 molecular-positive cases [135]. This innovative approach highlights the potential of surface plasmon resonance spectroscopy and QCM in enhancing the sensitivity and accuracy of COVID-19 diagnosis, marking a significant advancement in the realm of diagnostic methodologies. Examples of MIP-based mass-sensitive sensors and detection parameters of MIP-based sensors are presented in Tables 7 and 8 respectively.

**Table 8**
Comparison of MIP-based sensors for volatiles detection.

| VOC | Molecular Imprinting Layer | LOD | Range | Ref. |
|---|---|---|---|---|
| Acetaldehyde | MIP | – | ppm range | [108] |
| Acetone | MIP-AuNPs | 66 ppm | 50–300 ppm | [141] |
| Acetone, ammonia | $SnO_2$ nanostructures | Ppm level | – | [102] |
| Ethanethiol | Pyrrole on a GCE | 0.3 mg $L^{-1}$ | 0.3–3.1 mg $L^{-1}$ | [142] |
| Ethanol | MIP-multimode fiber region | – | 100–500 ppm | [143] |
| Ethanol/ methanol | cM-$SnO_2$ MIP | – | 50–500 ppm | [144] |
| Formaldehyde | PPy | ppm level | – | [109] |
| Furaneol | MIP-PANI | – | – | [105] |
| Hexanal | MIP-MWCNTs | 10 ppm | 10–200 ppm | [145] |
| Hexanal | MIP-Terahertz metamaterial sensor | – | 100–900 ppm | [146] |
| Hexanol | Au-MIP | 1.1 ppm | 2.5–300 ppm | [104] |
| Hydrogen peroxide | T-MIP-PtPd NFs | 0.005 μM | 0.01–5000 μM | [147] |
| Isopropanol | IPA-MIP | Ppb level | – | [27] |
| Methanol | MIP−graphite composite | 126 μmol $dm^{-3}$ | – | [129] |
| Nonanal | MIP-AuNPs | 4.5 ppm | 2.5–100 ppm | [14] |
| Pentane | MIP | – | 1–20 ppt | [148] |
| Trimethyloamine | ZnO–$SmFeO_3$ MIP | 5 ppm | – | [149] |

### 4.4. Applications of MIP-based sensors in volatile biomarkers detection

Currently, exogenous VOCs are bringing significant attention due to their interactions with biological systems, offering valuable insights into health and disease. Conversely, endogenous VOCs are generated through the body and are subsequently transported *via* the bloodstream. Inflammatory and abnormal metabolic pathways influence the concentration of endogenous VOCs making them potential specific biomarkers for clinical diagnosis and disease monitoring [55]. The primary volatile biomarkers associated with diseases in the human body are included in Tables 1 and 2 Hexanal is identified as a biomarker for LC, with its concentration found to be elevated in the breath of patients compared to that of healthy individuals [60]. Janfasa and colleagues used MIP nanoparticles (NPs) and multi-walled carbon nanotubes (MWCNTs) to develop a chemiresistive sensor for its detection [145]. These sensors, comprising a thin film of chemically sensitive material on an

**Table 7**
MIP-based mass-sensitive sensors for VOC analysis.

| Analyte | Sensor | Template molecule | Monomers for MIP preparation | Polymerization method | Detection method | Ref. |
|---|---|---|---|---|---|---|
| Formaldehyde | MIP-titanium dioxide nanotube array | Formaldehyde | Pyrrole | Electropolymerization | QCM | [109] |
| Formaldehyde | Hierarchical porous MIP-coated QCM | Formaldehyde | 2-(Trifluoromethyl) acrylic acid, ethylene glycol dimethacrylate, 1-hydroxycyclo-hexyl phenyl ketone | Photopolymerization | QCM | [133] |
| Formaldehyde | MIP-coated QCM | Formaldehyde | Methacrylic acid, ethylene glycol dimethacrylate, styrene, allyl amine, 2,2′-azobis-isobutyronitrile | Free radical polymerization | QCM | [136] |
| D-limonene, myrcene, α-pinene, decanal, linalool, β-ocimene | MIP-coated QCM | D-limonene, myrcene, α-pinene, decanal, linalool, β-ocimene | Methacrylic acid, ethylene glycol dimethacrylate, 2,2′-azobis-isobutyronitrile | Free radical polymerization | QCM | [137] |
| Propanoic acid, hexanoic acid, octanoic acid, | MIP-spin coated QCM | Propanoic acid, hexanoic acid, octanoic acid, | Acrylic acid | Free radical polymerization | QCM | [138] |
| Ammonia | MIP-polyvinyl acetate, boric acid coaed qcm | Ammonia | Vinyl acetate | Free radical polymerization | QCM | [139] |
| Dimethyl methyl phosphonate | MIP-coated SAW oscillator | Sarin acid | o-phenylenediamine | Cyclic voltammetry polymerization | SAW | [140] |

interdigitated electrode (IDE) platform, exhibit changes in electrical resistance when exposed VOCs. However, their broad responsiveness to a wide range of gas phase analytes has been a significant limitation. To enhance selectivity, the authors addressed this problem by utilizing polymeric nanocomposites based on MIP NPs as a thin film and incorporating MWCNTs to enhance conductivity. The underlying mechanism involves the nanocomposite film's increased electrical resistance upon exposure to the target analyte. This change is attributed to VOC adsorption and film swelling. Interaction of analytes with functional groups in the polymeric network of MIP NPs leads to polymer swelling. Hexanal-imprinted polymer NPs were synthesized *via* precipitation polymerization and the sensor was capable of detecting hexanal down to 10 ppm and distinguish it from other similar molecules. In a subsequent study conducted by Mousazadeh et al., the limit of detection (LOD) was significantly improved to 1 ppm [104]. This advancement was achieved through the utilization of a nanocomposite consisting of AuNPs and MIPs, drop-casted onto IDEs to form a thin sensing element. The sensor exhibited notable selectivity for hexanal over other potentially interfering analytes. Notably, the sensor demonstrated the capability to detect hexanal in the headspace of diverse biological matrices, including cell culture medium, serum, plasma, urine, and saliva. Additionally, an alternative approach to hexanal detection utilizing MIPs with terahertz spectroscopy and metamaterials has been documented [146]. Metamaterials, characterized by artificially designed structures with unique electromagnetic properties due to the periodic arrangement of subwavelength elements, play a crucial role in this method. Leveraging strong field enhancement effects, this approach enables the sensitive detection of minute quantities of both chemical and biological substances. MIPs-based detection of hexanal by a terahertz spectroscopy approach using metamaterials has also been reported. Metamaterials can be described as artificial materials with unique electromagnetic characteristics composed of periodically arranged subwavelength elements, which facilitates strong field enhancement effects and enables the sensitive detection of very small amounts of chemical and biological substances. In this method, the hexanal-imprinted MIPs coating on the metamaterial undergoes swelling upon specific hexanal adsorption. Consequently, this swelling induces a decrease in the effective RI of the MIPs, leading to a blue shift in the resonance of the modified metamaterial. The biosensor exhibited the capability to detect gaseous hexanal concentrations within the range of 100–900 ppm. Additionally, the authors demonstrated that the sensor can be reused at least three times by purging the surface with nitrogen, restoring it to its original state.

Nonanal, identified as a cancer cell metabolite and a biomarker for LC, also exhibits elevated concentrations in the exhalation of LC patients compared to healthy individuals [60]. According to the Cancer Odor Database (COD), nonanal also significantly increases in the biological matrices of patients with colorectal, breast, ovarian, gastric, and esophageal cancers in comparison to healthy individuals. Jahangiri-Manesh and collaborators reported the development of a chemiresistive sensor for nonanal detection [14]. The sensor utilized an active layer drop-casted onto IDEs, consisting of a conductive composite comprising MIPs and AuNPs synthesized in an organic solvent. The changes in conductivity induced by the presence of the target analyte were accurately measured using a potentiostat in a two-electrode system. The sensor demonstrated a LOD of 4.5 ppm and a linear range of 2.5–100 ppm. Furthermore, it successfully detected nonanal in the headspace of nonanal-spiked human plasma. To assess the sensor's selectivity, the MIP-coated electrodes were exposed to 100 ppm of various gas analytes. The sensor exhibited a notably higher response to nonanal compared to hexanoic acid, heptanoic acid, and decanal. In the case of hexanoic acid and heptanoic acid, both containing carboxyl functional groups, these analytes failed to interact with the cavities specifically imprinted for the aldehyde group of nonanal in the MIPs. Decanal, despite sharing the same functional group as the template molecule, encountered challenges entering the nonanal-specific cavities due to its larger hydrocarbon chain. However, interference from hexanal arises due to its identical functional groups (aldehyde) to the target analyte, coupled with a smaller volume resulting from a shorter hydrocarbon chain, leading to a greater diffusion rate than nonanal in the MIP.

Diabetes mellitus is frequently associated with specific volatile biomarkers, particularly isopropanol (IPA) and acetone, identifiable in the EB of individuals with the condition [71]. In a study by Pathak and colleagues, a cost-effective optical system was developed utilizing a glass slide coated with IPA-imprinted MIPs for the selective detection of IPA vapor, employing a wavelength interrogation technique [123]. The sensor's sensing layer was drop-casted onto a small glass slide, and optimization procedures were applied to enhance synthesis, polymerization, and exposure time. The results demonstrated a noticeable wavelength shift at elevated IPA concentrations, with a robust linear response maintained over 120 min of IPA exposure. To assess the selectivity of the IPA–MIP-coated sensor, experiments were conducted using pure ethanol and methanol, chosen for their similarity to alcohols present in the EB of diabetic patients. The findings revealed a more pronounced intensity for IPA, establishing the sensor's capability for selective detection amidst comparable compounds. Regarding acetone, a chemiresistive sensor has been described by Jahangiri-Manesh and collaborators [141]. The sensing layer was made of acetone-imprinted polymers and AuNPs synthesized in organic solvent as the conductive nanomaterials. Notably, this sensor operates at room temperature and demonstrates the capability to detect acetone with a limit of detection (LOD) of 66 ppm. To evaluate selectivity, the sensor underwent testing with various analytes. As anticipated, molecules with smaller dimensions but the same functional group exhibited greater penetration into the polymer cavities, resulting in a more substantial sensor response. This was evident in the cases of acetaldehyde and formaldehyde. In efforts to enhance differentiation and categorization of different analytes, the researchers employed multivariate classification, specifically principal component analysis (PCA)-linear discriminant analysis (LDA). The outcomes demonstrated that PCA-LDA successfully distinguished acetone from other non-target analytes, providing an advanced analytical approach for enhancing selectivity in acetone detection. Recently, a novel handheld electronic device for early LC detection by analyzing exhaled breath was presented by Emam et al. [148]. Utilizing an electrochemical gas sensor with a graphene and Prussian blue layer on a chromium-modified silicon substrate, the device employs MIPs for selective biomarkers binding. The device's efficacy is demonstrated through its ability to detect biomarker concentrations at the 1–20 ppt level. Equipped with a printed circuit board for resistance measurement and Bluetooth connectivity for data transmission to a smartphone app, this device offers promising potential for non-invasive LC diagnostics (Fig. 4).

MIPs are promising for the development of sensitive and selective sensors for organic vapor sensing. However, humidity interference remains a challenge for MIP gas sensors [151,152]. An unconventional approach to overcome this challenge involves incorporating pyrolyzed lotus leaves into the polymerization mixture, enhancing the final material's hydrophobic properties [153]. This hydrophobicity enhancement is attributed primarily to the nanostructure of the leaf; similar improvements have been observed when transitioning from MIP films to nanoparticles [136]. Another potential opportunity for exploiting this phenomenon involves imprinting with oligomers or polymers followed by crosslinking, as discussed previously [154]. Biologically sourced polymers could potentially enhance MIP performance while addressing environmental concerns. Recent advancements in silk-based MIP nanoparticles for aqueous applications lay the groundwork for this approach [155,156]. Especially fascinating is the possibility to prepare biological molecularly imprinted nanoparticles (BioMIPs), starting from called SilMA, a biocompatible and biodegradable natural protein extracted from silk [157,158], where peptides can be imprinted by using silk fibroin as the macromolecular monomer. Moreover, the fabrication

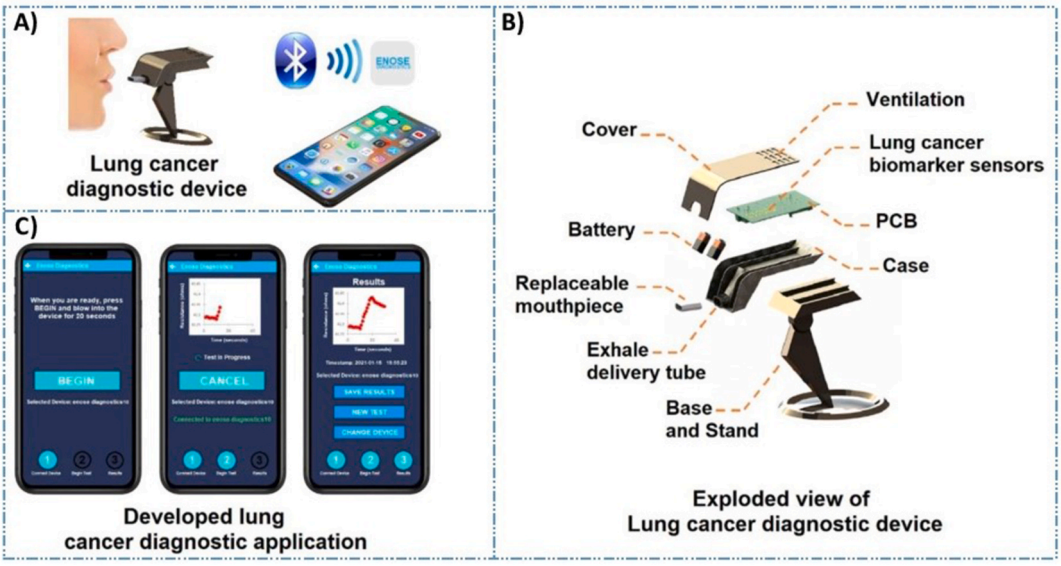


**Fig. 4.** Example of handheld LC diagnosis device based on MIP sensor. A) A patient blow into the replaceable mouthpiece and the results will be shown on his/her smartphone instantly. B) The mobile application that graph the data during the test, and C) the exploded view of the proposed lung cancer diagnosis handheld device. Reproduced with a permission from Ref. [148].

of chemiresistive sensors by inkjet printing is recognized as a breakthrough in gas-sensing applications. However, a challenge with this technology is in improving the cross-selectivity of the sensor array. Ye et al. [159] introduced ketjen black ink and molecularly imprinted sol–gel (MISG) inks to facilitate the production of a chemiresistive sensor array entirely printed using inkjet technology. This approach enables precise detection of volatile organic acids (biomarkers for colonic mucosa health diagnosis) at the molecular level. Furthermore, the proposed sensor array showed strong sensor robustness with excellent consistency, durability, bending, and humidity resistance.

## 5. Future prospects

Despite a few decades of development, sensors and biosensors' practical applications in diseases diagnostics is still in its infancy. MIP-based sensors call for significant improvements to become precise diagnostic tools. Following the efforts of the World Health Organization certain criteria were specified, the aim of which is improvement of efficiency of early diseases diagnostics, including application of the sensors and biosensors. Decent price, sensitivity, specificity, user friendliness, fast response, reliability and accessibility are the basic factors upon evaluation of disease diagnosis tests [160]. An emphasis on these factors influences on development of the biosensors, which seem to be best-suited tools due to their ability of point of care operation, fast response, specificity, sensitivity, possibility of miniaturization, reasonable price, *etc*. Commercialization of the MIP-based and micro/nanostructure-based sensing devices requires improvement of the mass-scale production methods [105]. Various techniques are available for production of imprinted polymers, which are currently popular for synthesizing them in nanoparticle form. While the processes for producing MIPs can be straightforward, they may pose risks to operators' health and the environment. Indeed, the manufacture of MIPs can be hazardous, particularly when involving dangerous reagents and solvents, and their usage and disposal can also raise health and environmental issues [161]. In the context of the United Nations' Sustainable Development Goals (SDGs) outlined in the 2030 Agenda for Sustainable Development, there is a current focus on minimizing risks associated with chemical synthesis. This can be achieved through the adoption of green chemistry principles, which aim to develop environmentally friendly chemical processes that enhance both human well-being and environmental quality. Furthermore, the envisioned large-scale production of MIPs necessitates the implementation of greener strategies. These strategies, encapsulated by the term GREENIFICATION, advocate for minimal waste generation and treatment, the utilization of renewable reagents, mild polymerization conditions, and the use of environmentally friendly solvents [162].

The selection of the appropriate nanomaterials should consider their compatibility with the fabrication process, their electrical and chemical properties, and their potential impact on the overall sensor performance. Utilizing nanomaterials in combination with printing techniques may be beneficial to realize the mass production of MIP-based electrochemical sensors [163]. Investigation of computational modelling MIPs structures capable of binding particular VOCs are still necessary. A progress in development of multiplexed devices, signal processing and parameters standardization is needed. The progress of MIP-based sensor technology has yielded numerous advantages in VOC detection. However, significant challenges persist in broadening their practical applicability. For instance, the optimization of manufacturing conditions for MIPs, such as the selection of appropriate monomers and solvents, can be labour-intensive, costly, and environmentally unsustainable. Furthermore, the utilization of single-template imprinting methodologies fails to provide active sites conducive to the selective detection of multiple VOC targets. Continuous microfluidic reactors offer a promising approach to ensuring the high quality of fabricated MIPs [164]. These reactors facilitate the creation of homogeneous products with enhanced attributes such as high capacity, selectivity, and binding affinity homogeneity. A deeper understanding of molecular interactions is crucial for the development of effective MIPs characterized by abundant specific binding sites and robust physical/chemical stability. Leveraging computer-assisted design strategies, such as second-order Moller–Plesset and density functional theory, can aid in designing and selecting functional and cross-linked monomers more efficiently. Such strategies have the potential to expedite MIP formulation, particularly when dealing with toxic or costly reactants, thereby reducing production time. To enhance the versatility of MIP-based sensors, efforts should be directed towards developing sensors capable of recognizing multiple target analytes simultaneously (Fig. 5). The multi-template imprinting method, which employs two or more targets as templates, holds promise in this regard. By incorporating multiple templates, a single MIP can be designed to possess multiple types of recognition sites, enabling it to

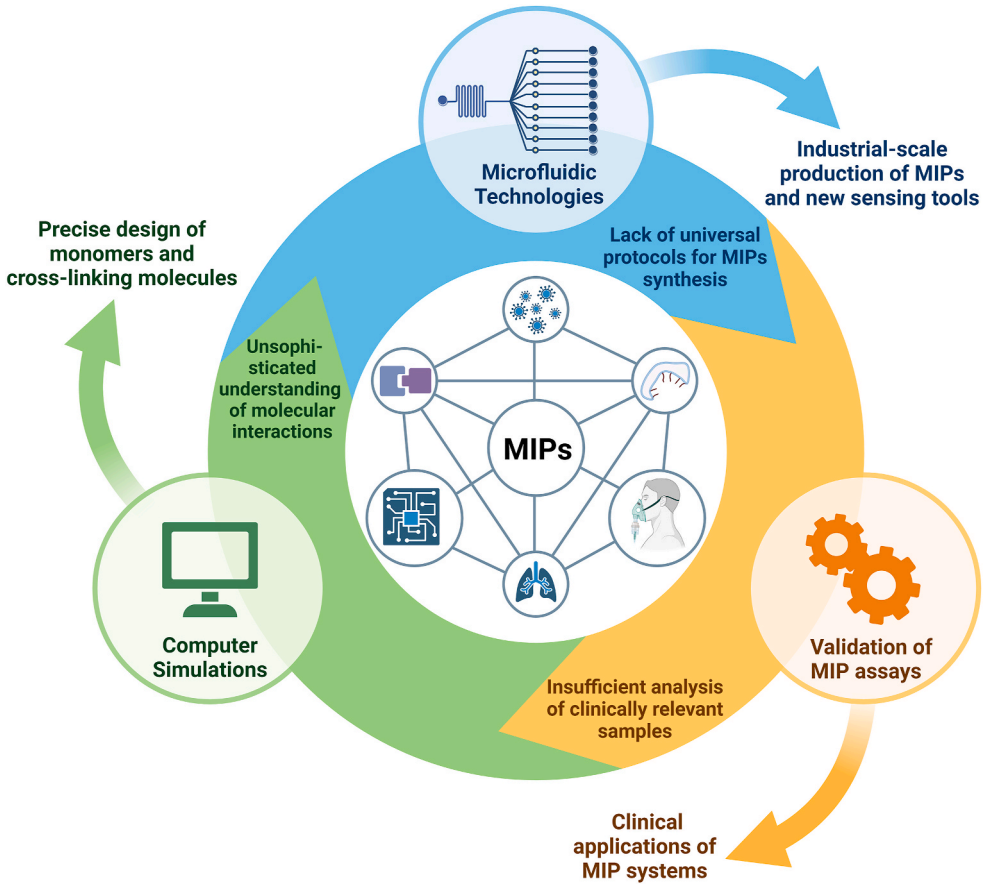


**Fig. 5.** A diagram with the main bottlenecks that impede progress in the field of MIP-based sensors and possible directions of outcomes and developments. Created with biorender.com.

bind various targets concurrently. It is essential to apply the template removal process uniformly to MIPs using a consistent methodology [31]. Additionally, the integration of modern devices and instruments for signal acquisition represents a viable approach for *in situ* analysis of trace-level targets such as volatile biomarkers. Microfluidic systems offer significant advantages for sensing applications, including high-speed serial processing, controlled structuring of cell size, and a high degree of parallelization, which are not achievable with traditional platforms. Integration of a chemiresistor with a microfluidic channel enables the fabrication of microfluidic platforms. The surface coatings on the microfluidic channel play a crucial role in influencing the diffusion, adsorption, and desorption of VOCs as they flow through the channel. Within a microfluidic platform, an MIP layer can be fabricated on the surface of a microchannel to serve as the recognition element. Consequently, such a platform can function as a portable, disposable, cost-effective, user-friendly, and highly sensitive/selective sensing tool for VOCs. Moreover, utilizing a combination of various sensors within a single sensing platform, such as the electrochemical QCM, can provide a comprehensive chemical information in a single measurement.

The incorporation of MIPs in biosensors for disease biomarker detection multifaceted set of advantages. Their customizable nature allows tailoring for a diverse array of biomolecules, encompassing proteins, peptides, and small organic molecules. Stability under varying conditions contributes to the robustness of biosensors over time, a critical factor for reliable diagnostics. Their customizable nature allows tailoring for a diverse array of biomolecules, encompassing proteins, peptides, and small organic molecules. Stability under varying conditions contributes to the robustness of biosensors over time, a critical factor for reliable diagnostics. Cost-effectiveness characterizes MIP synthesis, rendering these biosensors economically viable for large-scale production and potentially enhancing diagnostic accessibility [163]. Depending on design specifics, some MIP-based biosensors offer reusability, aligning with cost efficiency and environmental considerations. Their versatility extends across various biomarkers associated with different diseases, providing a broad diagnostic applicability. Additionally, some MIP-based biosensors enable real-time monitoring of biomarker concentrations, offering timely insights for disease diagnosis, progression tracking, and treatment monitoring.

However, implementation in a diagnostic context is also accompanied by a set of challenges. MIPs achieve high selectivity by imprinting the polymer with the target molecule's shape. While providing a promising solution to selectivity concerns, challenges arise when VOCs used as templates have few distinct functional groups, potentially causing imprinted sites to interact with chemically similar molecules and leading to cross-sensitivity. Similarly-sized interferences with comparable steric configurations may compete for MIPs binding sites, elevating the risk of false-positive results. In the healthcare context, this issue is critical, impacting disease detection accuracy and posing a risk of misdiagnosis and unnecessary medical interventions. In certain cases, MIPs may exhibit lower binding affinities compared to natural receptors. Assimilating diverse transduction methods to translate molecular recognition events into measurable signals demands a nuanced balance between sensitivity, specificity, and ease of integration. The effectiveness of MIP-based biosensors can be influenced within complex biological matrices, where the presence of numerous interfering substances may compromise sensor specificity. Inherent challenges arise from the variability of biological samples and the intricate complexities of real-world diseases, aspects often not comprehensively addressed in biosensor design. This highlights the importance of interdisciplinary collaboration and the imperative to conduct tests using actual patient

samples in developmental studies, aligning with regulatory requirements. These efforts are pivotal in enhancing the reliability of MIP-based biosensors in detecting target molecules. Such endeavors ensure the dependability and applicability of new efficient diagnostic tools across the spectrum of diseases in real-world diagnostic settings. Several diseases could share common VOC biomarkers, making the identification of disease-specific biomarkers difficult, when based only on breath analysis [165]. Although broad national and international collaborative research projects are hard to establish for state-of-the-art technologies, the standardization of protocols and guidelines for breath sample collection, analysis, and interpretation is crucial to ensure consistency across studies, facilitating result comparison from different research groups.

Most of the MIP-modified sensors developed to date have been utilized for the precise and selective identification of biomarkers in liquid samples [166]. In liquids, achieving selectivity can be pursued through various methods, although many of these are unsuitable for gas-phase analysis. However, when applied to gaseous samples, the spatial arrangement of imprinted recognition sites undergoes alterations upon drying in air. Moreover, in gaseous samples, the transfer of template molecules between the sample matrix and the imprinted recognition sites within the densely cross-linked polymer network is limited, often leading to extended sampling durations. The volatile nature of the compounds presents difficulties in ensuring consistent and reliable interactions with the imprinted cavities of the polymers. VOCs may have varying levels of volatility, which can affect their ability to bind to the polymer matrix effectively. Additionally, the kinetics of diffusion of volatile compounds into the polymer matrix can be slow, leading to prolonged response times and reduced sensitivity of the sensor. MIP-modified sensors designed for gaseous samples typically experience extended sampling durations. Unlike very volatile organic compounds (VVOCs) and VOCs, semi-volatile organic compounds (SVOCs) exhibit lower volatility, resulting in constrained concentrations in the air [167]. Cowen and Cheffena [33] suggested that porogen imprinting, holds significant promise in gas sensors technology and could potentially complement traditional template imprinting methods. However, the latter generally remains preferable for achieving selective and sensitive detection of gaseous molecules. There are speculations that porogen imprinting and template imprinting could be used together, for instance, in creating a porogen-imprinted switch. This material would demonstrate high affinity and sensitivity for a specific analyte in template-imprinted binding sites only upon exposure to a second porogen-imprinted substance [33]. It is crucial to delve deeper into the understanding of the interactions between VOCs and MIPs. This involves comprehensive studies on the selection of appropriate monomers and templates, as well as optimization of the synthesis conditions to enhance the affinity and selectivity of MIPs towards volatile compounds. Consequently, detecting SVOCs in the gas phase remains a significant challenge. Developing novel synthesis methodologies is essential to address the challenge of synthesizing MIPs for electrically charged and highly water-soluble chemical compounds in MIP technology. Furthermore, the development of novel synthesis methodologies tailored specifically for volatile compounds can facilitate the creation of MIPs with improved performance characteristics. In addition to synthesis optimization, advancements in sensors' design and integration are essential. Incorporating MIPs into sensor platforms that provide efficient diffusion of volatile compounds to the polymer matrix and rapid signal transduction can enhance the overall performance of the sensor. Integration of MIP-based sensors with complementary technologies, such as microfluidics or signal amplification techniques, can further improve sensitivity and response times. To address the general challenges associated with using MIPs for volatile compounds requires a cross-disciplinary combined research, involving expertise in polymer chemistry, biochemistry, sensor engineering, and analytical science [168]. By systematically investigating the underlying mechanisms and employing innovative strategies in synthesis and sensor design, it is possible to overcome these challenges and harness the full potential of MIPs for VOCs detection in sensor applications.

Researchers actively strive to enhance the selectivity of MIP-based biosensors, with ongoing research concentrating on advancements in design, optimization of synthesis processes, and innovative sensor configurations to minimize cross-sensitivity. Synthesis methods still exhibit occurrences of unintended adsorption of non-targeted molecules, consequently increasing the interference issues [169,170]. To address this issue, scientists have explored increasing the concentration of the template molecule. The aim is to occupy a large number of functional groups within the monomer, thus minimizing non-specific binding. However, this strategy frequently encounters a limitation, as surpassing a specific threshold of template concentration can hinder the polymerization process [171]. Alternative strategies have been explored by Ref. [172], where MIP-based sensors selectivity were improved by incorporating suitable surfactants into MIPs, effectively overcoming non-specific adsorption problems and thus improving target recognition accuracy. With the growing awareness of climate change and the call for a more environmentally friendly lab procedures, it is anticipated that the utilization of "green" electrochemical synthesis within the MIP research community continue to increase. Electro-polymerization might be categorized as an environmentally friendly approach for MIP synthesis, it allows for "greener" synthesis conditions, including the use of aqueous media and room temperature, while also eliminating the need for toxic and hazardous reagents [173]. Furthermore, advancements in sensor technology over time have facilitated the large-scale production of cost-effective, multiplex sensor components, such as SPEs and paper-based transducers compatible with electrochemical synthesis and analysis [174]. When combined with compact electrochemical devices, such as a portable potentiostat controlled by a mobile phone software, these components could open up new possibilities for creating a valuable alternative diagnostic platforms for screening diseases.

Additionally, the potential for MIP-based sensors in wearable applications is significant, combining electronics, materials science, and nanotechnology to develop highly efficient, adaptable, and user-friendly systems for personalized and real-time monitoring. By integrating MIPs with advanced microfluidic chip technology, signal processing, and transmission electronics, modern non-invasive devices for real-time analysis of disease biomarkers could become feasible [175]. As technology advances, this approach is expected to lead to more widespread and extensively utilized sensing applications [23].

Indeed, a breakthrough in this domain could pave the way for intelligent, personalized medicine, enabling initial screenings to be conducted comfortably at patients' homes and then directly accessed and evaluated by medical professionals before scheduled appointments. Enhanced effectiveness in therapeutic treatments, facilitated by the early detection of diseases through advanced technologies, contributes significantly to the objectives of precision medicine. These advancements aim to mitigate healthcare expenses, shorten hospital stays, and capitalize on preemptive, prophylactic interventions. By intervening prior to the onset of disease symptoms, such strategies aim to abbreviate the disease course, mitigate secondary infections, and potentially influence disease epidemiology by curbing exposure rates. By preempting or lessening the periods during which presymptomatic individuals are contagious through early interventions, there is potential to diminish the transmission of diseases from person to person and consequently reduce the exposure of healthy individuals.

## 6. Conclusions

In recent years, there has been a significant growth in the development of sensing platforms tailored for VOCs analysis alongside the concurrent advancement of associated analytical methodologies. Leveraging the inherent advantages of MIPs, such as their physical and chemical stability, as well as their selectivity, various MIP-based sensors have been devised utilizing chemiresistive, piezoelectric, and optical

techniques. The recommended performance exhibited by MIP-based sensors has spurred the refinement and deployment of economically viable devices for VOC detection. Chemiresistive sensors based on MIPs have demonstrated enhanced detection parameters compared to alternative MIP-based counterparts for VOC detection, including volatile biomarkers. Moreover, the utilization of MIPs in tandem with advanced materials such as nanoparticles (*e.g.*, gold NPs), carbon-based materials (*e.g.*, MWCNs), and conductive polymers (*e.g.*, poly3-hexylthiophene) holds promise to further augment the sensing capabilities.

Concentrations of volatile biomarkers in EB, often found at levels in the parts per trillion (ppt) and parts per billion (ppb) range. Therefore, distinguishing between a healthy patient and an individual with an illness based on their VOC profile is a formidable challenge, necessitating the deployment of purpose-built sensory systems. This approach has the potential to reduce expenditures associated with routine medical tests and minimize doctor's interventions. Above all, it holds the promise of lowering morbidity and mortality rates among patients. Through the implementation of well-designed POC sensors, it may be feasible to curtail expenses on laborious laboratory diagnostic tests, making early disease detection and timely medical intervention more likely.

The integration of MIPs into diagnostic platforms can furnish high measurement sensitivity and selectivity in POC mode. However, further developments, including adaptation and real-world testing involving patients, are imperative. Progress is also stimulated by micro- and nanotechnology, leading to innovative functional microfabricated sensor platforms. Integrated microfluidic technologies can combine sample pre-concentration and detection in a single device, potentially simplifying and standardizing diagnostic sample collection. Advancements in nanomaterials, such as nanoparticles, carbon nanotubes, graphene, and 2D materials, are enhancing signal processing and data quality.

Furthermore, it is vital for these systems to operate without requiring expert knowledge, especially in limited medical diagnostic scenarios, which holds substantial commercial significance. Commercial success appears to hinge on the customization of applications to meet the end-user's demands for a precise, cost-effective, and user-friendly biosensor. This objective seems attainable through the evolution of MIP-based sensor technology.

## CRediT authorship contribution statement

**Tomasz Wasilewski:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Funding acquisition, Conceptualization. **Sinem Orbay:** Writing – original draft, Conceptualization. **Nathália F. Brito:** Writing – original draft, Conceptualization. **Karol Sikora:** Writing – original draft. **Ana Claudia A. Melo:** Supervision. **Matias E. Melendez:** Supervision. **Bartosz Szulczyński:** Supervision. **Amitav Sanyal:** Supervision. **Wojciech Kamysz:** Supervision. **Jacek Gębicki:** Supervision.

## Declaration of competing interest

The 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.

## Data availability

No data was used for the research described in the article.

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